

Public Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research December 3, 2014 – January 29, 2015

Table of Contents

Commenter	Comment Number	Page Number
Academy Health	Comment #96	104
Alzheimer's Association	Comment #83	65
American Academy of Orthopaedic Surgeons	Comment #131	183
American Heart Association/American Stroke Association	Comment #76	52
American Psychological Association	Comment #140	207
American Physiological Society	Comment #79	59
American Society of Clinical Oncology (ASCO)	Comment #138	201
American Society of Hematology	Comment #108	132
Ascherio, Alberto	Comment #45	20
Association of American Medical Colleges	Comment #147	222
Assoc. of American Universities & Assoc. of Public and Land-grant Universities	Comment #151	232
Association of Clinical Research Organizations	Comment #123	162
Association of Clinical Research Professionals	Comment #142	210
Association for the Accreditation of Human Research Protection Programs	Comment #91	90
Beck, Roy W.	Comment #59	32
Benatar, Michael	Comment #56	25
Bertrand, Kimberly	Comment #48	21
Biomedical Research Alliance of New York (BRANY)	Comment #84	66
Blackwell, Karen	Comment #69	44
Brewer, Barry L.	Comment #57	29
Brigham and Women's Hospital	Comment #158	251
Brott, Thomas G.	Comment #20	9
Byars, William D.	Comment #43	20
Campbell, Thomas	Comment #117	153
Cancer Leadership Council	Comment #143	213
Chadwick, Gary	Comment #70	44
Cherokee Nation	Comment #149	228
Children's Hospital of Philadelphia	Comment #95	101
Christianson, Karen	Comment #68	43
Clayton, Anita H.	Comment #86	72
Cleveland Clinic	Comment #129	178
Cohen, Ezra	Comment #47	21
Collins, Linda M.	Comment #37	16
Community-Campus Partnerships for Health	Comment #157	247
Consortium of Independent Review Boards	Comment #152	235
Cotton, Mark	Comment #121	161
Council of Ivy League Presidents	Comment #115	150
Council on Governmental Relations	Comment #103	121
Cystic Fibrosis Foundation	Comment #127	170
Devon, Holli A.	Comment #28	172
East Carolina University	Comment #166	268
EMMES Corporation	Comment #153	237
Emory University	Comment #80	60

Public Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

Commenter	Comment Number	Page Number
Endocrine Society	Comment #92	93
Federation of American Societies for Experimental Biology	Comment #64	37
Feldman, James	Comment #67	40
Feun, Lynn	Comment #23	11
Fontana, Margherita	Comment #105	125
French, William J.	Comment #16	8
Gabbert, Sherri	Comment #13	7
Ganley-Leal, Lisa	Comment #54	23
Gidding, Samuel S.	Comment#2	5
Gilbert, Donald L.	Comment #19	9
Goodman, Sherry H.	Comment #15	8
Green, April	Comment #74	50
Halstead, Linda	Comment #141	209
Harabin, Andrea	Comment #18	9
Hartmann, Katherine E	Comment #159	257
Harvard Medical School	Comment #97	106
Harvard Medical School, Teaching Hospital	Comment #128	172
Heath, Erica	Comment #118	154
Heinritz, Patrick	Comment #36	16
Herndon, Mary R.	Comment#1	5
Hood, Robert	Comment #32	14
Horn, Evelyn	Comment #17	8
Hull, Pamela C	Comment #6	5
Hummingbird IRB	Comment #11	7
Imperato-McGinley, Julianne	Comment #40	17
Indian Health Services	Comment #164	266
Indiana University	Comment #134	194
Infectious Diseases Society of America	Comment #124	165
Johns Hopkins University Center for Clinical Trials	Comment #42	210
Johns Hopkins University School of Medicine	Comment #58	30
Jurnack, Joy	Comment #63	36
Kaiser Permanente	Comment #154	241
Kentucky Children's Hospital	Comment #72	46
Kato, Gregory	Comment #46	20
Khan, Seema	Comment #30	13
Kim, Emily	Comment #55	23
Koros, Paul	Comment #33	15
Klibanski, Anne	Comment #89	83
Kopras, Elizabeth	Comment #35	15
Kramer, Skyler	Comment #120	160
Leaders Engaged on Alzheimer's Disease	Comment #119	156
Ledger, Elizabeth	Comment #165	268
Linakis, James G.	Comment #22	10
Lok, Anna	Comment #53	23
Lowrance, Debra	Comment #10	6
Mallett, Gail	Comment #26	11
Massachusetts General Hospital	Comment #94	95
Mayo Clinic	Comment #75	51
McArthur, Jennifer	Comment #99	112
McFarlin, Barbara I.	Comment #9	6
McKinnell, James A.	Comment #8	6
McLean Hospital	Comment #128	172

Public Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

Commenter	Comment Number	Page Number
Medical University of South Carolina Children's Hospital	Comment #62	34
Mehta, Varsha	Comment #4	5
Miller, Jonathan E.	Comment #109	134
Morton, Jeremy	Comment #82	64
Mount Sinai Icahn School of Medicine	Comment #110	135
Nakaganda, Annet.	Comment #122	161
National Biomedical Research Ethics Council	Comment #107	129
National Science Board	Comment #163	264
NICHD Neonatal Research Network Members	Comment #87	73
N. American Society for Pediatric Gastroenterology, Hepatology & Nutrition	Comment #144	215
Northwestern University	Comment #126	168
Orthopaedic Research Society	Comment #104	123
Ozbolt, Judy	Comment #31	14
Papajorgji-Taylor, Dea	Comment #161	260
Parkinson's Iction Network	Comment #125	167
Partners Health Care System	Comment #88	77
Pediatric Dermatology Research Alliance	Comment #150	229
Pediatric Orthopaedic Society of North America	Comment #162	261
Percy, Alan	Comment #66	40
Peterson, Andrew R.	Comment #136	198
Pfizer Inc.	Comment #146	220
Pieper, Barbara	Comment #5	5
Public Responsibility in Medicine and Research (PRIM&R)	Comment #139	204
Q. Janice	Comment #130	181
Rare Diseases Clinical Research Network.	Comment #114	149
Regan, Susan	Comment #98	112
Reider, Carson Robert	Comment #29	13
Resnick, Barbara	Comment #34	15
Rodavita	Comment #156	246
Rodriguez, Melanie M. Domenech	Comment #49	21
Rothman, Michael	Comment #11	7
Ruppman, Joan B.	Comment #21	10
Russell-Einhorn, Michele K	Comment #65	38
Sames, Lori	Comment #60	32
Sayre, Shelly	Comment #51	22
Schernhammer, Eva	Comment #50	21
Scoliosis Research Society	Comment #162	261
Secretary's Advisory Committee on Human Research Protections	Comment #167	270
Shirtcliff, Elizabeth	Comment #24	11
Shulman, Robert J.	Comment #52	23
Shuster, Evelyne	Comment #39	17
Slingluff, Craig	Comment #38	16
Smith, William	Comment #90	89
Society for Clinical Research Sites	Comment #85	68
Society for Women's Health Research	Comment #155	244
Spaulding Rehabilitation Network	Comment #97	106
Srilatha, D.	Comment #41	17
Stampfer, Meir	Comment #44	20
Stanford University	Comment #116	151
START Treatment & Recovery Centers	Comment #93	94
Strittmatter, Stephen M.	Comment #7	6
Study of Women's Health across the Nation	Comment #78	57

Public Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

Commenter	Comment Number	Page Number
Takashima, Akira	Comment #71	45
Trachtman, Howard	Comment #81	64
Tuchman, Mendel	Comment #61	33
Tufts University Health Sciences	Comment #77	54
Tuma, Pepin	Comment #160	260
University of Florida	Comment #102	116
University of Kentucky, Kentucky Children's Hospital	Comment #72	46
University of Massachusetts Center for Clinical and Translational Science	Comment #111	137
University of Miami School of Education & Human Development	Comment #27	12
University of Michigan	Comment #135	196
University of Pittsburgh Department of Biomedical Informatics	Comment #112	139
University of Pittsburgh Office of the Vice Chancellor	Comment #137	199
University of Rochester	Comment #133	190
University of Toledo College of Medicine	Comment #71	45
University of Virginia	Comment #100	113
University of Washington	Comment #101	114
University of Wisconsin-Madison	Comment #113	142
Vandenbroucke, Ruth	Comment #25	11
Vanderbilt University Medical Center Response	Comment #132	184
Virginia Commonwealth University	Comment #145	217
Walicke, Patricia	Comment #14	8
Walter Reed Army Institute of Research (WRAIR)	Comment #106	126
Washington University in St. Louis	Comment #73	48
Wassenaar, Douglas R.	Comment #12	7
Weill Cornell CTSC	Comment #40	17
WIRB Copernicus Group	Comment #148	225
Woody, George	Comment #3	5

Comment#1

Commenter: Mary R. Herndon, CRA
Date of comment: December 3, 2014

Comment:

I think use of a single IRB for multiple-site clinical studies is brilliant!

Comment#2

Commenter: Samuel S. Gidding, MD
Date of comment: December 3, 2014

Comment:

I am fully supportive.

Comment #3

Commenter: George Woody, MD
Date of comment: December 3, 2014

Comment:

I think it's a good idea.

Comment #4

Commenter: Varsha Mehta
Date of comment: December 3, 2014

Comment:

I support this policy.

Comment #5

Commenter: Barbara Pieper
Date of comment: December 3, 2014

Comment:

Go with single submission.

Comment #6

Commenter: Pamela C. Hull, Ph.D.
Date of comment: December 3, 2014

Comment:

I think this is a great idea to help speed up the pace of research discoveries by eliminating duplication of bureaucratic processes at multiple institutions. The IRB review process is extremely important, but it does not need to be repeated at multiple institutions for the same study. Using a single IRB of record for review purposes would be much more efficient, both in terms of time and resources.

Comment #7

Commenter: Stephen Strittmatter, MD, PhD

Date of comment: December 3, 2014

Comment:

I encourage you to adopt this policy

Comment #8

Commenter: James McKinnell, MD

Date of comment: December 3, 2014

Comment:

I applaud your work in streamlining IRB review of clinical research. The IRB process is lengthy and as mentioned in your background is not ideally set up to protect research subjects, due to institutional biases.

I would strongly encourage you to clarify a few points.

It should be clearly stated that the policy applies to all phases of research, not simply Phase III or Phase IV clinical trials as has been applied in some institutions. Delaying early phase research can have consequence for drug development and research.

It should be clearly stated that the policy applies to pediatric and vulnerable populations. There is no reason that research in these populations should be further hampered than it already has been.

The following statement is problematic. "A duplicate IRB review at a participating site would be counter to the intent and goal of the Policy, but the Policy does not prohibit any participating site from carrying out its own IRB review. If this approach is taken, the participating site should expect to bear the cost of the additional review." This language creates a giant loophole whereby institutions may force investigators to go through the local IRB. I would recommend specific language stating that an investigator may choose to have additional IRB review at their own institution, but that it would be up to the discretion of the principal investigator and Site investigator.

Changing the language is crucial or the clause will defeat the purpose of this policy. Congratulations on an important step forward.

Comment #9

Commenter: Barbara McFarlin, PhD

Date of comment: December 3, 2014

Comment:

I am in total support of the single IRB plan. In Chicago I work at a medical center where the institutions may only be blocks apart but require separate IRB applications for multi-site studies. I have spent over 120 hours to get a small study approved. Furthermore, we have to apply for separate IRB applications when collaborating faculty are on two campuses of our University of Illinois. I applaud your leadership on this important issue

Comment #10

Commenter: Debra Lowrance

Date of comment: December 3, 2014

Comment:

I support a single IRB for multiple sites. The IRB process is already tedious enough...much is duplicative in nature!

Comment #11

Commenter: Michael Rothman, MD

Date of comment: December 4, 2014

Comment:

Hummingbird IRB was founded with the express purpose of being that hybrid IRB with the efficiency of the private sector but with the judicious eyes of academia. One window into the culture of an IRB is the character of the funders. HummingbirdIRB is funded by academics such as Tim Swager, the Chair of the department of chemistry at MIT, and Steve Buchwald, a celebrated chemist at MIT, and by physicians such as Burt Adelman. Our boards have specialists from the Boston medical community who understand increasingly complex protocols. Their board chair is the former Dean for Graduate Students at MIT, who understands the concerns of academic institutions. We would like to play a role in the single IRB policy, and hope to be contacted to discuss the vital new policy. Please feel encouraged to contact me, as I would like to be part of the solution.

Comment #12

Commenter: Douglas Wassenaar

Date of comment: December 4, 2014

Comment:

This policy should be more explicit in stating that it does not apply to international studies where approval from the host country is always required and that US IRB approval alone does not suffice. I chair an IRB with FWA in South Africa.

Comment #13

Commenter: Sherri Gabbert, PhD

Date of comment: December 4, 2014

Comment:

In spite of current guidance from OHRP on ceding to other IRBs, most local IRBs continue to refuse this approach and there is no apparent basis for this with respect to research subject rights and safety.

It is time for pressure from the appropriate entities to minimize the local hegemony of IRBs, which have aligned themselves inappropriately with risk and liability management for their institutions as well as exerted excessive control of submission content to the point of irrelevancy. I think the irony here is that the more they attempt to bring absolute conformity to submission content, the more work they make for themselves, which in turn leads to greater efforts to control in order to manage workload. The substance of oversight is lost when I am required to revise a consent document with a "better phrase" in the Benefits paragraph. I have had these issues escalated to committee because of my unwillingness to revise a consent for stylistic reasons. Frankly, this is insane.

It is not an exaggeration to state that my faculty is functionally terrorized by our IRB, through lack of

effective education and irrational and illogical demands made in order to approve research.

I have worked with 6 IRBs over my 18 year career and I have always had to “push” back at those IRBs when their demands were wholly irrelevant to protection of human subjects. This is not a good use of my time and energy, and it creates artificial delays that do not serve the regulated IRB mandate. Any and all efforts to corral this trend are greatly appreciated.

Comment #14

Commenter: Patricia Walicke, MD, PhD

Date of comment: December 4, 2014

Comment:

I am working with a trans-federal group to assemble an emergency medicine network. We just had our meeting to discuss central IRB use two days prior to release of the Request for Comments. We are highly supportive and in agreement. For our planning purposes, we would like to know your estimates for the end of review period and issuance of policy?

Comment #15

Commenter: Sherryl H. Goodman, PhD

Date of comment: December 4, 2014

Comment:

I fully and enthusiastically support the approval of the policy that would allow single IRB review of multi-site investigations. This would save much time of both investigators and IRB committee and staff members and address the other problems mentioned in the policy statement.

Comment #16

Commenter: William J. French, MD

Date of comment: December 4, 2014

Comment:

Several models work well for us.

The use of one central IRB (WIRB) has revolutionized the clinical trial process for us.

Local vs. central IRB modeling needs to be clarified.

A ‘local’ IRB can be the conduit to one or more central IRBs, the model we currently use.

Or the local IRB can deal with only one central IRB.

Or the local IRB is the only IRB.

Currently, in many clinical trials that we are involved in, several central IRBs may be involved in the same trial. All seems to work well with this model.

Comment #17

Commenter: Evelyn M. Horn

Date of comment: December 4, 2014

Comment:

I like the idea!

Comment #18

Commenter: Andrea Harabin, PhD

Date of comment: December 4, 2014

Comment:

I am in favor of central IRBs but have a question and comment.

By “fee-based” IRB, do you mean a commercial IRB.? How do you envision supporting the costs of a single IRB that is not a commercial? Are these costs to be included in direct costs as well? NHLBI is developing a single IRB for a new clinical trials network – PETAL, and there appear to be additional costs for this process that are not a part of F and A. It is certainly clear that the organization who takes on the role as the IRB has more work – negotiating reliance agreements, handling amendments, AEs etc. It appears our IRB will not be funded as fee-based, but rather by FTE support.

I would also comment that we don’t yet know that a central IRB actually produces efficiencies (or enhance safety). I expect this may turn out to be true (as evidenced by the fact that I am organizing one) but it is not yet known. We have promising anecdotes from NeuroNEXT, but I believe we know that NCI has dramatically revamped its CIRB from how it originally looked and functioned and cost. This remains an experiment in my mind.

It will be important that NIH have in place a plan to evaluate the success or failure (e.g., cost, timeliness, safety) of this process before it becomes policy.

Comment #19

Commenter: Donald L. Gilbert, MD, MS, FAAN FAAP

Date of comment: December 4, 2014

Comment:

Thank you for soliciting my input on this. I currently do NIH funded research in two studies funded through the Co-PI mechanism. I am in favor of a single IRB approach.

Comment #20

Commenter: Thomas G. Brott, MD

Date of comment: December 4, 2014

Comment:

I read your Rock Talk section about single IRBs and went to the links you provided. Our team here will be discussing the JCO article at our Tuesday team meeting. The citations are rather dated, and I did not see another paper likely to have pertinent numerical data comparing the CIRB model with the distributed model (I did not do a search). The NEJM piece was an editorial as you know, and the author could be perceived as having a COI given his role as director of OHRP.

Our own clinical trial experience would not support the “bandwagon” momentum I perceive for the CIRB model – at least not yet. As PI of very large randomized trial since the beginning of 2008, I have worked with our team at Rutgers, dealing with 2500+ elderly patients at 117 medical centers, and their IRBs. Despite the many complexities, the demands of an IDE, etc, etc, we have had very smooth sailing with this model since 2000 and continue to have smooth sailing (the grant runs through 2016). I also work as PI of a very new and very large randomized clinical trial which uses the CIRB model. We are just getting started. So far, despite the “above and beyond” efforts of the Chair of that CIRB, our CREST-2 team

members at Mayo and UAB have not seen nor do they foresee yet the “slam-dunk” advantages advocated by our beltway colleagues at NIH, OHRP, and I believe also, FDA.

My request to you and to your colleagues at NIH would be to proceed with the same level of rigor that you expect from your investigator-applicants in their grant applications -- when it comes to the pluses and minuses of the CIRB model. Look for numerical comparative data, admit when you don't have it, and be critical of the data you have. And please be aware of beltway bias: the model perceived to be best centrally, at NIH and at other government agencies, may not be the best in Utah, or Florida, or California, or Hawaii, etc. “Common sense” beliefs and hypotheses should be tested when they impact NIH clinical trial policy.

...and I love NIH by the way – outstanding people with a wonderful mission.

Comment #21

Commenter: Joan B. Ruppman, MS, RN

Date of comment: December 4, 2014

Comment:

Peoria, IL Community IRB has been in existence for about 15 years. This single entity is housed at the University of IL College of Medicine site in Peoria. Medical, nursing and other professional disciplines submit sponsored national studies or locally driven studies. The IRB is representative of our community. Local hospitals and health departments honor and accept IRB approved studies. This community formed the single IRB so researchers would not have to go to multiple sites and have multiple approvals prior to initiating studies.

Comment #22

Commenter: James Linakis, PhD, MD

Date of comment: December 4, 2014

Comment:

Although I am generally encouraged by the proposed policy, I'm confused by the line that notes, "A duplicate IRB review at a participating site would be counter to the intent and goal of the Policy, but the Policy does not prohibit any participating site from carrying out its own IRB review."

As I read this line, it permits ambiguity as to which IRB would prevail in a disagreement between the "IRB of record" and the site's IRB. Would the dissenting institution be compelled to drop out of the study? As we've already learned, many institution's IRBs are reluctant to relinquish control to a central IRB or another institution's IRB. So while one institution dropping out of a multicenter study may not have a damaging impact on the study, the possibility exists that many or all sites' IRBs in a multicenter study may choose to review the protocol independently of the IRB of record. What will happen if all or the majority of the "participating" sites IRBs dissent from the IRB of record's determination. Will all or the majority of sites be dropped? I'm not sure that would constitute an enhanced or streamline process.

I believe that a more clear statement of the contingencies should be made with regard to a major disagreement between the IRB of record and a duplicate IRB review at a participating site.

Thanks for your consideration.

Comment #23

Commenter: Lynn G. Feun

Date of comment: December 5, 2014

Comment:

I wholeheartedly support this concept and it would streamline approval of protocols without jeopardizing patient safety.

Comment #24

Commenter: Elizabeth Shirtcliff

Date of comment: December 5, 2014

Comment:

I read the policy and I think it is a great idea. I just want to add that another benefit of a single IRB is that minor fluctuations in requests and protocols across institutions can be eliminated by the single IRB. My experience is that each IRB raises slightly different concerns and I like to be responsive, but this can make the studies differ from site to site, even if slightly.

Comment #25

Commenter: Ruth Vandenbroucke

Date of comment: December 5, 2014

Comment:

I like the idea. I think it would provide more consistent and/or standardized adherence to the protocol; with the result of a more reliable data set.

Comment #26

Commenter: Gail Mallett, RN, BSN, CCRC

Date of comment: December 5, 2014

Comment:

I am in favor of this NIH proposal. Gratifying to know that the NIH is aware of and responsive to the burden of IRB submissions and continuing reviews borne by multi-site participants and has found an effective way to alleviate the time and cost burden without sacrificing subject safety. It is also my hope that interpretation of the proposed review mechanism by local IRBs will not negate the benefit and/or hinder the process.

Comment #27

Commenter: Pedro Villarreal III, Ph.D.

Date of Comment: December 5, 2014

Comment:

December 5, 2014

Re: Request for Comments, Rules Change (NOT-OD-15-026)

To Whom It May Concern

I submit this letter as my comments on the proposed rules change under consideration regarding the use of a single IRB for multi-site research. Whereas the current rules require the acquisition of multiple approvals through various institutional IRBs:

- The benefits received by the current policy have proved to be of little to no known social or public value or benefit.
- The loss of time and amount of human capital expended can lead to smaller scale study designs with limited generalizability.
- The implementation of the policy demonstrates little, if anything, to ensure greater safety of patients, subjects, or people involved in human subjects research.
- The effect of the policy may have led to an increasing number of study designs with shorter trajectories and time terms.
- The increase in acquiring additional IRB approvals may have led to greater inconsistencies in the research designs at the implementation of research, further compromising the rigor and internal validity of studies.

The savings, both financial and human capital, could be quite substantial over the course of several years, if NIH along with all federal and state agencies would follow the suggested recommendations for policy change. The NIH serves as a leading government agency in funding research on projects affecting individual persons and their health and well-being. Many state and other federal agencies including the Institute of Education Sciences (IES) see NIH as a model agency.

Given the significant constraints and limited returns to investment of the current policy under review, it is essential that we consider revising the policy. Consequently, I write to support the recommended policy changes as they are currently written and under discussion. I offer no alternative written suggestions for changes to the proposed policy as written. I base my support of the policy change on almost 10 years of academic research experience.

Sincerely,

Pedro Villarreal III, Ph.D.

Assistant Professor, Higher Education Program Educational & Psychological Studies Department School of Education & Human Development University of Miami

5202 University Drive 310-D Merrick Building Coral Gables, FL 33146

Ph: 305-284-3196

petev3@miami.edu

Comment #28

Commenter: Holli A. DeVon, PhD, RN, FAHA, FAAN

Date of comment: December 5, 2014

Comment:

As a long time scientist and former member of 2 institutional review boards, I strongly urge you to adopt the policy requiring only one IRB approval for multi-sites studies. I currently have 6 separate approvals for my study which is extremely burdensome to all sites.

Thanks for your efforts to change the current policy.

Comment #29

Commenter: Carson Reider, PhD

Date of comment: December 5, 2014

Comment:

It would be enlightening to add the attached reference to the notice or subsequent related announcement to offer another model approach beyond the central models presented in the next to last paragraph of the Background section of the Notice. Currently, readers only have the centralized model option presented. The Reliant is a novel one which has the option to be adopted by any combination of institutions; potentially sharing in the processes and workload than always deferring to a particular institution, e.g., NCI, Harvard, etc....

Clarity on the extent of “expected” would be beneficial, i.e., clarify how use (or not use) of a single IRB for a multi-center study will weigh in the review process of the proposal submitted to NIH.

Clarify if this pertains to all clinical research or just to clinical trials (as defined by NIH).

Thank you for taking these thoughts into consideration.

This is exciting stuff for us in this particular world of engagement!

Comment #30

Commenter: Seema Khan, MD

Date of comment: December 7, 2015

Comment:

This is long overdue. The approval of a multi-site protocol by the IRB of each site is redundant and wasteful of time and resources. The issue that I have encountered most frequently regarding review at multiple sites is the template language, which varies from place to place and the lawyers at each university are very adamant about using their specific template language (e.g. treatment of injury, confidentiality, risks of the fetus, compensation for the participant etc.). This would need to be resolved, so that individual institutions are willing to accept the template language of the single/originating IRB.... or that replacement of one template paragraph by an equivalent para would be done as an administrative action, not requiring full review.

The rules for compensation of subjects also vary from place to place, and we would need to reach some unanimity about these.

Comment #31

Commenter: Judy Ozbolt, PhD, RN, FAAN, FACMI, FAIMBE

Date of comment: December 7, 2015

Comment:

A hypothetical risk of abuse occurs if IRB approval from a single site is ratified by other sites in a multi-site study. An example of similar abuse is the use of flags of convenience by cargo ships selecting registration in a country known not to apply high standards of safety, crew treatment or other issues. IRBs, however, generally have checks and balances to prevent abuses. Furthermore, the culture of research in this country is such that it is unlikely that researchers from multiple sites would seek out a lax IRB to approve research of questionable ethics.

I believe that the benefits of single-site IRB approval for multi-site research outweigh the risks.

Comment #32

Commenter: Robert L. Hood, PhD

Date of comment: December 8, 2015

Comment:

Although all IRBs should have a process to ensure the quality and accuracy of review, the NIH policy should mandate that if a single IRB process is chosen, that the organization conducting IRB review have a process for quality assurance and meets quality standards, which at a minimum must include compliance with laws governing research. Preferably the quality assurance process should include external validation by someone unaffiliated with the organization, such as an accrediting body like the Association for Accreditation of Human Research Protection Programs, other accrediting organization, or an independent auditor.

The quality assurance process might validate that when the IRB reviews research in more than one jurisdiction, the IRB follows all applicable laws, including knowing who is a child in the research in all jurisdictions in which the research will occur and knowing who can serve as a legally authorized representative in all jurisdictions in which the research will occur.

The quality assurance process might validate that when the research involves non-compliance, including non-compliance by the IRB, that the organization follows policies for managing non-compliance, and reports non-compliance by the IRB to the NIH. For example, if an IRB is found to have not made required determinations for research involving children, pregnant women, or prisoners, then the policy should require the steps NIH would take to ensure participants are protected.

However, it is unclear why review by a single IRB is not satisfactory when the IRB reviews international research. The US criteria for approval (45 CFR 46.111) are the same, and the IRB has the same requirements to know and follow laws in the jurisdictions in which the research will occur, including laws governing quorum and IRB membership. The US requirement that the IRB have members with sufficient qualifications and expertise to review the research still applies when reviewing research conducted internationally. Whatever the reasons for not allowing a single IRB to review research conducted internationally, some evidence should be provided as to why those reasons would not also apply within the US.

These comments do not necessarily represent the views of the Florida Department of Health as an organization.

Comment #33

Commenter: Paul Koros, RN, CCRC

Date of comment: December 8, 2014

Comment:

I have reviewed a proposed policy change that would require NIH studies to use a single central IRB.

While I understand this plan may have benefits I believe it will negatively impact your cause overall in the following ways:

1. Some really good sites are required to use a local IRB. This policy would prevent these sites from doing the study which would negatively impact your enrolment goals/plans
2. You run some pretty big studies and I don't know that a single central IRB could be able to keep up with that level of work which would put you right back in the same position you are right now- not getting work done quickly enough.
3. It is typically better to diversify & not have all of your "eggs in one basket". We have seen some pretty scary things in the last several years and we have learned that no one is immune from it. If you were to lose your single IRB for whatever reason it would be a mess and very damaging.

You may want to consider the impact before implementing such a policy.

Thank you for allowing us to make comments.

Good Luck with this no matter which way it goes.

Comment #34

Commenter: Barbara Resnick, PhD, CRN

Date of comment: December 8, 2014

Comment:

This would be a fantastic help to those of us engaged in multisite projects and would also help study participants I believe. What I am not clear about is whether or not there will be clear guidelines to make a LAW so to speak. I just worry about different sites being able to give over the control so to speak. I hope this will be clearly articulated with a process in place that all have to agree to. Thank you for taking this initiative.

Comment #35

Commenter: Elizabeth Kopras

Date of comment: December 8, 2014

Comment:

I highly support the implementation of a single IRB for multi-center trials. It is a challenge to get "big name" academic research centers to rely on each other's IRBs, even though we are all following the same human subjects rules. Ownership among the bean-counters makes it incredibly challenging to get the research off the ground. We also have to deal with the "hairy arm" effect, where every IRB wants to fix something (that's not broken) in order to feel like they did a good review.

The only way we will get past these territorial issues is if the NIH makes it happen.

I appreciate that we all need oversight when dealing with people, but the rules (sometimes randomly

made up) of our IRBs impede discovery, keep us separate from the patient, and waste money. IRBs need to be pulled into the 21st century.

Comment #36

Commenter: Patrick Heinritz
Date of comment: December 8, 2014

Comment:

This is to voice enthusiastic support for the NIH policy proposal that all NIH-funded multi-site studies carried out in the U.S., whether supported through grants, contracts, or the NIH intramural program, should use a single, Central IRB (CIRB). Since 2003 I have served as Business Manager for a large NIH-funded clinical research consortium. As such, I have witnessed first-hand the inefficiencies inherent in a decentralized IRB of record system.

For our multi-center studies, it was "Standard Operating Procedure (SOP)" for the consortium to allow 4 months for the site IRB process. This typically involved 4 weeks of dedicated effort of at least 1.0 staff FTE to prepare and submit the IRB application, 8 weeks for IRB review, and then 4 more weeks for responding to questions and waiting for the IRB to generate approval documents. Additional staff effort was then required to upload or file approved forms and documents. Some IRBs meet infrequently so the processing time for responding to even minor questions could extend the time table by several months. Similarly, IRBs have varying scheduling requirements for submitting materials and missing a deadline by a day could delay review a month or more.

A less obvious but no less disruptive result of the time and resource consuming decentralized IRB process involved protocol changes. As with the initial study IRB submission, protocol changes required extraordinary planning, significant Investigator and staff processing effort and potentially delayed the implementation of important study improvements.

Consortium operating costs averaged \$1 million per month and while great care was taken to overlap studies and allow for extended IRB processing times, it was still relatively common for the IRB approval process to cause unproductive downtime. For the most part IRBs were unsympathetic to these logistical and economic implications.

In the current iteration of the consortium, we have embraced and incorporated the Central IRB (IRB) model into our SOPs. Based on results to date, we are confident that the CIRB will have a significant positive impact on study planning, start-up, and conduct. Thank you for the opportunity to comment on this important matter.

Comment #37

Commenter: Linda M. Collins
Date of comment: December 9, 2015

Comment:

In my view, the proposed single IRB policy is an excellent idea.

Comment #38

Commenter: Craig Slingluff
Date of comment: December 9, 2014

Comment:

I agree with this proposed policy. Thank you.

Comment #39

Commenter: Evelyne Shuster, PhD

Date of comment: December 9, 2014

Comment:

The National Institutes of Health policy designed to increase the use of single Institutional Review Boards (IRB) for multi- site domestic studies with the purpose of streamlining the research review process is misguided and will not achieve what it is intended to do. It is a bad idea, which if applied, will only substitute a research review process that is perceived as inefficient, time consuming, redundant and costly with another review process that is as time consuming, as redundant and as costly. In addition, single Institutional Review Boards will eliminate the benefits of local IRB, having what is needed for a complete and thorough protocol review within reach, and whose members are presumed to reflect the values of the community, and therefore the values of subjects themselves who are drawn from that community. Rather than streamlining the research review process, this policy adds another bureaucratic layer, for example, the agreement between the single IRB of record and participating sites, which would have the responsibilities of reporting, documenting, policing and ensuring that all research requirements for the protection of subjects are met. This new policy can only make things worse, i.e., more difficult, cumbersome and frustrating; it will not make things more efficient, more focused, less costly and readily actionable.

Comment #40

Commenter: Julianne Imperato-McGinley, MD

Date of comment: December 10, 2014

Comment:

The Weill Cornell CTSC is enthusiastic about the policy to promote the use of a single Institutional Review Board of record for domestic sites of multi-site studies funded by the NIH.

Comment #41

Commenter: D. Srilatha

Date of comment: December 10, 2014

Comment:

I would like to suggest that multi-site human trials be reviewed by at least one member of the 'single/sole Institutional Review Board' being present at each site; their suggestion could be put together into a single evaluation. I would also like to know whether IRBs oversee animal experiments.

Comment #42

Commenter: Curtis Meinert, Professor

Date of Comment: January 22, 2015

Comment:

22 January 2015

Memorandum

To: Office of Clinical Research and Bioethics Policy, Office of Science Policy, National Institutes of Health

6705 Rockledge Drive, Suite 750, Bethesda, MD 20892

via email: SingleIRBpolicy@mail.nih.gov

Fr: Curtis Meinert, Professor

The Johns Hopkins Bloomberg School of Public Health

Department of Epidemiology

Baltimore, Maryland

Re: Comments on proposed NIH policy on use of a single institutional review board for multi-site research (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-026.html>; release date 3 December 2014; response deadline 29 January 2015)

The expectation is that the change will save money. Good luck on that. The reality is that the change will increase costs given what IRBs of record have to do to acquire the necessary assurances and certifications.

The expectation also is that the single IRB will shorten the time to start, good luck on that one also. Times to start are driven largely by other factors like the time it takes for investigators to agree on a protocol, the time it takes to develop data forms and systems for data intake and, in the case of drug trials, the time it takes to get and package drugs for use in those trials.

Local IRBs under the proposal will retain responsibility for reviewing and approving consent forms and procedures for local use. Even if IRBs of record prepare prototype consents for local use, experience teaches that IRBs have predilections for wordsmithing. Hence, one can expect the most time consuming part of the approval process will be clearing consents for local use. The time may be considerable in network trials with, sometimes, as many protocols as there are clinics in a study.

The proposed change has downsides. An obvious one is what it does to local IRBs. There can be no question that the IRB system in place has been paramount in educating faculty and staff of academic institutions as to duties and ethical issues underlying the privilege of researching on human beings. Reducing the richness of exposure by siphoning away what is usually the most important and challenging research IRBs review will lessen their vitality and morale.

A likely unintended effect of the one IRB requirement is to further diminish the means and incentives for individual investigators to propose and initiate multicenter studies. As it is now, an ever increasing number of initiatives come from the NIH and fewer and fewer from investigators. A robust research environment needs balance between the two modes of initiation.

The argument by the proposers that there is no evidence that multiple IRB reviews enhance protections for human subjects is vacuous in the absence of detail. One can just as easily argue that there is no evidence of harm because of multiple reviews.

The proposers argue that the single IRB model may lead to enhanced protections by “minimizing

institutional conflicts of interest". As a researcher I am more interested in balance of conflicts than in minimizing them. There is information in the different philosophies and points of views of individual IRBs that, in all likelihood, add to protections.

An effect of the policy will be to increase free-standing IRBs not affiliated with any institutions. Even some for profit, perhaps. It is hard to see this as a step forward or a direction we should be headed.

The current system of institution-affiliated IRBs is robust because of their autonomy. Shutdown of one IRB because of failure to obtain renewals or by action of the OHRP does not effect other centers under other IRBs in a study. Everything shuts down with the single IRB model if the IRB of record fails to renew in time or if it is shutdown by the OHRP (as happened here in the summer of 2001 because of an unfortunate death in one of the research projects under the Medical School IRB).

Undertaking research on human beings is a high-risk activity. Trials, in particular, expose investigators to an array of risks. There is no doubt that I have had my share of disputes with my IRB, but I have also felt protected by my IRB if something bad were to happen on my watch. It is difficult to feel that same level of protection with a free-standing IRB comprised of members I do not know in some remote location that likely is more interested in protecting its own interests than mine.

There is no doubt that the existing IRB system is cumbersome and needs revision but that should be accomplished by legislation rather than by administrative fiat. The policy places responsibility for the change on the backs of researchers and the institutions housing them – already over stressed by endless streams of regulations. In any case, it is a mistake to characterize individual IRB reviews as duplicative any more than it would be to characterize multiple reviews of manuscripts as duplicative. Every IRB is different and sees and responds to different things. No single IRB, no matter how comprised, can be expected to have the coverage and breadth of knowledge as with a collective body of IRBs.

Certainly, the fussy language in the proposal regarding consents is not reassuring if I was to find myself called to task by an angry participant in my center for something I did or said.

With regard to assuring that local perspectives are addressed, the assessment of a study's risks and benefits and the adequacy of the informed consent should not generally require the perspective of a local IRB. Local contextual issues relevant to most studies (e.g., investigator competence and site suitability) can be addressed through mechanisms other than local IRB review, such as the involvement of ad hoc members or consultants with the necessary specialized knowledge or expertise, or by submission of information by the individual site(s). Even when certain vulnerable populations are targeted for recruitment, such alternative approaches may be appropriate.

My advice: Go slowly. We have had the current system in place for 40 plus years. We need time to assess the effect of changes and time to identify and understand unintended consequences of changes. The only allowable exceptions to the policy, as written, are if the designated single IRB is unable to meet the needs of specific populations or where local IRB review is required by federal, tribal, or state laws or regulations. The go for broke approach to implementation seems ill-advised especially when, all too often in government, something is implemented not even God can undo it.

Comment #43

Commenter: William D. Byars, MD

Date of comment: December 11, 2014

Comment:

Thank you for soliciting opinions on the single IRB issue. I've been doing clinical research for over 10 years now. My personal experience has been that dealing with local IRB's can be a confounding and inefficient process. Although the rulings of local IRB's have rarely had a significant impact on the conduct of a clinical study, in the long run the process of getting through a study that involves a local and a central IRB can be filled with headaches that I view as unnecessary. I've also noticed that some pharmaceutical companies avoid research sites which are tied to a local IRB.

Admittedly there are potential dangers in having a few central IRB's overseeing most of the clinical research in the US. However with good government oversight of those IRB's themselves, great research can be conducted with more efficiency.

Comment #44

Commenter: Meir Stampfer, MD, PhD

Date of comment: December 12, 2014

Comment:

Yes, I strongly favor this approach, which preserves the protection of Humans, while decreasing the (still enormous) burden on investigators. this would be a good opportunity to revisit the IRB requirements and burden for minimal risk research, to ease the administrative hassles even more. The hoop we must jump to be able to ask a person how often they eat spinach seem disproportionately great, compared to the risks.

Comment #45

Commenter: Alberto Ascherio, MD, DrPH

Date of comment: December 12, 2014

Comment:

This would definitely be a step forward and probably results in better protection of human subjects as well.

Comment #46

Commenter: Gregory Kato, MD

Date of comment: December 12, 2014

Comment:

I agree with the formulation of the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research, Notice Number: NOT-OD-15-026

My own anecdotal experience is that multiple IRBs does not improve patient safety. I think that individual institutional IRBs tend to contribute some additional attention to protecting interests of the institution, which impedes rather than enhances the main focus of the IRB in patient protection.

Comment #47

Commenter: Ezra Cohen

Date of comment: December 15, 2014

Comment:

Having been an investigator on several multi-institutional NIH sponsored studies, I believe this policy has several advantages. A single IRB review will increase efficiency of clinical trials; minimize heterogeneity in review and comments from different IRBs; and actually improve patient safety by setting a high bar for review by a central IRB. This is a definite step in the right direction for oncology clinical research.

Comment #48

Commenter: Kimberly Bertrand

Date of comment: December 16, 2014

Comment:

I am writing to provide my support for this Draft NIH Policy to require use of single IRB for multi-site studies. This process will streamline IRB review, reduce administrative burden, and improve efficiency in human subjects research. We have already used a single IRB of record for multi-site studies within our own institution, when allowed under the current policy, with great success.

Comment #49

Commenter: Melanie M. Domenech Rodriguez, PhD

Date of comment: December 17, 2014

Comment:

My comment is: THANK YOU. This is a great idea. IRBs will probably need some guidance on how to proceed. For example an adverse event at site 1, where a co-PI is located results in adverse event reporting at site 2, where the IRB of record is. Site 2 IRB manages the issue but site 1 never hears about it. This could be an issue, especially if the site 1 co-PI has a chronic pattern of problematic behavior. It seems guidance on how to best implement the IRB of record is warranted. The policy itself should be very helpful to those of us that conduct research across sites.

Comment #50

Commenter: Eva Schernhammer, MD, DrPH

Date of comment: December 17, 2014

Comment:

I welcome the new draft policy!

Comment #51

Commenter: Shelly L. Sayre

Date of comment: December 17, 2014

Comment:

I am writing today to provide comments on the draft policy for the use of a single IRB review for multisite trials. <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-026.html>

As part of an NHLBI cooperative agreement, our Network (Cardiovascular Cell Therapy Research Network) was funded to conduct multiple studies utilizing the same seven locations over a seven year period. The trials are focused on stem cell use in the treatment of cardiovascular diseases. In an effort to consolidate the number of IRB reviews, both within and across our trials, our Data Coordinating Center explored the opportunities for the use of IRBShare and also of the use of Inter-institutional agreements to allow the individual local IRBs to rely on a central IRB at the Data Coordinating Center Institution. As is outlined in the background of the draft policy, and many of its accompanying articles, our attempts have been met with similar challenges; with many IRBs indicating they only allow for the use of centralized IRBs for industry sponsored trials. Very few of our participating institutions utilize IRBShare, and as noted- this system makes available the review as an option for other local IRBs to adopt or to augment their own review (as opposed to simply relying on the review).

The IRB at the Data Coordinating Center's Institution is an AAHRPP accredited board that is willing to provide centralized review for all of our participating centers. In light of their willingness to serve in this role, we provided each local center with an introduction letter, the inter-institutional agreement, and an operational plan to each of the centers to provide to their IRBs. While many boards recognized the efficiencies gained by the use of a central IRB, they were not enthusiastic about entering into such an arrangement at this time. We were met with many a polite "no thank you," "not at this time," or not acknowledged at all. While some seemed appreciative that this option is being considered and an institution was willing to undertake it, they also did not seem to be interested in being test pilots. There would really almost need to be a champion at each of the local IRB offices to make this happen.

In my experience as an IRB member, for multi-site trials- the review decision of a study by the local IRB is often limited to a yes or no as to whether the trial can be conducted locally; alterations to the actual protocol that is being conducted at multiple locations are very rare. The document over which the local IRBs have the most influence is the informed consent. It has been my experience as a Sponsor, in reviewing the suggested recommendations from the local IRB reviews- that these are largely word-smithing edits and do not change the nature of the study or the risk/benefit level to the patients. However it does produce many person-hours of back and forth review with Sponsors, local reviewers, and sometimes board meetings to agree upon the wording.

I say all of this to note that our experience has been in keeping with that which has been outlined in the literature and that, even when the offer is readily available and extended, local IRBs tend to decline in favor of keeping control over their own review. They each have systems, forms, and processes in place that allow for this to work locally. My sense however is that until it is required, under grant specifications that a central IRB be identified and utilized as part of the funded project, many groups will not take advantage of such a model. I applaud the groups that have been willing to test the waters a bit through the Public Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research use of IRBShare in recognition that centralized review will one day be a reality for multi-site trials. I am encouraged that NIH is considering such a policy and look forward to future initiatives in this area.

Comment #52

Commenter: Robert J. Shulman, MD

Date of comment: December 17, 2014

Comment:

I urge you to support a single IRB policy for multisite research. This will expedite research endeavors without affecting subject safety.

Comment #53

Commenter: Anna Lok, MD, FAASLD

Date of comment: December 17, 2014

Comment:

As a clinical investigator who have participated in NIH funded multi-center clinical studies, either as PI of R01 grant being responsible for regulatory and scientific aspects of the study or as PI of U01 studies, this is like a dream come true. A single IRB will improve efficiency both regarding approval of protocols (initial and amendments) and in AE reporting and review. More importantly, science will not be bogged down by individual IRB idiosyncrasies. No longer will we need to deal with a site IRB requesting a change to the protocol after 15 other IRBs have approved the protocol and the study is well on its way.

I applaud the move to single IRB. This will save time, agony and cost; allow studies to proceed faster with no compromise to safety of study subjects.

Thanks for listening to our prayers.

Comment #54

Commenter: Lisa M. Ganley-Leal

Date of comment: December 19, 2014

Comment:

A single IRB should definitely be used for multi-site studies. Often times, the second or third IRB committee will spend months reviewing the protocol to make minor changes that do not impact the protection of the subjects. Furthermore, the clinical coordinator at the NIH will have addressed many of the concerns before submission, which all IRB should honor.

If all IRBs require a similar set of requirements to be certified, IRBs should feel comfortable deferring to a primary board. Besides, when reduced to practice, an institution will honor its own IRB approved protocol, not one modified by its collaborative site board, thereby wasting both time and money.

This policy should also apply to transferred grants that include human subject research. The primary institution's IRB approval should be allowed for the first year of the transferred project. Again, one IRB board should be equivalent to another despite the subjective opinions of unique board members.

Comment #55

Commenter: Emily Kim, MPH

Date of comment: December 19, 2014

Comment:

While I love the idea of this new policy, I wonder if the time it will take initially to get participating

centers to agree to the central IRB will obviate efficiencies created. Additionally, wouldn't local IRBs continue to track in some way or another that a study is ongoing at their site, whether it is approved by an IRB, etc? In which case, I wonder if local IRBs will need some time to create a system that can work with the requirement of a central IRB- perhaps the requirement should be staged in over a couple of years?

Thank you for the opportunity to comment.

Comment #56

Commenter: Michael Benatar

Date of comment: December 21, 2014

Comment: See highlights in Notice below

Notice Number:

NOT-OD-15-026

Key Dates

Release Date: December 3, 2014

Response Date: January 29, 2015

Related Announcements

None

Issued by

National Institutes of Health (NIH)

Purpose

The National Institutes of Health (NIH) is seeking public comments on a draft policy to promote the use of a single Institutional Review Board of record for domestic sites of multi-site studies funded by the NIH.

Background

The NIH is dedicated to improving the health of Americans by conducting and funding biomedical research through an extensive portfolio of human subjects research. While NIH-funded investigators must adhere to regulations for the protection of human subjects, the agency also looks for ways to reduce procedural inefficiencies so that human subjects research can proceed efficiently without compromising ethical principles and protections.

The Department of Health and Human Services (HHS) regulations for the Protection of Human Subjects at 45 CFR part 46 requires Institutional Review Board (IRB) review of non-exempt HHS conducted or supported human subjects research. IRBs are responsible for performing an ethical review of studies involving human subjects. Research protocols and informed consent documents must be approved by an IRB prior to the commencement of human subjects research. In 1975, when the HHS regulations for protection of human subjects were first published,¹ most clinical research was conducted primarily at a single institution. Since then, the research landscape has evolved, and many studies are carried out at multiple sites.

In order to avoid duplication of the effort, both the HHS regulations at 45 CFR part 46 and the IRB regulations of the Food and Drug Administration (FDA) at 21 CFR part 56 allow institutions that participate in multi-site studies to use joint review, rely on the review of another qualified IRB, or establish other arrangements.² FDA and the Office for Human Research Protections (OHRP) have also issued guidance on this topic.^{3,4} However, too few institutions involved in multi-site studies are taking advantage of the option.⁵

Proponents of the single IRB model maintain that review of a multi-site study by the IRB of each

participating site involves significant administrative burden in terms of IRB staff and members' time to perform duplicative reviews. When each participating institution's IRB conducts a review, the process can take many months and significantly delay the initiation of research projects and recruitment of human subjects into research studies. Use of single IRBs in multi-site studies, on the other hand, has been shown to decrease approval times for clinical protocols and may be more cost effective than local IRB review.⁶

Importantly, there is no evidence that multiple IRB reviews enhance protections for human subjects. In fact, the use of single IRBs may lead to enhanced protections for research participants by eliminating the problem of distributed accountability, minimizing institutional conflicts of interest, and refocusing IRB time and resources toward review of other studies.^{7,8} With regard to assuring that local perspectives are addressed, the assessment of a study's risks and benefits and the adequacy of the informed consent should not generally require the perspective of a local IRB. Local contextual issues relevant to most studies (e.g., investigator competence and site suitability) can be addressed through mechanisms other than local IRB review, such as the involvement of ad hoc members or consultants with the necessary specialized knowledge or expertise or by submission of information by the individual site(s). Even when certain vulnerable populations are targeted for recruitment, such alternative approaches may be appropriate.

Several extramural NIH programs already support the use of a single IRB for multi-sites studies. For example, the National Cancer Institute has had a Central Institutional Review Board (CIRB) in place for the review of NCI-sponsored clinical trials since 1999. The National Institute of Neurological Disorders and Stroke has incorporated the use of a single IRB for its Network for Excellence in Neuroscience Clinical Trials' (NeuroNEXT) and Network for Stroke Research (NIH StrokeNet).^{9,10}

The draft Policy proposes that NIH funded institutions will be expected to use a single IRB of record [MB1] for domestic sites of multi-site studies unless there is justification for an exception (see exceptions below). The draft Policy applies to all domestic sites participating in NIH conducted or supported multi -site studies, whether supported through grants, contracts, or the NIH intramural program. By expecting all domestic multi-site studies to use a single IRB, this Policy should help achieve greater efficiencies and speed the initiation of studies across NIH's entire clinical research portfolio. This Policy is also in keeping with one of the proposed changes being considered to the Common Rule.¹¹

Request for Comments

NIH encourages the public to provide comments on any aspect of the draft Policy. Comments should be submitted electronically by January 29, 2015, to the Office of Clinical Research and Bioethics Policy, Office of Science Policy, NIH, via email at SingleIRBpolicy@mail.nih.gov, mail at 6705 Rockledge Drive, Suite 750, Bethesda, MD 20892, or by fax at 301-496-9839.

Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

Purpose

The purpose of this Policy is to increase the use of single Institutional Review Boards (IRB) for multi-site studies funded by the National Institutes of Health (NIH). Its goal is to enhance and streamline the process of IRB review and reduce inefficiencies so that research can proceed efficiently without compromising ethical principles and protections.

Scope

NIH generally expects all domestic sites of multi-site NIH-funded studies to use a single IRB of record. The Policy applies to all domestic sites participating in NIH conducted or supported multi-site studies, whether supported through grants, contracts, or the NIH intramural program. While foreign sites in multi-site studies will not be expected to follow this Policy, they may elect to do so.

Responsibilities

All sites participating in a multi-site study will be expected to rely on a single IRB to carry out the functions that are required for institutional compliance with IRB review set forth in the HHS regulations for the Protection of Human Subjects. The single IRB will be the IRB of record for the other participating sites. The single IRB will be accountable for compliance with regulatory requirements for IRBs specified under the HHS regulations at 45 CFR part 46, such as providing initial and continuing review of the research.¹² All participating sites will be responsible for meeting other regulatory obligations, such as obtaining informed consent, overseeing the implementation of approved protocols, and, reporting unanticipated problems and adverse events to the single IRB of record.

Agreements between the single IRB of record and other participating sites will be needed in accordance with 45 CFR part 46. IRB Authorization Agreements [MB2] will document the delegation of responsibilities of IRB review to the designated IRB of record and that IRB site's acceptance of the responsibilities. [MB3] The agreement will set forth the specific responsibilities of each participating site. Participating sites will then rely on the IRB of record to satisfy the regulatory requirements relevant to the IRB review. The awardee or lead site for an NIH-funded, multi-site study will be responsible for maintaining authorization agreements [MB4] and should be prepared to provide copies of the authorization agreements and other necessary documentation to the NIH funding Institute or Center upon request. As necessary, mechanisms should be established to enable the single IRB of record to consider local context issues during its deliberations. A duplicate IRB review at a participating site would be counter to the intent and goal of the Policy, but the Policy does not prohibit any participating site from carrying out its own IRB review. [MB5] If this approach is taken, the participating site should expect to bear the cost of the additional review.

Identification of the IRB that will serve as the single IRB of record will be the responsibility of the extramural applicant or offerer, [MB6] or the intramural principal investigator. The funding NIH Institute or Center has final decisional authority for approving the selected single IRB. Use of the designated single IRB will be a term and condition of award. If the agreed-upon single IRB is a fee-based IRB, these costs will be included in the Notice of Award as a direct cost.

Compliance with this Policy will be a term and condition in the Notice of Award and a contract requirement in the Contract Award.

Exceptions

Exceptions to the expectation to use a single IRB may be made with appropriate justification. Exceptions will be allowed only if the designated single IRB is unable to meet the needs of specific populations or where local IRB review is required by federal, tribal, or state laws or regulations.¹³

******Comments******

Comment [MB1]: Is it important to differentiate the different types of models that might be used. For example, NeuroNEXT utilizes a central IRB, but this policy seems to indicate that an IRB of record would be sufficient.

Comment [MB2]: Will NIH be publishing a template IRB Authorization Agreement that sites may use in these multi-center initiatives?

Comment [MB3]: Unclear. Not sure what this last phrase is intended to mean.

Comment [MB4]: Would it make sense to allow any of the centers participating in a multi-center study to serve as the IRB of record rather than to require that this be the lead site or awardee? I ask because some sites may be less comfortable serving this role and this might impede individual investigators from applying for NIH funds to support multi-center trials. But if an investigator is limited by his/her institution in this way, they could propose to use the IRB of one of the other centers participating in the multi-center study.

Comment [MB5]: This sounds very much like an IRBShare model.

Comment [MB6]: ???

Comment #57

Commenter: Barry L. Brewer

Date of comment: December 23, 2014

Comment:

I am very strongly in favor of single IRB. I am also in favor of eliminating the RCA review process. RAC is simply not needed in today's drug approval process.

Comment #58

Commenter: Aravinda Chakravarti, PhD; Courtney Berrios, MSc, ScM

Date of Comment: December 30, 2014

Comment:

December 30, 2014

Office of Clinical Research and Bioethics Policy

Office of Science Policy, NIH

6705 Rockledge Drive, Suite 750

Bethesda, MD 20892

Re: Request for Comments on the NIH Draft Policy on the Use of a Single Institutional Review Board for Multi-Site Research

Dear Sir or Madam:

We are writing to provide comments in support of the NIH draft policy that would encourage use of a single Institutional Review Board (IRB) of record for multi-site research studies. We are involved in a multi-site research project as the Principal Investigator and Study Coordinator for the Hirschsprung Disease Research Collaborative (HDRC). The HDRC is an academic research collaboration involving geneticists, pediatric surgeons, pediatricians and gastroenterologists interested in a global analysis of Hirschsprung disease toward improving care for affected individuals. The HDRC is building a biorepository of data and samples collected in a detailed and standardized manner that will be used for correlation of disease and treatment outcomes with genetic, pathologic and clinical variation, as well as providing a resource for other HDRC member research projects.

The HDRC was initiated in the summer of 2011 after IRB approval at the HDRC Coordinating Center at Johns Hopkins University, and additional site approvals have trickled in since that time. To date, the HDRC includes 18 study sites with IRB approval to actively enroll study participants for the biorepository, 2 sites currently in the IRB review process, 9 sites who have indicated that they are preparing materials for IRB submission, and 5 sites referring patients to the HDRC Coordinating Center for study enrollment. More than 30 other investigators, at sites both within the US and internationally, have expressed interest in joining the HDRC. Barriers to HDRC participation, due to the administrative and time requirements of local IRB approval based on their prior experience, have been cited by potential collaborators at many institutions; particularly those still preparing their IRB applications, referring to the Coordinating Center, or who have expressed interest but not moved forward with joining.

At the Coordinating Center, we invest considerable time in maintaining our local IRB approval, but also invest a minimum of 3-4 hours assisting each actively enrolling site with its own initial IRB approval by providing study documents, answering questions, and reviewing each site's IRB application and consent form before submission to ensure they include all necessary study elements. For many sites, the time commitment for assistance is much greater as delays, unfamiliarity of collaborating clinicians with the application process, and requested revisions, require additional assistance. We comment here only on the time investment of the Coordinating Center study coordinator, but each approval also requires extensive time commitment of the site's own investigator, study staff, and, of course, the local IRB to obtain approval. The time commitment of both the Coordinating Center and local site staff then continues for each site's annual continuing review and any amendments to the initial approved protocol. The result of all this effort is redundant review and approval of the same study protocol with minor variations in the consent form based on each institutional IRB's consent form template. We are

confident that this does not improve protections for study participants, but actually decreases protection and consistency for participants as minor, but largely inconsequential, variations in study language are made to accommodate various IRB templates. The only substantive revisions by other IRBs thus far to the HDRC protocol have been changes in categories for racial and ethnic data collection for sites outside the US, which would still be accommodated by the draft policy.

Hirschsprung disease affects approximately 1 in 5000 newborns, is life threatening if not recognized and treated promptly, and despite recent advances continues to cause significant morbidity in affected individuals. Research, such as that carried out by the HDRC, is essential to improving treatment for this condition. The rare nature of the disease, the variation in its presentation and outcomes, and multidisciplinary nature of its care mean that multi-site studies are necessary to obtain the power and expertise needed for meaningful results. The HDRC is making significant steps toward overcoming barriers in Hirschsprung disease research, but the progress of the collaborative has been significantly hampered by the need for redundant IRB reviews as the addition of new collaborating study sites and revisions to study protocols are delayed by many months due to the time required for multiple IRB reviews. Therefore, we support the use of a single IRB of record for review of multi-site studies to both reduce redundant and unnecessary use of investigator and research staff effort and to improve protections and equality for study subjects.

Sincerely,

Aravinda Chakravarti, PhD
Professor of Medicine, Pediatrics, Molecular Biology & Genetics
Johns Hopkins School of Medicine; Professor of Biostatistics
Johns Hopkins Bloomberg School of Public Health

Courtney Berrios, MSc, ScM
Genetic Counselor/Study Coordinator

Comment #59

Commenter: Roy W. Beck, MD, PhD

Date of comment: December 31, 2014

Comment:

As the director of multi-center coordinating centers, I believe the proposed central IRB requirement will have major positive benefits towards creating greater efficiency in the conduct of trials and enhancing human subject protections. Study participants would be far better served by centralizing the responsibility for human subject protection rather than relying on an inefficient and sometimes ineffective system in which multiple IRBs duplicate effort in performing this function. In addition, it should be noted that there is further duplication of effort in many multi-center trials that have a Data and Safety Monitoring Board, comprised of individuals with qualifications and expertise specific for the trial to be conducted. There will be new logistical issues for a coordinating center to deal with in working with a central IRB and establishing agreements with each institution but these should be far less than what is currently required dealing with review by a large number of IRBs. Although OHRP has indicated its support for having a central IRB for multi-center trials, it has not issued a formal guidance in this regard. Thus, most institutions have not been willing to relinquish even partial control of the IRB review process. This new central IRB requirement by the NIH will force the reluctant institutions to accept a central IRB, and once established for NIH studies, this should become commonplace for studies conducted through other funding sources.

Comment #60

Commenter: Lori Sames

Date of comment: January 2, 2015

Comment:

Not only is a single IRB needed for multi-site NIH studies, but a single IRB is needed for all gene deliveries. Just as the FDA realized a different level of expertise was needed when they created the FDA Center for Biologics Evaluation and Review (CBER), as a separate entity than the Center for Drug evaluation and Review (CDER), the NIH IRBs must also adapt and change. CBER sees a ton of AAV data every day, and thus make fast, confident decisions.

The AAV9 gene delivery protocol we have developed went before the NIH Genome IRB. While the FDA CBER was amazingly responsive, the NIH IRB was painfully slow. We feel this is largely due to the fact that the Genome IRB members have no experience in the field of gene delivery, they have no accountability to a mandated turnaround time.

It pains us to think that every AAV gene delivery trial to go the 28 different NIH IRBs will go throughout the same wasteful, inefficient NIH IRB review process. A national IRB is needed for all gene deliveries, comprised of experts in the field, as well as immunologist(s)! AND, like the FDA, NIH IRBs they must have a 30 mandated turn-around time! IRB members should have a percentage of their salaried time allocated to their IRB responsibilities.

Patients have no time to waste and far too much time is being wasted with NIH IRBs. IRB members seem to forget that the protocol and consent forms have already gone before the NIH RAC and FDA CBER.

It was public outcry that resulted in the 30 required turnaround by the FDA. I am happy to lead the charge to obtain a 30 day mandated turn-around time for NIH IRB protocol reviews.

Comment #61

Commenter: Mendel Tuchman, MD

Date of comment: January 5, 2015

Comment:

Very few people will disagree that a central IRB for multisite clinical trials is warranted to reduce unnecessary and unproductive burden on investigators and to avoid duplications that have no additional benefits for patients. The main problem to tackle is how to get there. We have witnessed that setting up central IRBs among collaborative institutions creates a new bureaucracy which could negate the gains of this important initiative. Inter-institutional agreements on central IRBs typically involve legal and administrative considerations and once lawyers get involved, delays seem to be the rule. I would recommend to discuss how to make the process of setting up central IRBs more efficient. An easy and uniform path to accomplish this would go a long way to eliminate a large barrier to efficient conduct of clinical and translational research.

Comment #62

Commenter: Robert A. Cina, MD
Date of Comment: January 5, 2015

Comment:

January 5, 2015

Office of Clinical Research and Bioethics Policy Office of Science Policy, NIH
6705 Rockledge Drive, Suite 750 Bethesda, MD 20892

Re: Request for Comments on the NIH Draft Policy on the Use of a Single Institutional Review Board for Multi-Site Research

Dear Sir or Madam,

I am writing to provide comments in support of the NIH draft policy that would encourage use of a single Institutional Review Board (IRB) of record for multi-site research studies. My group is involved in a multi-site research project as a member in the Hirschsprung Disease Research Collaborative (HDRC). The HDRC is an academic research collaboration involving geneticists, pediatric surgeons, pediatricians and gastroenterologists interested in a global analysis of Hirschsprung disease toward improving care for affected individuals. The HDRC is building a biorepository of data and samples collected in a detailed and standardized manner that will be used for correlation of disease and treatment outcomes with genetic, pathologic and clinical variation, as well as providing a resource for other HDRC member research projects.

The HDRC was initiated in the summer of 2011 after IRB approval at the HDRC Coordinating Center at Johns Hopkins University School of Medicine, and additional site approvals have continued since that time. To date, the HDRC includes 18 study sites with IRB approval to actively enroll study participants for the biorepository, 2 sites currently in the IRB review process, 9 sites who have indicated that they are preparing materials for IRB submission, and 5 sites referring patients to the HDRC Coordinating Center for study enrollment. More than 30 other investigators, at sites both within the US and internationally, have expressed interest in joining the HDRC. We have an approved HDRC protocol which requires investigator and effort for initial approval and maintenance.

I estimate that initial approval required 40 hours of effort by our local study team, and approximately 20 hours of effort annually for continuing review and protocol changes. The result of this effort was approval of the study protocol provided by the HDRC Coordinating Center with minor variations in the application and consent form based on our institutional IRB's application and consent form template. I do not believe that local review improved protections for study participants due to the minor nature of any variations from the Coordinating Center's approved protocol. Furthermore, I believe that any local considerations used to make changes to the protocol could be accommodated by a single IRB of record or otherwise allowed by the proposed policy. The effort required for IRB review for multi-site collaborative studies is also recognized by the Global Alliance for Genomics and Health in its initiative to develop systems that support mutual recognition of ethics review.

Hirschsprung disease affects approximately 1 in 5,000 newborns, is life threatening if not recognized and treated promptly, and despite recent advances continues to cause significant morbidity in affected individuals. Research, such as that carried out by the HDRC, is essential to improving treatment for this condition. The rare nature of the disease, the variation in its presentation and outcomes, and multidisciplinary nature of its care mean that multi-site studies are necessary to obtain

the power and expertise needed for meaningful results. The HDRC is making significant steps toward overcoming barriers in Hirschsprung disease research, but the progress of the collaborative has been significantly hampered by the need for redundant IRB reviews as the addition of new collaborating study sites and revisions to study protocols are delayed by many months due to the time required for multiple IRB reviews. Therefore, I enthusiastically support the use of a single IRB of record for review of multi-site studies to both reduce redundant and unnecessary use of investigator and research staff effort and to improve protections and equality for study subjects.

Sincerely,

Robert A. Cina, MD
Associate Professor of Surgery and Pediatrics
The Medical University of South Carolina

Comment #63

Commenter: Joy Jurnack, RN, CCRC, DIP

Date of comment: January 6, 2015

Comment:

While I applaud the efforts to centralize efforts of human subject protection, I encourage serious thought on who will be writing these informed consent documents. As a research nurse for over 20 years, scientific jargon and difficult, dense ICF writing has been so standard within both NIH and Pharma that the time it takes for potential subjects to become subjects is labor intensive. NCI has made a lame effort to present comprehensive ICF's to multi-centered IRB's. As a fierce subject advocate, both in a previous position as a NHI Research Subject Advocate and currently as a research nurse in CKD, efforts must be made to ensure that any document sent to multi-centered sites is written with the true end user considered – the subject who speaks limited scientific language and has the right under the Belmont Report to have a document presented to her/him which is readable, understandable and provides a road map for the research they are consenting to participate. We, as in scientists, physicians – typical IRB members, read medical/scientific journals – subjects read People Magazine and Sports Illustrated. In a previous position, I was required to re-write pharma presented ICF's, as required by an independent IRB, no greater than a 9th grade reading level. It can be done. While presenting a challenge to me to keep the serious language of the scientific hypothesis, simplification of the document went a long way to providing a subject signs the ICF – adhering to protection of autonomy, beneficence and justice.

Comment #64

Commenter: Joseph R. Haywood, PhD FASEB President

Date of Comment: January 6, 2015

Comment:

January 6, 2015

Office of Clinical Research and Bioethics Policy Office of Science Policy, National Institutes of Health 6705 Rockledge Drive, Suite 750 Bethesda, MD 20892

Submitted electronically via: SingleIRBpolicy@mail.nih.gov

Dear NIH Clinical Research and Bioethics Policy Team,

The Federation of American Societies for Experimental Biology (FASEB) appreciates the opportunity to comment on the National Institutes of Health's (NIH's) draft Policy to promote the use of a single Institutional Review Board (IRB) of record for domestic sites of multi-site clinical studies funded by NIH (NOT-OD-15-026). FASEB is composed of 27 scientific societies, collectively representing over 120,000 biological and biomedical researchers. The Federation has long advocated for widespread use of a single IRB of record for multi-site studies, and we applaud NIH for this proposed Policy.

In our [response](#) to the 2011 Department of Health and Human Services Advance Notice of Proposed Rulemaking, "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators," FASEB agreed that the Department should mandate use of a single IRB of record for all domestic multi-site studies. In these comments, we noted that "[t]his change would facilitate collaborative review arrangements and reduce the obstacles that investigators encounter when embarking on multi-center projects." This perspective was reiterated in our [response](#) to a 2013 Request for Information from the National Science Board on "Reducing Investigator's Administrative Workload for Federally Funded Research."

FASEB commends NIH for proposing this Policy that will increase the efficiency of clinical studies. Use of single IRB of record for multi-site studies will decrease administrative burden for clinical research staff and reduce delays in patient recruitment.

Thank you for considering FASEB's comments. Please do not hesitate to contact me if we can provide you with additional information.

Sincerely,

Joseph R. Haywood, PhD

FASEB President

Comment #65

Commenter: Michele K. Russell-Einhorn, JD

Date of comment: January 7, 2015

Comment:

Please accept the following as comments in response to the NIH Draft Policy on the Use of a Single Institutional Review Board for Multi-Site Research.

1. The Exception to use of a single IRB is currently described as including only situations where the IRB is unable to meet the needs of a specific population or where local IRB review is required because of a state or local regulation or law.

This exception should be broadened to include situations where:

1. The IRB review time frame from submission of a protocol to IRB approval is an average of under 30 days. If the purpose of the policy is to address delays in the review process, this should not apply where an IRB can demonstrate a speedy and efficient IRB review process.
 2. The relying IRB determines in the review process that there are differing views about safety issues in the reviews conducted by the reviewing IRB. The relying IRB should have the option of terminating the relationship but remaining as an institutional participant in the research.
 3. The IRB Chair verifies that the type of research warrants local IRB review. Research such as first in human research may well be safer where the local IRB has reviewed the consent and the protocol and can adapt the consent to specific experiences that the institution has had with the investigational agent or like agents. For example, at the DF/HCC, first in human research protocols involve many issues regarding dosing changes and require a close working relationship with research pharmacy. Dose changes; changes in cohorts, increases in subject population all require an IRB review. Management of protocol violations, deviations and eligibility exceptions, common in phase I research, is very difficult to manage when the requests have to go to an outside Institutional Review Board. In fact, it can take much longer to go through an outside IRB.
 4. Resources and issues relating to feasibility warrant the use of a local IRB. Use of an independent IRB requires a significant cost. Where an institution is chosen to be the single IRB of record, that institution takes on a significant burden both in terms of resources and operations. Institutions have varying levels of support, processes and resources for their own research portfolio. Operating as a single IRB for several sites requires a significant financial commitment that should not be one done only for a few years during the time that the institution operates as single IRB for an NIH trial. Incorporating separate reviews such as conflicts of interest and radiation safety reviews have proved problematic when relying on outside IRBs. These reviews must take place in the same review process that the IRB is conducting for the consent and the protocol.
- A. Further justification for increasing the number of reasons for more exceptions include the following:
- (i) Local context review becomes another process that has to be implemented in order to ensure that the reviewing IRB has information about competing trials and possible subject population at the relying site.
 - (ii) Protocols often need to be changed during the IRB review because a process, a test, or a procedure that is described in the protocol violates the institutions' policies. These are situations that get worked out during the IRB review. With a single IRB review, required, there will be no ability to manage these types of issues. For example, a protocol calls for a dip stick urine test and the institution does not do dip stick urine tests. This would be discovered after

the single IRB reviewed the protocol and, if that single IRB review is required, the relying institution would have no choice but to pull out. This could occur with many point of service tests. Another example is where institutional policy calls for a cardiac echo in lieu of a MUGA. An institution may decline to perform CT scans in addition to PET-CT. Working these issues out involves requiring the PI to contact the sponsor; negotiations regarding changes in the protocol; negotiations regarding changes in the consent; or, requirements that embodied in local site only documents. These types of issues are very difficult to manage when relying upon a single IRB.

- (iii) Investigator competence and site suitability are in part issues determined during the IRB process. A new process would have to be created to manage these issues.
- (iv) Institutions and IRBs would experience an increase in administrative burden from the management of numerous IRB authorization agreements as well as approvals and management of protocol related events. Along these lines, institutions may well have different responsibilities delegated and managing and tracking those will be an administrative burden for all institutions. Institutions have systems in place to manage their typical processes. Incorporating review oversight of many different institutions may well require significant re-tooling of existing systems.

To summarize, “encouraging” the use of a single IRB is laudable. “Requiring” the use of a single IRB with few limited exceptions will only delay research and raise the specter of unsafe research, additional substitute administrative processes, and increased cost to institutions.

Comment #66

Commenter: Alan Percy, MD

Date of comment: January 8, 2015

Comment:

Having been involved with multi-site studies now for more than ten years, this policy would greatly benefit the efficiency of protocol approval at the IRB level. The delays that have resulted in one or more sites weakens the primary purpose of the research. Assuming that the protocol passes this critical step at a single site should allow these multi-site studies to function uniformly. The commentary of Menikoff referenced here suggests the obvious positives, but highlights the possible difficulties with relying on each institution's IRB in that the outcome could be negatively influenced with biased or misguided results.

What is also important is to separate the critical ethical role of the IRB and the influence of the institutional responsibility. The latter has seemed to become intertwined when it in fact subverts the IRBs role.

For these reasons alone, I am fully supportive of the proposed policy.

Comment #67

Commenter: James Feldman, MD MPH FACEP

Date of comment: January 8, 2015

Comment:

The NIH in support of the draft policy for single center review of a multicenter study states that, "Importantly, there is no evidence that multiple IRB reviews enhance protections for human subjects. In fact, the use of single IRBs may lead to enhanced protections for research participants by eliminating the problem of distributed accountability, minimizing institutional conflicts of interest, and refocusing IRB time and resources toward review of other studies." The absence of evidence that multiple IRB reviews enhance protections for research subjects could be a result of the lack of research that has formally evaluated the effects of local IRB reviews rather than confirming that such reviews have had no effects or that a single center review was preferable.

The major problem with multiple IRB reviews for multicenter studies was that there was no procedure for reconciling discordant reviews or providing some kind of analysis where there were differences as to whether these differences were substantive. The human subject regulations recognize the role of robust discussion by requiring that minutes of IRB meetings summarize "controverted issues and their resolution" 45CFR46.115(a). Requiring a single center review would be more efficient. However, there is no assurance that a single center might not make serious errors in its review of a study. The SUPPORT Trial, for example, could arguably have been more efficient if the Alabama IRB had been the single center IRB of record. As stated by OHRP, "It was alleged, and we determine, that the IRB approved informed consent documents for this study failed to include or adequately address the following basic element required by HHS regulations at 45 CFR 46.116(a)." How would a single center IRB review have prevented this occurrence?

If NIH is going to implement the requirement for a single center review of multicenter NIH funded research, NIH must establish an explicit procedure where local IRBs or others can appeal the determination or raise controverted issues concerning the central IRB's determinations. The following are two contemporary examples where the central IRB that was suggested as the IRB of record made

determinations that the local IRB questioned. In the absence of a formal policy and procedure for challenging the central IRB findings, important questions about risks, benefits and risk/benefit could not be appealed.

Example 1:

This is an NIH funded investigation. The central IRB determined that this was a “minimal risk study” as stated in the Informed Consent document and the only risk was loss of confidentiality:

The following is the statement that was approved by the central IRB in the Informed Consent Document:

RISKS AND DISCOMFORTS

What Are The Risks Of The Study?

As described above (“Purpose of the study”), there are likely pros and cons to remaining on 5 mg prednisone. Because both of these approaches to prednisone dosing are considered to be “standard of care,” participation in this study is considered to cause you “minimal risk.” That means that the risks associated with this study are the same as what you face every day. The only risk to those who take part in this study is the potential loss of privacy if you choose to share your condition through online social media.

Side Effects of Prednisone

Prednisone may cause weight gain, cataracts, weak muscles and fragile skin that may bruise easily. Prednisone can also cause bone changes which include bone thinning (osteoporosis), bone fractures, and avascular necrosis which is a type of bone fracture that most often affects the hips or shoulders. Prednisone can also cause an increased risk of infections, diabetes, high blood pressure, stomach irritation, and can affect some people’s mood.

Questionnaires

There is no physical risk to answering the questions. The medical interview and questionnaires used are not expected to be psychologically harmful or stressful

Our IRB disagreed with this characterization of the risks of this comparative effectiveness study. In conference call with OHRP (8/14), it was my impression that OHRP had concerns about the central IRB’s characterization of this study as well. We also questioned the risks that were included in the informed consent document (prednisone, questionnaires, confidentiality) and those that were omitted (risk of relapse for those who were randomized to taper to 0 mg prednisone).

Example 2:

This is an NIH/NIMH funded comparative effectiveness trial that compares methadone to morphine in the treatment of neonatal abstinence syndrome.

The central IRB determined that the study satisfied 45 CFR 46 405 and 21 CFR 50.52 for inclusion of minors as greater than minimal risk but presents the prospect of direct benefit to the individual subjects.

The benefit to the individual subjects in the central IRB approved Informed Consent Document stated, “The behavioral and developmental assessments will provide important information for you and your baby’s doctor on how your baby is doing and whether the treatment has contributed to any significant health problem.”

Our local IRB noted that “the actual direct benefit that would accrue to the child subjects was not adequately defined or justified...The Benefit to subjects as stated in the Informed consent document is that “The behavioral and developmental assessments will provide important information for you and

your baby's doctor on how your baby is doing and whether the treatment has contributed to any significant health problem." The Board noted that the standard of clinical developmental assessment both in the hospital and in routine follow up is not described. The Board could not determine the incremental direct benefit if any that would be derived for the child subjects as a direct result of the research."

The local IRB also questioned whether such a statement could be coercive to a vulnerable population where refusing participation in the research study could preclude access to "important" or "special" evaluations about the baby's development.

These specific examples are provided to counter the claim that the central IRB review is per se more informed, ethical or valid in terms of application of the research regulations.

I believe strongly that IF the NIH mandates a central IRB for multicenter NIH funded studies, NIH MUST establish a formal procedure whereby one can appeal or question the findings or determinations of the central IRB and that such a procedure will result in a written and publicly available analysis of the issues raised.

Comment #68

Commenter: Karen Christianson, RN, BSN, CCRP

Date of comment: January 9, 2015

Comment:

This email is in response to the request for comments on the draft NIH policy on the use of a single institutional review board for multi-site research. The opinions expressed in this email are my own and are not intended to represent the viewpoint of my employer, the HRP Consulting Group.

While I commend the desire to improve efficiency of IRB review, I also have concerns regarding the draft policy based upon my experiences as a research subject, as research nurse, as a HRPP Quality Assurance and Education Specialist, as a HRPP Director, as an AAHRPP Site Visitor, and as a consultant in the field of human research protections.

First, I urge NIH to consider restricting the policy to those multi-site projects that involve a large number of centers (e.g., greater than 10), extended periods of human subjects activity (e.g., 3 years or longer requiring IRB oversight), and not involving methods or populations that are likely to require more complex local context considerations (e.g., planned emergency research). My concern is that the time, resources, and effort spent establishing the standard operating procedures for the single relied-upon IRB, negotiating and executing institutional agreements, educating local sites, and gathering and considering local context information would negate or exceed any gain in efficiency that the policy is intended to achieve for this sub-set of studies.

Second, I encourage NIH to allow exclusions for those centers with accredited HRPPs. A functional HRPP enhances human subjects protections and promotes efficiency through the coordination of effort and information-sharing that is inherent in such systems. To gain accreditation, an organization must have procedures in place to ensure coordination of IRB review with other internal reviews such as Conflict of Interest, Biosafety, Radiation Safety, Scientific Review, Privacy Review, and Departmental or Leadership Review. Further there must be quality monitoring and initial and ongoing training and education efforts all of which communicate and coordinate with IRB. Quality assurance findings drive educational priorities and inform IRB review. Common issues identified in IRB reviews drive quality assurance and education plans. Feedback obtained during education and training informs IRB and quality assurance activities. Requiring such organizations to rely upon multiple external IRBs in order to participate in desirable NIH research has the potential to diminish the effectiveness of the HRPP by virtue of removing an essential component from the feedback loops that characterize and drive HRPPs and by forcing organizations to constantly adapt their processes to accommodate the standard operating procedures of an ever-changing stream of IRBs.

Finally, I offer an observation based upon my experience with organizations that currently choose to rely upon multiple IRBs. I have observed an increase in what I can only describe as unintentional noncompliance on the part of investigators as they attempt to comply with the varying requirements of each of the IRBs. I have seen extremely complex charts developed by regulatory specialists in an attempt to create a reference guide capturing what needs to be reported to whom and when. This IRB defines a protocol deviation as this and requires reporting within X business days. This IRB defines a major protocol violation as this and a minor as this, major violations must be reported within X business days, minor violations must be summarized at continuing review. This IRB requires reporting of all subject complaints, this IRB only requires reporting of subject complaints that can't be resolved by the investigator. This IRB requires review of any changes to study personnel, this IRB only requires review of any changes to principal investigator. And on and on. As the investigators become increasingly frustrated trying to navigate the varying requirements it is not at all uncommon that they begin to avoid reporting

which in turn can lead to significant issues not being pro-actively identified and managed. I suggest that any initiative to mandate centralized review also be accompanied by the development of a common set of standards that will apply to IRB review of studies under the initiative to minimize the confusion, mistakes, and harm that may occur without common standards.

Thank you for your consideration of my comments, I commend NIH's efforts to improve the human protections system.

Comment #69

Commenter: Karen Blackwell, MS, CIP

Date of comment: January 9, 2015

Comment:

Thank you for requesting comments on the draft policy for use of a single IRB for multi-site research. Overall, we are supportive. Our institution has extensive experience with single IRB review through existing agreements with NCI CIRB, NeuroNext, our regional CTSA network and a newly developed IRB consortium for our PCORI CDRN.

My comment pertains to the policy's section on exceptions. Would there be a circumstance where NIH would fund a surgery trial? At this time, our policy is not to rely on another IRB for a clinical trial involving surgery. For surgery studies, risks are much more focused and dependent on the local setting: the skills of the local surgeons, local hospital resources and processes and other risks/protections that may or may not be present at every location.

Thank you for considering this issue as a possible exception, if applicable to NIH funded studies.

Comment #70

Commenter: Gary Chadwick, PharmD, MPH, CIP

Date of comment: January 12, 2015

Comment:

1. The federal regulations at 45CFR46 do NOT require reporting adverse events to IRBs. This requirement should be removed from the NIH Policy for consistency. ("All participating sites will be responsible for meeting other regulatory obligations, such as obtaining informed consent, overseeing the implementation of approved protocols, and, reporting unanticipated problems and adverse events to the single IRB of record." Reviewing adverse effects is a responsibility of sponsors (NIH funding Institutes and Centers), which typically are handled by a Data and Safety Monitoring Committee/Board (DMC/DSMB). The policy for single IRB review should also require a study-wide DMC/DSMB to work with the IRB.
2. Being the single IRB of record for multi-site studies is expensive and it requires effort beyond that needed for the typical IRB review. The Policy should require the "applicant" (the extramural applicant or offerer, or the intramural principal investigator) to justify selection of the single IRB; show that resources exist to negotiate and track Authorization Agreements; show what the costs for review and management will be and how those costs will be met; and require a statement of support from the nominated IRB and, if applicable, its governing institution.
3. If NIH is to require a single IRB of record, then that should be a "direct cost" in the budget. The draft Policy states that only "fee-based IRBs" will be compensated for the expense of operation. This is not justifiable. The standard for multi-site trials as set by "industry sponsors" is to pay the

reasonable costs for all ethics reviews (IRB). NIH needs to meet its financial responsibilities for requiring single IRB review, or abandon the Policy. The Policy should be revised to clearly state that the costs of single IRB review will be included in the Notice of Award as a direct cost for all awards.

Comment #71

Commenter: Akira Takashima, MD, PhD

Date of comment: January 14, 2015

Comment:

At the University of Toledo College of Medicine, we discussed the draft policy with the Vice President of Research (Bill Messer, Ph.D.) and the IRB Chair (Roland Skeel, M.D.). We all support the concept of the use of a single IRB for NIH-funded multi-site studies.

Comment #72

Commenter: Sean C. Skinner, M.D.

Date of Comment: January 15, 2015

Comment:

January 15, 2015

Office of Clinical Research and Bioethics Policy
Office of Science Policy, NIH
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Re: Request for Comments on the NIH Draft Policy on the Use of a Single Institutional Review Board for Multi-Site Research

Dear Sir or Madam,

I am writing to provide comments in support of the NIH draft policy that would encourage use of a single Institutional Review Board (IRB) of record for multi-site research studies. We are involved in a multi-site research project as members and investigators in the Hirschsprung Disease Research Collaborative (HDRC). The HDRC is an academic research collaboration involving geneticists, pediatric surgeons, pediatricians and gastroenterologists interested in a global analysis of Hirschsprung disease toward improving care for affected individuals. The HDRC is building a biorepository of data and samples collected in a detailed and standardized manner that will be used for correlation of disease and treatment outcomes with genetic, pathologic and clinical variation, as well as providing a resource for other HDRC member research projects.

The HDRC was initiated in the summer of 2011 after IRB approval at the HDRC Coordinating Center at Johns Hopkins University School of Medicine, and additional site approvals have continued since that time. To date, the HDRC includes 18 study sites with IRB approval to actively enroll study participants for the biorepository, 2 sites currently in the IRB review process, 9 sites who have indicated that they are preparing materials for IRB submission, and 5 sites referring patients to the HDRC Coordinating Center for study enrollment. More than 30 other investigators, at sites both within the US and internationally, have expressed interest in joining the HDRC. We have an approved HDRC protocol which requires investigator and effort for initial approval and maintenance. I am working toward obtaining IRB approval with the input of investigator and study staff effort. We are interested in joining the HDRC, but have found barriers to participating including the time and effort required to prepare documents for local IRB review.

I estimate that initial approval will require 60 hours of effort by our local study team, and approximately 30 hours of effort annually for continuing review and protocol changes. The result of this effort is likely to be approval of the study protocol provided by the HDRC Coordinating Center with no substantial changes/minor variations in the application and consent form based on our institutional IRB's application and consent form template. We do not believe that local review will improve protections for study participants due to the minor nature of any variations from the Coordinating Center's approved protocol. We believe that any local considerations used to make changes to the protocol could be accommodated by a single IRB of record or otherwise allowed by the proposed policy. The effort required for IRB review for multi-site collaborative studies is also recognized by the Global Alliance for Genomics and Health in its initiative to develop systems that support mutual recognition of ethics review.

Hirschsprung disease affects approximately 1 in 5000 newborns, is life threatening if not recognized and treated promptly, and despite recent advances continues to cause significant morbidity in affected individuals. Research, such as that carried out by the HDRC, is essential to improving treatment for this condition. The rare nature of the disease, the variation in its presentation and outcomes, and multidisciplinary nature of its care mean that multi-site studies are necessary to obtain the power and expertise needed for meaningful results. The HDRC is making significant steps toward overcoming barriers in Hirschsprung disease research, but the progress of the collaborative has been significantly hampered by the need for redundant IRB reviews as the addition of new collaborating study sites and revisions to study protocols are delayed by many months due to the time required for multiple IRB reviews. Therefore, I support the use of a single IRB of record for review of multisite studies to both reduce redundant and unnecessary use of investigator and research staff effort and to improve protections and equality for study subjects.

Sincerely,

Sean C. Skinner, M.D.

Assistant Professor Surgery and Pediatrics, Division of Pediatric Surgery

Comment #73

Commenter: Evan Kharasch, M.D., Ph.D.

Date of Comment: January 12, 2015

Comment:

January 12, 2015

Office of Clinical Research and Bioethics Policy Office of Science Policy
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892
via: SingleIRBpolicy@mail.nih.gov

RE: Request for Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research, NOT-OD-15-026

This letter serves to support the proposed NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research with the greatest possible enthusiasm, and to endorse its implementation at the earliest possible time.

I am a translational and clinical investigator with more than two decades of clinical research experience (both single- and multi-site studies), more than two decades of peer-reviewed federal research funding, and have more than 225 peer-reviewed publications. I am the former Vice Chancellor for Research and Institutional Official for Human Subjects Research at Washington University in St. Louis, and am an elected member of the Institute of Medicine of the National Academy of Sciences. I am writing in my personal capacity.

The proposed Policy is directly responsive and partially curative to the indisputable need for reform of the IRB process. Specifically, the Policy will refocus IRB process on the primary mission of ethical review and protecting human subjects, increase quality and diminish the variability of IRB reviews, enhance and streamline the IRB review process, increase research efficiency, diminish time- and dollar-cost expenditures on research administration by investigators and institutions, and increase the overall cost-effectiveness and return on federal investment in clinical research. Single IRB review of multi-site research should be the NIH standard, and the federal standard more broadly.

The Policy as written does merit a clarification. As written, "NIH generally expects all domestic sites of multi-site NIH-funded studies to use a single IRB of record. The Policy applies to all domestic sites participating in NIH conducted or supported multi-site studies, whether supported through grants, contracts, or the NIH intramural program". Nevertheless, it is not clear whether the Policy applies only to the NIH-supported multi-site studies (specifically), or more generally to any domestic site of any multi-site NIH-funded study (which would make the Policy applicable to an Institution which receives any NIH funds, for all their multi-center studies, regardless of the source of support). Given the extreme importance of the proposed Policy and its underlying need, I endorse the principle that the Policy apply broadly to any and all multi-site studies performed at an institution receiving any NIH funds.

Furthermore, while highly meritorious, the Policy applies only to multi-site studies (which would now be reviewed by a single IRB). Nonetheless, there is opportunity for additional positive impact of the proposed Policy. Specifically, the Policy should be enlarged to include the principle and statement that *single-site studies should also only be reviewed by a single IRB*. Presently, some single-site studies are subject to jurisdiction (and multiple reviews) by multiple IRBs. For example, FDA requires all human subjects research conducted by, supported, or funded in whole or in part by FDA, to be reviewed by the

FDA IRB (and every local IRB as well); (c.f. <http://first.fda.gov/Rihsc/document/RIHSCwrittenproceduresfinal.doc>). This multi- IRB review of a single-site study violates the same principles motivating the NIH Policy on single IRB review, and NIH is encouraged to correct this also in the new Policy.

Implementation of the draft Policy, with clarifications and additions as enumerated above, is important because other agencies and funding organizations so often pattern their guidelines on those of NIH. Implementing single-IRB review is consonant with and would accomplish the goals articulated above and in the proposed NIH Policy.

I applaud and thank NIH for proposing this needed and long-overdue Policy, and most emphatically endorse its adoption (and expansion, as above). Please do not hesitate to contact me if you have further questions of considerations.

Very truly yours,

Evan Kharasch, M.D., Ph.D.
Russell D. and Mary B. Shelden Professor of Anesthesiology
Director, Division of Clinical and Translational Research
Professor of Biochemistry and Molecular Biophysics

Comment #74

Commenter: April Green

Date of comment: January 16, 2015

Comment:

I think that a centralized IRB for multi-center study is a great idea it will help save a lot of time and cut down on costs. I would also like to submit a public comment for the NIH policy for the use of single Institutional Review Boards.

I suggest that the centralized IRB reviewing the study be a separate entity from the site who owns the protocol so that there is no conflict of interest when reviewing the protocol. IRBs may feel pressure at their institution to approve and continue to approve large multi-center studies so the study can receive revenue and so that the institution can receive credit for creating/conducting large multi-center studies.

Comment #75

Commenter: Gregory J. Gores, M .D.; Sundeep Khosla, M.D.; William J. Tremaine, M .D.

Date of Comment: January 6, 2015

Comment:

January 6, 2015

Office of Clinical Research and Bioethics Policy Office of Science Policy
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, Maryland 20892

Re: Request for Comments

Draft NIH Policy on the Use of a Single Institutional Review Board for Multi- Site Research
NOT-OD-15-026

To Whom It May Concern:

Thank you for the opportunity to comment upon the draft N IH policy regarding the use of a single Institutional Review Board (IRB) of record for domestic multi-site research funded by the N IH.

We respectfully provide the following comments and suggestions for your consideration:

We are fully supportive of a single, full-reliance IR B model as proposed in this draft policy. In addition, and in the interest of further reducing administrative burden across multiple local sites, we suggest the creation of discipline-specific central IRBs at the federal level consistent with the National Cancer Institute Central Institutional Review Board (NCI CIRB). If, however, IRBs at local sites will function as the IRBs of record for sites engaged in the research, we recommend that these sites maintain accreditation by a national organization such as the Association for the Accreditation of Human Research Protection Programs (AAHRPP).

We appreciate your consideration of our response.

Sincerely,

Gregory J. Gores, M.D.
Executive Dean for Research, Mayo Clinic

William J. Tremaine, M .D.
Director, Institutional Review Board, Mayo Clinic

Sundeep Khosla, M.D.
Director, Center for Clinical and Translational Science, Mayo Clinic

Comment #76

Commenter: Elliott M. Antman, MD FAHA President

Date of Comment: January 20, 2015

Comment:

January 20, 2015

Office of Clinical Research and Bioethics Policy Office of Science Policy
National Institutes of Health 6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Re: Notice Number NOT-OD-15-026

The American Heart Association applauds the National Institutes of Health draft policy promoting the use of single institutional review boards or IRBs, in multi-site clinical research studies as per the above named notice.

Importance of Clinical Trials

Since 1949, the American Heart Association has invested more than \$3.7 billion in research to increase our knowledge about cardiovascular diseases and stroke and currently funds more than 2,000 scientists around the United States. As a leading funder of heart disease- and stroke-related research, the AHA has developed unparalleled competencies in the administration of large-scale research enterprises. In our last fiscal year, we recruited 1,500 expert volunteers to review over 6,100 applications in order to award grants across our research enterprise, which includes a mix of both investigator-initiated and strategic research platforms that span across basic, clinical and population health research disciplines.

The AHA affirms the pivotal importance of clinical trials as a key base for the development of evidence-based clinical practice guidelines in support of our mission. In order to provide clinicians with best practice recommendations that will help them improve outcomes at point-of-care, there is an urgent need to conduct research that addresses current gaps. To this end, streamlining of the processes required to design and execute knowledge-generating clinical trials is of critical importance in advancing care.

Value of Single IRB review of Clinical Trials

As an organization that channels almost 30 cents of every publicly donated dollar to our research programs, the AHA supports any administrative efficiencies that could result in a greater proportion of funds supporting the conduct of research. Use of a single IRB has the potential to shift many internal costs and create such efficiencies.

We fully support the recommendation to encourage single IRBs in domestic multi-site clinical research studies funded by the NIH, given that this would allow for the acceleration of research and the timely generation of findings that have the potential to improve outcomes. There is a successful precedent for the concept of an IRB reliance agreement in the CTSA consortium where trials that are NIH-funded as well as those that are not are being conducted. (<http://www.ncats.nih.gov/news-and-events/features/irb-reliance.html>).

Suggestions for Implementing the Single IRB Program for Domestic NIH-Funded Multisite Clinical Trials

To facilitate the efforts of participating sites in implementing the Single IRB Program it would be helpful if the NIH posted on its website:

1. A list of IRBs that have agreed to participate in the Single IRB Program
2. A set of template documents that specify the minimum criteria for IRBs to participate in the reliance program. An example of the criteria as developed by one of the CTSA programs can be found at <http://catalyst.harvard.edu/programs/regulatory/reliance.html>

We look forward to the evolution of the NIH draft policy and ultimately to the widespread adoption of the proposals therein since we believe it will help improve and extend people's lives.

Sincerely,

Elliott M. Antman, MD FAHA
President

Comment #77

Commenter: Susan Blanchard, VP Research Administration; Diane L. Souvaine, PhD Vice Provost for Research Tufts University

Date of Comment: January 14, 2015

Comment:

January 14, 2015

Office of Clinical Research and Bioethics Policy Office of Science Policy

National Institutes of Health

6705 Rockledge Drive Suite 750

Bethesda, MD 20892

Email: SingleIRBpolicy@mail.nih.gov

RE: Comments in response to the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-026.html>

NIH takes step to speed the initiation of clinical research by ensuring use of single IRB

Tufts Medical Center and Tufts University support this proposed policy. We are proponents of the single IRB model, have successfully utilized the CIRB since it began, and have implemented a variety of IRB reliance agreements. We fully support new policies that seek to speed up the initiation of studies and decrease administrative burden for investigators and institutions.

Thank you for considering the following comments and requests for additional details on NIH's draft policy to promote the use of a single Institutional Review Board of record.

Creating an "NUIRB":

We think the best option for Investigators, IRBs, and institutions would be for the NIH to create a central Institutional Review Board (IRB) for NIH studies, like the National Cancer Institute CIRB.

This would create an even playing field for every institution, big or small, regardless of whether their own IRB has the resources to act as the single IRB of record. Having the option to use an NIH central IRB would also alleviate concerns that grant proposals will be less competitive if the principal investigator's institution cannot serve as a central IRB.

Otherwise, it may only be feasible for a commercial IRB to be named as the single IRB of record, since other IRBs, including academic IRBs, may not have the resources to conduct local context reviews, ensure compliance (monitoring), and comply with state or local laws that govern the conduct of research at each institution across the country.

Creating a Shared/Facilitated Review Model:

If creating an NIH IRB is not feasible, another option would be to create a standard "facilitated review" model, whereby a single IRB of record would exist, but would share responsibility with local IRBs who would review for local context, local compliance, and local laws. In our experience, this type of shared model is efficient and decreases administrative burden while maintaining oversight of local context. A template IRB Authorization Agreement could be provided that allows for delegation of responsibilities.

How to Address Local Contextual Issues across Multiple Sites and Locations:

There is the potential that multiple sites from various locations across the US and even internationally may participate in a single NIH funded study. Please provide additional details and template forms for

information to be collected from each site to address local contextual issues (e.g., investigator competence and site suitability, state laws and community standards, etc.) In addition, provide details about when ad hoc members or consultants would be necessary to review local contextual issues.

In addition, please note that for each participating site, institutional committee review might still be necessary, such as radiation safety review, pharmacy review, etc. Therefore, each site will need to have a process to ensure appropriate institutional committee review, even when ceding IRB review to a single IRB of record.

Clarify whether one consent form would be approved by the single IRB of record for use at all sites, or whether each site would add the site's boilerplate language to the template consent approved by the single IRB of record.

Additional Guidance Requested:

Please provide additional guidance about how the use of a single IRB of record should be proposed at the grant level. Consider whether acknowledgment from the proposed IRB of record will be required, and provide details about the NIH review and approval process for a proposed IRB of record.

The draft policy states "If the agreed-upon single IRB is a fee-based IRB, these costs will be included in the Notice of Award as a direct cost."

- Please define "fee-based IRB." Is this intended to refer only to commercial IRBs or to any IRB that has costs associated with IRB review?
- Would a proposed single IRB of record need to have existing resources to act as the single IRB of record, or could they use NIH funds to hire additional staff, etc.?
- Please clarify if use of a model such as the existing IRBShare model would be consistent with the proposed policy to utilize a central IRB model.

What would be the anticipated timeline for implementing large scale IRB Authorization Agreements for many sites? Although use of a single IRB decreases administrative burden over the life of the study, executing the agreements for all sites, and preparing a review for multiple sites with which the IRB may be unfamiliar would take a significant amount of time and effort for the institution serving as the central IRB.

The proposed policy states "A duplicate IRB review at a participating site would be counter to the intent and goal of the Policy, but the Policy does not prohibit any participating site from carrying out its own IRB review." How would issues identified during a duplicate review be addressed and resolved?

Standard/Template Documents Requested:

Please provide the following standard template documents/guidance:

1. A template IRB Authorization Agreement that specifies the responsibilities of each participating site and the single IRB of record.
3. Guidance and tools to enable the single IRB of record to consider local context issues during its deliberations, such as a standard form to collect local context information from each site.

Guidance for institutions that cede review to central IRBs regarding the best practices for maintaining oversight of research reviewed and approved by a non-institutional IRB- consider creating a standard tracking spreadsheet or a web-based tracking system.

Sincerely,

Andreas K. Klein, M.D.

IRB Chair

Susan Blanchard

Vice President Research Administration

Tufts Medical Center

Diane L. Souvaine, PhD

Vice Provost for Research

Tufts University

Comment #78

Commenter: The Study of Women's Health Across the Nation (SWAN) Steering Committee

Date of Comment: January 21, 2015

Comment:

To: Office of Clinical Research and Bioethics Policy

From: The Study of Women's Health Across the Nation (SWAN) Steering Committee

Re: Response to the NIH Draft Policy on the Use of Single Institutional Review Boards

Date: January 21, 2015

We, the Steering Committee of the multi-site study, Study of Women's Health Across the Nation (SWAN), are responding to the NIH request for comments on the draft policy (dated 12/3/2104) regarding use of a single IRB in multi-site studies. We recognize that a single IRB may result in increased efficiency and reduced cost and effort for certain types of multi-site studies. In particular, this model may be ideal for a multi-site clinical trial with a specific common protocol and a Coordinating Center that is responsible for developing and making all changes to the protocol. In contrast, in many multi-site studies, particularly epidemiological studies, the disadvantages of a single IRB would far outweigh the advantages, as described below.

In our experience with SWAN, a multi-site longitudinal observational cohort study of women's mid-life aging and menopause conducted at 7 sites, the recruitment and retention strategies had to vary across the sites because each involved a distinct population of racial/ethnic groups and communities. To identify the potential participant pool, some sites used random digit dialing; others contacted women from driver registrations, a health maintenance organization, or utility company lists; others used household surveys to identify relevant participants; another used snowball sampling in which enrolled participants identified friends who might be eligible. Furthermore, as the study initially progressed, new methods of recruitment and retention had to be developed at most of the sites to meet overall recruitment goals for specific racial/ethnic groups. Some of the sites were required to translate all materials into languages appropriate for the target population. It would be challenging for a single IRB to review the diverse methods used and to consider the different needs of the participant populations.

While each SWAN site was required to conduct a protocol that was common across sites, each site also directed additional site-specific protocols. To have adequate statistical power and have access to local expert investigators, some of the site-specific studies were conducted at several SWAN sites, resulting in various combinations of protocols among the 7 sites. In addition, sites requested permission from participants to obtain medical records to verify specific clinical events. Local IRBs vary in terms of the permission that they require research studies to obtain in order to link protected health information while adhering to HIPAA rules for ensuring privacy of individually identifiable health information. When protocols vary across sites and institutional regulations require that certain site-specific information is contained in informed consent documents, it might be difficult for participating sites to use the documents that would be created by a centralized IRB that would be responsible while also satisfying individual site IRB requirements. This situation is not infrequent in current studies that use a centralized IRB.

We have listed important challenges that might confront incorporation of a single IRB to cover the protocols for multi-site studies. Others have been cited by Klitzman (BMC Medical Ethics 2011, 12:13; <http://www.biomedcentral.com/1472-6939/12/13>). We hope that our points about the inefficiencies introduced by a single IRB are clear, but we are happy to clarify any remaining uncertainties about our concerns.

We recommend that multi-site studies be permitted to request either a single IRB or multiple site-specific IRBs at the time of the study inception. A statement explaining the rationale should accompany the request.

Comment #79

Commenter: David M. Pollock, President, APS

Date of Comment: January 22, 2015

Comment:

January 22, 2015

Office of Clinical Research and Bioethics Policy
Office of Science Policy, National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Submitted electronically via: SingleIRBpolicy@mail.nih.gov

Dear NIH Clinical Research and Bioethics Policy Team,

The American Physiological Society (APS) appreciates the opportunity to respond to the request for comments on the use of a single institutional review board (IRB) for multi-site research (NOT-OD-15-026).

The current lack of uniformity in IRB review is an obstacle to multi-site collaboration, requiring duplicative effort on the part of investigators and administrators. Collaboration between institutions to accept single IRB review has the potential to promote uniformity in study review, reduce administrative burden and improve efficiency for multi-site studies and improve the quality of review thereby enhancing participant safety.

A critical aspect of single or central IRB review will be assuring the high quality of reviews. Monitoring the quality of reviews could be achieved through a program of accreditation. The current accreditation system in place through the Association for the Accreditation of Human Research Protection Programs (AAHRPP) may need to be adapted to accommodate single or central IRB review for multi-site studies. Institutions holding federal grants will need to invest significant effort upfront to establish agreements with other institutions to accept reviews from external IRBs and modify internal policies to accommodate those changes. However, this upfront investment of effort will be offset by improved efficiency over time. We note that the draft policy outlines a number of possible exceptions for single or central IRB review. We recommend allowing exceptions in cases where institutional policy requires an in-house IRB review.

The APS thanks you for considering these comments and for your efforts to increase the efficiency of research and reduce administrative burden. The APS is a professional society dedicated to fostering research and education as well as the dissemination of scientific knowledge concerning how the organs and systems of the body work. The Society was founded in 1887 and now has more than 10,000 member physiologists. Our members conduct federally-supported research at colleges, universities, medical schools, and other public and private research institutions across the U.S.

Sincerely,

David M. Pollock
President

Comment #80

Commenter: David L. Wynes, Ph.D., VP for Research Administration Emory University

Date of Comment: January 21, 2015

Comment:

January 21, 2015

Office of Clinical Research and Bioethics Policy Office of Science Policy
National Institutes of Health

To Whom It May Concern:

I am writing in response to your request for comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research (NOT-OD-15-026). Emory University is a leading institution of higher education, which includes a research portfolio exceeding \$500 million per year in externally sponsored programs. The primary sponsor of our research is the National Institutes of Health. Our AAHRPP-accredited human research program encompasses over 3,000 active protocols including over 1,500 clinical research studies.

Emory's NIH-funded research portfolio during the prior University fiscal year includes approximately 90 grants and contracts that involved human subject research at nearly 350 subcontract sites, and nearly 200 NIH awards involving human subject research under which Emory is a subcontractor.

Emory has a history of embracing the use of central IRBs for many of its multi-site research studies. For approximately seven years, Emory has used the Western IRB (WIRB) for review of its industry-sponsored multi-site Phase III and some Phase II clinical trials. We have also participated in other central IRB initiatives such as the NCI CIRB, the Hutchinson Center's Cancer Immunotherapy Trials Network (CITN) central IRB, NeuroNEXT StrokeNet, and others. We also make discriminating use of reliance agreements for collaborating individual and institutional investigators. Through this extensive experience with single IRBs for multi-site research, we have gained insights into the advantages, disadvantages, and recommended strategies in partnering with other institutions in the reliance on a single IRB.

Furthermore, as a past Chair of the Council on Accreditation for AAHRPP and site visitor at multiple institutions and organizations, I believe that I have a comprehensive understanding of ways in which central/single IRBs can operate effectively and efficiently.

Emory's comments on your Draft Policy are enumerated below.

1. The Draft Policy does not clearly state that it would apply only to multi-site studies in which a single protocol is implemented at all sites. As stated in the Draft Policy all of the Emory studies listed above would fall under this Policy because they involve human subjects research at multiple sites. In a December 10, 2014 telephone conference call with several NIH administrators, however, it was clarified that only a subset of the Emory studies would meet the intended requirement for a single IRB. NIH should revise its Policy to state that it applies only to multi-site studies in which a single protocol is implemented at all sites.
2. The Draft Policy does not recognize the time and effort required to establish a central IRB. The Draft Policy contemplates establishing a new central IRB de novo for each multi-site grant. In-depth conversations with IRB professionals at institutions that have established central IRBs reinforce the length of time it takes to establish a central IRB as well as to enter into agreements with all of the partner sites. Our experience is that it is often much faster for each site to review the study individually if the central IRB is only going to be used for a single study. The efficiencies are only realized if a model calls for review of several studies at many of the same participating sites over

time to be reviewed through the central IRB,. This leverages the time it takes to negotiate the SOPs and reliance agreements with all sites, and allows for more established lines of communication as well as time to establish an agreed upon process for use template consent language unique to each institution (e.g., HIPAA, subject injury).

3. The growing number of “central” IRBs poses a logistical problem for large research institutions. As with most institutions of our size and complexity, Emory has developed an electronic IRB system. Like many, our system is a customized commercially available software package, while other institutions have system developed entirely in-house. IRBs do not function in a vacuum within our institutions. They exist as a component of a larger Human Research Protections Program (HRPP). The HRPP includes units such as the Investigational Drug Pharmacy, Office of Clinical Research, Health Care Office of Quality (including Office of Nursing), Biosafety Program, Radiation Safety Program, Conflict of Interest, and Office of Sponsored Programs. Our software system is programmed to send notifications to partnering units based on answers to questions in the IRB application. This not only reduces institutional administrative costs and assures proper notification of other units, but it also allows the IRB to hold the release of approved consents if other institutional concerns arise. This system also eliminates a substantial amount of duplicate entry of information by the research team into stand-alone systems. Every time an external central IRB is used, the automated notification and information-sharing system is disrupted. This not only increases the risk of non-compliance with institutional, regulatory, and sponsor requirement but also forces investigators to enter information into independent systems for these other units. These systems can be adjusted via programming special workflows for a limited number of central or commercial IRBs and we have implemented these workflows to rely on WIRB and NCI’s CIRB, for example. What is not feasible is to program unique workflows for the number of new central-IRBs contemplated by this Draft Policy because each central IRB invariably has different SOPs and a different division of duties between central IRB and the local site. In that scenario, the efficiency of our single, central institutional system is lost.
4. The model currently in use by NIH Institutes (other than the NCI) of employing varying single IRBs for multi-site studies adds to the difficulties of initiating studies. The proposed Draft Policy complicates this scenario even further. The critical issue is that each institution designated as a single IRB for multi-site studies develops its own SOPs and partnering agreements. These SOPs reflect a) the experience of the IRB as a central IRB, b) unique institutional policies and practices, c) the institution’s legal counsel requirements to comply with state law and limit institutional liability for research at other sites, and d) resources available for interacting with collaborating sites. Understanding and negotiating the relationship for both our investigators and our institution can take months depending on the central IRB’s requirements and capabilities. The end result is a growing mosaic of idiosyncratic IRB roles and responsibilities that our investigators and institutional IRB must learn and follow.
5. Reliance on an external IRB does not save administrative costs to our institution. Our experience is that we simply have to shift resources from supporting internal IRBs to managing the external relationships as well as managing the loss of automated communications between our internal IRB system and other units referenced above. We have resisted serving as a central IRB when approached in the past because coordinating this would be an additional, unrecovered cost.
6. Like the NIH, Emory’s HRPP is accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). One of the principles of accreditation is that an accredited institution will largely only rely on other accredited institutions except in limited situations. Currently, when asked to rely on another institution, accreditation status is a standard question we ask. Under the proposed Draft Policy, this does not appear to be a requirement. Even if it were a

requirement, it would shift the burden of serving as the central IRB to a subset of all grant recipients without funding the added burden of this role.

7. Our current decisions to enter into reliance agreements with other institutions on a study-by-study basis include a review of both the nature of the study as well as the knowledge and experience of the other IRB. Additionally, we evaluate the means by which we can be assured that the IRB on which we are relying is properly carrying out its duties. In this regard, I require an explanation of the role of investigators at each institution as well as the accreditation status of the other institution (if Emory is relying on its IRB) as a part of that evaluation. All of these considerations are rendered meaningless if a blanket requirement is implemented. Further, blanket use of single IRBs without regard to experience, accreditation status, etc. will require our institution to implement significant monitoring processes to ensure that the IRBs on which we rely are in compliance with their oversight responsibilities.
8. One of the key challenges we have identified in using a central IRB is the review and management of an investigator's Significant Financial Interests related to the performance of the study. Many external IRBs require that they have the final say on management of COI. In situations where we can exert an option, we keep all studies involving investigator Conflict of Interest internal to Emory for IRB review. However, some of the central IRBs established under the NINDS group-by-group model do not permit this. We believe that this exposes Emory to potential criticism on an issue over which we have been forced to cede control. This, in fact, has been one issue that has resulted in lengthy negotiations with the central IRB institution. We are concerned that under the proposed Draft Policy we will not have an option to not participate in the central review without an explicit NIH exemption from the single IRB review policy for investigator COI.
9. The institutional cost of operating the IRB system as proposed under this Draft Policy is of significant concern. The Draft Policy states that the costs of using a fee-based IRB can be included in the direct costs of the grant, however, there is no accommodation made for institutions which include the cost of the IRB in the Administration component of the F&A rate. This is the majority of academic institutions. As the NIH leadership is well aware, the majority of research universities have an Administrative Rate that exceeds the 26% cap imposed in 1991. Therefore, the added cost of operating as a central IRB will be an unfunded mandate. As noted above, there is no savings in relying on outside institutions because of the added burden of communicating between IRBs and monitoring compliance of unknown entities. The net result will be more costs with little or no time savings for investigators if each relationship is new with each grant.

Given the challenges I have outlined above, I propose that NIH consider the following approach to address the need for more use of single IRB reviews of multi-site studies.

1. Development of a central/single IRB policy by NIH should have, at its core, the principle of keeping the number of central/single IRBs to a minimum.
2. Expanded use of NCI CIRB. The NIH could first require the use of the NCI CIRB for all studies that are currently reviewed by that Board as long as the NCI CIRB maintains its accreditation. There should be allowances for local IRB review in specific cases such as when a local investigator has a COI.
3. The NCI CIRB should expand to cover the review of all NCI-funded multi-site studies. The NCI IRB is already in place and has over a decade of experience. Rather than create a cottage industry of new, inexperienced central IRBs, NIH should expand its currently operating model.
4. This same model of a single IRB managed by an Institute should be extended to other Institutes at the NIH. This can be done by a) hiring an external contractor to operate the Institute's central IRB as in the NCI case, b) contracting with an external commercial IRB, or c) funding the establishment of a central IRB at an academic or other research institution to perform this central role on behalf of the

Institute. The specific model chosen is, perhaps, less important than the point that as few central IRBs as possible should exist, in the interest of study, investigator, and administrative efficiency

Other comments related to the Draft Policy

1. The Draft Policy includes as a part of its justification that use of a single IRB can be useful in “minimizing institutional conflicts of interest...” I believe that it is ill-advised to justify this policy by saying that it can manage an issue for which there is no federal policy, regulation, or law.
2. Justification of this Draft Policy because it is “in keeping with one of the proposed changes being considered to the Common Rule” is of great concern. First, the ANPRM for this change was issued over 3 years ago with no action since that time.

Second, implementing a policy in advance of the rule, or even the NPRM, is a practice that should be avoided at all costs. Rather, policy and guidance should be promulgated only after final regulations have been issued.

In summary, Emory embraces the concept of single IRB review of multi---site studies. However, we believe that there are serious flaws in the Draft Policy which we strongly urge you to address prior to releasing a final policy.

Sincerely,

David L. Wynes, Ph.D.
Vice President for Research Administration
Emory University

Comment #81

Commenter: Howard Trachtman

Date of comment: January 23, 2015

Comment:

I have had the opportunity to read the proposal to implement a single IRB review for multicenter trials.

As a clinical investigator who has been the PI for such studies in kidney disease, both observational and interventional, this seems like a long overdue change. I realize that there are many issues that will need to deal with prior to implementation. I anticipate that the costs at the single IRB approving the protocol may go up in terms of distributing and maintaining valid materials and authorizations. But it should be more than offset by the savings incurred by eliminating charges at each participating site. Moreover, it should shorten the timeline for start-up of trials and further promote a reduction in the costs of clinical studies of all types.

I would offer one suggestion. It would be very helpful if NIH was able to maintain a list of qualified sites that have demonstrated the facility and administrative organization needed to carry out this IRB function. This could be maintained within each institute with focused expertise in the clinical conditions that they fund. This would help study PIs select a single IRB site with a proven track record. This would in turn help them promote the credentials of the single IRB site and foster acceptance by the roster of participating sites in a clinical trial consortium.

Thanks for soliciting input from the community and moving forward with this initiative.

Comment #82

Commenter: Jeremy Morton, MD

Date of comment: January 23, 2015

Comment:

I would support the single IRB proposal as long as each participating institution retains the option of submitting any study to an internal review should there arise a significant ethical or other issue.

Comment #83

Commenter: Robert Egge, Executive Vice President, Alzheimer's Association

Date of Comment: January 23, 2015

Comment:

Francis S. Collins, MD, PhD, Director
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, Maryland 20892

January 23, 2015

Re: Draft Policy, Single Institutional Review Board for Multi-Site Research

Dear Dr. Collins,

The Alzheimer's Association appreciates the opportunity to comment on the National Institutes of Health's (NIH) proposed policy on a single Institutional Review Board (IRB). As the largest non-profit funder of Alzheimer's research, the Association is committed to accelerating the progress of new treatments, preventions, and ultimately, a cure. We applaud NIH's efforts to improve safety for research volunteers, reduce approval times for clinical protocols, and safely expedite research progress.

As NIH notes, there is evidence that a single IRB for multi-site studies can lead to enhanced protections for patients through increased accountability, a decrease in conflicts of interest, and improved efficiency through a refocusing of resources. These benefits plus the acceleration of the pace of research is particularly important to individuals affected by Alzheimer's disease and other dementias. Alzheimer's remains the sixth leading cause of death in the United States, and the only cause of death among the top 10 without a way to prevent, cure, or even slow its progression.¹ The problems associated with multi-site IRB reviews are particularly relevant for neurodegenerative diseases such as Alzheimer's and other dementing illnesses: these diseases require already-lengthy trials and the need for sites to apply through each of their IRBs can delay progress for an additional year or more. The Alzheimer's research community overwhelmingly supports the concept of a centralized IRB, as have participants in several expert think tank and strategy meetings, including the 2012 Alzheimer's Disease Research Summit and meetings of the Advisory Council on Alzheimer's Research, Care, and Services.

Thank you for your leadership in these efforts. The Alzheimer's Association looks forward to our continued partnership with NIH. Please contact Laura Thornhill, Manager of Regulatory Affairs, at 202-638-7042 or lthornhill@alz.org if you have questions or if we can be of assistance.

Sincerely,

Robert Egge
Executive Vice President

Footnotes:

¹ Alzheimer's Association. (2014). 2014 Alzheimer's Disease Facts and Figures.

Comment #84

Commenter: Kimberly Irvine, CIP, CIM, Executive VP and Chief Operating Officer
Raffaella Hart, CIP, VP, IRB and IBC Services

Date of Comment: January 22, 2015

Comment:

January 22, 2015

Office of Clinical Research and Bioethics Policy, Office of Science Policy, NIH
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892
Email: SingleIRBpolicy@mail.nih.gov

Re: Request for Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

To Whom It May Concern:

On behalf of Biomedical Research Alliance of New York LLC (BRANY), we would like to thank you for the opportunity to comment on the Draft National Institutes of Health (NIH) Policy on the Use of a Single Institutional Review Board for Multi-Site Research. We fully support NIH's leadership to pursue efficiency in the conduct of human subject research. Implementation of the Draft Policy would go a long way to achieving that goal.

BRANY IRB was organized in 1998, as an initiative of the New York Academy of Medicine by five preeminent academic medical centers in New York with the expressed purpose of streamlining the IRB review process to make approval more efficient and effective. BRANY IRB has demonstrated time and again that approval turnaround time and cost can be reduced while maintaining high-quality IRB review. Four of the original founding organizations remain BRANY's owners today; they include North Shore LIJ Health System, NYU School of Medicine, Montefiore Medical Center, and Icahn School of Medicine at Mount Sinai. In addition to reviewing multi-site studies for its member institutions, BRANY IRB is the IRB of record for over 40 universities and hospitals. BRANY is an independent IRB primarily focusing on academic institutions and hospitals.

As a company, BRANY's core objective is to offer an array of comprehensive and efficient clinical trial support services to institutions that conduct research. Beyond IRB review services, BRANY also provides institutions with outsourcing options for Medicare Coverage Analysis, contract and budget negotiation, clinical trial start-up, protocol writing software, and monitoring for investigator-initiated trials. BRANY is a proponent of providing researchers and institutions with a solid and effective research support platform that will facilitate new, innovative interventions that promote health and improve quality of life.

We offer the following specific comments on the Policy:

1. We recommend NIH make available a template IRB Authorization Agreement paired with guidelines for de-coupling institutional obligations from the IRB review process, when applicable. Such a resource would promote an expedited agreement negotiation process and better prepare institutions that have not previously relied on an external IRB. The IRB is only one component in an institution's system for human subject protection, and is often embedded in the processes as a gate-keeper for all other institutional requirements. Failure to recognize the need to provide procedural guidance in this area will simply shift burden and time constraints rather than add efficiency

The draft Policy states that in accordance with 45 CFR part 46, IRB Authorization Agreements will

need to be established between the single IRB of record and the sites relying on it. BRANY IRB frequently negotiates such IRB Authorization Agreements for both single site and multi-site studies, and concurs these agreements are necessary to document the delegation of responsibilities to the single IRB of record. However, it is our experience that because institutions frequently co-mingle the duties of the IRB with other institutional duties, extraction of the responsibilities of the IRB from the other institutional duties can be operationally challenging for the institution, and negotiating the IRB Authorization Agreement is often the first time an institution is confronted with this prospect. Additionally, some organizations wish to limit these agreements to a particular study, such that reliance on the same single IRB of record for a future study would require another agreement. The result is lengthy negotiations of these agreements. Given these agreements need to be in place before the research can be reviewed by the single IRB of record, they may constitute a rate-limiting step in the process and negate any efficiency gained by centralizing the IRB review process.

2. We recommend that the final Policy include specific selection criteria or minimum requirements that extramural applicants or offerors, and/or intramural principal investigators will rely on when selecting a single IRB. Such criteria could include elements such as registration in accordance with 45 CFR part 46, subpart E, full accreditation AAHRPP status, availability of staff to support review of multiple sites, and use of electronic IRB management software. The Policy should also stipulate the criteria that NIH will use to approve the selected single IRB for studies funded by NIH, or at a minimum specify the criteria it would use to disapprove the selected single IRB.
3. We recommend that the final Policy specifically state that the single IRB may be an independent IRB. The draft Policy refers to a fee-based IRB but does not define the term. This term could be narrowly interpreted to include only institutionally based IRBs that charge a fee when reviewing a protocol external to the organization. To achieve the greatest amount of efficiency, we recommend that NIH include partnerships between grantees and independent IRBs that could serve as the single IRB for review of multi-site studies.

Thank you again for the opportunity to provide comments on the draft Policy. BRANY IRB has continually encouraged efficiency in research without compromising human subject protections, and applauds the Draft NIH Policy's alignment with this goal.

Please contact us if you have any questions or concerns.

Sincerely,

Kimberly Irvine, CIP, CIM
Executive VP and Chief Operating Officer

Raffaella Hart, CIP
VP, IRB and IBC Services

Comment #85

Commenter:

Date of Comment:

Comment:

Request for Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research (Notice Number: NOT-OD-15-026)

Key Dates

Release Date: December 3, 2014

Response Date: January 29, 2015

The Society for Clinical Research Sites (SCRS) thanks the National Institutes of Health (NIH) for providing the research community with opportunity to comment on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research (Notice Number: NOT-OD-15-026)

SCRS was founded in 2012 with a mission to unify the voice of the global clinical research site community for greater site sustainability. It is the first trade association established to represent global clinical research sites, providing the sites a voice and a community focused on sustainability. SCRS represents 1,750 sites in 39 countries; 90% are private/free standing sites and 10% are academic or institutional sites. Our community believes in the value of human research protections and the Institutional Review Board (IRB) system in the United States. However we also recognize that the clinical research environment has become increasingly multi-disciplinary and multicenter with the era of a single site and therefore single corresponding IRB review long over. In fact the majority of our independent site members already rely on Central IRBs or a single IRB review for industry sponsored multicenter clinical trials.

In developing a response to NIH's request for comment, we constituted a workgroup from amongst our community to include members of human research protections program staff and clinical research investigators and their staff from both independent and institutional sites. As a result, our response is a consensus document that reflects practical concerns and solutions from those who touch the process. We welcome the implementation of a policy requiring use of a single IRB for NIH funded multicenter clinical trials as we believe such a review would be more efficacious, will provide better quality, and will be more sustainable in the long term. Our workgroup discussions therefore focused on implementation of such a policy and practical items for consideration.

This letter represents a summary of those discussions and areas we believe critical to the goal of increased protections for human research protections and streamlined administrative burden. Three main recommendations emerged:

1. The NIH should draft implementation guidance to be disseminated with the final policy.
 - a. There will be operational, compliance, and financial impact to organizations who agree to rely on a single IRB of record and to organizations who agree to serve as a single IRB of record. Guidance around these issues is required and is discussed in greater detail below.
 - b. Guidance should clearly define the role and responsibilities of "a single IRB of record" and that of the institution, with concrete suggestions for implementation.
2. NIH should publish clear guidance on the criteria NIH will use for evaluation of Single/Central IRBs when selecting a Single IRB for a specific multicenter clinical trial and the criteria Single/Central IRBs

should use for evaluation of a specific site. The suggested criteria for evaluation are discussed in greater detail below.

3. We believe that the intent of the policy to reduce administrative burden and improve the process for human research protections are best achieved through clarification of terms and/or additional guidance to standardize IRB and institutional processes. We therefore recommend that NIH mandate use of a standard IRB Authorization Agreement and process for reliance.

Summary of specific recommendations

1. The NIH should draft implementation guidance to be disseminated with the final policy that addresses the Impact of an Institution's Reliance on a Single IRB for Multi-Site Research and the Impact of an Institution/Local IRB Serving as a Single IRB for Multi-Site Research: Guidance should be developed which calls attention to the following
 - a. Operational Impact
 - i. Institutions should consider the impact on the institution's Human Research Protection Program (HRPP) goals and business goals for clinical research
 - ii. Institutions may need to review and revise their human research protection policies and standard operating procedures to apply regardless of IRB utilized.
 - iii. Accredited human research protection programs may need to assess the impact on their accreditation status
 - iv. Institutions should assess their business processes and decouple institutional and IRB responsibilities. NIH guidance should reinforce and educate about Institutional Responsibilities versus IRB Responsibilities. For example, the Clinical Trials Transformation Initiative published a Considerations Document in 2013 which outlines outline categories of legal and ethical responsibilities of an institution and those of an IRB in overseeing the conduct of clinical trials. This document is meant to support communication between institutions and external central IRBs when responsibilities are being assigned for multicenter clinical trial protocols that are using a central IRB.
 - v. Institution/Local IRBs should assess and determine impact on their IRB application process, whether electronic or on paper
 - vi. Institutions should assess and determine the impact on electronic systems used in HRPP data collection.
 - b. Compliance/Legal Impact
 - i. Institutions should assess governance of their human research protection programs and determine who within the institution will provide institutional approval for a study to proceed regardless of IRB of record. Care should be taken to ensure that additional administrative burden is not introduced in place of local IRB review.
 - ii. Institutions may need to review and revise the terms of other institutional policies such as their medical staff bylaws or other governing documents if they reference requirements for use of an institutional IRB or reporting of IRB decisions.
 - iii. Institutions may need to review and/or revise the contractual terms or obligations of their physicians if their employment agreements require use of the institutional IRB.
 - iv. Institutions should review any other agreements with outside parties to assure that there are no provisions preventing the use of a central IRB.
 - v. Institutions may need to review and revise procedures for other non-HRPP compliance related activities such as Clinical Trial Agreement and consent form language

- concurrency, Conflict of Interest or Export Control reviews if those items had been previously integrated with IRB review.
- vi. Institutions should review their insurance policies and provisions to ensure adequate coverage is in place.
 - vii. NIH should convey and Institutions should clearly define who is responsible for ensuring investigator compliance.
- c. Financial Impact
- i. NIH should clarify the statement, "If the agreed-upon single IRB is a fee-based IRB, these costs will be included in the Notice of Award as a direct cost." The majority of Institutional/Local IRBs charge industry sponsors for IRB review and costs of Institutional/Local IRB review may also included in Facilities & Administrative (F&A) cost calculation. However F&A cost calculations did not anticipate IRB work to be performed for sites external to the Institutional/Local IRB performing the review and the administrative costs associated with that work. As a result we believe that
 - 1. Costs associated with Institutional/Local IRBs serving as a central IRB should be treated as a direct cost when an Institutional/Local IRB is providing the single IRB review for a multicenter project as long as that Institutional/Local IRB has a published fee schedule.
 - 2. The direct costs of providing single IRB review should be reimbursed above or outside of the scientific budget so as not to dilute project funds.
 - ii. The NIH should review and revise the NIH POLICY ON DIRECT COST CHARGES FOR IRB REVIEW, May 22, 2003 and the NIH Grant Policy Statement to conform with changes in policy
 - iii. NIH should review and coordinate with the Office of Management and Budget (OMB) to ensure compliance with Title 2 Subtitle A Chapter II
[Part 200 Uniform Administrative Requirements, Cost Principles, and Audit Requirements for Federal Awards.](#)
2. NIH should publish clear guidance on the criteria for evaluation of Central IRBs when selecting a Single IRB for a specific multicenter clinical trial and the criteria Single/Central IRBs should use for evaluation of a specific site.
- a. *NIH criteria for evaluation of Central IRBs when selecting a Single IRB for a specific multicenter clinical trial* We recommend that NIH Consider IRB's certifications and accreditation; Investigate compliance history of the IRB; Review qualifications of board members including therapeutic expertise; Request references and review organization's history of working with institutions and/or sponsors; Evaluate IRB's ability to step seamlessly into the process (including state laws and local considerations); Determine scope and associated costs of services provided; Establish communication process between institution, investigator, and IRB; Assess operational processes (frequency of board meetings, document management, capacity, turnaround time, QA processes: internal and external); and Inquire about technology used by Central IRB and compatibility with existing systems/programs.
 - b. *Single/Central IRBs criteria for evaluation of a specific site.* Investigate compliance history of the institution; Determine relevant laws, local regulations, institutional norms and values, requirements; Specify point(s) of contact at the institution and lines of communication; Establish level of involvement in unanticipated problems, and other problems; Review

institution's experience working with outside IRBs; Gauge institution's expectations regarding central IRB's performance and metrics.

3. NIH should mandate use of a standard IRB Authorization Agreement and process for reliance. We note that intent of the policy is to build efficiency into the system. However those efficiencies may be lost if institutions and IRBs need to negotiate a new agreement each time they enter into a reliance relationship.
 - a. Multiple other trade groups and organizations, such as the Clinical Trials Transformation Initiative (CTTI), the MRCT Center at Harvard, and the NIH NCAT program amongst others have been working to develop standardized IRB Authorization Agreement for use by their members which could be broadly used as a reliance document. These groups should be brought together to develop a standard NIH IRB Authorization Agreement.
 - b. The standard NIH IRB Authorization Agreement could then be managed by NIH or a trade group partner such as PRIMR and relied upon by all signatories to the agreement much in the same way that AUTM the Association of University Technology Managers manages the Uniform Biological Materials Transfer Agreement (UBMTA) after the National Institutes of Health in 1995 published the final version of the Uniform Biological Material Transfer Agreement (UBMTA) and a Simple Letter Agreement for the Transfer of Non-Proprietary Biological Material. For institutions that have signed the UBMTA Master Agreement, materials can be transferred under the terms of the UBMTA upon execution of an Implementing Letter for the particular transfer. A similar process should be developed for IRB reliance.

Again we thank NIH for the opportunity to comment on this important initiative. Please contact Christine Pierre, at 410.696.5080 ext. 120 or via e-mail at christine.pierre@myscrs.org if you would like to discuss any of our recommendations or comments. We look forward to next steps and your continued work in the protection of human subjects who participate in research.

Sincerely,

The Society for Clinical Research Sites

Comment #86

Commenter: Anita H. Clayton, MD

Date of comment: January 25, 2015

Comment:

As an academic researcher for 25 years, I wholeheartedly support the proposal to encourage use of a single IRB for multi-center trials. This would be far more efficient than multiple local IRBs at academic medical centers requiring modifying the multi center protocol to their local template and requiring multiple minor/grammatical changes to suit their local preferences. The required changes almost never improve the science or safety of subjects. Local IRBs don't add value over central IRBs, but do add significant time and financial costs, thus, the process is less efficient. Local IRBs (at least, our local IRB which is the University of Virginia) are overly concerned about their legal liability leading to excessive restrictions (e.g. requiring phone calls, then calling emergency contacts, and potentially going to the subject's home to ensure they are ok when subjects fail to show up for a scheduled appointment), length of consent forms (which makes them lack of consent forms as subjects stop listening when we read them and don't personally read 26 pages thoroughly), and unnecessary requirements (e.g. obtaining a federal certificate of confidentiality whenever a UDS is part of the protocol even though state laws protect study subject data). VCU began to use a central IRB several years ago, and this puts UVA researchers at a competitive disadvantage with them (e.g. for competitive enrollment) as we must use our local IRB and are always delayed significantly by their procedures. In the world today, there is no "unique local context." Local IRBs do not seem to provide any advantage over central IRBs, yet they cost far more in time and money.

Given the data that knowledge doesn't increase IRB comfort with central / single IRBs, but experience does, please do more than encourage this process which would provide significant savings. Please require unless the IRB can provide a reason for an exception.

Comment #87

Commenter: Carl T. D'Angio, M.D., et.al.

Date of Comment: January 26, 2015

Comment:

January 26, 2015

RE: NOT-OD-15-026

We, the undersigned, are clinical investigators, research coordinators and/or parents of premature infants who are also members of the NICHD Neonatal Research Network (NRN) Steering Committee's Research Participants Subcommittee. The views expressed herein are our personal observations and do not reflect the opinions of the NRN or its investigators, or our institutions. We welcome the opportunity to comment on the draft NIH Policy on the Use of a Single Institutional Review Board (IRB) for Multi-Site Research. Several of us have experience with using single or central IRB's, and our comments in part reflect our experiences.

As the draft policy notes, using a single IRB of record for multi-site research could enhance the quality and streamline the process of human subjects' protection review of protocols that will be instituted at multiple sites. However, use of a single IRB potentially adds complexity to the review of many multi-site trials and has potential drawbacks as well as benefits.

Potential Advantages

In keeping with the examples of the NCI Central IRB or NINDS NeuroNEXT single IRB system, use of single IRB's has proven useful when applied to established multi-center research groups who can submit trials to a consistent, established, strong, well-resourced, central IRB. A single or central IRB may, in some instances, improve both the time from submission to the approval of a study and the quality, clarity and specificity of reviews. We could envision such a system being helpful in other, established, NIH-funded multi-center groups, perhaps including the NRN. Indeed, the NRN has explored the prospect of a reliance IRB model in the past. In addition to the potential advantages listed in the Background of the Draft Policy, use of a single IRB would limit the difficulty of reconciling conflicting local opinions about non-local matters regarding protocols, research practices and consent documents. The consistent encouragement from NIH would also give interested universities and other groups the opportunity to develop "best practices" for multi-center research review among a core contingent of IRB's.

Potential Challenges

The blanket requirement to use a single IRB of reference for all multi-center studies would also face several, significant challenges:

1. The examples of NeuroNEXT and other cooperative group central or single IRB's show that these IRB's are very difficult and complicated to set up, train and maintain. The investment of resources to do so would be significant. An ideal central IRB for neonatal trials, for instance, would need extensive expertise in neonatal medicine (or access to such expertise), clear delineation of authority, defined reporting structures, exceptional ability to balance risks and benefits for a high risk population, and staff capable of helping investigators simplify permission documents while expressing clearly the issues that parents find most important.
2. As a result of the resource-intensive nature of establishing a single IRB of record, it is not clear that any economies of scale or advantages of centralization would accrue for *ad hoc* multicenter groups

brought together for a single, multi-site study; small groups; or groups performing low-risk studies. Attempts to require a single IRB for such studies might be premature and wasteful.

4. Some cooperative groups offer tiers of participation in a single IRB process, ranging from complete reliance to individual local review. Each degree of participation has advantages and disadvantages, as does even allowing a tiered model, which allows individual institutions choice, but can be chaotic. The Draft Policy should carefully consider and address whether such a tiered model would be allowed.
5. The current Draft Policy offers little detail regarding preferred models for the single IRB itself.
While it might not be appropriate to mandate a single model, potential models vary widely, from one site in a multi-site trial being named the central IRB for all sites, to using independent IRBs, to having the NIH itself create and administer additional IRB's similar to the NCI CIRB. It would be likely to be inefficient not to establish some preference among the models.
6. IRB review is only a small part of a local institution's responsibility for the safety of research participants. Single IRB review would not significantly reduce or simplify an individual institution's responsibility or burden (nor should it). The reference in the Draft Policy to 45 CFR 46.114 makes it very clear that the individual institution remains "responsible for safeguarding the rights and welfare of human subjects and for complying with [the Common Rule]."
7. The issues of responsibility and liability in the event of adverse events or complaints are complex and are not well addressed in the Draft Policy. Unless the single IRB assumes the responsibility and liability normally accrued to local institution IRBs, it is unlikely that institutions would be willing to cede much of their authority to the single IRB, resulting in potential duplication and increased delays. Indeed, even nominal shifting of responsibility and liability may not produce an actual shift (see point #15).
8. It is appropriate that the Draft Policy provides for payment for single IRB's, since this would be an expensive endeavor for any institution. However, this makes it likely that the overall cost of adopting single IRB's is likely to be more, rather than less, than the current system.
9. Unless a central or single IRB has appropriate resources, overburdened central IRB's can result in longer, rather than shorter, review and approval times. Well-resourced IRB's with rapid turnaround are expensive.
10. While a single or central IRB might result in faster approval, approval times can vary widely from one institution to another. Even an efficient central IRB might not offer faster turnaround than local IRB's at a plurality of institutions, and thus might not speed study startup overall. This is particularly true when the local, non-IRB-dependent steps in study startup are included.
11. The proposed mechanisms for addressing local concerns (creating a local, non-IRB level of review or adding members with expertise regarding local issues) are potentially feasible. The former approach is frequently practiced at several of our centers that use central IRB's for some protocols. We note that it adds, rather than removes, a level of review. Done well, it can be effective and efficient. Done poorly, it could slow review significantly. The latter approach might be practical in the setting of a central IRB intimately familiar with the sites submitting to it, but would be difficult for *ad hoc* single IRB's.
12. The issues of addressing local, institutional variations in standard of care are complex. For example, there are differences among NRR centers in standard-of-care uses of drugs or interventions under study in some of the protocols. Under a single IRB model, these variations would continue to need to be considered in reviews and reflected in each local consent document when differentiating between what is local standard of care and what a research protocol requires. While a local IRB

should have representation from members who are knowledgeable about local standards and are able to comment on that through the IRB review process, it would be difficult for a single or central IRB to obtain this expertise *for each site for each protocol*.

13. Explaining what would be, by nature, a more complicated IRB process to participants and/or families would need to be a part of the consent process – and might in itself prove confusing.
14. Relying on a single or central IRB removes the locus of decision making one step further from the local investigator and investigative team. (Conversely, it provides the advantage of putting that locus one step closer to the overall PI of the study.) While the cooperative group might benefit from a single “answer,” a single IRB model could make it more, rather than less, difficult for individual sites to communicate with the central IRB regarding site-specific issues. Many experienced clinical trial investigators have built close working relationships with local IRB’s that generally improve the speed and comprehensiveness of review and communication. These relationships would have to be sacrificed or rebuilt.
15. Moving to a single IRB model may also increase the workload (and thus need for increased funding) at the cooperative group coordinating centers charged with handling the communication flow between the centers and the central IRB.
16. Some have proposed that a single IRB model would prevent the diffusion of responsibility that occurs with multiple IRB’s reviewing a multi-site protocol.¹ However, the case mentioned in the Draft Policy’s reference #4 (http://www.hhs.gov/ohrp/detrm_lettrs/YR09/jun09c.pdf) suggests that central IRB review could result in a new and different diffusion of responsibility. In that case, OHRP absolved the university in question of responsibility for a consent form (reviewed and approved by the Cooperative [sic] Oncology Group and the National Cancer Institute’s Pediatric Central IRB) it felt was inadequate, but not from the consequences of having used the form.
17. While the Draft Policy provides a framework for choosing the single IRB for any given study, NIH would face the additional burden of confirming that the chosen IRB was appropriate, was able to handle the complexities of a multi-site trial and had the appropriate expertise in place.

While requiring accreditation from a national organization such as the Association for Accreditation of Human Research Protection Programs (AAHRPP) is a reasonable first confirmatory step, it is likely that few IRB’s would have the broad and deep expertise needed to review and manage multicenter studies. The existing network of independent IRB’s (which are often familiar with multisite trials) might or might not be able to absorb the additional volume the policy would generate, and would be an expensive alternative.

18. Institutional Review Boards are not asked to review the science of any given protocol – it is assumed that this has been reviewed and found worthy before a protocol is submitted. Our accumulated experience suggests that an NIH grant review committee cannot, in reviewing a 12-page proposal, assess how well the crucial process of converting a grant into a complete and working protocol that remains scientifically valid will proceed. Several of our institutions have developed robust scientific review processes that consistently result in scientific improvements to protocols. How would NIH propose to assure that adequate scientific review of the protocol had occurred? There are multiple potential approaches, but they need to be specified.

Summary

In summary, promoting the use of a single IRB for multi-site studies, if carefully and thoughtfully implemented, may offer significant advantages to large, existing research networks like the NRN. The complexities inherent in a single-IRB system make it unlikely, however, that requiring such a model for “all domestic sites of multi-site NIH-funded studies” would improve the quality of IRB review, streamline

such review, save resources or significantly further the rights and welfare of human subjects. Any central or single IRB that is developed should and must expect to be held to the highest standards, including, but not limited to, accreditation by one of the IRB-accrediting organizations. Any success of a single system would be magnified, but any failure would be similarly magnified. Any policy promulgated at the moment should be narrowly targeted (with their consent) at the cooperative groups most likely to be able to arrange and benefit from single-IRB review, should include the appropriate resources to implement the policy over the long term, and should be flexible enough to allow modification as those groups learn from their experience. Finally, the implementation of any such policy should be rigorously and pragmatically evaluated, as was the implementation of the NCI central IRB.

Carl T. D'Angio, MD

Professor of Pediatrics and Medical Humanities & Bioethics University of Rochester School of Medicine and Dentistry

David G. Russell, CIP

Clinical Research Regulatory Coordinator Indiana University School of Medicine

Nancy Newman, BA., RN Research Coordinator

Case Western Reserve University

Luc P. Brion, MD Professor of Pediatrics

The University of Texas Southwestern Medical Center at Dallas

Jon E. Tyson, MD, MPH Professor of Pediatrics

The University of Texas Health Science Center at Houston

Abhik Das, PhD

Biostatistician

Brenda Poindexter, MD, MS Professor of Pediatrics

Cincinnati Children's Hospital Medical Center

Barbara J. Stoll, MD

Professor and Chair of Pediatrics Emory University School of Medicine

Michele Walsh, MD Professor of Pediatrics

Case Western Reserve University

Footnotes:

¹Menikoff J. The paradoxical problem with multiple-IRB review. *New Engl J Med.* 2010;363(17):1591-1593.

Comment #88

Commenter: P. Perl O'Rourke, M.D.

Date of Comment: January 27, 2015

Comment:

JANUARY 27, 2015

Thank you very much for providing the opportunity to comment on the NIH Draft Policy entitled: *Use of Single Institutional Review Board for Multi Site Research* (Draft Policy). I am writing in my role as Director of Human Research Affairs at Partners HealthCare System (Partners). I oversee the IRB system for several of its member hospitals: Brigham and Women's Hospital (BWH), Massachusetts General Hospital (MGH), McLean Hospital (McLean), and North Shore Hospital. Partners is one of the nation's leading non-profit biomedical research organizations and its hospitals are the principal teaching affiliates of Harvard Medical School. In FY 14, Partners hospitals received approximately \$700 million in federal research funding. Thus, reform of policies pertaining to Institutional Review Boards is of critical importance to the Partners research enterprise.

As a participant in multiple single IRB (SIRB) arrangements, including as a Central IRB, we strongly support the development and facilitation of SIRB review. However, we believe that the Draft Policy as written is premature in its breadth and inflexibility and does not adequately acknowledge or address the gaps in current knowledge about the relative benefits and costs of SIRB systems. As indicated in our detailed comments below, we propose that more research be conducted before mandating SIRB review for all types of multi-site studies and that the initial policy focus on a more limited set of research.

Our comments are organized into three sections: 1) comments on the assumptions/assertions made in the introduction to the Draft Policy; 2) comments on the specific proposals of the Draft Policy and 3) suggestions for alternate approaches.

Introductory assumptions/assertions:

Use of an SIRB for domestic multi-site research is promoted as promising potential advantages of efficiency, decreased time to study start-up and consistency of review and even conduct of the research. However, there is currently little research or data to demonstrate that these potential benefits will materialize in particular types of multi-site research, that they can be realized with no accompanying decrease in human subject protections, or that they outweigh the significant costs and resource investments required to implement a single IRB system in which all parties can have confidence.

A few specific comments:

The Draft Policy presumes that there will be efficiency in the initiation/initial review of a study. In our experience with serving as the SIRB and relying on other SIRBs, the efficiency has not been in the initial review of the protocol, but rather in the addition of sites after initial protocol review as well as in the subsequent reviews through the life of the protocol; e.g., continuing review, unanticipated problems (UAPs).

The Draft Policy asserts that local IRB review is not needed for assessing local context. While we agree this is not an IRB regulatory requirement, we note that it is generally the local IRB or at least the local IRB office that is most knowledgeable about the local context and about the application of local rules and norms to the conduct of research. Therefore recognition of the practical reality of ongoing IRB office, if not IRB, involvement is necessary.

The Draft Policy casts use of a SIRB as more cost effective than local IRB review. More information is

needed before this can be accepted as a benefit.

Details of the Draft Guidance:

Our comments on specific proposals or aspects of the Draft Policy are listed here. Discussion of each item immediately follows this list.

1. The broad scope of the mandate – all multi-site domestic research with NIH funding – without regard to the type of research or number and type of sites and to the existence of central infrastructure to support the SIRB
2. The limited scope for exceptions
3. Lack of details and proposed financial support for management of the necessary research oversight processes at the reviewing SIRB and the relying sites, and for required communication between them
4. Lack of details regarding expectations when the local IRB elects to review a project subject to the policy
5. Absence of information about the selection/approval criteria for the SIRB, including whether the SIRB's willingness/ability to serve as a HIPAA Privacy
6. Board will be a factor
7. Apparent lack of coordination with other proposed mandates and/or regulatory changes regarding the use of SIRBs, including the 2009 and 2011 ANPRMs referenced in the Draft Policy

1. The broad scope of the mandate:

The Draft Policy describes in general the requisite responsibilities for both the reviewing SIRB and the relying institutions. But it fails to recognize how different types of studies require vastly different logistics and resources for both the SIRB and the relying institution. Due to these differences, there are multi-site studies that fit more easily into an SIRB approach and there are others that do not.

In our experience, examples of factors to consider before deciding that SIRB review is appropriate include:

- Number of institutions: a study involving 2 sites versus one with 75 will have very different impact on coordination, workflow and resources needed.
- Types of institutions: The success of SIRBs is predicated on trust and mutually agreed-upon processes. The SIRB must have confidence that the sites relying on the SIRB have good HRPPs that can provide all of the institutional requirements. And the relying sites must trust that the SIRB is a quality IRB that will be accessible to the each site. This trust grows from various factors, including the sites' and SIRBs' level of experience conducting or reviewing the type of studies at issue, the size of the respective research programs, and familiarity with one another's state and local rules and culture. Mandating a SIRB arrangement among several academic medical centers in the same area that are frequent collaborators is very different than mandating SIRB review among these centers and small private physician practices in different states.
- Types of studies: Minimal risk studies generally have few ancillary committee reviews as well as few amendments and UAPs over the course of the study. In contrast, more than minimal risk studies generally have ancillary committee reviews as well as frequent amendments and UAPs that require IRB review. The logistics and resources needed for SIRB review vary as a function of the type of research; hence adequacy of infrastructure must be assessed for each study.
- Types of study teams: Multi-site studies require some level of study team coordination. However, the degree of coordination that is customary and readily achievable varies: robust research networks

with clinical and data coordinating committees are vastly different from one-time affiliations of several colleagues with no existing infrastructure. The ‘one-time-affiliations’ often lack the skills as well as funding to coordinate with a SIRB.

- **Resources for the SIRB system:** If an institution is expected to provide SIRB services as an ‘add-on’ with no additional resources, then its overall capacity will be severely limited. For example, a 50-site high risk interventional study would easily require a full-time liaison to simply handle communications between all sites for initial review, continuing review, adverse events, amendments, etc. In addition, information technology (IT) resources must be in place to accommodate handling the processes between the participating institutions. In many situations, this requires either a new system or a work-around of an existing IT system.
- **Resources for investigators:** Study teams will have to assume much of the coordination functions between the sites – this will require resources.

The Draft Policy does not currently allow for consideration of such heterogeneity. A minimal risk study conducted at 4 institutions that are members of an existing network defies comparison with an interventional high-risk study conducted at 25 institutions that have been newly brought together for specific research, in terms of capabilities, comfort level, and resources needed.

2. The limited scope for exceptions is not adequate

The Draft Policy states that “exceptions will be allowed only if the designated SIRB is unable to meet the needs of specific populations or where local IRB review is required by federal, tribal, or state laws or regulations;” For all of the reasons addressed above, if the final policy adopts the broad scope that is proposed, we believe that there are many other factors that should be considered as justification for an alternate approach or an exception, including the type of study, types and numbers of involved institutions, and type of study team. In addition, it is unclear what sorts of situations would constitute inability to meet the needs of specific populations or why this could not be assessed before any particular IRB is designated as the SIRB.

3. Lack of details and proposed financial resources to support the processes at both the reviewing SIRB as well as the relying sites

The default in any reliance arrangement is that the only task that is ceded is the IRB regulatory review; all institutional responsibilities generally remain with the local sites and some in fact cannot be ceded. Institutional responsibilities include, for example, HIPAA determinations related to the study, ancillary committee reviews, compliance with state laws, COI, CMS, and training of investigators. Tasks like ancillary committee reviews necessarily *must* remain with the local sites, as must ultimate responsibility for compliance with state laws. Hence in ceded review, the relying sites retain significant tasks. These are tasks that in many institutions are completed by the IRB (such as in the case of HIPAA) or otherwise by the IRB office and closely integrated into the overall review of a protocol. When IRB review is ceded, the relying institution must develop processes and systems (often new IT systems) by which they not only coordinate these institutional responsibilities but also communicate their determinations to the SIRB.

Providing SIRB capacity requires planning and process development including identification of resources needed for both setting up the SIRB as well as completing the protocol review. The tasks for setting up a SIRB include for example: negotiation of reliance agreements; performance of due diligence of the relying sites; development of SOPs that address processes for communication between the SIRB and all relying sites, processes for obtaining and considering relying site issues such as HIPAA authorizations or waiver of authorization determinations, ancillary committee reviews, COI, CMS, sign-off on PI training, processes for dealing with noncompliance and required reporting, etc. Once these systems are set up, the SIRB must then be able to conduct all regulatory reviews (initial, continuing, amendments, UAPs etc)

after obtaining appropriate input from local sites.

As noted above, the level of resources needed for serving as a SIRB as well as relying on a SIRB will be informed by the type of study; e.g., complexity of the study, number of sites, structure of the study team etc.

We (institutions, IRBs, sponsors, regulatory agencies) do not yet have accurate information on these costs. Without this information, it will be difficult for institutions to responsibly serve as a SIRB or agree to rely. This discussion is further complicated by the paucity of data regarding the cost of local IRB review. As noted above, most IRB offices are responsible for much more than the regulatory review and it may be difficult to disentangle the costs of that regulatory review from all of the other tasks that the IRB/IRB office performs.

Adding to the comments made above – is the fact that we are currently in a time of evolving and multiplying SIRB models. At present there are a number of different models which share some features, but which each have their own approach. IRBShare is an example of a “share model” in which IRB regulatory review is shared between the SIRB and local IRBs. In contrast are the “nonshare” models in which all regulatory review is completed by the SIRB; examples include systems used by the VA, NCI and NeuroNEXT. Mandating SIRB review at this time without review and analysis of the relative benefits and costs of each model or determination which is most appropriate for different types of NIH-funded research just adds another requirement to the explosion of different models and approaches. A single institution may be faced with serving as a SIRB for several completely different types of research as well as relying on several other SIRBs, each of which has their own policies and procedures. If the Draft Policy is finalized as proposed, different SIRB systems would be developed. This would then require that relying institutions have the infrastructure and resources needed to maintain working interfaces with multiple somewhat different systems. This could in fact decrease the efficiency of protocol review.

The proposal states that if the identified central IRB is a for-fee IRB, then that cost can be included in the budget. IRBs based at academic centers are typically not fee based, at least not for all reviews they perform – yet they will have to assume significant increases in work, as well as development of systems to comply with this proposal. How will that be funded?

4. Suggestion of SIRB AND local IRB review

The Draft Policy allows for parallel reviews, as we agree is appropriate in the absence of any current regulatory mandate for SIRB review. However, the policy does not discuss the implications of a situation in which both a designated SIRB and a local IRB(s) perform a regulatory review of a study. From a regulatory perspective, we presume that NIH agrees that both IRBs would have authority, and as a practical matter, the result is that the most stringent (protective of human subjects) requirements must govern. How does NIH intend for this concurrent review scenario to work, and what communication will occur to ensure that the designated SIRB selected by NIH is aware of the other IRBs’ reviews?

5. Selection criteria for the SIRB

The Draft Policy does not indicate what criteria will be used by NIH to evaluate and select the SIRB. Transparency around this determination is critical for institutions and IRBs participating in trials subject to the policy to understand NIH’s expectations and to develop robust proposals if they are interested in being designated as the SIRB.

Without limiting this general comment, we note that the Draft Policy does not mention the requirements of the HIPAA Privacy Rule for use or disclosure of Protected Health Information for research. Depending on the type of study at issue, the researchers may request a waiver of authorization for use/disclosure of PHI. Under the HIPAA Privacy Rule, a Privacy Board must determine whether a waiver is appropriate for

the study and document that determination. In practice, many IRBs serve as the Privacy Boards for their institutions. In our experience, including reliance arrangements where NIH's IRBs are designated as the SIRB, the designated IRB is not always willing to serve as a Privacy Board for the relying institutions. In such situations, the relying institutions (and specifically, their IRBs) must then review the study sufficiently to be able to apply the HIPAA waiver criteria and make the waiver determination. When this occurs, the potential efficiencies of the SIRB review are diminished. Does NIH intend to require willingness to serve as a HIPAA Privacy Board in order for an IRB to be selected as the SIRB under this policy?

6. Lack of coordination with other proposed mandates and/or regulatory changes regarding the use of SIRBs

As noted in the Draft Policy, there are two outstanding ANPRMs, from 2009 and 2011, that contain proposals relevant to reliance arrangements and requirements for use of single IRBs. It is not clear to us whether HHS intends to proceed with proposed regulatory change as discussed in the 2009 ANPRM, that would clarify regulatory responsibilities of each of the parties in a reliance arrangement and establish direct regulatory liability of IRBs. It is also not clear to us whether single IRB review will be mandated as a result of the 2011 ANPRM, and if so, for what scope of studies. Establishing a funding policy mandating broad use of single IRBs in advance of the resolution of these two regulatory initiatives may create confusion or result in inconsistencies if and when regulatory changes are adopted. We believe that it makes more sense for NIH's focus at the present time to be on funding additional research examining the potential benefits and costs of single IRB use as suggested above.

Suggestions for alternate approaches:

As noted above, we strongly support the development and facilitation of SIRBs for some multi-site research. We also note that the use of external IRBs is not a new concept and there is an experience upon which to build. Most academic medical centers (AMC) have experience relying on an IRB at another AMC; these arrangements are often limited to no more than minimal risk research conducted at two or three sites. In addition, many AMCs have experience relying on commercial/independent IRBs for a select category of research - most often industry-sponsored and initiated, phase 3 and 4 multi-site research. What is new with the NIH Draft Policy is the inclusion of all NIH-funded multi-site research regardless of type of study or number of institutions.

Given the current evolution of SIRB models and the paucity of data regarding these models, we suggest a more tempered approach. Instead of broadly requiring a SIRB for any NIH-funded multi-site research, we propose refining the policy either to be limited (for now) to minimal risk research involving no more than several sites or, if it remains broad, to including a process whereby flexibility be built into the policy to account for various types of research and other specific factors more fully discussed above. In this way, use of a SIRB could be considered case-by-case before being required by NIH as a condition of funding.

We also suggest that NIH simultaneously fund research on existing SIRB models to evaluate potential benefits and costs for both the SIRB site as well as relying sites. This could include research focused at models that are currently reviewing NIH-funded research or NIH could also identify a cohort of clinical research for which the NIH will fund a SIRB and as a condition of grant award require research on the SIRB itself.

All of these approaches would inform the process going forward.

In addition, NIH could convene expert panels to focus on a number of SIRB-related issues; such as, developing criteria to identify research best reviewed by a SIRB; identifying the elements and resources needed to provide SIRB services within an AMC; and evaluating the pros and cons of various reliance

models.

Finally, NIH could support the development of tools that could facilitate SIRB processes – this would include working with groups that have already begun to address some of these. Examples of tools include: Reliance Agreement templates, Standard Operating Procedures, approaches to HIPAA.

Thank you for the opportunity to provide comments on this draft guidance. Please contact us with any questions or requests for clarification. We are very interested in working with you to develop a successful future for SIRBs.

Sincerely,

P. Pearl O'Rourke, M.D.
Director, Human Research Affairs Partners HealthCare
Boston, MA

Comment #89

Commenter: Anna Klibanski, M.D. and Laurie Carrol Guthart, Professor

Date of Comment: January 27, 2015

Comment:

JANUARY 27, 2015

Thank you very much for providing the opportunity to comment on the NIH Draft Policy entitled: *Use of Single Institutional Review Board for Multi Site Research* (Draft Policy). I am writing on behalf of Partners HealthCare System (Partners) which provides financial and administrative oversight of research grants and clinical trials awarded to its member hospitals: Brigham and Women's Hospital (BWH), Massachusetts General Hospital (MGH), McLean Hospital (McLean), and Spaulding Rehabilitation Hospital (SRH.) Partners is one of the nation's leading non-profit biomedical research organizations and its hospitals are the principal teaching affiliates of Harvard Medical School. In FY 14, Partners hospitals received approximately \$700 million in federal research funding. Thus, reform of policies pertaining to Institutional Review Boards is of critical importance to the Partners research enterprise.

As a participant in multiple single IRB (SIRB) arrangements, including as a Central IRB, we strongly support the development and facilitation of SIRB review. However, we believe that the Draft Policy as written is premature in its breadth and inflexibility and does not adequately acknowledge or address the gaps in current knowledge about the relative benefits and costs of SIRB systems. As indicated in our detailed comments below, we propose that more research be conducted before mandating SIRB review for all types of multi-site studies and that the initial policy focus on a more limited set of research.

Our comments are organized into three sections: 1) comments on the assumptions/assertions made in the introduction to the Draft Policy; 2) comments on the specific proposals of the Draft Policy and 3) suggestions for alternate approaches.

Introductory assumptions/assertions:

Use of an SIRB for domestic multi-site research is promoted as promising potential advantages of efficiency, decreased time to study start-up and consistency of review and even conduct of the research. However, there is currently little research or data to demonstrate that these potential benefits will materialize in particular types of multi-site research, that they can be realized with no accompanying decrease in human subject protections, or that they outweigh the significant costs and resource investments required to implement a single IRB system in which all parties can have confidence.

A few specific comments:

The Draft Policy presumes that there will be efficiency in the initiation/initial review of a study. In our experience with serving as the SIRB and relying on other SIRBs, the efficiency has not been in the initial review of the protocol, but rather in the addition of sites after initial protocol review as well as in the subsequent reviews through the life of the protocol; e.g., continuing review, unanticipated problems (UAPs).

The Draft Policy asserts that local IRB review is not needed for assessing local context. While we agree this is not an IRB regulatory requirement, we note that it is generally the local IRB or at least the local IRB office that is most knowledgeable about the local context and about the application of local rules and norms to the conduct of research. Therefore recognition of the practical reality of ongoing IRB office, if not IRB, involvement is necessary.

The Draft Policy casts use of a SIRB as more cost effective than local IRB review. More information is

needed before this can be accepted as a benefit.

Details of the Draft Guidance:

Our comments on specific proposals or aspects of the Draft Policy are listed here. Discussion of each item immediately follows this list.

1. The broad scope of the mandate – all multi-site domestic research with NIH funding – without regard to the type of research or number and type of sites and to the existence of central infrastructure to support the SIRB
2. The limited scope for exceptions
3. Lack of details and proposed financial support for management of the necessary research oversight processes at the reviewing SIRB and the relying sites, and for required communication between them
4. Lack of details regarding expectations when the local IRB elects to review a project subject to the policy
5. Absence of information about the selection/approval criteria for the SIRB, including whether the SIRB's willingness/ability to serve as a HIPAA Privacy Board will be a factor
6. Apparent lack of coordination with other proposed mandates and/or regulatory changes regarding the use of SIRBs, including the 2009 and 2011
7. ANPRMs referenced in the Draft Policy

1. The broad scope of the mandate:

The Draft Policy describes in general the requisite responsibilities for both the reviewing SIRB and the relying institutions. But it fails to recognize how different types of studies require vastly different logistics and resources for both the SIRB and the relying institution. Due to these differences, there are multi-site studies that fit more easily into an SIRB approach and there are others that do not.

In our experience, examples of factors to consider before deciding that SIRB review is appropriate include:

- **Number of institutions:** a study involving 2 sites versus one with 75 will have very different impact on coordination, workflow and resources needed.
- **Types of institutions:** The success of SIRBs is predicated on trust and mutually agreed-upon processes. The SIRB must have confidence that the sites relying on the SIRB have good HRPPs that can provide all of the institutional requirements. And the relying sites must trust that the SIRB is a quality IRB that will be accessible to the each site. This trust grows from various factors, including the sites' and SIRBs' level of experience conducting or reviewing the type of studies at issue, the size of the respective research programs, and familiarity with one another's state and local rules and culture. Mandating a SIRB arrangement among several academic medical centers in the same area that are frequent collaborators is very different than mandating SIRB review among these centers and small private physician practices in different states.
- **Types of studies:** Minimal risk studies generally have few ancillary committee reviews as well as few amendments and UAPs over the course of the study. In contrast, more than minimal risk studies generally have ancillary committee reviews as well as frequent amendments and UAPs that require IRB review. The logistics and resources needed for SIRB review vary as a function of the type of research; hence adequacy of infrastructure must be assessed for each study.
- **Types of study teams:** Multi-site studies require some level of study team coordination. However, the degree of coordination that is customary and readily achievable varies: robust research networks

with clinical and data coordinating committees are vastly different from one-time affiliations of several colleagues with no existing infrastructure. The ‘one-time-affiliations’ often lack the skills as well as funding to coordinate with a SIRB.

- Resources for the SIRB system: If an institution is expected to provide SIRB services as an ‘add-on’ with no additional resources, then its overall capacity will be severely limited. For example, a 50 site high risk interventional study would easily require a full-time liaison to simply handle communications between all sites for initial review, continuing review, adverse events, amendments, etc. In addition, information technology (IT) resources must be in place to accommodate handling the processes between the participating institutions. In many situations this requires either a new system or a work-around of an existing IT system.
- Resources for investigators: Study teams will have to assume much of the coordination functions between the sites – this will require resources.

The Draft Policy does not currently allow for consideration of such heterogeneity. A minimal risk study conducted at 4 institutions that are members of an existing network defies comparison with an interventional high risk study conducted at 25 institutions that have been newly brought together for specific research, in terms of capabilities, comfort level, and resources needed.

2. The limited scope for exceptions is not adequate

The Draft Policy states that “exceptions will be allowed only if the designated SIRB is unable to meet the needs of specific populations or where local IRB review is required by federal, tribal, or state laws or regulations.” For all of the reasons addressed above, if the final policy adopts the broad scope that is proposed, we believe that there are many other factors that should be considered as justification for an alternate approach or an exception, including the type of study, types and numbers of involved institutions, and type of study team. In addition, it is unclear what sorts of situations would constitute inability to meet the needs of specific populations or why this could not be assessed before any particular IRB is designated as the SIRB.

3. Lack of details and proposed financial resources to support the processes at both the reviewing SIRB as well as the relying sites

The default in any reliance arrangement is that the only task that is ceded is the IRB regulatory review; all institutional responsibilities generally remain with the local sites and some in fact cannot be ceded. Institutional responsibilities include, for example, HIPAA determinations related to the study, ancillary committee reviews, compliance with state laws, COI, CMS, and training of investigators. Tasks like ancillary committee reviews necessarily *must* remain with the local sites, as must ultimate responsibility for compliance with state laws. Hence in ceded review, the relying sites retain significant tasks. These are tasks that in many institutions are completed by the IRB (such as in the case of HIPAA) or otherwise by the IRB office and closely integrated into the overall review of a protocol. When IRB review is ceded, the relying institution must develop processes and systems (often new IT systems) by which they not only coordinate these institutional responsibilities but also communicate their determinations to the SIRB.

Providing SIRB capacity requires planning and process development including identification of resources needed for both setting up the SIRB as well as completing the protocol review. The tasks for setting up a SIRB include for example: negotiation of reliance agreements; performance of due diligence of the relying sites; development of SOPs that address processes for communication between the SIRB and all relying sites, processes for obtaining and considering relying site issues such as HIPAA authorizations or waiver of authorization determinations, ancillary committee reviews, COI, CMS, sign-off on PI training, processes for dealing with noncompliance and required reporting, etc. Once these systems are set up, the SIRB must then be able to conduct all regulatory reviews (initial, continuing, amendments, UAPs etc)

after obtaining appropriate input from local sites.

As noted above, the level of resources needed for serving as a SIRB as well as relying on a SIRB will be informed by the type of study; e.g., complexity of the study, number of sites, structure of the study team etc.

We (institutions, IRBs, sponsors, regulatory agencies) do not yet have accurate information on these costs. Without this information, it will be difficult for institutions to responsibly serve as a SIRB or agree to rely. This discussion is further complicated by the paucity of data regarding the cost of local IRB review. As noted above, most IRB offices are responsible for much more than the regulatory review and it may be difficult to disentangle the costs of that regulatory review from all of the other tasks that the IRB/IRB office performs.

Adding to the comments made above – is the fact that we are currently in a time of evolving and multiplying SIRB models. At present there are a number of different models which share some features, but which each have their own approach. IRBShare is an example of a “share model” in which IRB regulatory review is shared between the SIRB and local IRBs. In contrast are the “nonshare” models in which all regulatory review is completed by the SIRB; examples include systems used by the VA, NCI and NeuroNEXT. Mandating SIRB review at this time without review and analysis of the relative benefits and costs of each model or determination which is most appropriate for different types of NIH-funded research just adds another requirement to the explosion of different models and approaches. A single institution may be faced with serving as a SIRB for several completely different types of research as well as relying on several other SIRBs, each of which has their own policies and procedures. If the Draft Policy is finalized as proposed, different SIRB systems would be developed. This would then require that relying institutions have the infrastructure and resources needed to maintain working interfaces with multiple somewhat different systems. This could in fact decrease the efficiency of protocol review.

The proposal states that if the identified central IRB is a for-fee IRB, then that cost can be included in the budget. IRBs based at academic centers are typically not fee based, at least not for all reviews they perform – yet they will have to assume significant increases in work, as well as development of systems to comply with this proposal. How will that be funded?

4. Suggestion of SIRB AND local IRB review

The Draft Policy allows for parallel reviews, as we agree is appropriate in the absence of any current regulatory mandate for SIRB review. However, the policy does not discuss the implications of a situation in which both a designated SIRB and a local IRB(s) perform a regulatory review of a study. From a regulatory perspective, we presume that NIH agrees that both IRBs would have authority, and as a practical matter, the result is that the most stringent (protective of human subjects) requirements must govern. How does NIH intend for this concurrent review scenario to work, and what communication will occur to ensure that the designated SIRB selected by NIH is aware of the other IRBs’ reviews?

5. Selection criteria for the SIRB

The Draft Policy does not indicate what criteria will be used by NIH to evaluate and select the SIRB. Transparency around this determination is critical for institutions and IRBs participating in trials subject to the policy to understand NIH’s expectations and to develop robust proposals if they are interested in being designated as the SIRB.

Without limiting this general comment, we note that the Draft Policy does not mention the requirements of the HIPAA Privacy Rule for use or disclosure of Protected Health Information for research. Depending on the type of study at issue, the researchers may request a waiver of authorization for use/disclosure of PHI. Under the HIPAA Privacy Rule, a Privacy Board must determine whether a waiver is appropriate for

the study and document that determination. In practice, many IRBs serve as the Privacy Boards for their institutions. In our experience, including reliance arrangements where NIH's IRBs are designated as the SIRB, the designated IRB is not always willing to serve as a Privacy Board for the relying institutions. In such situations, the relying institutions (and specifically, their IRBs) must then review the study sufficiently to be able to apply the HIPAA waiver criteria and make the waiver determination. When this occurs, the potential efficiencies of the SIRB review are diminished. Does NIH intend to require willingness to serve as a HIPAA Privacy Board in order for an IRB to be selected as the SIRB under this policy?

6. Lack of coordination with other proposed mandates and/or regulatory changes regarding the use of SIRBs

As noted in the Draft Policy, there are two outstanding ANPRMs, from 2009 and 2011, that contain proposals relevant to reliance arrangements and requirements for use of single IRBs. It is not clear to us whether HHS intends to proceed with proposed regulatory change as discussed in the 2009 ANPRM, that would clarify regulatory responsibilities of each of the parties in a reliance arrangement and establish direct regulatory liability of IRBs. It is also not clear to us whether single IRB review will be mandated as a result of the 2011 ANPRM, and if so, for what scope of studies. Establishing a funding policy mandating broad use of single IRBs in advance of the resolution of these two regulatory initiatives may create confusion or result in inconsistencies if and when regulatory changes are adopted. We believe that it makes more sense for NIH's focus at the present time to be on funding additional research examining the potential benefits and costs of single IRB use as suggested above.

Suggestions for alternate approaches:

As noted above, we strongly support the development and facilitation of SIRBs for some multi-site research. We also note that the use of external IRBs is not a new concept and there is an experience upon which to build. Most academic medical centers (AMC) have experience relying on an IRB at another AMC; these arrangements are often limited to no more than minimal risk research conducted at two or three sites. In addition, many AMCs have experience relying on commercial/independent IRBs for a select category of research - most often industry-sponsored and initiated, phase 3 and 4 multi-site research. What is new with the NIH Draft Policy is the inclusion of all NIH-funded multi-site research regardless of type of study or number of institutions.

Given the current evolution of SIRB models and the paucity of data regarding these models, we suggest a more tempered approach. Instead of broadly requiring a SIRB for any NIH-funded multi-site research, we propose refining the policy either to be limited (for now) to minimal risk research involving no more than several sites or, if it remains broad, to including a process whereby flexibility be built into the policy to account for various types of research and other specific factors more fully discussed above. In this way, use of a SIRB could be considered case-by-case before being required by NIH as a condition of funding.

We also suggest that NIH simultaneously fund research on existing SIRB models to evaluate potential benefits and costs for both the SIRB site as well as relying sites. This could include research focused at models that are currently reviewing NIH-funded research or NIH could also identify a cohort of clinical research for which the NIH will fund a SIRB and as a condition of grant award require research on the SIRB itself.

All of these approaches would inform the process going forward.

In addition, NIH could convene expert panels to focus on a number of SIRB-related issues; such as, developing criteria to identify research best reviewed by a SIRB; identifying the elements and resources needed to provide SIRB services within an AMC; and evaluating the pros and cons of various reliance models.

Finally, NIH could support the development of tools that could facilitate SIRB processes – this would include working with groups that have already begun to address some of these. Examples of tools include: Reliance Agreement templates, Standard Operating Procedures, approaches to HIPAA.

Thank you for the opportunity to provide comments on this draft guidance. Please contact us with any questions or requests for clarification. We are very interested in working with you to develop a successful future for SIRBs.

Sincerely,

Anne Klibanski, M.D.
Chief Academic Officer, Partners HealthCare

Laurie Carrol Guthart,
Professor of Medicine, Harvard Medical School

Comment #90

Commenter: William Smith, JD

Date of comment: January 27, 2015

Comment:

In regards to the Draft Guidance, I have a concern about the language, “Exceptions to the expectation to use a single IRB may be made with appropriate justification. Exceptions will be allowed only if the designated single IRB is unable to meet the needs of specific populations or where local IRB review is required by federal, tribal, or state laws or regulations.”

State and local laws as pertaining to IRB review do not mention IRBs or require local IRB review, yet bring to bear many potential issues of which centralized or single IRBs might not be aware. In Florida, HIV test results have specific guidelines for disclosure (Title XXIX, Chapter 381.004, (2)(a)-(h)). These provisions do not require a separate IRB review; however, they do require localized knowledge to avoid local sites being non-compliant with state/local laws. The Draft Guidance is unclear on how the single IRB will obtain this localized knowledge, and, whom, if not the single IRB, would be responsible for possessing such knowledge, informing the single IRB of these provisions, and monitoring sites for compliance of these provisions when approved by the single IRB.

Solutions to such issues are not discussed by the guidance but would be problematic even if they were so discussed. Local sites’ IRBs might have to review research approved by single IRBs for compliance with local laws without the authority to require changes at the local level. This would defeat the purpose of single IRB review as research would go through multiple IRB reviews, requests for changes would be made from multiple IRBs and have to be approved individually by a single and central IRB.

Alternatively, the single IRB would have to be responsible for understanding and applying 50 or more different state laws, which is a task ill-suited to all but the larger commercial IRBs. This solution would all but require multisite NIH-funded research to use a large commercial IRB.

I am generally supportive of removing duplicative review of research across multiple sites as this rarely adds to the protection of human subjects. However, responsible IRB reviews require knowing and adjusting for state and local laws, which is something missing from the draft guidance.

Comment #91

Commenter:

Date of Comment:

Comment:

Human Research Protection Programs, Inc.®

January 27, 2015

Office of Clinical Research and Bioethics Policy
Office of Science Policy
National Institutes of Health

Via email to: SingleIRBpolicy@mail.nih.gov

The Association for the Accreditation of Human Research Protection Programs, Inc.© (AAHRPP) appreciates the opportunity to provide comments on the "Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research" (Policy). AAHRPP applauds NIH on its efforts to bring greater efficiency to the process of IRB review and approval of high-quality, ethically sound research. AAHRPP generally supports the proposed NIH requirement that, whenever appropriate, a single IRB will perform the review of multi-site studies.

AAHRPP is an independent, non-profit, 501(c)(3) organization that accredits human research protection programs (HRPPs) in the United States and around the world. Currently, more than 200 organizations-representing every sector of the human research enterprise - have earned AAHRPP accreditation.

Among AAHRPP's accredited organizations are almost three-quarters of NIH's top 50 funded institutions. In addition, the intramural program of NIH is itself AAHRPP-accredited. (We should note that comments expressed in this letter do not necessarily reflect the opinion of AAHRPP-accredited organizations. We have encouraged them to respond to you separately.)

AAHRPP promotes high-quality research principally through accreditation activities that help organizations worldwide strengthen their HRPPs. AAHRPP uses a voluntary, peer-driven model to ensure that HRPPs meet rigorous standards for quality and protection of research participants. In its ordinary course of operations, AAHRPP reviews tangible evidence-through a peer review of policies, procedures, and practices-that verify an organization's commitment to scientifically and ethically sound research as well as evidence of a focus on continuous improvement.

AAHRPP partners with research organizations, researchers, sponsors, and the public to identify, encourage, and promote effective, efficient, and innovative systems of protection for human research participants. AAHRPP's comments are based on nearly 15 years of experience and more than 500 site visits to review organizations' HRPPs. No other non-governmental entity has such extensive, firsthand experience in assessing the implementation of human research protections. Given the breadth and depth of AAHRPP's reach across the human research enterprise, we bring a singular perspective to the issues raised in the draft NIH Policy.

As noted above, AAHRPP generally supports the proposed requirement that a single IRB review multi-site studies. However, there are many open questions relating to the draft Policy that will need to be addressed prior to its finalization or implementation. Rather than addressing all of these issues, which other commenters undoubtedly will do, AAHRPP's comments are largely addressed to those issues that have clear implications for organizations that are AAHRPP-accredited, currently working toward achieving AAHRPP accreditation, or considering AAHRPP accreditation.

The draft Policy describes a single IRB of record "default" that suggests that it will be the norm regardless of what type of research is being proposed. That is, the draft Policy uses the multi-site feature of a proposed study as the trigger for single IRB review (in most cases) and does not differentiate between types of research, such as clinical trials, epidemiologic studies, and smaller multi-site studies (e.g. a community-based intervention study involving two to five local institutions). While, on its face, this may appear to be a rational approach, it is not clear whether this "one size fits all" requirement will actually lessen institutional burden, given the infrastructure and administrative complexity of becoming or ceding to a single IRB of record.

Laudably, in certain areas the draft Policy sets a somewhat clearer expectation of the responsibilities of local IRBs that currently review multi-site research. This is a positive development because in clinical trials and other large multi-site studies (e.g., epidemiological studies), local IRBs have a false expectation that they can change the protocol, leading to frustration and unnecessary burden on the local IRB. Local IRBs are typically limited to 1) deciding whether the local institution will participate in the study and 2) slightly altering the consent process and document to meet local institutional requirements. Currently, local changes to consent documents pose significant burdens on researchers, and there is no evidence they improve protections. A parallel and also potentially beneficial aspect of this proposal is that whereas, as stated, local IRBs typically have little or no power to change a study, having a single IRB of record can strengthen IRB review to the extent that an IRB of record (theoretically representing scores of research sites) may have more leverage with the sponsor on issues of human subject protection.

Separately, the draft Policy also states that the single IRB of record will be "accountable for compliance with regulatory requirements for IRBs...under ...45 CFR part 46" but then goes on to provide an in-exhaustive list of examples of regulatory responsibilities that will remain with participating sites. Therefore, further guidance from NIH will be needed on the respective roles of the single IRB and the participating sites in areas such as review of modifications to approved research, addition of research sites, and other post-approval monitoring issues including the relationship between the IRB and a data monitoring committee (such as a data and safety monitoring board). Guidance will also be required on applying state laws, identifying and managing individual financial COI, validating the experience and expertise of members of the research team, and funding the single IRB (this topic is mentioned but not elaborated upon in the draft, especially as to what will constitute a "fee-based" IRB). In short, guidance should delineate more specifically the responsibilities of the single reviewing IRB and the research sites, any shared responsibilities, and any responsibilities that may be negotiated by the reviewing IRB and the research site. Guidance should make clear who will be responsible—the institution, the IRB, or the researcher—for specific regulatory requirements—and, correspondingly, who is liable when a problem emerges.

Finally, the selection process of the single IRB for review of a specific study is of paramount importance. The IRB must have the appropriate expertise and experience to review the proposed research and the capacity to review the protocol and sites participating in the study. In other words, the single IRB of record must be of high quality and exist within a robust HRPP. An oft-cited reason given for institutional reluctance to cede IRB review to another institution is the perception that the "ceded-to" IRB is simply not as good as the institution's own IRB. Therefore, in order to make the new Policy not just a mandated requirement but one that is well-received by the research community, guidance should specify criteria for selecting the single IRB of record.

This is where AAHRPP accreditation plays a key role. As mentioned above, NIH itself has achieved full AAHRPP accreditation for its intramural program, an important public affirmation by the world's premier research organization of the value of AAHRPP accreditation as a meaningful component in efforts to help assure the safety and welfare of human research participants. AAHRPP believes that the logical

next step for NIH would be to expand this commitment to its extramural research program. Therefore, in the final Policy, NIH should either require or evince a strong preference for AAHRPP-accredited HRPPs to serve as the IRB of record for multi-site research studies.

AAHRPP and NIH are united in our mission to support and encourage excellent research conducted at the highest ethical level for the ultimate benefit of the public. Though questions remain as to the precise content and implementation framework of the proposed NIH Policy, its issuance represents an important first step toward improving the processes for the review and approval of research involving human participants. AAHRPP appreciates the opportunity to participate in this public process to thoughtfully refine and improve upon what is undeniably a good idea whose time has come.

Sincerely,

Elyse I. Summers, J.D. President and CEO

Comment #92

Commenter:

Date of Comment:

Comment:

January 27, 2015

Acting Director Sarah Carr
Office of Clinical Research and Bioethics Policy
Office of Science Policy
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Dear Acting Director Carr,

The Endocrine Society appreciates the opportunity to comment on the draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research. Founded in 1916, the Endocrine Society is the world's oldest, largest, and most active organization devoted to research on hormones and the clinical practice of endocrinology. The Endocrine Society's membership of over 18,000 includes many clinical researchers who conduct clinical, translational, and epidemiological research with human participants, necessitating approval by IRBs. We support the new policy to "promote the use of a single Institutional Review Board of record for domestic sites of multi-site studies funded by the NIH" and look forward to additional details regarding implementation.

The Society applauds the recognition in the notice of the draft policy that multiple-IRB reviews have increased the burdens faced by administrators and researchers in efforts to reduce liability and ensure compliance. Moreover, as we noted in our response to the National Science Board Task Force on Administrative Burden¹, many of the expanded regulations are unnecessarily cumbersome, cause substantial delays, and do not affect patient safety. We expect that the new policy will therefore streamline the overall process for clinical trials and improve the efficiency of the biomedical research enterprise.

The Endocrine Society looks forward to the issuance of the final policy and specific procedural guidance to facilitate implementation, as indicated in the notice. We would welcome the opportunity to work with you as you implement the policy and we are prepared to help with the dissemination of the information to our members once policy is final. If we can be of any assistance in your efforts please do not hesitate to contact Dr. Joseph Laakso, Associate Director of Science Policy at jlaakso@endocrine.org.

Sincerely,

Richard J. Santen, MD President, Endocrine Society

Footnotes:

¹<https://www.endocrine.org/~media/endosociety/Files/Advocacy%20and%20Outreach/Society%20Letters/TE%20Comments%20on%20Administrative%20Burden%20RFI%20FINAL.pdf>

Comment #93

Commenter: Steven Kritz, MD

Date of comment: January 27, 2015

Comment:

On behalf of START Treatment & Recovery Centers' Board of Trustees, leadership, and Institutional Review Board (IRB), I present the following response to your call for public comment to your draft policy for the use of single IRBs in multi-site clinical research studies.

As an agency that provides medication-assisted opioid treatment and drug-free treatment for chemical dependency, primary medical and behavioral care (including HIV/AIDS services), and clinical research to a population that experiences significant disparities due to race/ethnicity, socioeconomic status, and stigma; any loss of oversight or autonomy by our in-house IRB would likely be detrimental.

I state this, not as a theoretical possibility, but as an experiential one. Despite the well-documented reluctance of the patients described above to participate in research, we have had considerable success in that arena. Our IRB, which has a similar racial/ethnic make-up to the patients we serve, has usually found areas for amendment in protocols reviewed that were missed by the PIs or other IRBs. Had these amendments not been made, it would likely have impacted patients' willingness to participate in the study. For example, there were amendments made by our IRB to a NIDA Clinical Trials Network study (CTN- 0002) that tightened confidentiality requirements. As a result, our agency not only recruited at least as many participants as any other study site nationwide; we recruited approximately 90% of the African American participants nationwide.

In the case of a non-NIH international study by a major pharmaceutical manufacturer, our IRB found a confidentiality issue in one portion of the study that was missed by the 200+ other participating sites worldwide (including dozens of IRBs). The pharmaceutical firm acknowledged the point and even stated that they needed to address our issues in future protocols. However, due to the logistical challenges of changing a protocol that was already ongoing, they could not make the requested amendments. As a result, our IRB denied our agency's participation in that element of the study.

The point is; we are a minority institution with an IRB that reviews research protocols with our vulnerable populations uppermost in mind. As a result of these efforts, we have developed a level of trust with the population we serve that must continue to be cultivated. This is consistent with one of the main tenets of community-based research.

Therefore, we believe that at the very least, statements in this new policy allowing for exceptions, must be broad enough to cover agencies such as ours to allow us to capitalize on our unique experience and continue to review research impacting our especially vulnerable populations.

Comment #94

Commenter: Harry W. Orf, PhD

Date of Comment: 27 January 2015

Comment:

JANUARY 27, 2015

Thank you very much for providing the opportunity to comment on the NIH Draft Policy entitled: Use of Single Institutional Review Board for Multi Site Research (Draft Policy). I am writing on behalf of the Massachusetts General Hospital (Mass General), a principal teaching affiliate of Harvard Medical School.

The Mass General is the third oldest general hospital in the United States and the original and largest teaching hospital of Harvard Medical School. A founding member of Partners HealthCare System, Mass General conducts the largest hospital- based research program in the U.S, encompassing both basic science and clinical research, and is consistently ranked among the top two hospitals nationally receiving NIH funding. In FY 14, Mass General received approximately \$350 million in research funding from the NIH. Thus, reform of policies pertaining to Institutional Review Boards is of critical importance to the Mass General research enterprise.

As a participant in multiple single IRB (SIRB) arrangements, including as a Central IRB, we strongly support the development and facilitation of SIRB review. However, we believe that the Draft Policy as written is premature in its breadth and inflexibility and does not adequately acknowledge or address the gaps in current knowledge about the relative benefits and costs of SIRB systems. As indicated in our detailed comments below, we propose that more research be conducted before mandating SIRB review for all types of multi-site studies and that the initial policy focus on a more limited set of research.

Our comments are organized into three sections: 1) comments on the assumptions/assertions made in the introduction to the Draft Policy; 2) comments on the specific proposals of the Draft Policy and 3) suggestions for alternate approaches.

Introductory assumptions/assertions:

Use of an SIRB for domestic multi-site research is promoted as promising potential advantages of efficiency, decreased time to study start-up and consistency of review and even conduct of the research. However, there is currently little research or data to demonstrate that these potential benefits will materialize in particular types of multi-site research, that they can be realized with no accompanying decrease in human subject protections, or that they outweigh the significant costs and resource investments required to implement a single IRB system in which all parties can have confidence.

A few specific comments:

The Draft Policy presumes that there will be efficiency in the initiation/initial review of a study. In our experience with serving as the SIRB and relying on other SIRBs, the efficiency has not been in the initial review of the protocol, but rather in the addition of sites after initial protocol review as well as in the subsequent reviews through the life of the protocol; e.g., continuing review, unanticipated problems (UAPs).

The Draft Policy asserts that local IRB review is not needed for assessing local context. While we agree this is not an IRB regulatory requirement, we note that it is generally the local IRB or at least the local IRB office that is most knowledgeable about the local context and about the application of local rules and norms to the conduct of research. Therefore recognition of the practical reality of ongoing IRB office, if not IRB, involvement is necessary.

The Draft Policy casts use of a SIRB as more cost effective than local IRB review. More information is needed before this can be accepted as a benefit.

Details of the Draft Guidance:

Our comments on specific proposals or aspects of the Draft Policy are listed here. Discussion of each item immediately follows this list.

1. The broad scope of the mandate – all multi-site domestic research with NIH
2. funding – without regard to the type of research or number and type of sites and to the existence of central infrastructure to support the SIRB
3. The limited scope for exceptions
4. Lack of details and proposed financial support for management of the necessary research oversight processes at the reviewing SIRB and the relying sites, and for required communication between them
5. Lack of details regarding expectations when the local IRB elects to review a
6. project subject to the policy
7. Absence of information about the selection/approval criteria for the SIRB, including whether the SIRB's willingness/ability to serve as a HIPAA Privacy Board will be a factor
8. Apparent lack of coordination with other proposed mandates and/or regulatory changes regarding the use of SIRBs, including the 2009 and 2011 ANPRMs referenced in the Draft Policy

1. The broad scope of the mandate:

The Draft Policy describes in general the requisite responsibilities for both the reviewing SIRB and the relying institutions. But it fails to recognize how different types of studies require vastly different logistics and resources for both the SIRB and the relying institution. Due to these differences, there are multi-site studies that fit more easily into an SIRB approach and there are others that do not.

In our experience, examples of factors to consider before deciding that SIRB review is appropriate include:

- Number of institutions: a study involving 2 sites versus one with 75 will have very different impact on coordination, workflow and resources needed.
- Types of institutions: The success of SIRBs is predicated on trust and mutually agreed-upon processes. The SIRB must have confidence that the sites relying on the SIRB have good HRPPs that can provide all of the institutional requirements. And the relying sites must trust that the SIRB is a quality IRB that will be accessible to the each site. This trust grows from various factors, including the sites' and SIRBs' level of experience conducting or reviewing the type of studies at issue, the size of the respective research programs, and familiarity with one another's state and local rules and culture. Mandating a SIRB arrangement among several academic medical centers in the same area that are frequent collaborators is very different than mandating SIRB review among these centers and small private physician practices in different states.
- Types of studies: Minimal risk studies generally have few ancillary committee reviews as well as few amendments and UAPs over the course of the study. In contrast, more than minimal risk studies generally have ancillary committee reviews as well as frequent amendments and UAPs that require IRB review. The logistics and resources needed for SIRB review vary as a function of the type of research; hence adequacy of infrastructure must be assessed for each study.
- Types of study teams: Multi-site studies require some level of study team coordination. However, the degree of coordination that is customary and readily achievable varies: robust research networks

with clinical and data coordinating committees are vastly different from one-time affiliations of several colleagues with no existing infrastructure. The 'one-time-affiliations' often lack the skills as well as funding to coordinate with a SIRB.

- Resources for the SIRB system: If an institution is expected to provide SIRB services as an 'add-on' with no additional resources, then its overall capacity will be severely limited. For example, a 50 site high risk interventional study would easily require a full-time liaison to simply handle communications between all sites for initial review, continuing review, adverse events, amendments, etc. In addition, information technology (IT) resources must be in place to accommodate handling the processes between the participating institutions. In many situations this requires either a new system or a work-around of an existing IT system.
- Resources for investigators: Study teams will have to assume much of the coordination functions between the sites – this will require resources.

The Draft Policy does not currently allow for consideration of such heterogeneity. A minimal risk study conducted at 4 institutions that are members of an existing network defies comparison with an interventional high risk study conducted at 25 institutions that have been newly brought together for specific research, in terms of capabilities, comfort level, and resources needed.

2. The limited scope for exceptions is not adequate

The Draft Policy states that "exceptions will be allowed only if the designated SIRB is unable to meet the needs of specific populations or where local IRB review is required by federal, tribal, or state laws or regulations." For all of the reasons addressed above, if the final policy adopts the broad scope that is proposed, we believe that there are many other factors that should be considered as justification for an alternate approach or an exception, including the type of study, types and numbers of involved institutions, and type of study team. In addition, it is unclear what sorts of situations would constitute inability to meet the needs of specific populations or why this could not be assessed before any particular IRB is designated as the SIRB.

3. Lack of details and proposed financial resources to support the processes at both the reviewing SIRB as well as the relying sites

The default in any reliance arrangement is that the only task that is ceded is the IRB regulatory review; all institutional responsibilities generally remain with the local sites and some in fact cannot be ceded. Institutional responsibilities include, for example, HIPAA determinations related to the study, ancillary committee reviews, compliance with state laws, COI, CMS, and training of investigators. Tasks like ancillary committee reviews necessarily *must* remain with the local sites, as must ultimate responsibility for compliance with state laws. Hence in ceded review, the relying sites retain significant tasks. These are tasks that in many institutions are completed by the IRB (such as in the case of HIPAA) or otherwise by the IRB office and closely integrated into the overall review of a protocol. When IRB review is ceded, the relying institution must develop processes and systems (often new IT systems) by which they not only coordinate these institutional responsibilities but also communicate their determinations to the SIRB.

Providing SIRB capacity requires planning and process development including identification of resources needed for both setting up the SIRB as well as completing the protocol review. The tasks for setting up a SIRB include for example: negotiation of reliance agreements; performance of due diligence of the relying sites; development of SOPs that address processes for communication between the SIRB and all relying sites, processes for obtaining and considering relying site issues such as HIPAA authorizations or waiver of authorization determinations, ancillary committee reviews, COI, CMS, sign-off on PI training, processes for dealing with noncompliance and required reporting, etc. Once these systems are set up, the SIRB must then be able to conduct all regulatory reviews (initial, continuing, amendments, UAPs etc)

after obtaining appropriate input from local sites.

As noted above, the level of resources needed for serving as a SIRB as well as relying on a SIRB will be informed by the type of study; e.g., complexity of the study, number of sites, structure of the study team etc.

We (institutions, IRBs, sponsors, regulatory agencies) do not yet have accurate information on these costs. Without this information, it will be difficult for institutions to responsibly serve as a SIRB or agree to rely. This discussion is further complicated by the paucity of data regarding the cost of local IRB review. As noted above, most IRB offices are responsible for much more than the regulatory review and it may be difficult to disentangle the costs of that regulatory review from all of the other tasks that the IRB/IRB office performs.

Adding to the comments made above – is the fact that we are currently in a time of evolving and multiplying SIRB models. At present there are a number of different models which share some features, but which each have their own approach. IRBShare is an example of a “share model” in which IRB regulatory review is shared between the SIRB and local IRBs. In contrast are the “nonshare” models in which all regulatory review is completed by the SIRB; examples include systems used by the VA, NCI and NeuroNEXT. Mandating SIRB review at this time without review and analysis of the relative benefits and costs of each model or determination which is most appropriate for different types of NIH-funded research just adds another requirement to the explosion of different models and approaches. A single institution may be faced with serving as a SIRB for several completely different types of research as well as relying on several other SIRBs, each of which has their own policies and procedures. If the Draft Policy is finalized as proposed, different SIRB systems would be developed. This would then require that relying institutions have the infrastructure and resources needed to maintain working interfaces with multiple somewhat different systems. This could in fact decrease the efficiency of protocol review.

The proposal states that if the identified central IRB is a for-fee IRB, then that cost can be included in the budget. IRBs based at academic centers are typically not fee based, at least not for all reviews they perform – yet they will have to assume significant increases in work, as well as development of systems to comply with this proposal. How will that be funded?

4. Suggestion of SIRB AND local IRB review

The Draft Policy allows for parallel reviews, as we agree is appropriate in the absence of any current regulatory mandate for SIRB review. However, the policy does not discuss the implications of a situation in which both a designated SIRB and a local IRB(s) perform a regulatory review of a study. From a regulatory perspective, we presume that NIH agrees that both IRBs would have authority, and as a practical matter, the result is that the most stringent (protective of human subjects) requirements must govern. How does NIH intend for this concurrent review scenario to work, and what communication will occur to ensure that the designated SIRB selected by NIH is aware of the other IRBs’ reviews?

5. Selection criteria for the SIRB

The Draft Policy does not indicate what criteria will be used by NIH to evaluate and select the SIRB. Transparency around this determination is critical for institutions and IRBs participating in trials subject to the policy to understand NIH’s expectations and to develop robust proposals if they are interested in being designated as the SIRB.

Without limiting this general comment, we note that the Draft Policy does not mention the requirements of the HIPAA Privacy Rule for use or disclosure of Protected Health Information for research. Depending on the type of study at issue, the researchers may request a waiver of authorization for use/disclosure of PHI. Under the HIPAA Privacy Rule, a Privacy Board must determine whether a waiver is appropriate for

the study and document that determination. In practice, many IRBs serve as the Privacy Boards for their institutions. In our experience, including reliance arrangements where NIH's IRBs are designated as the SIRB, the designated IRB is not always willing to serve as a Privacy Board for the relying institutions. In such situations, the relying institutions (and specifically, their IRBs) must then review the study sufficiently to be able to apply the HIPAA waiver criteria and make the waiver determination. When this occurs, the potential efficiencies of the SIRB review are diminished. Does NIH intend to require willingness to serve as a HIPAA Privacy Board in order for an IRB to be selected as the SIRB under this policy?

6. Lack of coordination with other proposed mandates and/or regulatory changes regarding the use of SIRBs

As noted in the Draft Policy, there are two outstanding ANPRMs, from 2009 and 2011, that contain proposals relevant to reliance arrangements and requirements for use of single IRBs. It is not clear to us whether HHS intends to proceed with proposed regulatory change as discussed in the 2009 ANPRM, that would clarify regulatory responsibilities of each of the parties in a reliance arrangement and establish direct regulatory liability of IRBs. It is also not clear to us whether single IRB review will be mandated as a result of the 2011 ANPRM, and if so, for what scope of studies. Establishing a funding policy mandating broad use of single IRBs in advance of the resolution of these two regulatory initiatives may create confusion or result in inconsistencies if and when regulatory changes are adopted. We believe that it makes more sense for NIH's focus at the present time to be on funding additional research examining the potential benefits and costs of single IRB use as suggested above.

Suggestions for alternate approaches:

As noted above, we strongly support the development and facilitation of SIRBs for some multi-site research. We also note that the use of external IRBs is not a new concept and there is an experience upon which to build. Most academic medical centers (AMC) have experience relying on an IRB at another AMC; these arrangements are often limited to no more than minimal risk research conducted at two or three sites. In addition, many AMCs have experience relying on commercial/independent IRBs for a select category of research—most often industry-sponsored and initiated, phase 3 and 4 multi-site research. What is new with the NIH Draft Policy is the inclusion of all NIH-funded multi-site research regardless of type of study or number of institutions.

Given the current evolution of SIRB models and the paucity of data regarding these models, we suggest a more tempered approach. Instead of broadly requiring a SIRB for any NIH-funded multi-site research, we propose refining the policy either to be limited (for now) to minimal risk research involving no more than several sites or, if it remains broad, to including a process whereby flexibility be built into the policy to account for various types of research and other specific factors more fully discussed above. In this way, use of a SIRB could be considered case-by-case before being required by NIH as a condition of funding.

We also suggest that NIH simultaneously fund research on existing SIRB models to evaluate potential benefits and costs for both the SIRB site as well as relying sites. This could include research focused at models that are currently reviewing NIH-funded research or NIH could also identify a cohort of clinical research for which the NIH will fund a SIRB and as a condition of grant award require research on the SIRB itself.

All of these approaches would inform the process going forward.

In addition, NIH could convene expert panels to focus on a number of SIRB-related issues; such as, developing criteria to identify research best reviewed by a SIRB; identifying the elements and resources needed to provide SIRB services within an AMC; and evaluating the pros and cons of various reliance

models.

Finally, NIH could support the development of tools that could facilitate SIRB processes – this would include working with groups that have already begun to address some of these. Examples of tools include: Reliance Agreement templates, Standard Operating Procedures, approaches to HIPAA.

Thank you for the opportunity to provide comments on this draft guidance. Please contact us with any questions or requests for clarification. We are very interested in working with you to develop a successful future for SIRBs.

Sincerely,

Harry W. Orf, PhD

Senior Vice President for Research Massachusetts General Hospital
Boston, Massachusetts 02114

Comment #95

Commenter:

Date of Comment:

Comment:

January 28, 2015

Office of Clinical Research and Bioethics Policy

Office of Science Policy, NIH

6705 Rockledge Drive, Suite 750

Bethesda, MD 20892

email: SingleIRBpolicy@mail.nih.gov

Re: NIH Draft Policy on the Use of a Single IRB for Multi-Site Research. Dear Sir or Madam:

Thank you for allowing us the opportunity to comment on the NIH draft policy on the use of a single IRB for multi-site research.

Experience with Central Review at The Children's Hospital of Philadelphia

For over a decade, The Children's Hospital of Philadelphia has aggressively sought and entered into cooperative IRB reliance agreements with other institutions. We believe that doing so reduces the regulatory burden on investigators and on our IRB and avoids unnecessary replication of effort. We have also publicly advocated that IRB's rethink their aversion to the use of central IRBs and instead, enter into more cooperative agreements (Schreiner MS, Engel BC. *We Have Met the Enemy and He Is Us*, AJOB Primary Research, 2:2, 39-41, 2011 <http://dx.doi.org/10.1080/21507716.2011.605420>).

Some examples of our support for central review include:

- Our long-standing agreement with the University of Pennsylvania that has covered many hundreds of studies;
- Our early participation in the NCI CIRB;
- Advocacy for (as a participant on the IRB sub-committee) and participation in the National Children's Study central IRB;
- Our recently negotiated Master Reliance Agreements with CCHMC and BCH. This agreement formed the basis for the Master Reliance Agreement negotiated between the eight PEDSnet (PCORI grant) institutions. This agreement is open to other pediatric centers who wish to participate.

In addition to the above examples, we have universally accepted the concept of a central IRB for all NIH-funded multicenter studies where this was a condition of grant.

Based on our actions and experience, CHOP welcomes NIH's plan to develop a formal policy for the use of a single IRB for multi-site research. However, our extensive experiences with central IRBs have identified numerous potential issues that are either not addressed or incompletely addressed in the draft policy.

Issues Encountered as Part of Central Review

Quality of the Reviewing IRB.

A vital consideration when entering into an agreement is an understanding of the quality and relevant expertise of the reviewing IRB. The draft policy does not address any standards or criteria to establish

the qualifications of the proposed central IRB. Will IRB selection be based on the awardee site, the NIH's decision or some other process? How will other sites know that the reviewing IRB has both the expertise to review the research and the infrastructure required to effectively communicate to the various sites participating in the research?

We had multiple experiences with external IRBs which have repeatedly made major regulatory errors and who failed to identify important issues.

Transparency in Communications.

Communications between the reviewing IRB and the relying site is extremely important and not addressed in the Draft Guidance. The Reviewing IRB approval letter is often insufficient evidence to demonstrate that the study underwent substantive review. To address this issue, the NCI IRB makes the reviewers' notes and the meeting minutes available for the Relying IRBs. This level of transparency has been essential for building trust.

Regulatory Errors Made by the Reviewing IRB

When it is difficult to obtain essential information from an external, reviewing IRB, it is difficult to assess whether or not it is appropriate to accept them as the reviewing IRB. The final guidance needs to provide relying IRBs recourse to opt out if they find that the determinations made by the reviewing IRB fail to meet regulatory requirements. We have had dozens of studies where the reviewing IRB made major errors including:

Inappropriate Waiver of Consent.

We have experienced IRBs that waive consent for control groups and for comparative effectiveness studies involving two or more FDA-regulated but approved test articles. These IRB seemed unaware of difference in the requirements for waiver of consent for studies that fall under the FDA regulations at 21 CFR 50 and 56 as compared to studies that only needed to satisfy the waiver requirements at 45 CFR 46.116(d).

Failure to Address IND Requirements.

We have been frequently surprised that external IRBs have approved studies that involved FDA-approved drugs that were being tested for new indications or in a new population (children) without also determining that the study met the FDA exemption criteria. For one recent multicenter study we were the only IRB out of approximately 20 that required the steering committee to either obtain a letter of exemption or an IND from the FDA. The study was approved by all of the other sites. After review, the FDA required an IND to conduct the study.

Failure to Make All Required Determinations.

For many studies, particularly those involving adults and children, we have required revisions from the reviewing IRB because they failed to make a Subpart D determination.

Failure to Identify All Research Subjects.

In studies where more than one group of participants is involved (both a parent and their child, the physician and their patients, etc.), the reviewing IRB failed to identify and address the human subjects issues for all groups of subjects. In a particularly egregious example, CHOP was asked to participate in a study already approved at over 200 sites. Our IRB recognized that the intervention was aimed directly at the physicians and only indirectly at the patients. None of the other sites recognized that the physicians were the primary subjects of the research and as such, needed to provide consent to participate.

Proposed Remedies

We think that the NIH final policy would be improved if it addressed the issues identified above and summarized below.

- Guidance is needed to establish the requisite qualifications that must be satisfied before an IRB could serve as the reviewing IRB for a multicenter study
- Assurance that there is an adequate infrastructure in place to support the central IRB activity.
- Communications standards should be established for sharing reviews, minutes and approval information in a timely and transparent manner to ensure relying institutions that the study has had substantive review.
- Institutions must have the ability to opt out of the agreement or to appeal the reviewing IRB's determinations when, in the relying institution's IRB, the reviewing IRB has made one or more regulatory errors.

Sincerely,

Mark S. Schreiner, MD.
Executive Vice-Chair

Barbara Engel, MD, PhD
Chair

Amy Schwarzhoff
Director, Human Subjects Research

Deborah Barnard, M.S.
Director, Research Compliance and Regulatory Affairs

Heather Cathrall, MBE
Assistant Director, IRB Operations

Comment #96

Commenter:

Date of Comment:

Comment:

January 28, 2015

Office of Clinical Research and Bioethics Policy
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, Maryland 20892

Re: NOT-OD-15-026 (Comments on Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research)

AcademyHealth, as the nonpartisan, professional home for more than 5,000 health services researchers, policy analysts, and practitioners, welcomes the opportunity to respond to the Office of Clinical Research and Bioethics Policy's request for comment on the Draft National Institutes of Health (NIH) Policy on the Use of a Single Institutional Review Board (IRB) for Multi-Site Research.

Human subjects research protections are a moral compass critical to the public good. Health services researchers—from an array of disciplines ranging from outcomes research to health economics—are subject to the Common Rule, which ensures that the individuals who participate in health services research are protected, and that the data with which we work are collected, used, and stored ethically and appropriately. In revising its multi-site IRB policy, NIH will speed the initiation of studies by reducing administrative burdens that unnecessarily hinder scientific innovation and progress while assuring the rigorous and potentially enhanced protection of human subjects.

Utilization of a single IRB review of record for domestic sites of multi-site studies would undoubtedly reduce administrative burden and enhance the timeliness of research and represent a significant improvement to the current process, whereby the review processes and variations in determination associated with multi-site reviews can often delay for months even low-risk projects. However, the policy change is not without its political, administrative, and legal complexities. For instance, what criteria should be used to identify the single IRB in a multi-site study, e.g., principal investigator location, IRB specialty, reputation, or existing relationships with an IRB? Many protocols currently direct subjects to contact the institution's IRB with issues or questions. How do you address institutional accountability when there is a single IRB for a multi-site study? How does NIH address secondary consequences, such as how to allocate liability, and whether an appeals process is necessary? The draft policy itself does not directly address these questions, leaving much of these critical decisions to the investigators and institutions themselves.

Given the complexities, AcademyHealth encourages NIH to develop guidance and training for investigators and institutions on the implementation of the policy. Such guidance could be derived from the experiences of IRB systems that have already implemented more centralized IRB review processes, such as the National Cancer Institute Central Institutional Review Board, as well as the Veterans Health Administration's VA Central Institutional Review Board. Experiences and best practices from these and other centralized IRB systems would provide useful insights for NIH-funded investigators and institutions and facilitate the implementation of NIH's new policy.

AcademyHealth also encourages the Office of Clinical Research and Bioethics Policy to periodically assess the effectiveness of its single-site IRB policy to ensure that it does indeed streamline the

research process and assure appropriate protections for human subjects. Such regular assessment would ensure the policy is responsive and flexible to evolving research needs and practice.

We support NIH's efforts to modernize its IRB policy while reducing the burden, delay, and ambiguity for investigators to produce valuable research. We hope that NIH's efforts spur continued dialogue on the conduct of research—such as long-awaited revisions to the Common Rule—that succeeds in further protecting human subjects rights and incentivizing innovative health care research.

Thank you for the opportunity to submit these comments. Should you have any questions, please contact me directly at 202.292.6700 or lisa.simpson@academyhealth.org.

Sincerely,

Lisa Simpson, M.B., B.Ch., M.P.H., F.A.A.P.
President and CEO AcademyHealth

Comment #97

Commenter:

Date of Comment:

Comment:

JANUARY 27, 2015

Thank you very much for providing the opportunity to comment on the NIH Draft Policy entitled: Use of Single Institutional Review Board for Multi Site Research (Draft Policy).

I am writing on behalf of the Spaulding Rehabilitation Hospital (Spaulding), the primary physical medicine and rehabilitation hospital of the Harvard Medical School (HMS), and a member of the Partners HealthCare System. A major HMS teaching facility, Spaulding clinicians and researchers participate in research studies focused on improving neurological and musculoskeletal functions; understanding the effects of physical activity, inactivity, and exercise; or developing and evaluating the efficacy of new techniques. Clinical areas of research include traumatic brain injury, aging/geriatrics, cardiovascular rehab, motion analysis, muscle cell physiology, robotic therapy, spinal cord injury and stroke. In FY 14, Spaulding received approximately \$1.5 million in research funding from the NIH. Thus, reform of policies pertaining to Institutional Review Boards is of critical importance to Spaulding's research enterprise.

Based on the experience of affiliated hospitals who have participated in multiple single IRB (sIRB) arrangements, including as a Central IRB, we strongly support the development and facilitation of sIRB review. However, we believe that the Draft Policy as written is premature in its breadth and inflexibility, and does not adequately acknowledge or address the gaps in current knowledge about the relative benefits and costs of sIRB systems. As indicated in our detailed comments below, we propose that more research be conducted before mandating sIRB review for all types of multi-site studies, and that the initial policy focus on a more limited set of research.

Our comments are organized into three sections: 1) comments on the assumptions/assertions made in the introduction to the Draft Policy; 2) comments on the specific proposals of the Draft Policy; and 3) suggestions for alternate approaches.

Introductory assumptions/assertions:

Use of an sIRB for domestic multi-site research is promoted as promising potential advantages of efficiency, decreased time to study start-up and consistency of review, and even conduct of the research. However, there is currently little research or data to demonstrate that these potential benefits will materialize in particular types of multi-site research, that they can be realized with no accompanying decrease in human subject protections, or that they outweigh the significant costs and resource investments required to implement a single IRB system in which all parties can have confidence.

A few specific comments:

The Draft Policy presumes that there will be efficiency in the initiation/initial review of a study. In our experience with serving as the sIRB and relying on other sIRBs, the efficiency has not been in the initial review of the protocol, but rather in the addition of sites after initial protocol review, as well as in the subsequent reviews through the life of the protocol, e.g., continuing review, unanticipated problems (UAPs).

The Draft Policy asserts that local IRB review is not needed for assessing local context. While we agree this is not an IRB regulatory requirement, we note that it is generally the local IRB, or at least the local

IRB office, that is most knowledgeable about the local context and about the application of local rules and norms to the conduct of research. Therefore, recognition of the practical reality of ongoing IRB office, if not IRB, involvement is necessary.

The Draft Policy casts use of a sIRB as more cost effective than local IRB review. More information is needed before this can be accepted as a benefit.

Details of the Draft Guidance:

Our comments on specific proposals or aspects of the Draft Policy are listed here. Discussion of each item immediately follows this list.

1. The broad scope of the mandate- all multi-site domestic research with NIH funding- without regard to the type of research or number and type of sites and to the existence of central infrastructure to support the sIRB and the limited scope for exceptions
2. Lack of details and proposed financial support for management of the necessary research oversight processes at the reviewing sIRB and the relying sites, and for required communication between them
3. Lack of details regarding expectations when the local IRB elects to review a project subject to the policy
4. Absence of information about the selection/approval criteria for the SIRB, including whether the sIRB's willingness/ability to serve as a HIPAA Privacy Board will be a factor
5. Apparent lack of coordination with other proposed mandates and/or regulatory changes regarding the use of sIRBs, including the 2009 and 2011 ANPRMs referenced in the Draft Policy

1. The broad scope of the mandate:

The Draft Policy describes in general the requisite responsibilities for both the reviewing sIRB and the relying institutions. But it fails to recognize how different types of studies require vastly different logistics and resources for both the sIRB and the relying institution. Due to these differences, there are multi-site studies that fit more easily into an SIRB approach and there are others that do not.

In our experience, examples of factors to consider before deciding that SIRB review is appropriate include:

- Number of institutions: a study involving two sites versus one with 75 will have very different impact on coordination, workflow and resources needed.
- Types of institutions: The success of sIRBs is predicated on trust and mutually agreed-upon processes. The sIRB must have confidence that the sites relying on the sIRB have good HRPPs that can provide all of the institutional requirements. And the relying sites must trust that the sIRB is a quality IRB that will be accessible to the each site. This trust grows from various factors, including the sites' and sIRBs' level of experience conducting or reviewing the type of studies at issue, the size of the respective research programs, and familiarity with one another's state and local rules and culture. Mandating a sIRB arrangement among several academic medical centers in the same area that are frequent collaborators is very different than mandating sIRB review among these centers and small private physician practices in different states.
- Types of studies: Minimal risk studies generally have few ancillary committee reviews as well as few amendments and UAPs over the course of the study. In contrast, more than minimal risk studies generally have ancillary committee reviews as well as frequent amendments and UAPs that require IRB review. The logistics and resources needed for sIRB review vary as a function of the type of research; hence adequacy of infrastructure must be assessed for each study.

- Types of study teams: Multi-site studies require some level of study team coordination. However, the degree of coordination that is customary and readily achievable varies: robust research networks with clinical and data coordinating committees are vastly different from one-time affiliations of several colleagues with no existing infrastructure. The 'one-time-affiliations' often lack the skills as well as funding to coordinate with a sIRB.
- Resources for the sIRB system: If an institution is expected to provide sIRB services as an 'add-on' with no additional resources, then its overall capacity will be severely limited. For example, an SO site high risk interventional study would easily require a full-time liaison to simply handle communications between all sites for initial review, continuing review, adverse events, amendments, etc. In addition, information technology (IT) resources must be in place to accommodate handling the processes between the participating institutions. In many situations this requires either a new system or a work-around of an existing IT system.
- Resources for investigators: Study teams will have to assume much of the coordination functions between the sites- this will require resources.

The Draft Policy does not currently allow for consideration of such heterogeneity. A minimal risk study conducted at 4 institutions that are members of an existing network defies comparison with an interventional high risk study conducted at 25 institutions that have been newly brought together for specific research, in terms of capabilities, comfort level, and resources needed.

2. The limited scope for exceptions is not adequate

The Draft Policy states that "exceptions will be allowed only if the designated sIRB is unable to meet the needs of specific populations or where local IRB review is required by federal, tribal, or state laws or regulations." For all of the reasons addressed above, if the final policy adopts the broad scope that is proposed, we believe that there are many other factors that should be considered as justification for an alternate approach or an exception, including the type of study, types and numbers of involved institutions, and type of study team. In addition, it is unclear what sorts of situations would constitute inability to meet the needs of specific populations or why this could not be assessed before any particular IRB is designated as the sIRB.

3. Lack of details and proposed financial resources to support the processes at both the reviewing sIRB as well as the relying sites

The default in any reliance arrangement is that the only task that is ceded is the IRB regulatory review; all institutional responsibilities generally remain with the local sites and some in fact cannot be ceded. Institutional responsibilities include, for example, HIPAA determinations related to the study, ancillary committee reviews, compliance with state laws, COI, CMS, and training of investigators. Tasks like ancillary committee reviews necessarily *must* remain with the local sites, as must ultimate responsibility for compliance with state laws. Hence in ceded review, the relying sites retain significant tasks. These are tasks that in many institutions are completed by the IRB (such as in the case of HIPAA) or otherwise by the IRB office and closely integrated into the overall review of a protocol. When IRB review is ceded, the relying institution must develop processes and systems (often new IT systems) by which they not only coordinate these institutional responsibilities but also communicate their determinations to the sIRB.

Providing sIRB capacity requires planning and process development including identification of resources needed for both setting up the sIRB as well as completing the protocol review. The tasks for setting up a sIRB include for example: negotiation of reliance agreements; performance of due diligence of the relying sites; development of SOPs that address processes for communication between the sIRBs and all relying sites, processes for obtaining and considering relying site issues such as HIPAA authorizations or

waiver of authorization determinations, ancillary committee reviews, COI, CMS, sign-off on PI training, processes for dealing with noncompliance and required reporting, etc. Once these systems are set up, the sIRB must then be able to conduct all regulatory reviews (initial, continuing, amendments, UAPs etc) after obtaining appropriate input from local sites.

As noted above, the level of resources needed for serving as a sIRB as well as relying on a sIRB will be informed by the type of study; e.g., complexity of the study, number of sites, structure of the study team etc.

We (institutions, IRBs, sponsors, regulatory agencies) do not yet have accurate information on these costs. Without this information, it will be difficult for institutions to responsibly serve as a sIRB or agree to rely. This discussion is further complicated by the paucity of data regarding the cost of local IRB review. As noted above, most IRB offices are responsible for much more than the regulatory review and it may be difficult to disentangle the costs of that regulatory review from all of the other tasks that the IRB/IRS office performs.

Adding to the comments made above- is the fact that we are currently in a time of evolving and multiplying sIRB models. At present there are a number of different models which share some features, but which each have their own approach. IRBShare is an example of a "share model" in which IRB regulatory review is shared between the sIRB and local IRBs. In contrast are the "nonshare" models in which all regulatory review is completed by the sIRB; examples include systems used by the VA, NCI and NeuroN EXT. Mandating sIRB review at this time without review and analysis of the relative benefits and costs of each model or determination which is most appropriate for different types of NIH-funded research just adds another requirement to the explosion of different models and approaches. A single institution may be faced with serving as a sIRB for several completely different types of research as well as relying on several other sIRBs, each of which has their own policies and procedures. If the Draft Policy is finalized as proposed, different sIRB systems would be developed. This would then require that relying institutions have the infrastructure and resources needed to maintain working interfaces with multiple somewhat different systems. This could in fact decrease the efficiency of protocol review.

The proposal states that if the identified central IRB is a for-fee IRB, then that cost can be included in the budget. IRBs based at academic centers are typically not fee based, at least not for all reviews they perform -yet they will have to assume significant increases in work, as well as development of systems to comply with this proposal. How will that be funded?

4. Suggestion of sIRB and local IRB review

The Draft Policy allows for parallel reviews, as we agree is appropriate in the absence of any current regulatory mandate for sIRB review. However, the policy does not discuss the implications of a situation in which both a designated sIRB and a local IRB(s) perform a regulatory review of a study. From a regulatory perspective, we presume that NIH agrees that both IRBs would have authority, and as a practical matter, the result is that the most stringent (protective of human subjects) requirements must govern. How does NIH intend for this concurrent review scenario to work, and what communication will occur to ensure that the designated sIRB selected by NIH is aware of the other IRBs' reviews?

5. Selection criteria for the sIRB

The Draft Policy does not indicate what criteria will be used by NIH to evaluate and select the sIRB. Transparency around this determination is critical for institutions and IRBs participating in trials subject to the policy to understand NIH's expectations and to develop robust proposals if they are interested in being designated as the sIRB.

Without limiting this general comment, we note that the Draft Policy does not mention the

requirements of the HIPAA Privacy Rule for use or disclosure of Protected Health Information for research. Depending on the type of study at issue, the researchers may request a waiver of authorization for use/disclosure of PHI. Under the HIPAA Privacy Rule, a Privacy Board must determine whether a waiver is appropriate for the study and document that determination. In practice, many IRBs serve as the Privacy Boards for their institutions. In our experience, including reliance arrangements where NIH's IRBs are designated as the sIRB, the designated IRB is not always willing to serve as a Privacy Board for the relying institutions. In such situations, the relying institutions (and specifically, their IRBs) must then review the study sufficiently to be able to apply the HIPAA waiver criteria and make the waiver determination. When this occurs, the potential efficiencies of the sIRB review are diminished. Does NIH intend to require willingness to serve as a HIPAA Privacy Board in order for an IRB to be selected as the sIRB under this policy?

6. Lack of coordination with other proposed mandates and/or regulatory changes regarding the use of sIRBs

As noted in the Draft Policy, there are two outstanding ANPRMs, from 2009 and 2011, that contain proposals relevant to reliance arrangements and requirements for use of single IRBs. It is not clear to us whether HHS intends to proceed with proposed regulatory change as discussed in the 2009 ANPRM, that would clarify regulatory responsibilities of each of the parties in a reliance arrangement and establish direct regulatory liability of IRBs. It is also not clear to us whether single IRB review will be mandated as a result of the 2011 ANPRM, and if so, for what scope of studies. Establishing a funding policy mandating broad use of single IRBs in advance of the resolution of these two regulatory initiatives may create confusion or result in inconsistencies if and when regulatory changes are adopted. We believe that it makes more sense for NIH's focus at the present time to be on funding additional research examining the potential benefits and costs of single IRB use as suggested above.

Suggestions for alternate approaches:

As noted above, we strongly support the development and facilitation of sIRBs for some multi-site research. We also note that the use of external IRBs is not a new concept and there is an experience upon which to build. Most academic medical centers (AMC) have experience relying on an IRB at another AMC; these arrangements are often limited to no more than minimal risk research conducted at two or three sites. In addition, many AMCs have experience relying on commercial/independent IRBs for a select category of research—most often industry-sponsored and initiated, phase 3 and 4 multi-site research. What is new with the NIH Draft Policy is the inclusion of all NIH-funded multi-site research regardless of type of study or number of institutions.

Given the current evolution of sIRB models and the paucity of data regarding these models, we suggest a more tempered approach. Instead of broadly requiring a sIRB for any NIH-funded multi-site research, we propose refining the policy either to be limited (for now) to minimal risk research involving no more than several sites or, if it remains broad, to including a process whereby flexibility be built into the policy to account for various types of research and other specific factors more fully discussed above. In this way, use of a sIRB could be considered case-by-case before being required by NIH as a condition of funding.

We also suggest that NIH simultaneously fund research on existing sIRB models to evaluate potential benefits and costs for both the sIRB site as well as relying sites. This could include research focused at models that are currently reviewing NIH-funded research or NIH could also identify a cohort of clinical research for which the NIH will fund a sIRB and as a condition of grant award require research on the sIRB itself.

All of these approaches would inform the process going forward.

In addition, NIH could convene expert panels to focus on a number of sIRB-related issues; such as, developing criteria to identify research best reviewed by a sIRB; identifying the elements and resources needed to provide sIRB services within an AMC; and evaluating the pros and cons of various reliance models.

Finally, NIH could support the development of tools that could facilitate sIRB processes- this would include working with groups that have already begun to address some of these. Examples of tools include: Reliance Agreement templates, Standard Operating Procedures, approaches to HIPAA.

Thank you for the opportunity to provide comments on this draft guidance. Please contact us with any questions or requests for clarification. We are very interested in working with you to develop a successful future for sIRBs.

Best regards,

Ross Zafonte, DO

Earle P. and Ida S. Charlton Professor and Chair

Department of Physical Medicine and Rehabilitation

Harvard Medical School

Chief, Physical Medicine and Rehabilitation

Massachusetts General Hospital

Chief, Physical Medicine and Rehabilitation Brigham and Women's Hospital

Senior Vice President of Medical Affairs, Research and Education

Spaulding Rehabilitation Network

300 First Avenue, Charlestown, MA 02129

www.spauldingrehab.org

Comment #98

Commenter: Susan Regan

Date of comment: January 28, 2015

Comment:

Our IRB is sponsored by an agency that focuses on home and community based research, and virtually all of our studies involve participants who are vulnerable due to age, dementing illness, or social and cultural barriers. For this reason we frequently find that consent documents approved by other IRBs are not appropriate to the needs of participants at our site. Often such forms are aimed at a too advanced educational level or are too legalistic for our participants to understand. While we are very supportive of the goal of eliminating multiple reviews for multi-site studies, we would like to be assured that we would have, as a subsidiary site, the opportunity to amend consent forms that have been approved by the single IRB of record. It is not clear in the proposed draft if the reservation of the right to amend the consent document would require that our site receive an exception to the single IRB (we think that is not the best result), or whether we would have the opportunity, in the development of the IRB Authorization Agreement, to require amendment to consent documents as they affect participants at our site. We therefore would appreciate clarification of how the process would work in a way that preserves the benefits of single IRB review but also protects the particular participants in sites such as ours.

Comment #99

Commenter: Jennifer McArthur, DO

Date of comment: January 28, 2015

Comment:

I strongly support the efforts by the NIH to incentivize the use of Central IRBs. As a researcher involved in multi-site trials and an IRB member for several years, I have seen first-hand the inefficiencies involved in multiple IRBs reviewing the same study. It is frustrating to both researchers and IRB members. Multiple IRB reviews place undue burden and expense upon researchers, delays the start of trials and wastes valuable time in finding answers to important clinical questions that these trials are trying to answer. Furthermore, it does not add any further protection to research subjects. If anything, it provides less protection as local IRBs are reviewing SAEs in their institution's silo and without having access to the big picture across the entire landscape of the trial. This can cause problems covering the range of unnecessary panic to uneducated complacency.

You have described adequately the importance of having a mechanism by which local differences (local resources available to conduct the trial, local customs that may influence how the trial is viewed locally) must be taken into account by the central IRB. I applaud your efforts to break down this cumbersome and unnecessary barrier to conducting important research.

Comment #100

Commenter:

Date of Comment:

Comment:

SingleIRBpolicy@mail.nih.gov

Office of Clinical Research and Bioethics, Policy Office of Science Policy
6705 Rockledge Drive, Suite 750, Bethesda, MD 20992

Re: Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

In the context of research with human participants, the University of Virginia wholeheartedly agrees that policies and procedures which increase administrative burden without improving the protection of human subjects should be carefully reviewed, and where possible be modified, streamlined or eliminated.

Our researchers (and their staffs) have experience participating in the NCI CIRB and the NINDS NeuroNEXT and this favorable experience affirms the value of the proposed central IRB review system.

We do have some concerns and some comments on the proposed policy on the use of a single IRB for multi-site research.

One benefit of the present, local-review, approach is that researchers and their staff member develop an extensive experience base working with their local IRB. This benefit might be lost as these teams may need to acquire experience with multiple external IRBs which may be chosen to fill the central IRB role. There is no doubt that this shift from multiple IRBs to a single, central IRB will reduce the effort required at the IRB review and approval step, but this might be offset by an increase in effort required by the researchers and staff as they learn to prepare and submit documents to central IRBs.

Our research staffs also comment that an advantage of working with an institutional IRB is access to IRB staff. They express concern that such ease of access may be lost or decreased by a central system. A central IRB might not be in our time zone, for example, or be available on weekends.

We understand that the applicant will identify the single IRB at the time of application, and this suggests that this need not be the IRB of the applicant institution. The authority to approve the proposed IRB will rest with the funding NIH Institute or Center. We wonder if the evaluation of the proposed central IRB will be a criterion in the grant review. Specifically, if the proposed central IRB were not acceptable to the Institute or Center, would this be reason to withhold funding, or would the Institute or Center propose an alternative?

We suggest that a number of these concerns could be addressed if NIH Institutes and Centers maintained their own central IRBs which could function as central IRBs in a manner similar to that of the NCI.

Further we would suggest that the implementation procedures (the IRB Authorization Agreements) be simplified and standardized so that time is not lost negotiating complicated agreements for each new central-IRB study. Standard agreement language would be a substantial aid. The NIH role in the development of the Uniform Biological Material Transfer Agreement is an example of this leadership.

David Hudson

Associate Vice President for Research University of Virginia

Comment #101

Commenter:

Date of Comment:

Comment:

January 28, 2015

Office of Clinical Research and Bioethics Policy

Office of Science Policy

National Institutes of Health

Re: Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

(NOT-OD-15-026)

To whom it may concern:

I am writing on behalf of the University of Washington Human Research Protection Program, in response to your request for comments on the above-mentioned draft policy.

CONTEXT

The University of Washington is the leading research university in the Pacific Northwest. Our research portfolio exceeds \$1.4 billion per year in externally sponsored programs. The National Institutes of Health is one of our primary research sponsors. Our IRB is responsible for managing over 6,000 active human subjects research studies. Not surprisingly, given the size of our program, we have used central IRBs and reliance agreements for many years. For example, we have used WIRB for the review of all industry-sponsored trials since 2005. We also rely upon the NCI central IRB and the StrokeNet central IRB. Our experience with these arrangements and with our diverse portfolio is the basis for the comments and suggestion offered here.

COMMENTS

1. Time and effort to establish and implement a central IRB, and impact on study startup time.

The draft policy implies that a new central IRB will be established for each multi-site study. Significant time and effort is required to establish a central IRB as well as the agreements with the partner sites. In our experience, these activities require as much or more time than would have elapsed if each site had reviewed the study individually. We believe that the efficiencies associated with a central IRB will be realized only in situations involving the review of several studies at many of the same participating sites over time by the same central IRB. This leverages the time and effort to negotiate reliance agreements, SOPs, site-specific template consent language, infra-structure, and communication channels.

2. Differences among central IRBs.

Each central IRB develops its own SOPs, reliance agreements, infra-structure, and division of duties between the central IRB and the local sites. Among other factors, these reflect: (1) idiosyncratic institutional policies and practices; (2) applicable state laws; (3) guidance and requirements from legal counsel; (4) institutional compliance/administrative structure and philosophy; and (5) available (or not) supporting resources. Navigating these institutional differences and negotiating the relationship between the central IRB and local sites can require many months or more. The result: a widely-varying accumulation of different roles, responsibilities, and agreements that require each local institution and local investigator to spend valuable study start-up time to learn and navigate.

3. Cost of establishing and maintaining a central IRB.

The cost to an institution of establishing and operating a central IRB is significant. For most academic institutions (including ours), IRB costs are considered to be a component of the F&A rate on grants. It is not clear whether NIH would allow such institutions to establish a fee -based system (i.e., separate from F&A costs) for recovering the cost of central IRB review from participating sites and whether such fees could be included in the direct costs of grants. If not, the added cost of operating as a central IRB would be an unfunded mandate. The University of Washington has not been able to serve as a central IRB when approached in the past because establishing and operating the central IRB would be an additional, unrecovered, cost for which we do not have the resources.

Summary

The central IRB policy as currently articulated will result in more costs with little or no time savings for investigators if a central IRB must be established for each multi-site grant.

SUGGESTION

The University of Washington strongly agrees with NIH about the potential value of a central IRB policy. To realize this value, we believe it is necessary to keep the number of central IRB to a minimum and to allow a straight-forward mechanism for recovering costs. To maximize cost- effectiveness and efficiency for all parties involved, NIH might consider the following options that would provide a central IRB mechanism while still preserving an appropriate "firewall" between NIH as a research sponsor and the independent review of NIH-supported research:

- Funding the development and operations of a central IRB at an academic or other institution, to operate on behalf of NIH (or a specific Institute at NIH);
- Contracting with one or more accredited commercial IRBs that can scale up its operations;
- Contracting with an entity to establish and operate one or more NIH central IRBs.

We appreciate the opportunity to comment on this high-impact draft policy.

Sincerely,

Karen Moe, PhD
Director, Human Subjects Division
Assistant Vice Provost for Research

Comment #102

Commenter:

Date of Comment:

Comment:

Request for Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

Notice Number: NOT-OD-15-026

The **University of Florida** supports enhancing current policy that would allow for use of a single IRB. We also support supplementing existing policy by providing incentives and flexible examples (but not a prescriptive or exhaustive list) of a variety of single IRB structures for institutions to consider. However, as currently formulated, the NIH proposal to require a single “IRB of record” to be responsible for the regulatory oversight of all Multi-Site NIH funded research, while reflecting a positive intention, would have unintended adverse consequences for important biomedical research, particularly with its mandatory application to all NIH research projects that involve human subjects.

The University of Florida has had a voluntary agreement with the Western IRB (WIRB) for over 17 years to serve as our IRB of record for certain industry sponsored protocols. Significant time and effort was required to establish agreements and processes to bridge between WIRB and UF. Local input guidance was established, annual WIRB meetings are attended by UF staff, etc. Having to establish this rapport with a different “IRB of Record” for each NIH funded study will be a continual, time and dollar consuming effort.

A voluntary “market-driven” approach, encouraging use of a single IRB through incentives when that would be most efficient for research costs and schedule, would better achieve the efficiency and quality-driven purposes of the proposal. Although there are circumstances when a single IRB can reduce duplication of effort and delays, while also performing to high quality standards, this is not the case in all research endeavors that involve human subjects.

The establishment and ongoing use of a single IRB for multiple sites requires a significant up front and ongoing investment of time and resources by all involved institutions. All institutions involved must determine the expertise of the proposed IRB and the compatibility of its processes and policies with those of the participating institutions. Systems for coordinating administrative and compliance processes must also be developed and agreed upon. All institutions must then negotiate and accept the terms of a legal agreement with the IRB institution, without creating inconsistencies among these agreements that would create conflicting obligations, and inefficiencies and problems, for the single IRB and its institution. These agreements must also allocate responsibilities and liabilities and address many other administrative matters. The more institutions, the greater the task, but these inter-institutional agreements alone can take many months to complete and their terms will need to vary according to local law. These substantial single IRB-associated start up burdens on projects are real, and they are in addition to the other start-up costs, discussed below, that will be incurred whether there is a single IRB or not. IRB review will still be needed, of course, even if it is through one IRB, and as discussed below, local IRBs will still be involved. These up front endeavors take substantial time. While a single IRB will make sense in some situations, in others, mandating single IRBs will cause projects to incur greater delays than going through the IRB process at several institutions or will merely substitute one cause of delay (i.e. single IRB start up) for another unnecessary duplicative review).

Mandating a single “IRB of record” for **every** multi-site protocol, or even for every project where the same protocol is used to collect data from multiple sites, would create a chaotic system. Each institution

would need to administer and try to comply with the requirements of multiple “IRB’s of Record,” depending on the number of multi-site protocols they participate in. Managing this could quickly become an immense administrative undertaking for institutions with a significant research volume, demanding manpower and other resources that are disproportionate to the benefits gained. At its worst, a site with inadequate experience and infrastructure, or with inadequate understanding of the participating institutions and their investigators and support systems, could be tasked with overseeing a multi-site protocol, while lacking the ability necessary to adequately oversee it. Evaluating experience, compatibility and resources can be difficult or impossible in advance of institutions and research teams having extensive experience working together.

Even with a single IRB, each participating institution on a project would need to retain certain mandatory local responsibilities, including monitoring of compliance, response to adverse incidents and breaches; application of state law requirements and local standards of care, etc., that only its local IRB can perform. Only a local institution will know its investigators’ capabilities and reliability for certain types of responsibilities, which is critical factor in developing appropriate protocols. Other common IRB responsibilities, while not required by NIH to be performed by the IRB, include customary use of IRBs to coordinate a variety of important compliance obligations efficiently. IRBs are often used for this purpose because, in performing their mandatory duties, IRBs gain the full breadth of detailed factual and contextual information about the research project, the investigators and the subjects, that no other single body at the institution usually has. This information is necessary to facilitate the proper handling of a variety of compliance obligations. If IRBs do not have this information, other costly and time consuming methods of gathering the information and facilitating compliance would be needed. This would merely shift burdens on research, and likely increase such burdens, not reduce them.

The implication that the use of a single IRB will eliminate or greatly reduce delays and unnecessary costs in initiating research in every project involving human subjects, or even in every project where the similar data are collected from multiple sites under a single protocol is unfounded. The steps involved when coordinating a multi- site project, regardless of the number of IRBs involved, include establishing the local principal investigator (PI) and study team, contracting with the site, addressing any conflicts of interest (both PI and institutional), and establishing and resolving billing issues, privacy issues, radiation safety issues and biosafety issues, in addition to review by the IRB. These matters must be addressed in any event and contribute significantly to start up costs of human subjects research.

Where, among other factors, the combination of

- the frequency or expected lengthy period of work among particular institutions and particular research teams will provide necessary experience with and information about all participating institutions, their researchers and the capability of the proposed central IRB—and will allow initial up front investments to be recouped over the period of joint research,
- the compatibility of administrative processes and ability to confirm compatible standards among institutions will make joint operations feasible, and
- the need to follow a single protocol to collect the same data from multiple sites in a long-running project, and other factors, make the scope of work by a central IRB manageable, provide real opportunities for efficiency and make the up front and ongoing investment in a single IRB worthwhile, institutions could be incentivized by NIH to use a single IRB.

However, unless the lost efficiency in management of a variety of compliance obligations and the upfront costs and unavoidable delays in establishing a single IRB are offset by associated savings, there will be increased burdens and inefficiencies for the research endeavor. Incentives for institutions to evaluate the circumstances and use a single IRB when most efficient, will yield better results.

It is also important to provide significant time for institutions to explore when single IRBs really do make sense and experiment with different approaches/models. This requires a policy that is flexible and based on market incentives for voluntary participation. It may make sense to use a well constructed and succinct survey to gather data from voluntary participants to determine the benefits and detriments of single IRBs and to begin to demonstrate the factors that determine when they are useful and when they are not useful. These data could be de-identified and shared to encourage use of single IRBs in the appropriate situations.

Additional Discussion and Issues with Proposal:

Even if the upfront contracting, coordination, and compliance burdens are not disproportionate to the benefits realized, there are a number of practical challenges that need to be addressed. Again, the resources and time needed to address these challenges must be worthwhile in relation to benefits obtained. There also needs to be a source to fund the efforts needed to establish and operate a central IRB. While the proposed policy indicates the ability to direct charge these costs, which is appreciated, it is unclear that the objective is full funding of all associated costs.

1. Some local review will be required in any event; this was confirmed directly by Dr. Menikoff, the Director of OHRP during a PRIM&R AER 2014 session with OHRP. To be effective in duties remaining with each local IRB, each IRB needs to have a thorough understanding of the project and individuals involved, which can only be obtained by either duplicating the central IRB's review (at least in part) or having at least some members of the local IRBs participate on the central IRB when that is feasible. Who will conduct the review of that local input was not addressed. To be clear, important local issues can include:
 - a. Issues related to the competencies and work styles of the local PI and study staff, as well as the nature and robustness of local support capabilities and systems, which widely vary both within a single institution and among different institutions, and are crucial to the development of appropriate protocols
 - b. Any state laws or regulations, and institutional policies (i.e. state laws on pregnant minors, subject compensation, legally authorized representatives)
 - c. Sovereign immunity for state institutions
 - d. Local standards of care
 - e. Descriptions of where the study is being conducted, who to call if there are regulatory concerns
 - f. Drug or device formulary issues (the drug in question may be on one formulary and thus available, but not on another which could result in an added cost)
 - g. Conflicts of Interest (both the PI and institutional)
2. Systems, including those listed below will need to be established to record and track the numerous C-IRB's governing various protocols:
 - a. Submission software
 - b. Tracking
 - i. Approval status
 - ii. AE\Unanticipated results
 - iii. Continuing review requirement
 - iv. IAAs and any additional legal services

3. Some process needs to be in place to evaluate the IRB of record before a local site would agree to participate:
 - a. What is their current status with OHRP?
 - b. Have they been an IRB of record in the past?
 - c. What systems and staff are in place to support their status as the IRB of record?
 - d. Will their approach be compatible with the local context and requirements?
 - e. How will the local IRB obtain the depth of knowledge to competently perform retained
 - f. responsibilities?
 - g. Is adequate insurance and/or sovereign immunity available to address risks assumed by the central IRB, including when projects involve both immune and non-immune institutions?
4. Processes must be available to communicate to study staff, and in some cases the local IRB regarding revisions, serious local adverse events, suspensions, closures, etc.
5. Significant investment will be necessary to administer projects under a large number of different IRBs for institutions participating in many multi-site projects.

Recommendations to the NIH:

1. The NIH should structure a market-driven, voluntary regime and require that IRBs be registered with the NIH and provide central NIH repository information to support informed decision-making by demonstrating their level of capability to provide central “IRB of Record” services; !HRPP accreditation should neither be required nor would it be sufficient since such accreditation does not consider “IRB of Record” needs; Minimum information to demonstrate level of capability should include:
 - a. Consistency of the IRB’s policies and procedures with guidelines that NIH and the research community could collaborate to develop
 - b. Experience of the IRB serving as a central IRB for other multi-site protocols or demonstrated readiness to do so (with indicia being developed by NIH collaboratively with the research community)
 - c. Whether the IRB has significant outstanding or recent FDA, OHRP, or OCR violations and the nature of those violations
 - d. Availability of an on line submission process with access provided to the local IRB’s to review documents
 - e. Compliance of electronic transmissions, data storage, etc. with customary security standards.
 - f. Availability of data feeds (protocol numbers, approval dates, etc.) to allow for tracking by companion IRBs.
 - g. Availability of a DSMB for all studies, with reports sent to all sites
 - h. How local IRBs will be able to provide input to the IRB of record regarding the status of the local research team
 - i. Availability of video conferencing to connect local IRB representatives into the “IRB of Record’s”
 - j. Meeting during the discussion of the protocol in question. How this would be structured to allow the participating sites to voice any concerns and potentially have them incorporated with the “IRB of Record’s” review. For example, would the local IRB representatives have

voting rights or serve as ad-hoc consultants to the “IRB of Record” which is allowed under the federal regulations.

2. NIH’s work with the research community to develop some sample (not mandatory) clauses for frequent terms in inter-institutional agreements could aid in the negotiation of agreements and help to improve the efficiency of a central IRB system. However, it must be recognized that state laws governing contracts differ, certain provisions that public and private institutions can agree to differ (e.g., state institutions are often prohibited or limited in providing indemnities, public records requirements will apply to public institutions), insurance provisions and availability of sovereign immunity differ, and costs to negotiate these agreements are unavoidable. NIH should require, however, that the IRB of Record takes sole responsibility that the protocol has been approved according to all required regulatory bodies (with the exception of the local addenda governing matters for which the local IRBs retain explicit responsibility). Reporting serious or continuing non-compliance by a local investigator should be the responsibility of the local institution.
3. The “IRB of Record” should approve the core consent form, which describes the procedures, risks and benefits in a standardized consent form template as determined by the NIH. Local IRBs should complete an addendum to the consent that contains sections addressing local issues. The local consents addendums should be signed off by the local IRB, and must be submitted to the “IRB of Record” prior to their meeting date.
4. The IRB of Record should serve as the Privacy Board for all sites, at least as to a defined universe of federal privacy requirements.
5. The Human Use of Radioisotopes and Radiation Committee (HURRC), and local billing issues should be addressed locally and be included in the local consent addendum; this is an unavoidable cost.
6. Clinical Trials.gov requirements should be the responsibility of the primary awarded institution.

The concept of the proposed mandatory “IRB of Record” to function as the regulatory oversight on all multi-site NIH funded research is well intended to minimize duplication in the current system. However, some duplication will be necessary to meet local requirements. Careful consideration must be given to the many other time- consuming efforts involved in initiating a human subject’s trial at various research sites, and to the significant infrastructure that would need to be created at each participating institution. We would welcome the opportunity for local experienced individuals at the University of Florida to participate in further communications with NIH to further develop a worthwhile central IRB regime and to address other issues that delay the initiation of human research protocols.

Comment #103

Commenter:

Date of Comment:

Comment:

January 28, 2015

Office of Clinical Research and Bioethics Policy

Office of Science Policy, NIH

Email: SingleIRBPolicy@mail.nih.gov

Dear Comment Review Board:

The Council on Governmental Relations (COGR) is an association of 190 research universities, and their affiliated academic medical centers and research institutes. COGR concerns itself with the influence of federal regulations, policies, and practices on the performance of research conducted at its member institutions.

We appreciate the opportunity to provide our comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research (NOT-OD-15-026) and understand, although not stated in the draft guidance, that this applies only to multi-site research with a single protocol. While we recognize the need to reduce regulatory burden and support efforts to make IRB processes more efficient, we are concerned that the proposed policy as currently written will create new burdens for institutions conducting NIH-supported human research and would be very hard for our member institutions to accommodate in such a short timeframe.

For several years, many of our University members have embraced the use of single IRBs (e.g., Western IRB [WIRB], NCI CIRB, the Hutchinson Center's Cancer Immunotherapy Trials Network [CITN] single IRB, NeuroNEXT, and StrokeNet), but it took many years and great effort for our members to obtain the support of their institutional leadership and to implement the new processes required. The draft guidance as currently written does not recognize the amount of time and effort it will take to get all NIH-funded institutions to adopt this approach, nor the effort it takes to develop and negotiate agreements with multiple clinical sites, each with its own policies and procedures, regulations, and institutional systems.

Our member institutions that have experience with single IRB review models have learned that it can be a good investment and can save time when there are multiple studies planned for the same participating sites, but it can be time consuming and expensive when used for only a single study. This is particularly true for institutions that utilize information management systems that need to be customized to allow for local review by ancillary committees such as investigational drug services, radiation safety review, and institutional biosafety committee review of gene therapies. Generally, reliance on an external IRB does not save administrative costs to our institutions, but rather shifts resources from supporting internal IRBs to managing the external relationships and reporting requirements.

Some of our member schools with no experience ceding IRB review have echoed the above concerns about electronic systems and the ancillary review process. In support of having a local IRB, many member schools cite institutional culture as an important consideration. A central IRB may not have, or be aware of, certain values and norms that can help guide decisions. Further, a local IRB contact often proves critical, particularly when sites span the nation and are several time zones away from the IRB of record. For smaller institutions, the extra administrative burden of external reporting and responding to audits might prohibit participation in multi-site trials.

While we appreciate that the proposed policy indicates that the costs of using a fee-based IRB can be included as a direct cost of a grant, the majority of academic institutions already include the cost of operating IRBs in the Administration component (capped at 26% since 1991) of their Facilities and Administrative cost rate. Therefore, for academic institutions, the added cost of operating as the single IRB of Record will be yet another unfunded mandate with zero cost savings due to the added burden of communicating between IRBs and monitoring compliance of unknown entities. The net result will be more costs with little or no time-savings for investigators when new reliance agreements need to be established.

While we endorse the concept of a single IRB review of multi-site studies and the goal to accelerate timeliness and reduce duplicative processes, we urge you to move us towards this goal by encouraging the use of a single IRB for certain types of multi-site clinical trials (e.g., those that can follow the NCI model or other established models) rather than to mandate this for all NIH-funded multi-site studies.

With the vast amount of research that has been done over the years suggesting models for IRB improvements, some currently in practice or being piloted, we believe that other efforts can be made to streamline IRB review with minimal cost impact to our members. We believe that with more emphasis on education regarding IRB reliance agreements, a concerted effort towards change management, i.e., changing from a from culture fed by fear of non-compliance or legal liability, combined with efforts of the NIH to pilot the NCI model with other NIH institutes will be a more productive course of action. In addition, we caution against any policy implementation prior to clarification of the status of the ANPRM regarding human research; as it will be costly for our members to implement and operationalize regulatory change in a piecemeal approach.

Thank you for the opportunity to comment.

Sincerely,

Anthony P. DeCrappeo
President

Comment #104

Commenter:

Date of Comment:

Comment:

January 26, 2015

National Institutes of Health
Office of Clinical Research and Bioethics Policy Office of Science Policy
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Re: NOT-OD-15-026; Draft policy to promote the use of a single IRB of record

The Orthopaedic Research Society (ORS), representing over 2,900 researchers in the field of musculoskeletal science, welcomes the opportunity to respond to the draft policy from the National Institutes of Health (NIH). We appreciate the efforts that the NIH has made in reaching out to the society's membership, and we hope that the comments that we are contributing are helpful.

This response was prepared on behalf of the ORS by Jennifer Racine, MBA and members of the ORS Clinical Research Committee including Kurt P. Spindler, MD, Chair, Roy K. Aaron, MD, Saam Morshed, MD, George F. Muschler, MD, Kristy L. Weber, MD, Michael J. Yaszemski, MD, PhD, and Theodore Miclau, MD

This draft Policy proposes that NIH funded institutions will be "expected to use a single IRB of record for domestic sites of multisite studies unless there is justification for an exception." We would like to address this opportunity in support of it.

Response:

Many orthopaedic surgeons and clinical research centers participate in and lead multicenter clinical research. We strongly support the use of a single IRB process in light of the enormous time and expense wasted on multiple pending institutions' human subjects' protection committees, in effect, duplicating, and sometimes triplicating the same work. There are times we must wait up to 3-6 months while IRB applications are bounced between various academic institutions and then government funding sources. For example, the MOON study has 7 IRBs, while the MARS study has 51. The amount of effort, time, and money spent on IRBs alone is enormous and adds nothing to research.

NIH Exception Rule:

"Exceptions will be allowed only if the designated single IRB is unable to meet the needs of specific populations or where local IRB review is required by federal, tribal, or state laws or regulations. Assuring that local perspectives are addressed, the assessment of a study's risks and benefits and the adequacy of the informed consent should not generally require the perspective of a local IRB. Local contextual issues relevant to most studies (e.g., investigator competence and site suitability) can be addressed through mechanisms other than local IRB review, such as the involvement of ad hoc members or consultants with the necessary specialized knowledge or expertise or by submission of information by the individual site(s). Even when certain vulnerable populations are targeted for recruitment, such alternative approaches may be appropriate."

Response:

Equal access to research studies would have to be assured to prevent disparities in participation

when considering the individuality of each center.

Sincerely,

Mary B. Goldring, PhD
President, ORS

Kurt P. Spindler, MD
Chair, ORS Clinical Research Committee

cc:

Roy K. Aaron, MD

Saam Morshed, MD

George F. Muschler, MD

Kristy L. Weber, MD

Michael J. Yaszemski, MD, PhD.

Theodore Miclau, MD

Jennifer Racine, MBA

Brenda A. Frederick, Executive Director, ORS

Comment #105

Commenter: Margherita Fontana, DDS, PhD

Date of comment: January 28, 2015

Comment:

I am the PI of a multisite clinical study (Predicting Caries Risk in Underserved Toddlers in Primary Healthcare Settings, 1U01DE021412-01A1), and as such would like to write to offer my strong support to this draft policy. The amount of time and effort at all 4 sites involved in our study, including the DCC, that has been spent to develop materials suitable to all 4 involved IRB's, and ensure continuous communications between each site and its IRB, and then between each site with the DCC regarding IRB related matters has been enormous (and thus extremely costly). The process would be greatly enhanced, and would be much more efficient, by using a single IRB. In addition to the time saved for applications, amendments, etc., and the IRBs boards' review time, it would ensure all sites involved (especially the DCC) are aware of all IRB communications. Additionally, each site IRB has unique policies, titles for documents, times for reviews and amendments, etc. The single IRB would streamline processes, documents, approvals and use a universal language which all could easily understand.

However, I think implementation may be difficult unless some changes are made to the draft policy. In my experience academic institutions' IRBs are not used to functioning in this matter, and in fact many do not offer this option, which is probably why this is not being taken advantage off already. I am afraid that unless the policy includes some provision to ensure IRBs associated with funded studies are willing to serve as a single IRB, that this may become an added burden to investigators to try to figure out. In addition, I can easily see the scenario were IRB's forced to move to this new model would start charging significant fees to serve as a single IRB for these studies, which when added to the direct costs of funded studies may significantly impact the amount of science to be carried out. These costs should come from indirect costs associated with the study.

Comment #106

Commenter: Human Subjects Protection Branch (HSPB), Walter Reed Army Institute of Research (WRAIR), 503 Robert Grant Avenue, Silver Spring, Maryland 20910-7500

Date of comment: January 28, 2015

Comment:

1. The draft policy states that this policy will only be applicable for domestic studies. As many multi-site studies involve both domestic and international sites and/or partnerships, the policy will have international implications.
 - How does NIH plan to address this requirement when a study involves both domestic and international sites?
2. We understand that the goal of permitting use of a single IRB is to enhance and streamline the process of IRB review for multisite studies. But no data are provided to support that this approach will decrease time to approval. IRBs often find that for the bulk of the approval time, the protocol is with the Investigator or the sponsor, not with the IRB. Moreover, the literature referenced in the draft policy is outdated and only presents one perspective (NCI), not those of institutions carrying out research or performing IRB reviews and the challenges faced with regard to incomplete protocol submissions or poorly written protocols.
 - So, please clarify how the IRB review time will be reduced and in which phase of the review process such decrease may or will occur?
 - What is the supporting evidence?
 - Were there any studies done exploring this issue?
3. What does “Multi-site” mean in the context of this draft policy? Does this mean physical locations where subjects are located or does this mean multiple collaborators from more than one institution?
4. No data are provided to address how safety of subjects will or will not be impacted by this policy. The Policy simply states that there is no evidence that multiple IRB reviews better protect subjects. On the other hand, there is no converse evidence that multiple IRB reviews do not. Permitting use of a single IRB may enhance and streamline the process of IRB review for multisite studies, so that research can proceed efficiently. It is, however, important to ensure use of a single IRB does not compromise ethical principles and protections. How does NIH plan to ensure that?
5. The draft policy states that the funding NIH institute or center has the final decision authority for selecting the single IRB. All IRBs are not created equal. Currently, at the WRAIR, this is approached based on PI location, subject/patient location, funding, IRB’s expertise, etc. It seems that without additional information, research teams will “shop” for the fastest IRB, not necessarily taking into account other considerations. From the draft policy, it is not clear how a single IRB will be selected.
 - Will the NIH issue minimum requirements for the “IRB of record” to have in order to serve in that capacity?
 - Who within the funding NIH Institute or Center will be responsible for approving the selected single reviewing IRB? What factors will determine approval or denial?
6. The draft policy states that some commenters were concerned that a single IRB could lead to increased liability and diminished accountability for participating sites, and decreased consideration of local context. While a single IRB may save time and more cost effective, it could also lead to increased workload for the single IRB, thus leading to decreased consideration of local context and less accountability. The activities that are carried on at the sites might not be as easily tracked as

- when there was an IRB overseeing that site. So if these are in fact concerns, then the operating procedures that are followed need to address these issues and ensure that they don't happen.
7. Reliance is about communication. University systems with multiple IRBs often cannot communicate effectively amongst themselves, let alone with an outside organization. Will the NIH be providing communication plan SOP templates to ensure the IRB of record communicates to other organizations in real time?
 8. We have found that reliance on other IRBs does not always save time or effort for the IRB Administrative office. In fact, the workload simply shifts to the IRB offices, as opposed to the IRB itself. Besides, an in-house IRB may be reluctant to assume review and approval responsibility for multiple sites. Unless the IRB of record is a commercial entity, the added work for an IRB may be counterproductive to achieving the stated goals of this policy. We envision institutions issuing pre-submission requirements (local regulatory review) prior to entering into a deferral agreement. This has occurred with the use of the NCI and Neuronext review boards and therefore does not reduce time to approval if that is intent of this policy.
 - How does NIH plan to address resource issues for the IRB of Record (who will now be charged with the oversight of all sites) and also the extra burden on the IRB offices?
 9. This policy takes "institutional" out of IRB. This promotes the use of central, fee for service (for profit) IRBs. The policy states that ..."If this approach is taken, the participating site should expect to bear the cost of the additional review." Aren't they already doing so, unless fee for service IRB is in play?
 10. In relation to item 9 above, institutions often have their own local policies that usually impact the institution's human subjects protection policies and procedures. How does NIH plan to harmonize the different requirements originated from different institutional policies and local practices, so as to ensure the single IRB's approval of a protocol is consistent with local policies?
 11. IRBs are responsible for monitoring (See 45 CFR 46 and 21 CFR 56.), how will this function be upheld if they are reviewing on behalf of another institution? How does NIH ensure the local context factors are adequately considered?
 12. It would have been helpful for the NIH to provide more specific procedural guidance on how to facilitate implementation of this policy with the issuance of the draft policy. The policy sounds good in theory, but it would be helpful to see the procedural guidance as to how this policy will be operationalized.
 13. The draft policy states that compliance with this Policy will be a term and condition in the Notice of Award and a contract requirement in the Contract Award. This statement seems to contradict another statement in the draft policy, "the policy does not prohibit any participating site from carrying out its own IRB review." In addition, the use of the word "expectation" in the statement, "Exceptions to the expectation to use a single IRB may be made with appropriate justification" can be interpreted to indicate that the policy is optional.
 14. Obtaining IRB Authorization Agreements from multiple site IRBs could be a time consuming process and hinder the NIH's goals of enhancing and streamlining the IRB review process. I would hope that an IRB would review a protocol prior to agreeing to defer review and approval to a commercial IRB or an IRB at another site. The deferring IRB will need to update its FWA application agreement naming the IRB of record as the reviewer of a particular study, is this correct?
 15. The draft policy states that the effective date will also apply to intramural multi-site studies submitted for initial review after that date. It is unclear what this means. If the project is already approved for funding, will this policy apply? Will these projects not have grandfather status?

16. The following statement in the draft policy appears to be open-ended items that need more consideration: "As necessary, mechanisms should be established to enable the single IRB of record to consider local context issues during its deliberations."

- What entity will establish these mechanisms?
- How will the local context issues be made known to the IRB of record?

Comment #107

Commenter:

Date of Comment:

Comment:

January 27, 2015

Office of Clinical Research and Bioethics Policy

Office of Science Policy

National Institutes of Health

6705 Rockledge Drive, Suite 750

Bethesda, MD 20892

SingleIRBpolicy@mail.nih.gov

Subject: Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

Dear Madam/Sir,

The aging cohort of 78 million baby boomers remains an important catalyst that has influenced a re-engineering process of the broader national biomedical research infrastructure towards the concepts of “disease prevention”. To this end, the recent “Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research (NOT-OD-15-026),” represents one critical step forward in this overall effort. The National Biomedical Research Ethics Council, the Campaign to Prevent Alzheimer’s by 2020, the Alzheimer’s Association, the Alzheimer’s Drug Discovery Foundation, the Alzheimer’s Disease Cooperative Study, Canadian Consortium on Neurodegeneration of Aging, and the Imaging Dementia—Evidence for Amyloid Scanning Study applaud and support the efforts of the Office of Clinical Research and Bioethics Policy, Office of Science Policy, NIH. The undersigned offer the following comments.

The growing burden of disorders that impair memory, movement, and mood is a significant threat to our nation’s public health. There is an urgent need for new technologies to detect diseases at the very earliest stages, often before symptoms first emerge. There also is the competing and ever-pressing need to develop effective interventions that may delay, halt or ultimately prevent the onset of these conditions. Yet, the achievement of these national priorities is hampered by many inherent problems in our current research systems.

One example is the conduct of clinical trials among persons with symptomatic Alzheimer’s disease. As is true for other chronic diseases, these investigations are often complex and difficult for local IRBs who lack the specific disease expertise. Within related symptomatic trials, the difficulties are compounded by methodological enhancements necessitating larger and longer studies. Additional complications arise from the need to recruit from dozens of sites that inevitably increases the variability in local IRB quality. This situation greatly diminishes the quality of the ethics reviews and certainly reduces the efficiency of initiating a trial.

There are also two specific problems in the conduct of multisite research specifically aimed at prevention. For many chronic diseases, such as Alzheimer’s, Parkinson’s and Huntington’s, the high cost for clinical trials and the lack of appropriate research infrastructure represent huge obstacles for advancement. Even more so than current clinical trials for symptomatic treatments, prevention trials require the need for long follow-up periods, recruitment of large numbers of volunteers (i.e., in excess of 5,000 persons), and highly stratified samples of research volunteers spanning from the general population to tertiary care. Another important challenge for prevention research is the need to discover and validate new technologies, tools, and biomarkers for early detection of the disease in the

asymptomatic stages. This objective has led many to contemplate the creation of large hybrid clinical-population databases and national registries comprised of research volunteers from many different geographical, age groups, ethnic, gender and socio-economic strata.

In addition, there is growing global acceptance of the concept to establish transnational institutional review boards for neurodegenerative diseases and other chronic conditions. Internationally, governments, patient advocacy groups, trial sponsors, and the research community recognize that centralized IRBs as one of the most practical and achievable solutions to improve volunteer participation in biomedical research and speed development of new interventions and diagnostics. Especially for rare diseases, such as frontotemporal degeneration, progressive supranuclear palsy or Huntington disease, to name but a few, international collaboration is essential to ensure sufficient power to conduct definitive efficacy trials.

NIH's interest in the use of single IRBs for multi-site research coincides with recognition by many, including NIH, that the current system where complex and large multi-center trials are overseen by local (decentralized) IRBs is outmoded. The draft policy recommendation is an important step toward fixing the time consuming delays and the increased possibility for ethical oversight problems currently encountered in research. The undersigned commend NIH's draft policy initiative as a means to:

1. Enhance volunteer safety in biomedical research
2. Increase the efficiency for clinical trials
3. Provide an important pathway to advance international prevention research

From a practical point of view, NIH support for central IRBs for multicenter studies ultimately will be cost neutral for the NIH because of the enhanced efficiency with which trials can be initiated and monitored.

The undersigned encourage NIH to state clearly "that patient and research volunteer safety is the penultimate mission for research ethics review." As a bedrock principle of the final policy statement, the undersigned request that the historical background be amended to briefly include notable historical examples of research ethics abuses. Such an inclusion will serve as a vivid reminder to all involved in research—particularly newly minted centralized IRBs.

The undersigned recommend that the final policy statement acknowledge that chronic, debilitating diseases are among the most important threats to public health. The "failures of our success" now points to many individuals living longer with debilitating diseases. Today, disease morbidity exacts crippling emotional expenditures and increasing healthcare costs that magnify the need to develop new interventions. However, the recruitment for volunteers for randomized clinical is becoming more difficult. For low prevalence diseases, the sampling frames require larger geographical areas and larger number of sites. For orphan drug development, this reality is more acute. Often this problem presents as a disincentive to research and as an insurmountable obstacles for trial sponsors.

The undersigned believe that NIH's draft policy guidance will influence international development and advancement of prevention research. The new policy will increase the probability of the discovery of new classes of disease prevention-interventions, the validation of instruments for disease diagnosis/assessment/ monitoring, and for the development of new, robust systems to obtain macro- and micro-health economic data. The policy guidance, once finalized, will enable U.S.-based researchers to attract even greater numbers of international collaborators and set the stage for future international harmonization standards on research integrity and ethics.

Given the public health challenges posed by Alzheimer's disease, neurodegenerative conditions that affect memory, movement and mood, and other chronic diseases the establishment of single institutional review board for multi-site research is welcomed. The undersigned affirm that the

development of national IRBs for chronic diseases will significantly alter the therapy-development landscape and expand public health efforts to control and ultimately prevent many debilitating and disabling conditions.

Respectfully,

Ara S. Khachaturian

Chair and Interim President, National Biomedical Research Ethics Council
Executive Editor, Alzheimer's & Dementia
Email: adj_xed@kra.net

Maria Carrillo

Trustee, National Biomedical Research Ethics Council
Chief Science Officer, Medical & Scientific Relations, Alzheimer's Association

David S. Knopman

Trustee, National Biomedical Research Ethics Council
Professor of Neurology, Mayo Clinic College of Medicine and Consultant in Neurology,
Mayo Clinic

Peter J. Snyder

Trustee, National Biomedical Research Ethics Council
Senior Vice-President and Chief Research Officer, Lifespan Hospital System
Professor of Neurology, Alpert Medical School of Brown University

Howard Fillit

Founding Executive Director and Chief Science Officer, The Alzheimer's Drug Discovery Foundation
Clinical Professor of Geriatric Medicine, Palliative Care, and Neuroscience,
The Ichan School of Medicine at Mount Sinai
Physician, The Rockefeller University Hospital

Zaven S. Khachaturian

President, Campaign to Prevent Alzheimer's by 2020 Editor-in-Chief, Alzheimer's & Dementia

Paul Aisen

Director, Alzheimer's Disease Cooperative Study Professor of Neurosciences, UCSD

Serge Gauthier

Chair, Ethical, legal and social implications Committee, Canadian Consortium on Neurodegeneration of Aging

Director, AD Research Unit, McGill University Research Centre for Studies in Aging

Gil Rabinovici

Associate Professor in Neurology, University of California, San Francisco (UCSF)
Study Chair, Imaging Dementia Evidence for Amyloid Scanning Study

Incorporated as a 501c(3) non-profit corporation on August 27, 2012, National Biomedical Research Ethics Council (NBREC), has lead the establishment for a central, national institutional review board for human research of neurodegenerative and other chronic diseases. The twin mission of NBREC is to enhance the protection of human volunteers in clinical research and to increase the efficiency of initiating large multi-center studies. In this way, NBREC aims to help accelerate the development of safe and effective novel diagnostics and therapeutics for many devastating illnesses.

Comment #108

Commenter:

Date of Comment:

Comment:

January 28, 2015

Office of Clinical Research and Bioethics Policy
Office of Science Policy, National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Via Electronic Submission to: SingleIRBpolicy@mail.nih.gov

RE: Notice Number: NOT-OD-15-026

Dear NIH Clinical Research and Bioethics Policy Team:

The American Society of Hematology (ASH) appreciates this opportunity to comment on the National Institutes of Health's (NIH) Draft Policy to promote the use of a single Institutional Review Board (IRB) of record for domestic sites of multi-site clinical studies funded by NIH (NOT-OD-15-026).

ASH represents over 15,000 clinicians and scientists committed to the study and treatment of blood and blood-related diseases. Our members strongly believe that the protection of human subjects must be a top priority. At the same time, inefficiencies in the oversight and review of clinical research can slow clinical innovation and increase costs without necessarily enhancing protections for individual subjects. ASH previously submitted comments to the Department of Health and Human Services (HHS) supporting the streamlining of IRB review of multi-site studies. In the same spirit, ASH applauds the efforts made in the Draft Policy to promote the use of single IRBs for multi-site studies receiving NIH funding.

As noted in the Draft Policy, a substantial amount of human subject clinical research is performed in multi-site studies. Both HHS and Food and Drug Administration (FDA) regulations allow participating institutions to forego the stand and use of local IRBs in favor of joint review, review by another qualified IRB, or establishing other arrangements. However, utilization of a single IRB to review multi-site research is currently not required, and many institutions are reluctant to relinquish review by their local IRB.

As such, it is common for local IRBs at each institution in a multi-site trial to independently review the research protocol, informed consent documents, and other materials - sometimes resulting in hundreds of reviews for a single study. Further, if any of the local IRBs require changes to the research protocol adopted for the study, investigators must resubmit the revised protocol to all of the reviewing IRBs. This process can be lengthy and burdensome, significantly delaying the initiation of clinical studies and, ultimately, the translation of biomedical research discoveries into therapies and treatments for patients with debilitating or life-threatening diseases.

The future of hematology requires that research in diverse areas of basic and clinical science be expeditiously translated into novel, decisive therapies that will effectively prevent and treat serious diseases. This requires human clinical trials and, in many cases, the research goals are enhanced by enrolling patients at multiple sites. A single IRB for multi-site trials will ease regulatory and administrative burdens and increase the harmonization of such trials, thus increasing patient access to promising treatments. Expecting all institutions participating in a multi-site study to rely on a single designated IRB as a condition of receiving a funding award is a much-needed step toward making the

review process more efficient.

There may be exceptional circumstances in which local IRBs are needed, such as when a designated single IRB is unable to meet the needs of specific populations, or where local IRB review is required by federal, tribal, or state regulations. In these cases, the Draft Policy rightly allows institutions to provide appropriate justifications for an exception. In addition, local IRB review is not prohibited by the Draft Policy; rather, the individual institution must simply bear the full cost of performing the review. This important distinction will give flexibility and autonomy to individual institutions while promoting a change in the overall culture of IRB use.

ASH is happy to provide further information and be a resource for the Office of Clinical Research and Bioethics Policy and the NIH. Please contact ASH Legislative Advocacy Manager Tracy Roades at 202-776-0544 or trodes@hematology.org if you have any questions or would like any additional information.

Sincerely,

David A. Williams, MD President

Comment #109

Commenter: Jonathan E. Miller

Date of comment: January 28, 2015

Comment:

We appreciate the opportunity to comment on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research.

In our experience, much of the time involved in the startup of IRB reliance arrangements is spent negotiating the agreement between the reviewing IRB and relying institution(s). As such, it would be helpful if a more robust template agreement were provided that delineates responsibilities (IRB versus institutional), and assigns institutional responsibilities to either the reviewing or relying institution. Institutions should have the flexibility to revise the template agreement and the assignment of institutional responsibilities as needed. However, beginning the discussions with a more comprehensive template agreement would make these negotiations more efficient.

Comment #110

Commenter:

Date of Comment:

Comment:

January 28, 2015

Office of Clinical Research and Bioethics Policy

Office of Science Policy

National Institutes of Health

6705 Rockledge Drive, Suite 750

Bethesda, MD 20892

Via email: SingleIRBpolicy@mail.nih.gov

To Whom It May Concern,

This is a response to Notice Number: NOT-OD-15-026: Request for Comments on the Draft NIH Policy on the Use of a single Institutional Review Board for Multi-Site Research.

I am an active NIH funded investigator who has conducted multicenter trials and has participated in many multicenter industry sponsored trials. I am also the Senior Associate Dean for Research and the Executive Director of the Program for the Protection of Human Subjects at the Icahn School of Medicine. In this position, I have engaged as a participant in central IRBs as a member of StrokeNet, as a participant in the CIRBs from the NCI, and have worked extensively with a number of commercial IRBs. We also have the infrastructure to serve as a central IRB, specifically for the CoFAR network.

I write this response as the Draft Policy on the use of a single review board for multi- site research is broad, non-specific and proposes no operational structure. These are extremely important issues as Dr. Collins' statement that single IRBs will "... reduce duplication of effort, speed the initiation of important research, and save time and taxpayer funds" is potentially untrue and misleading.

Applicability: The idea of a central or single IRB for multi-site research is extremely valuable and useful in circumstances such as NeuroNExt and StrokeNet in which a network is established with the idea of conducting multiple multi-site projects. The experience with both of these entities is that the upfront effort required to establish the central IRB structure is extensive, time consuming and expensive. This effort has a significant return on investment once established. However, the idea that every single multi-center study will benefit from this type of central organization is not supported by current experience. If this work were required to establish a single trial that had no other associated projects it is highly likely that it will slow the initiation of important research, waste significant amounts of time and cost someone, if not directly the NIH, significant funds. Therefore, I recommend that the idea of single IRB for one time multi-center trials that do not have an existing central IRB formed prior to submission of a grant proposal not be required to use such a mechanism unless it can be demonstrated that Dr. Collins' endpoints can be achieved.

Organization: The NeuroNext model has been very effective. It requires that the research organization (e.g. the data management center) has an individual who is responsible for the organization of all of the central IRB interactions. This is a crucial organizational issue that should be required of all projects that are proposing to establish or utilize central IRBs. The NIH should be aware that there are state regulations regarding research that have to be incorporated into the review process and consent documents, so someone has to be able to manage this diversity that will not disappear with a single IRB review.

Investigators, in my experience, approach their IRBs to inquire if they would participate in a central IRB and acquire verbal agreement. Subsequently, when I contact the IRBs to begin working on centralized IRB work they either deny ever having ever agreed or indicate that they agreed only in principle awaiting the details to make a final decision. If a central IRB plan is adopted, the Supplemental Instructions for Preparing the Human Subjects Section of the Research Plan in the SF424 (R&R) Application Guide for NIH and Other PHS Agencies should be amended to include substantial detail of central IRB plans, management and documentation of agreement by the participating centers for the specific plan included in the grant application. Either reviewers at CSR or institute program staff will need training to evaluate these plans and assure that they are indeed viable. Investigators will need more training than is typically available to understand how such plans should be organized. If the point of having a single IRB for a multi-site project is to diminish the time until startup, these organizational issues are vital.

Failure to organize this properly will result in chaos and trials that fail to start at all.

Cost: To date our experience with central IRBs has not saved any money. The review by a board of qualified experts and other members as required by regulation does not really have a defined cost. Some institutions do pay their IRB members but most don't. None pay them on a per project basis, so outsourcing projects only decreases that expenditure when the number of projects decrease sufficiently to decrease the number of boards required or their frequency of meeting. Most of the cost of IRB review at the academic institutions that partner with the National Institutes of Health on multi-site research is contained in the internal staff. The experience at the Icahn School of Medicine, as well as that reported by all other institutions at the recent PRIM&R meeting, is that staff time is directed to different activities associated with managing these external relationships. It is unclear from where Dr. Collins believes the cost saving of this proposal will arise. In the case of commercial IRBs, my experience is that costs are extremely high and generally above the original estimate – an issue that does not arise with academic IRBs. In a recent industry study I just completed (I do not have permission to identify the sponsor or the managing entity and prefer not to identify the central IRB), the management core estimated it would cost about \$3000 per center from the central IRB. By the time we completed our enrollment, we had generated in excess of \$6000 in IRB charges including amendments, etc. For the expected 35 sites, the estimate was \$105,000. If our charges were reproduced at the other centers, the cost would be \$210,000, just for IRB services for a 454 patient study. At between \$230 and \$460 of IRB costs per patient enrolled, this is not a cost savings for taxpayers. Eleven centers in this trial enrolled 2 patients or less, making the IRB investment per patient even higher for those centers.

In summary, the proposal to require a single IRB for multi-site research might achieve the goals put forward by Dr. Collins if the NIH adopts this model in appropriate circumstances, primarily cooperative group projects, creates the appropriate application and review process and conscientiously evaluates the costs associated with this alteration in policy. The policy as put forward to date accomplishes will not achieve the goal put forward by the NIH director.

Sincerely yours,

Jeffrey H. Silverstein, MD, MS, AGSF Executive Director
Senior Associate Dean for Research Professor of Anesthesiology, Surgery, Geriatrics & Palliative Medicine

Comment #111

Commenter:

Date of Comment:

Comment:

January 28, 2015

Response to Single IRB Policy (Notice Number: NOT-OD-15-026) Draft: 1.9.15

Thank you for the opportunity to respond to NOT-OD-15-026 regarding the draft policy to promote the use of a single IRB of record for domestic sites of multi-site studies funded by the NIH. In principle, we fully support the idea of using a single IRB for multi-site domestic studies. We believe this will result in the uniform application of human research protect principles across multi-sites studies. This policy has the potential to increase efficiency and decrease workload and administrative burden on investigators as well as IRB's. However, we are suggesting that immediate execution of the Secretary's Advisory Committee on Human Research (SACHRP; October 2012) recommendations that calls for the harmonization of the FDA's 2006 guidance on use of a single IRB with OHRP's guidance be a top priority and be implemented prior to this mandate. Additionally SACHRP's recommendations that a list of resources outlining state laws relevant to human subject research be developed and made available to IRBs of record and a set of guidelines be developed for how the single IRB of record will apply local standards, knowledge of institutional policies, institutional capacity issues, investigator and study staff qualifications, as well as community and subject considerations to the review of multi-center studies is urgently needed. We also believe that guidance on best practices for managing conflict of interest disclosures and mitigation plans at the local level when a single IRB is used needs to be developed.

It is our recommendation that the NIH, in collaboration with DHHS, convene a panel of IRB professionals with the goal of establishing a draft IAA document to replace the current outdated draft which exists on the DHHS website. This panel should collaborate and draw from the expertise of NIH institutes (e.g. NCATS, NCI) in order to develop common policies or procedures. Significant time is spent reviewing different versions of agreements because there is no common or accepted draft available. Since each institution is left to write their own agreements, many times each agreement needs to be reviewed by multiple parties including legal counsel and institutional officials which cause a delay in executing the agreements. Having a standard or widely accepted draft IAA, endorsed by the NIH and DHHS, would greatly reduce delays in execution. This draft should clearly specify the expectations and responsibilities of each of the Institutions involved in the agreement. If a draft agreement is endorsed by DHHS and the NIH which delineates the responsibilities of each institution, this may encourage trust between IRBs. This panel should also outline the agreement execution process.

The NIH should consider a central warehouse or software system whereby all federally funded research would be submitted for review by the IRB of record. This mechanism would eliminate the need to submit paperwork to each IRB for tracking purposes. This system can also be built to provide important notifications to the research sites (i.e. any unanticipated problems involving subjects or others, issues of serious or continued non-compliance) or other events that the institutions would want to be kept abreast of.

In conclusion, we are also recommending that the policy address the responsibilities of the local IRB related to the use of a single IRB, and how the IRB of record will be reimbursed. NOT-OD-15-026 indicates that this will be included as a direct cost in the notice of award; however, guidance is needed to include a fee structure to help Investigators develop reasonable budgets. All of the above measures need to be considered before the single IRB requirement for NIH studies is executed.

Katherine Luzuriaga, Director, UMCCTS
Vice Provost, Clinical and Translational Research Professor, Molecular Medicine, Pediatrics, and
Medicine

Carol Bova, PhD, RN, ANP
Chair, UMMS Institutional Review Board Professor, Graduate School of Nursing

Comment #112

Commenter:

Date of Comment:

Comment:

TO: SingleIRBpolicy@mail.nih.gov

RE: Request for Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research (NOT-OD-15-026) January 28, 2015

As biomedical researchers, we are committed to the use of safe, effective, and humane best practices in the conduct of studies that inform our understanding of human biology and disease. We are acutely aware of the impact of our studies on the lives of the individuals who participate in our work, and upon their families. Ensuring appropriate concern for the critical concepts of respects for persons, beneficence, and justice is a core consideration in our work.

Ensuring the efficient use of limited research funding is also of vital concern. Few studies are funded at levels sufficient to meet the aspirations of researchers, funding agencies, and patients. The identification of areas where costs can be reduced without sacrificing participant safety or scientific integrity is a constant struggle.

The proposed use of Single Institutional Review Boards (SIRBs) for multi-site research presents a rare opportunity to tackle both of these concerns at once, providing improved cost-efficiency without introducing risks for participants. We wholeheartedly endorse this proposal. We also suggest that relevant observations from our experience with current IRBs identify issues that should be considered in defining specific policies for SIRBs:

Human-subjects review practices for multi-site projects are often inconsistent and opaque. Although basic definitions of IRB requirements such as expedited and exempt categories and HIPAA rule are reasonably well-defined, jurisdictional policies dictating when each site must have its own local IRB approval and what content must be included in consent forms are much murkier. In one recent case, a subcontractor site on a multi-site project told the local principal investigator that a local IRB review was needed, even though the prime awardee's institution had already determined that such review was not necessary. Removing human judgment and interpretation from the IRB process is certainly not possible, but lack of predictability certainly complicates the process.

Variations in practice necessitate a complex and time-consuming process for achieving cross-site approval: Generally, the lead site will submit materials to their IRB, making changes for local approval. Materials are then disseminated to collaborating institutions, who may identify further changes that need to be made to satisfy their IRBs. Any such changes may require re-review at the initiating institution and any others that may have approved the original submissions. This iterative process is time-consuming and expensive.

Protocol modifications are difficult and time consuming: Many, if not all, complex projects find that aspects of the protocols need to be revised midstream. These changes might, for example, involve modification of inclusion/exclusion criteria to reflect difficulties in recruiting that otherwise might prevent successful enrollment of the desired number of participants. As approval at the lead center (or coordinating center) is required before each site can submit the changes, the amount of time needed to make implement a change is nearly doubled. As a result, embarking on protocol modifications that might impact multiple sites is a daunting process that might complicate ongoing enrollment and impact the overall quality of the study.

Adverse event reporting requirements are similarly inconsistent: Safety monitoring, including procedures for reporting unanticipated events, is a key component of a robust approach to the protection of research participants. Unfortunately, adverse event reporting can often be as seemingly arbitrary as initial review requirements, with institutions differing on their definitions of what must be reported when, and to whom. In some cases of multi-site research, some IRBs might require review of reportable events by both subcontracting and prime awardees. This latter practice is particularly problematic if one institution requests a review of an incident from a second institution that does not consider the incident reportable.

Data use agreements introduce further complexity: Biomedical research involving sensitive genomic, demographic, or clinical data generally requires data use agreements (DUAs). As these agreements often require review by institutional Offices of Research, the addition of DUAs throws an additional set of constraints on this already time-consuming process.

Multi-site IRB approval might never be a trivial process, but changes that balance the reduction of the impact of some of these bottlenecks with the critical goal of protecting research participants will provide welcome improvements to research efficiency.

Although we strongly favor the proposed single IRB review process, we would like to bring attention to several concerns that will impact the viability of the proposed changes. We suggest several principles that should drive the implementation of single IRB review policies:

- *Protection of human subjects should be foremost:* The goal of the human subjects review process must continue to be the protection of the rights and concerns of participants in research studies. Although institutional concerns are not irrelevant, concerns for respect for persons, justice, and beneficence, must take priority.
- *Institutional concerns must be addressed:* Institutional review boards operate in the context of institutional research support, interacting with faculty, offices of research, and university legal counsel. As any proposed revisions to IRB procedures will impact all of these groups, input from these various perspectives -should be considered in policy formation. This might require soliciting input from groups who might not respond via the NIH RFI process.
- Participation in multi-site IRB policies must not be contingent upon accreditation or other requirements that might present burdensome expenses: Accreditation of human research participants practices may be seen as an effective means of reviewing and maintaining best practices. However, accreditation fees may be substantial and burdensome, particularly for institutions that host a large number of research studies without significant federal funding. Requirements that tie participation to accreditation or similar expenses might lead some institutions to opt-out, thus weakening the utility of multi-site IRB.
- *Processes and requirements must be clearly and explicitly defined,* thus avoiding the ambiguity described above. Policies that might require additional contractual arrangements such as data use agreements must be particularly clear, given the involvement of institutional research offices.
- *Duplicative local review must be minimized:* As discussed above, we are sensitive to the concerns of individual institutions, and we understand the motivation behind the provision for local IRB review. However, we are concerned that the statement that “A duplicate IRB review at a participating site would be counter to the intent and goal of the Policy” does not go far enough. Local reviews would turn the single IRB review process into a multi-stage process that might rival, if not exceed, the complexity of the current regime. Clear policies should be established to minimize this local review. For example, local review might be an option only for studies that require full board review (neither expedited nor exempt) and/or involve protected health information.
- *Policies and personnel covering the entire spectrum of human subjects research must be included:*

Although perhaps the most visible component of the human subjects research process, initial review and approval cannot be the only focus of Single IRB policies. Subsequent monitoring and adverse event reporting must be included in appropriate policies, with appropriate staff available for handling compliance and oversight. A Single IRB model that, for example, centralized review while leaving adverse event handling in the hands of individual institutions would replicate many of the cumbersome features of the current situation.

- *Multi-site policies should be coordinated across other funding agencies to the greatest extent possible:* The use of different rules and procedures by different funding agencies will cause unnecessary confusion. Proposed changes to NIH policy should be aligned with any comparable proposals from NSF, DARPA, and other major funders of human subjects research.

Respectfully Submitted,

Harry Hochheiser, PhD Assistant Professor
Department of Biomedical Informatics and Intelligent Systems Program University of Pittsburgh

Michael J. Becich, MD, PhD
Chairman, Department of Biomedical Informatics
Professor of Pathology, Information Sciences/Telecommunications and Clinical/Translational Sciences
Associate Director for Cancer Informatics (UPCI), Associate Director, Clinical and Translational Science Institute (CTSI)

Steve Wisniewski
Professor
Epidemiology
University of Pittsburgh

Michael Tarr, PhD
Professor and Department Head
Department of Psychology
Carnegie-Mellon University

Marlene Behrmann, PhD
George A. and Helen Dunham Cowan Professor of Cognitive Neuroscience
Center for the Neural Basis of Cognition and Department of Psychology
Carnegie Mellon University

Comment #113

Commenter:

Date of Comment

Comment:

January 28, 2015

Office of Clinical Research and Bioethics Policy Office of Science Policy
National Institutes of Health 6705 Rockledge Drive
Suite 750
Bethesda, MD 20892

RE: FR Document, Draft NIH Policy on the Use of a Single Institutional Review Board for Multi- Site Research

Dear Members of the Office of Clinical Research and Bioethics Policy Team,

Thank you very much for allowing public comments on the proposed NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research (“draft Policy”). The University of Wisconsin-Madison Health Sciences IRBs (HS-IRBs) have significant experience with developing a variety of arrangements to provide more efficient IRB review for multi-site research. Therefore, we hope that you find our comments helpful to your consideration and implementation of the draft Policy.

Based on our experience, we think the UW-Madison HS-IRBs are national leaders in streamlining IRB review processes for multi-site research and welcome the opportunity to share our experiences as they relate to the draft Policy. For example, we are currently significantly involved in an effort funded by the National Center for Advancing Translation Science (NCATS) and led by Clinical & Translational Sciences Award (CTSA) institutions to promote and support the use of a single IRB for multi-site trials. This effort involves creating a template agreement and standard operating procedures, identifying the roles of the study team, reviewing IRB and relying institutions, and developing best practices and other infrastructure (e.g., web-based platform for reliant review decisions). Significant progress has been made in this project, which could provide institutions the support they need to effectively transition to an NIH policy requiring single IRB review.

Below, please see our general observations, as well as questions and responses to specific directives located in the “Responsibilities” portion of the draft Policy.

I. General Observations

Comments: Creating a model to shorten IRB review times across multi-site studies is a commendable effort and one we support based on our own experience and empiric studies appear to show that the use of a single IRB review may shorten the time to study activation and first subject enrollment. In addition, when important changes are required to a protocol, these changes can be implemented more quickly.

Although we understand why the draft Policy has been proposed and see the potential advantages single IRB review offers, implementing this model would pose significant challenges to academic institution IRBs such as UW-Madison and others. For this response, we culled several sections of the draft Policy, and provided comments and suggestions for review. It is our hope that these suggestions may help to clarify the attendant support required to transition to a single IRB model as well as cases where single IRB review may not be appropriate.

II. Specific Observations

Excerpt 1: NIH generally expects all domestic sites of multi-site NIH funded studies to use a single IRB of record. All sites participating in a multi-site study will be expected to rely on a single IRB to carry out the functions that are required for institutional compliance with IRB review set forth in the HHS regulations for the Protections of Human Subjects. The single IRB will be the IRB of record for other participating sites. The single IRB will be accountable for compliance with regulatory requirements for IRBs specified under the HHS regulations at 45 CFR 46, such as providing initial and continuing review of the research. All participating sites will be responsible for meeting other regulatory obligations, such as obtaining informed consent, overseeing the implementation of approved protocols, and, reporting unanticipated problems and adverse events to the single IRB of record.

Comments: Although the draft Policy indicates that NIH “general expects” that a single IRB will be used for each study, this language raises some questions for us. One concern is that there appears to be an opportunity for IRBs to opt out of the expectation of a single IRB review. Aside from the disincentive of an IRB “bearing the cost” of an additional review, what other processes will be in place to ensure that the single IRB model will be followed? We believe it is important that institutions are held to the principles that are set forth in the draft Policy. Without these processes in place, the potential for confusion and noncompliance will be significant concerns for both the reviewing IRB and those IRBs relying on the single IRB review.

Having noted the challenges with the exception, cases exist where single IRB review would not be desired or tenable. For example, there are cases, as noted in the draft policy, where the selected reviewing IRB may not have the appropriate roster or procedures in place to review for certain subject populations (e.g., prisoners, children, pregnant women, veterans). Moreover, there are situations we have encountered where the IRB of record has refused to serve as the Privacy Board for purposes of compliance with the Health Insurance Portability and Privacy Act (HIPAA), which would have resulted in the need for our institution to develop a separate board and processes simply to conduct the HIPAA component of the review. The HIPAA considerations are so intertwined with the Common Rule review (e.g., considerations of subject identification, privacy protections, and consent form language) that their separation does not make sense. The forced use of a reviewing IRB that will not act as a HIPAA Privacy Board as well creates concerns for us because it will result in duplicative effort.

While one of the main goals of the single IRB model is to shorten IRB review time, factors will remain that can lead to a longer approval time than some may desire. At many academic medical centers, several types of review must be completed before study activities can begin. In many cases, for example, institutional policies do not allow a study to be approved by the IRB until the clinical research unit, medical records department, and investigational pharmacy have signed off on the study. It is our experience that these types of approvals will be required at nearly all sites that are participating in NIH studies. Because many institutions use the local IRB as the gatekeeper for these and other approvals, a forced ceding of IRB review without recognition of the impact of other process on IRB review or the significant restructuring many institutions may need to undergo both in terms of personnel and electronic tracking systems should be addressed and not underestimated. The changes in processes may simply shift rather than eliminate costs.

The draft Policy should address the differences between institutional policies on reporting timeframes for reportable events, as well as for the differences in the definition used for “reportable events”, which is often the overarching term used to encompass new information that should be reported to the IRB as well as noncompliance and unanticipated problems. In our experience, there is little consistency between institutional policies on reportable events. This variation exists despite attempts by the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) to provide guidance, for example, about unanticipated problems. As written, the draft Policy does not acknowledge

these differences, nor does it provide any direction as to which reporting requirements relying sites must adhere to. Further, this variability in institutional requirements for reportable events could inadvertently lead to noncompliance as study teams must become familiar with a variety of institutional policies, depending on the number of IRBs they use; thus, it will be a challenge for study teams to understand what to report to whom and when. We think the draft Policy must be revised to acknowledge that these differences exist and which reporting requirements relying sites should follow (e.g., set a standard for reporting or suggest that the reviewing IRB's policies for reportable events should be followed).

Additionally, local IRB offices may still require local study teams to submit reportable events to the local IRB. Some factors leading local IRB offices to require this would include trusting local processes over the processes of another institution, lack of understanding of the reporting requirements, and a continued need to maintain compliance with their local Human Research Protection Program requirements. This could result in the type duplication of effort that the draft Policy is trying to avoid.

We are concerned about the potential burden that would be created by the draft Policy on the IRB serving as the IRB of record. As presently constituted, many IRBs are not equipped to handle the additional responsibilities of serving as a central IRB, especially for a large number of sites. For instance, an academic institution's IRB may find it onerous to monitor ongoing studies at numerous sites across the country because of staffing and infrastructure shortfalls. Examples of oversight activities that are either unique to a central IRB or are more pronounced for multi-site studies which likely require more resources include: applying State laws; ensuring institutionally-required language is included in consent documents for sites ceding IRB review; and review of reportable events. Additional resources would undoubtedly be required for an academic institution's IRB to meet the requirements of serving as a single IRB. Guidance on how to obtain these additional resources or allowing such expenses to be included as direct costs in grant proposals would be a critical component of successfully implementing this draft Policy.

The UW-Madison HS-IRBs have considerable experience in organizing IRB review processes for multi-site studies. As part of this experience, we have seen that many IRBs and researchers may not have the same experience. We think that the shift of multi-site NIH studies to a single IRB review model will include a steep learning curve for many institutions that are not familiar with this process both for the regulatory infrastructure and study teams. For example, there are additional expectations for study teams engaged in multi-site studies, such as identifying a lead team that will work with the central IRB and collate information from the other participating study teams to present to the IRB. The draft Policy should discuss the fact that significant time and education of various constituents will be required in order to implement this Policy.

Recommendations:

1. Update the draft Policy to clarify the occasions when a study site can opt out of the single IRB model.
2. Provide information on whether a specific timeframe should be followed when obtaining required institutional approvals.
3. Update the draft Policy to clearly state that relying sites will remain in regulatory compliance if their researchers follow reporting requirements for an IRB of record that differ from their home institution.
4. Include a provision in the draft Policy allowing for additional funds for support of regulatory entities in the Notice of Award as a direct cost. Consideration should be given to also allowing costs that the single IRB may incur while increasing IRB staff or improving infrastructure.

5. Indicate what resources, if any, NIH will make available to assist in training IRBs and researchers regarding single IRB review. Furthermore, indicate what resources, if any, NIH will provide to those study teams serving as the lead site/coordinating center.

Excerpt 2: Agreements between the single IRB of record and other participating sites will be needed in accordance with 45 CFR 46. IRB authorization agreements will document the delegation of responsibilities of IRB review to the designated IRB of record and that IRB site's acceptance of the responsibilities. The agreement will set forth the specific responsibilities of each participating site. Participating sites will then rely on the IRB of record to satisfy the regulatory requirements relevant to the IRB review. The awardee or lead site for an NIH-funded, multi-site study will be responsible for maintaining authorization agreements and should be prepared to provide copies of the authorization agreements and other necessary documentation to the NIH funding Institute or Center upon request.

Comments: As written, the proposed policy does not recognize several obstacles to ceding IRB oversight to a single IRB. Institutions accredited by AAHRPP (Association for Accreditation of Human Research Protection Programs) may be unwilling to cede oversight to an IRB that is not AAHRPP accredited. The HRPP at UW-Madison (and other accredited institutions) must adhere to the standard set by AAHRPP for accreditation. The HS-IRBs take into account whether the proposed IRB is AAHRPP-accredited or has an HRPP that is comparable to AAHRPP standards. If the proposed IRB of record does not meet those standards, it is unlikely the HS-IRBs would consider ceding IRB oversight to that institution. Therefore, guidance is requested as to how accredited institutions should proceed when the single IRB is not accredited or does not meet AAHRPP standards.

In addition, many institutions do not use the template IRB Authorization Agreement (IAA) provided by OHRP. This can cause lengthy delays in getting an agreement between institutions signed, and there have been situations where it took as much as 6 months to get an IAA signed. In these instances, it took more time to have an IAA signed than it would have taken to have the respective local IRBs review the protocol. Therefore, guidance is requested as to whether a specific template IAA will be required. If not, please provide guidance on how to streamline the process of obtaining IAAs. Of note, one potential solution to the IAA challenge is an effort led by the CTSAs institutions to develop a national template IAA along with standard operating procedures.

In your "Reliance Agreements Frequently Asked Questions" (<http://www.niaid.nih.gov/LabsAndResources/resources/toolkit/Pages/fag.aspx>), you indicate "Institutions may have several concerns regarding the delegation of IRB review to an outside entity...include(ing) 1) ensuring quality and thoroughness of external review; 2) local context issues; 3) institutional liability; 4) complexity of shared control and accountability." While the draft Policy sets out specific requirements, it does not implicitly include information that would work to alleviate any of these concerns or any substantive steps that can be taken to work through these issues. Therefore, we would request specific guidance as to how we can be assured that these challenges can be addressed while maintaining compliance within the draft Policy.

A question we have is whether the use of IRB reliance agreements already in place for consortia or networks would be permitted under the draft Policy. As discussed at <http://www.ncats.nih.gov/news-and-events/features/irb-reliance.htm>, under a reliance model, "institutions develop networks in which each of the IRBs in a multi-site study agrees to rely on a single involved IRB to review, approve and monitor the study." UW-Madison participates in several reliance agreements, including the Wisconsin IRB Consortium and the Greater Plains Consortium, and is assisting to create a national model along with other CTSAs as mentioned above. In our experience, these agreements work to provide models that other institutions can replicate.

Recommendations:

1. Update draft Policy to indicate alternatives to the single IRB requirement when study sites may have a) concerns regarding the constitution of the designated reviewing IRB or that IRBs' experience reviewing a particular type of research, or b) if relying on the single IRB would contradict AAHRPP requirements.
2. Incentivize sites to use a common IRB Authorization Agreement template. This would further streamline the approval of multi-site studies, as well as eliminate any concerns that institutions may have about agreement language.
3. Provide assurance that current IRB review networks and consortia in existence would be acceptable under the draft Policy.

Excerpt 3. As necessary, mechanisms should be established to enable the single IRB of record to consider local context issues during its deliberations.

Response: Guidance will be required on how the single IRB of record can take into account the local context issues of other study sites, along with how IRBs can add infrastructure to meet such requirements as provide specific standards that an IRB of record will need to meet to ensure adequate review of local context, however defined.

Recommendations:

1. Provide template information packets, to be completed by individual sites, which will serve to provide acceptable local context information to the single IRB. As currently written, ambiguity will persist as IRBs struggle with making local context determinations.
2. Provide guidance on the qualifications of who can serve as an ad hoc member or consultant and the impact on the regulatory requirements for IRB composition and quorum. For instance, would an IRB liaison from the study site be an appropriate individual or perhaps a researcher from a study site who is not involved with the study being reviewed by the single IRB?
3. Provide guidance on what is meant by local context and what standards for review of
4. Local context must be met by an IRB of record.

As noted above there is a current CTSA-led effort underway that is developing standard operating procedures and tools in support of a single IRB review model that NIH may consider drawing upon.

Excerpt 4. A duplicate IRB review at a participating site would be counter to the intent and goal of the Policy, but the Policy does not prohibit any participating site from carrying out its own IRB review. If this approach is taken, the participating site should expect to bear the cost of the additional review.

Response: We read this section to suggest that an institution would need to calculate the indirect costs involved in IRB review and pay back this amount to the funding agency. If this is the case, it is unclear how IRB review costs would be monitored for, calculated, and returned to the funding agency, especially given that IRBs do not tend to charge fees for review of federally supported research and the exact cost of review would be impossible to determine.

Similarly, this language does not acknowledge or address the legitimate circumstances that may cause or require an institution to retain IRB oversight for a study. For example, if the proposed IRB of record does not have the appropriate expertise to review the study in question or, as previously noted, is not accredited, an institution may have sound cause to retain IRB oversight and indeed may have legal obligation to do so. Any policy advocating for single IRB review must take such situations into account.

Recommendations:

1. Revise the current draft Policy language to specify under which circumstances an institution may legitimately retain IRB oversight without incurring additional cost or penalty.
2. Consider having the funding agency monitor how many times a participating site opts
3. Out of single IRB review and take that into future funding considerations rather than asking institutions to calculate and segregate the costs of IRB review if they decline to cede such review.
4. Provide funding or other incentives for institutions to rely on a single IRB of record.

Excerpt 5. Identification of the IRB that will serve as the single IRB of record will be the responsibility of the extramural applicant or offerer, or the intramural principal investigator. The funding NIH Institute or Center has final decision authority for approving the selected single IRB. Use of a designated single IRB will be a term and condition of the award. If the agreed-upon single IRB is a fee-based IRB, these costs will be included in the Notice of Award as a direct cost. Compliance with this Policy will be a term and condition in the Notice of Award and a contract requirement in the Contract Award. Exceptions to the expectation to use a single IRB may be made with appropriate justification. Exceptions will be allowed only if the designated single IRB is unable to meet the needs of specific populations or where local IRB review is required by federal, tribal, or state laws or regulations.

Response: This language is highly problematic in that it leaves a number of critical questions unanswered, including:

- What will be the process for selecting a single IRB of record?
- What criteria will be used in selecting the single IRB and who will assess whether these criteria have been met? For example, will the IRB serving the applicant/offerer always be named as the single IRB?
- Under what circumstances may the funding NIH Institute or Center override the selection of the applicant/offerer?
- How will it be ensured that the IRB identified as the single reviewing IRB will accept this responsibility?
- How will this Policy address the issue of IRB shopping on the part of investigators or funding agencies? According to the draft Policy, use of a designated single IRB will be a term and condition of the award. Would the applicant/offerer be held liable if one (or several) sites had their local IRBs review a study? Similarly, will sites electing to retain IRB oversight lose the opportunity to participate in study?

Recommendations:

1. Expand the potential criteria for a site opting out of using a particular IRB to include cases where the reviewing IRB does not have adequate standard operating procedures and policies in place that address serving as a central IRB, the IRB is not constituted to oversee the research due to the study topic, or the IRB will not serve as a Privacy Board for relying sites that are covered entities.
2. Provide clarification as to what (if any) criteria will be used in selecting the single IRB.
3. Indicate under what circumstances the NIH could override the IRB choice of the applicant/offerer.
4. Clarify whether a coordinating site will be out of compliance if any additional sites opt out of a multi-site agreement and insist on local IRB review.

5. Address whether a site will be in noncompliance if they choose to have a duplicate review performed by their local IRB.
6. Directly address the question of IRB shopping and how this will be prevented.
7. Address the issue of the often additional function of IRB as Privacy Board.

Thank you for your consideration of these comments. Please do not hesitate to contact me if you have any questions.

Sincerely,

Nichelle Cobb
Director, Health Sciences IRBs Office NC/mfb/cap

Comment #114

Commenter:

Date of Comment:

Comment:

January 28, 2015

Re: NOT-OD-15-026: Request for comments on the draft NIH policy on the use of a single institutional review board for multi-site research

On behalf of the 22 Consortia, over 500 investigators, and 221 domestic and 85 international sites that form the Rare Diseases Clinical Research Network (RDCRN) supported by the Office of Rare Disease Research, National Center for Advancing Translational Sciences, and 10 NIH institutes, we would like to offer our supportive comments on NOT-OD-15-026: a new NIH requirement that there be a single IRB of record for multi-center studies funded by NIH.

As researchers whose focus is on rare diseases affecting fewer than 200,000 Americans, we feel this requirement will be particularly helpful in speeding research in our areas. Because of the rarity of our disorders, participants in our trials are often spread over many institutions with each site enrolling only a few participants. In addition, although high-risk clinical trials are certainly being conducted in rare disorders, a lot of research is also observational or primarily supportive where risks to participants are low or minimal. The regulatory burden per participant of meeting all of the current requirements at multiple sites slows the research enterprise considerably without enhancing protections for research subjects.

The proposed change to require a single lead IRB will be very helpful, particularly if attention is paid to the implementation of this requirement, so that burdens on investigators do not increase. Under the current approval mechanisms, for our low or minimal risk studies, a disproportionate share of RDCRN resources is devoted to meeting the requirements of all the local IRBs without, we believe, contributing to patient safety. However, to ensure that the transition to this system does not harm investigators and their research productivity, inclusion of an expectation that institutions and IRBs (perhaps with the pressure of withholding OHRP accreditation) will facilitate a single lead IRB is also very important. We are pleased that the draft NIH policy recognizes that some investigator costs could rise, and that a mechanism for cost recovery is included so that research funds do not need to be used for this purpose. We also hope the policy will clearly delineate how "single IRB" is defined and allow for several acceptable models. Finally, we assume the policy will apply to newly funded studies and groups and not to ongoing protocols or consortia, and this should be clearly specified.

Thank you for your efforts to make clinical research more efficient and effective, thereby improving the clinical trial enterprise for all stakeholders and maximizing the amount of information gained per research dollar spent.

Comment #115

Commenter: Council of Ivy League Presidents

Date of Comment:

Comment:

Request for Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

Submitted by the Council of Ivy League Presidents

During the past few years, the leadership groups of the Big Ten and Ivy League conferences have been discussing the feasibility and benefits of a collaborative research initiative that would bring together the academic and research expertise of their institutions. This initiative would allow the coordination of ongoing efforts by each conference to study various aspects of sports-related concussions in college athletics. A national collegiate database for sports-related injuries is needed not only to help identify and monitor risk factors for concussions, but to also develop injury prevention strategies based on epidemiologic evidence. With these goals in mind, the Ivy League began enrolling student athletes into a study on concussions throughout the 2013-2014 academic year. The purpose of this multi-institutional, observational study is to characterize the epidemiology of concussions among student athletes. More recently, a select group of Big Ten schools were invited to participate in the current 2014-2015 academic year. However, there have been significant hardships executing the IRB submissions and approvals required to conduct this study at multiple institutions, as described in the bullet points below.

- It took more than half the year for all 8 Ivy League institutions to receive IRB approval to participate in this observational study. The approval dates ranged from January 2013 to August 2013. The study was scheduled to begin in August 2013, but only if all 8 schools had IRB approval, so we just barely met the deadline with the last school getting approved only days before the study initiation date.
- This is an observational study involving a questionnaire to be administered to the concussed student athlete, with no interventions involved. Yet, 8 independent IRBs were required to review the same study protocol, questionnaire, and consent forms which resulted in unnecessary duplication of efforts and expense, and potentially jeopardized the start of the study.
- In addition, the yearly IRB renewal process at each of the 8 Ivy League institutions has been plagued with administrative delays despite minimal changes to the study protocol.
- Of the 8 independent IRBs that reviewed this study protocol, only one deemed it exempt while the rest gave it an expedited review.
- The Ivy League Concussion Study is now in its second year of enrollment and has opened up enrollment to a select group of Big Ten schools. The inclusion of 5 Big Ten schools began in June 2014, and the IRB process is still ongoing as of January 2015.
- A centralized review process by a single IRB, perhaps the IRB overseeing the Data Coordinating Center for this study, would have streamlined the approval process and helped expedite the initiation of the study at all sites. Alternatively, a single joint review by a designated IRB with representatives from each of the participating institutions would also have helped expedite the process, thereby saving time and money for all involved.
- We recommend the use of single IRBs for multi-site studies, particularly for observational studies that pose minimal risk to its participants, as it would reduce inefficiencies without compromising the protection of research subjects and accountability of participating sites.
- We do not believe that multiple IRB reviews by each participating institution enhances protection of research subjects, especially with respect to observational studies, and only delays reporting of important research findings to the community.

Comment #116

Commenter:

Date of Comment:

Comment:

January 28, 2015

Ms. Sarah Carr, Acting Director
Office of Clinical Research and Bioethics Policy
Office of Science Policy, NIH
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

SingleIRBpolicy@mail.nih.gov

RE: Proposed NIH Policy on the Use of a Single Institutional Review Board for Multi-site Research

Dear Ms. Carr:

Stanford University appreciates the opportunity to respond to the draft *NIH Policy on the Use of a Single Institutional Review Board for Multi-site Research*. While we believe that the concept of a central IRB is a worthy ambition and we support the goal of this policy, we do not believe there is sufficient data, empirical or otherwise, to substantiate the claims that the use of single IRBs will “enhance and streamline IRB review” or “reduce inefficiencies without compromising ethical principles and protections.” Furthermore, this policy fails to address how institutions should implement the policy; it only states that they must.

Although the policy allows for lead institution funding, we fear that resources needed to support this mandate will be taken out of the researchers’ funding, leaving less to conduct their research, or will increase costs for the institution. In any case, implementing this policy will create new administrative burdens for the researchers, local IRBs, and the institution at a time when strategies to reduce these burdens are being sought.

Academic institutions have been cautious about participating in central IRBs among the many models that have been created, with each maintaining its own set of local responsibilities. Stanford’s experiences as a participant with the single IRB models for multi-site research have been mixed. As an early adopter of NCI’s CIRB with its facilitated review, we worked through the growing pains of that organization, adjusting our local SOPs each time changes were initiated. We concur that the NCI CIRB, with its independent review model, is working well at this time, but it has taken nearly 15 years since its inception in 1999, while being generously funded by NCI and managed by a well-established Contract Research Organization (EMMES). This is far from what NIH is now proposing: academic institutions are being asked to create their own models without guidance or best practices derived from reliable data.

A case in point is our experience with one of NIH’s Institutes setting up its own single IRB for studies to be conducted under an NIH grant, with Harvard University as the coordinating center. Our first request to rely on this single IRB came in May 2014, with initial enrollment planned to begin in July 2014. At this writing in January 2015, the protocol, consent documents and Reliance Agreements are still in the process of being revised and finalized. This is far longer than the anticipated three month set-up time.

The proposed policy indicates that “a duplicate IRB review at a participating site would be counter to the intent and goal of the policy”. However, it would not be possible to comply with this policy and “...be responsible for meeting other regulatory obligations, such as...overseeing the implementation of

approved protocols”, without performing a local review. We believe that no NIH mandate can or should relieve participating institutions from their fundamental obligation to protect human subjects involved in their research. At the same time, it is unreasonable to require the institution to undertake liability for the proper execution of this responsibility without performing the requisite review.

Contrary to the stated goal, “reducing procedural inefficiencies so that research can proceed efficiently...,” this policy will instead serve to create highly burdensome procedures. Researchers and their staff will be required to learn multiple new and different electronic systems, forms and submission requirements; and highly trained research staff will be required to shift their duties away from faculty support to mastering new and evolving administrative requirements. IRB staff will be required to design new processes, new ways of monitoring and tracking research, and executing Agreements between the single IRB of record and other participating sites, while still maintaining all of the local IRB responsibilities for the majority of the ongoing research administration not subject to single IRB review.

As stated in Petra Kaufmann and Pearl O’Rourke’s article entitled “Central Institutional Review Board Review for an Academic Trial Network,”¹ the NeuroNext (NN) CIRB which is supported by an NIH grant, is “still in the pilot stages” and “there has not yet been the opportunity to test how the model functions in case of incidents that require quality correction, such as major protocol violations.” The authors conclude that it is “not reasonable to generalize from a single completed protocol review process.”

Before mandating this new policy, we urge that serious consideration be given to expanding the NCI independent model that is NIH-funded and run by a contract research organization. This CIRB performs a single IRB review process which many academic institutions are already familiar with and support. We also believe that it would be prudent to await the results of the research to be supported by the newly proposed R01 grant, *Empirical Research on Ethical Issues Related to Central IRBs and Consent for Research Using Clinical Records and Data*. Further review of existing single IRB models, or a pilot project to test the implementation of this policy in a limited and controlled environment, may be necessary to determine the best ways to design and implement a single IRB review in multi-site research.

We are deeply concerned that this unfunded mandate may push institutions into processes hastily assembled, poorly funded, and lacking in quality controls or rigorous empirical data needed to sustain the goals of streamlining, efficiency, and ethical protection of human research participants.

Sincerely yours,

Ann M. Arvin, MD, Vice Provost and Dean of Research
Penelope Eckert, PhD, Chair IRB 2
David Oakes, MD, Chair, IRBs 1, 6, and 8
David Spiegel, MD, Chair, IRB/SCRO
Ronald Ariagno, MD, Chair, IRB 4
Michael Amylon, MD, Chair, IRB 7
Darrell Wilson, MD, Chair, IRB 5

Footnotes

¹ Kaufman, Petra and O’Rourke, P. Pearl, “Central Institutional Review Board Review for an Academic Trial Network,” *Academic Medicine* Volume 89, December 2014: pgs. 1575-1696

Comment #117

Commenter: Thomas Campbell, MD

Date of comment: January 28, 2015

Comment:

An NIH policy on the use of a single IRB for multi-institutional studies is long overdue and I am glad to see that this is now being addressed. I expect that this will have a big impact on the speed of clinical research implementation.

Comment #118

Commenter:

Date of Comment:

Comment:

TO: Office of Clinical Research and Bioethics Policy, Office of Science
Policy, NIH SingleIRBpolicy@mail.nih.gov
DATE: 1/28/15
FROM: Erica Heath, CIP
RE: Comments re Single IRB for Multi-Site Research

I am writing as an individual not representing any agency or company. I have 14 years experience with an academic IRB (1970-1984) and 32 years with independent IRBs much of which involves being a central IRB.

I am writing to discourage implementation of this draft policy. While it is sure to increase efficiency in some parts of the grant world, it is sure to generate far less efficiency in other parts. My belief is that the net outcome is likely to be less efficiency.

What is the current problem?

There have been multiple studies conducted purporting to show that IRBs are at fault for slowing down the time from idea to funding. This is likely true of a segment of grants but I suspect that were you to look across all grant types and sizes it would appear different. These reports all involved very large clinical studies. They don't often drill down to find causes of delay such as time in the PIs hands, submission of incorrect forms, and education. I suspect that non-clinical (SBER) grants might present a different picture.

Please base this decision on empirical evidence that is representative of all types of grants and of various solutions. Perhaps it is true but you have shown no basis for such a massive change and no evidence that a single IRB is the optimal solution.

What is wrong with consolidation?

The original rule was local institutional review and that did not change for 34 years. After 2000, when OHRP began to accept (not encourage, but accept) external review, there was little reward for accepting external review and major fear of penalty. Only in the last decade have the policies been changed enough to encourage institutions to rely on one another. Even then, there has been no carrot, no reason or encouragement to give up jurisdiction.

With this change the trend has been toward consolidation. Many more institutions are agreeing to rely on central review by independent IRBs for FDA regulated studies.

There are more regional and system-wide IRBs (e.g., Kaiser, Partners). More institutions are considering agreeing to rely on another recognized (peer level) IRB. This is a trend that is seeking its way to efficiency. It should be encouraged.

You are proposing going from one end of the spectrum to the other. Having one IRB certainly solves the inconsistency and inefficiency problem. Having 100 IRBs for one study is very inefficient and allows inconsistency. Shifting from one paradigm to the other could create its own very different set of new problems. Perhaps consolidation is a preferable outcome.

What is wrong with the proposed policy?

The recognized models—NeuroNet and Stroke Net – should be seen as experimental models. They took several years to create and were led by recognized leaders in our field. They are still working out policies and procedures and, at last report, have very few studies under their care. You are now asking the wide range of grants and IRB administrators to create new options very quickly without models or evidence. What you are likely to generate is chaos rather than efficiency.

It is important to consider the unintended consequences and avoid creating new problems. For example, you will require written agreements. Today they range from the OHRP 1 page to 20 or 25 legal language pages. Implementing these agreements is likely to extend the grants process.

This is a policy that will affect grants at large academic centers that have the resources to adapt and have already been thinking about this issue. It will also affect middle and small size institutions dealing with 2 and 3 site studies. Some of these institutions are far less sophisticated. To expect them to change systems immediately is very optimistic.

In each institution there is going to be a new job description for a person to keep track of the wide variety of networks and arrangements and their agreements; NCI studies here and NINDS studies there, epidemiology ceded to institution A and one sociology grant to institution X plus all of those agreement where others are relying on you. I doubt there is any software covering this yet.

Can the goal be met?

Your goal is to increase efficiency “without compromising ethical principles and protections”. Logically this cannot be done as any diminution of local review is sure to negatively impact protection. Whether it is enough to make a difference is unknown and would depend entirely on what is being measured.

Efficiency without serious compromise may be possible but only with a well thought out and tested alternative adopted with care.

Local review is the major loser. Your 83 words can hardly do it justice. Human subjects are protected not only by the IRB but also by the IRB’s function within a larger setting. When a study or group of studies is no longer reviewed locally, many relationships are severed and functions lost. Any change of policy must account for the internal changes required to adjust.

What is the alternative?

The answer may well be a broad single (or reduced) IRB requirement but it cannot be imposed immediately.

- Prejudice against any external review remains. This prejudice needs to be replaced with excitement.
- Penalties are thought to remain. There should be evidence that reliance is not to be penalized.
- Models should be publicized. The large central IRB (e.g., NeuroNet) is fine for an institute-wide or discipline-wide group of studies but models should be offered for all of the other kinds of studies funded by other institutes.
- Models for internal controls when the IRB is externalized should be encouraged
- There is no evidence of urgency. Any such policy should be phased in as the methods and mechanics become available.
- Consolidation should be an acceptable outcome.

Comment #119

Commenter:

Date of Comment:

Comment:

January 28, 2015

Sarah Carr, Acting Director
Office of Clinical Research and Bioethics Policy
Office of Science Policy
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

via electronic delivery to SingleIRBpolicy@mail.nih.gov

Dear Acting Director Carr:

We write in response to NOT-OD-15-026¹ and offer our strong support for the NIH draft policy to promote the use of a single Institutional Review Board (single IRB) of record for domestic sites of multi-site studies funded by the National Institutes of Health (NIH).

The LEAD Coalition is committed to accelerating the science needed to achieve the National Plan to Address Alzheimer's Disease goal number one of preventing and effectively treating Alzheimer's disease and related dementias by 2025.² We have supported increasing federal research resources, modernizing the regulatory environment, and implementing more efficient research practices and trial recruitment methods. In each area, measurable progress is being achieved through strategic collaborations, catalytic innovation, and the broadly embraced recognition that business as usual is as scientifically unacceptable as it is ethically indefensible. While not a silver bullet, we believe the single IRB policy is an important next step toward accelerated trials without compromising trial quality, ethical standards or – most important – research participant safety.

IRBs are essential to the clinical trial process. Assuring more consistent standards will provide greater study integrity, efficient use of finite public and private resources, and thorough protection of research participants. The single IRB policy will replace the outdated, fragmented status quo that all too often has resulted in:

- costly bureaucratic delays in study approval and start up;
- underutilization of academic research sites; and
- the unintended and counter-intuitive exclusion of people living with Alzheimer's disease and related dementias, informal caregivers and dementia research experts from local IRBs.

The single IRB policy will help enhance and accelerate research vital to addressing the current and projected health and financial threats posed by Alzheimer's disease and related dementias. Today our nation is spending more than \$150 billion annually in Medicare and Medicaid costs to care for people living with ADRD.³ Alzheimer's disease alone contributes to the deaths of approximately 500,000 Americans each year, making it the third leading cause of death in the United States.⁴ These figures will explode over the coming decades as our population ages, but a modernized and more robust research enterprise can help us prevent this future and move us closer to achieving our 2025 goal.⁵

Congress, the President and NIH Director Dr. Francis Collins have overcome enormous obstacles to

increase funding and prioritization of Alzheimer's disease and related dementias research over the past several years while the Food and Drug Administration (FDA) has worked tirelessly and effectively to encourage new avenues of research with substantially clarified paths to regulatory approval. The National Institute on Aging (NIA) and other NIH institutes—such as the National Institute of Neurological Disorders and Stroke, the National Institute of Biomedical Imaging and Bioengineering, the National Institute of Mental Health and the National Institute of Child Health and Human Development – are supporting a number of promising research projects to: understand the genetic risk factors;⁶ address the disproportionate impact on women,⁷ African Americans,⁸ Hispanics,⁹ and persons with intellectual disabilities;¹⁰ and pursue cutting-edge but costly and time consuming trials aimed at preventing or substantially slowing disease progression by administering treatments much earlier in the disease process.¹¹ These resources of time, talent and treasure are precious. We owe it to the taxpayers, to the research community and – most of all – to people living with, or at risk of, Alzheimer's disease and related disorders to apply those resources in the most efficient and ethically consistent manner possible.

The single IRB policy is an indispensable step in this direction, particularly as an increasing number of Alzheimer's disease and related disorders trials involve multiple sites, including groundbreaking "prevention" trials that seek to determine if treatments administered when the disease is in earliest stages can slow, delay or amend its progression. Given this potential, we again offer our **strong support for the NIH draft policy to promote the use of a single Institutional Review Board of record for domestic sites of multi-site studies funded by the National Institutes of Health.**

Thank you for considering our views and for your commitment to overcoming Alzheimer's disease and related disorders. Please contact Ian Kremer from Leaders Engaged on Alzheimer's Disease (the LEAD Coalition)¹² at ikremer@leadcoalition.org or (571) 383-9916, with questions or for additional information.

Sincerely,

Academy of Radiology Research Activists Against Alzheimer's
African American Network Against Alzheimer's
Alliance for Aging Research Alzheimer's & Dementia Alliance of Wisconsin
Alzheimer's Drug Discovery Foundation
Alzheimer's Foundation of America, LEAD Coalition co-convenor
Alzheimer's Tennessee American Academy of Neurology
American Association for Long Term Care Nursing
American Federation for Aging Research (AFAR)
American Geriatrics Society American Society of Nephrology Assisted Living Federation of America
Laura D. Baker, PhD (Wake Forest School of Medicine*)
Banner Alzheimer's Institute Beating Alzheimer's by Embracing Science Biogen Idec
Biotechnology Industry Organization
Blanchette Rockefeller Neurosciences Institute
B'nai B'rith International
James Brewer, M.D., Ph.D. (UC San Diego and Alzheimer's Disease Cooperative Study*)
BrightFocus Foundation Caregiver Action Network
Center for Alzheimer Research and Treatment, Harvard Medical School
Center for BrainHealth at The University of Texas at Dallas
Center to Advance Palliative Care Sandra Bond Chapman, PhD (Center for BrainHealth at The University

of Texas at Dallas*)

ClergyAgainstAlzheimer's Coalition for Imaging and Bioengineering Research Cognition Therapeutics

Suzanne Craft, PhD (Wake Forest School of Medicine*)

Critical Path Institute

Jeffrey Cummings, MD, ScD (Cleveland Clinic Lou Ruvo Center for Brain Health*)

Cure Alzheimer's Fund

Darrell K. Royal Fund for Alzheimer's Research

Department of Neurology, Washington University School of Medicine

Rachelle S. Doody, MD, PhD (Baylor College of Medicine*)

Geoffrey Beene Foundation Alzheimer's Initiative

Georgetown University Medical Center Memory Disorders Program

Gerontological Society of America Global Coalition on Aging

David Holtzman, MD (Washington University School of Medicine, Department of Neurology*)

Home Instead Senior Care Huntington's Disease Society of America

Janssen Research & Development, LLC

Diana R Kerwin, MD (Texas Alzheimer's and Memory Disorders)

Walter A. Kukull, PhD (School of Public Health, University of Washington*)

LatinosAgainstAlzheimer's Latino Alzheimer's and Memory Disorders Alliance LeadingAge

Lewy Body Dementia Association LinkedSenior

LuMind Foundation (formerly Down Syndrome Research and Treatment Foundation)

Mary Mittelman, DrPH (New York University Medical Center*)

David G. Morgan, PhD (Byrd Alzheimer's Institute, University of South Florida*)

National Alliance for Caregiving National Association of States United for Aging and Disabilities

National Certification Council for Activity Professionals

National Consumer Voice for Quality Long-Term Care

National Down Syndrome Society National Task Group on Intellectual

Disabilities and Dementia Practices

Neurocern

Neurotechnology Industry Organization New York Academy of Sciences

NYU Alzheimer's Disease Center

OWL-The Voice of Women 40+ Pioneer Network

Piramal Imaging S.A. Presence Care Project

Peter Reed, PhD (Sanford Center for Aging, University of Nevada Reno*)

Eric Reiman, MD (Banner Alzheimer's Institute*)

ResearchersAgainstAlzheimer's Reisa A. Sperling, MD, MMSc (Center

for Alzheimer Research and Treatment, Harvard Medical School*)

Rudolph Tanzi, PhD (Department of Neurology, MGH/Harvard Medical School*)

Taos Health Systems

The Association for Frontotemporal Degeneration

The Eden Alternative

The Evangelical Lutheran Good Samaritan Society

THE GREEN HOUSE® Project

R. Scott Turner, MD, PhD (Georgetown University Memory Disorders Program*)

USAgainstAlzheimer's, LEAD Coalition co-convener

USF Health Byrd Alzheimer's Institute Volunteers of America

Michael W. Weiner, MD (University of California San Francisco*)

Women Against Alzheimer's

* Affiliations of individual researchers are for identification purposes only and do not necessarily represent the endorsement of the affiliated institution

Footnotes

¹ <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-026.html>

² <http://aspe.hhs.gov/daltcp/napa/NatlPlan.pdf>

³ <http://www.nejm.org/doi/pdf/10.1056/NEJMs1204629>

⁴ <http://www.neurology.org/content/early/2014/03/05/WNL.0000000000000240>

⁵ <http://www.alz.org/trajectory>

⁶ <http://www.nia.nih.gov/alzheimers/publication/2012-2013-alzheimers-disease-progress-report/genetics-alzheimers-disease>

⁷ http://www.alz.org/downloads/facts_figures_2014.pdf

⁸ http://www.usagainstalzheimers.org/sites/default/files/USA2_AAN_CostsReport.pdf

⁹ <http://www.nhcoa.org/wp-content/uploads/2013/05/NHCOA-Alzheimers-Executive-Summary.pdf> and http://www.usagainstalzheimers.org/sites/all/themes/alzheimers_networks/files/LatinosAgainstAlzheimers_Issue_Brief.pdf

¹⁰ http://aadmd.org/sites/default/files/NTG_Thinker_Report.pdf

¹¹ <http://www.nia.nih.gov/alzheimers/publication/2012-2013-alzheimers-disease-progress-report/advancing-discovery-alzheimers#priorities>

¹² <http://www.leadcoalition.org> Leaders Engaged on Alzheimer's Disease (the LEAD Coalition) is a diverse national coalition of member organizations including patient advocacy and voluntary health non-profits, philanthropies and foundations, trade and professional associations, academic research and clinical institutions, and homecare, biotechnology and pharmaceutical companies. The LEAD Coalition works collaboratively to focus the nation's strategic attention on Alzheimer's disease and related dementias -- including vascular, Lewy body or frontotemporal dementia -- and to accelerate transformational progress in detection and diagnosis, care and support, and research leading to prevention, effective treatment and eventual cure. One or more participants may have a financial interest in the subjects addressed.

Comment #120

Commenter: Skyler Kramer

Date of comment: January 28, 2015

Comment:

Please note that the viewpoints below are mine alone and do not represent the views of my employer or any other organization.

My name is Skyler Kramer and I am a CRO Study Startup professional at inVentiv Health and I work with central IRB and local IRB sites/studies on a daily basis. It seems that most people within the CRO industry are in favor of utilizing central IRB reviews for more studies and fewer local IRB reviews. Overall, central IRB review is faster than most local institutional reviews and if we can trim timelines and get drugs to market faster, then patients can have access to treatments more quickly. This is sound logic and there is no doubt that many of the local IRB review administrative processes can be more of a hindrance than a help to the research process. However, I do think there is another side to this that must be considered.

On several occasions, most often on complex trials like oncology or gene therapy, I have seen commercial central IRB reviews that do not yield any questions or comments upon review of the protocol whereas multiple local IRB reviews yield comments and concerns. Oftentimes, these comments and concerns are just precautionary, but other times they can be significant findings that result in an amendment to the protocol. These findings are usually not ethical findings per se, but rather scientific improvements to the protocol that could enhance the validity of the trial data or improve the efficiency of the trial. I think that these local IRB reviews do have something to offer in that regard and I fear that we would miss some of those ideas from the local institutions that actually perform the research on a daily basis.

Nevertheless, recognizing that the status quo involves too many unnecessary administrative delays, I think that there is another solution here. Many of these local IRB sites (typically universities and hospitals) have scientific review committees (SRC) or protocol review committees (PRC) that those institutions mandate must review the protocol to determine the scientific merit and oftentimes feasibility of the protocol to be run at the trial site. These committees also often yield useful comments or ideas that can improve the study from a data, safety or efficiency standpoint. Furthermore, these committees are already in place and are reviewing most of the trials that fall under local IRB jurisdiction. I think it would be a very good idea to have a central IRB for all clinical trials in the USA, but to also have a scientific review be encouraged or required by federal guidance in order to maintain independent scientific reviews of the protocol. Each trial should undergo at least one scientific review process (could be a separate committee at central commercial IRB or local IRB sites) in addition to the IRB review process. The scientific review would focus on how to improve the protocol from a scientific standpoint while the IRB could then focus on the ethics and protecting welfare of subjects. This would allow us to maintain the benefit of potential protocol enhancement through multiple scientific reviews of the protocol (that already occur at many local IRB sites) while also improving trial efficiency by reducing IRB review timelines.

Comment #121

Commenter: Mark Cotton

Date of comment: January 28, 2015

Comment:

Important question is applicability to international sites It will require some capacity but a central IRB for South Africa could work; our local IRB is now much slower due to its own limited capacity; I think it would work It may be more difficult to have a central IRB for the Continent, although with time, could work
Sincerely Mark Cotton PI Stellenbosch University CTU for ACTG & IMPAACT

Comment #122

Commenter: Annet Nakaganda

Date of comment: January 29, 2015

Comment:

As stated this can only work in USA. But if study sites involve other institutions outside USA, we shall need review and approval of local IRBS to implement the trials.

Comment #123

Commenter:

Date of Comment:

Comment:

January 29, 2015

Office of Clinical Research and Bioethics Policy

Office of Science Policy

National Institutes of Health (NIH)

6705 Rockledge Drive, Suite 750

Bethesda, MD 20892

SingleIRBpolicy@mail.nih.gov

RE: NOT-OD-15-026: Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

Dear Sir/Madam:

The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from discovery, pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. With more than 110,000 employees engaged in research activities around the world, ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research.

Each year, ACRO member companies conduct more than 11,000 clinical trials involving nearly two million research participants in 115 countries. On average, each of our member companies works with more than 500 research sponsors annually, including as sub-contractors to NIH grantees, and we have a broad and unique understanding of the roles, responsibilities and behavior of all the stakeholders – research sponsors, investigators, Institutional Review Boards (IRBs,) clinical trial participants and ancillary providers of all types – that are part of the research enterprise.

ACRO thanks the NIH (the Agency) for issuing this Draft Policy and is pleased to support the use of a single IRB for multi-site research projects in the comments to follow.

Duplicative IRB Review Delays the Initiation of Multi-Site Studies

As the Agency points out in the Background section of the draft policy, “there is no evidence that multiple IRB reviews enhance protections for human subjects.” The FDA (2006) and the Office for Human Research Protections (OHRP) in 2010 have issued guidance to allow institutions participating in multi-site studies to use joint review, rely on the review of another qualified IRB (besides the institution’s own,) or establish other arrangements for avoiding duplication of effort. Notwithstanding the encouragement provided by the FDA and NIH and longstanding examples of successful implementation, such as the Central Institutional Review Board (CIRB) utilized for the review of NCI-sponsored clinical trials, adoption of single (or central or lead) IRB review models has occurred in only a small percentage of multi-site research projects.

Some institutions express concerns about a potential lack of clarity concerning regulatory and legal liability of cooperative IRB review arrangements. But the practical result of this is that multi-site research studies are delayed. Data provided by several of our member companies suggests that in commercially-sponsored research duplicative IRB review results in significant delays; for example, from initiating a

multi-site study in less than 50 days with a central IRB model to well over 100 days with duplicative local reviews. We believe the magnitude of delay is worse for NIH-sponsored multi-site studies. The time savings of a single IRB model has a meaningful impact, not only on the costs and time to develop a new product or treatment, but on the ultimate availability of drugs, device and treatments for the patients who are waiting.

The Draft Policy moves from “May” to “Should” and relevant Guidances Must Catch Up

Beyond the institutional turf and lack of trust issues that may underlie resistance to the use of a single IRB model, it is certainly possible that the overlapping and potentially contradictory requirements of Common Rule and FDA regulations make a complicated situation even more so. For example, the Common Rule (45 CFR Part 46) at 46.114 states, “In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy [emphasis added.] With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements to avoid duplication of effort.” By contrast, FDA regulation (21 CFR Part 56) at 56.114 says, “In complying with these regulations, institutions involved in multi- institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.” It seems to us that this emphasis on the responsibility of “each institution” has exacerbated institutional concerns about the potential liability of shared review arrangements, and we believe it would be helpful for OHRP to issue an interpretation of 46.114 that aligns with the straightforward and unambiguous encouragement of avoidance of duplication of 56.114 in order to facilitate acceptance of this Draft Policy.

The Draft Policy distinguishes between the accountability of the single IRB for a multi-site project as the IRB of record, and the responsibility of participating sites to meet other regulatory obligations, such as obtaining informed consent, overseeing the implementation of approved protocols, reporting adverse events to the single IRB, etc. Further to the question of needed guidance, we believe it would be useful for OHRP to issue, prior to implementation of the Draft Policy, guidance discussing the kinds of “mechanisms” that should be established for the consideration of local issues, involvement of vulnerable populations, and the like.

The Draft Policy stipulates exceptions to the use of a single IRB, including as required by federal, tribal, or state laws or regulations, which makes sense. However, the Policy indicates that the NIH will not “prohibit any participating site from carrying out its own IRB review” if it chooses to. While the Draft Policy says that the cost of such duplicative review must be borne by the site, we would suggest that the Agency reinforce the importance of not delaying multi-site studies by stipulating that any additional review, beyond that of the single IRB of record, must be completed within 10 days of the institution’s agreement to participate as a research site.

Concluding Remarks

By proposing to make compliance with the use of a single IRB for multi-site research a term and condition of NIH awards and contracts, the Agency is committing to achieving greater efficiencies of review and speeding the initiation of studies across the NIH’s clinical research portfolio. ACRO salutes this bold stroke, which we believe will have a significant and salutary impact on FDA-regulated, multi-site studies, as well.

Public Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

Please do not hesitate to contact ACRO if we can provide further information (knoonan@acrohealth.org or 202-464-9340). We look forward to opportunities to collaborate with the Agency in implementing this needed change in order to facilitate the timely initiation of multi-site research projects.

Respectfully submitted,

Karen Noonan
Vice President, Global Regulatory Policy

Comment #124

Commenter:

Date of Comment:

Comment:

January 29, 2015

[By email to singleirbpolicy@mail.nih.gov]

Office of Clinical Research and Bioethics Policy

Office of Science Policy, NIH

Telephone: 301-496-9838

Re: NOT-OD-15-026: “Request for Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research”

Dear Sir/Madam:

The Infectious Diseases Society of America (IDSA) is pleased to offer comments on the draft National Institutes of Health (NIH) policy on “The use of a single institutional review board (IRB) for multi-site research.” IDSA represents over 10,000 infectious diseases physicians and scientists devoted to patient care, disease prevention, public health, education, and research in the area of infectious diseases. Our members care for patients of all ages with serious infections, including meningitis, pneumonia, tuberculosis, HIV/AIDS, antibiotic-resistant bacterial infections such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) vancomycin-resistant enterococci (VRE), and Gram-negative bacterial infections such as *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, and, finally, emerging infections such as Ebola virus, enterovirus D68, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and bacteria containing the New Delhi metallo-beta-lactamase (NDM) enzyme that makes them resistant to a broad range of antibacterial drugs.

IDSA has long supported efforts to streamline the regulatory process while maintaining research participant protections. As highlighted in our [2009 letter](#) to the National Institutes of Allergy and Infectious Diseases (NIAID) and [2011 response](#) to the Department of Health and Human Services (DHHS) Advance Notice of Proposed Rulemaking “Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Researchers”, IDSA strongly supports a mandated central IRB for NIH funded domestic multi-site research studies.

While IDSA applauds the draft policy and agrees central IRBs will streamline the regulatory process for multi-site trials, we advise the NIH to consider several points as it finalizes this policy. IDSA recommends that the NIH clearly delineates the responsibilities for patient safety between the central IRB and its partner institutions in order to avoid ambiguity in accountability and liability in multi-site trials. During the review process, the central IRB and partners should also maintain transparency by communicating who on the committee is reviewing a given protocol.

In the current period of fiscal austerity, it is important to verify how funding will impact the administration of a central IRB. In the unlikely event that funding for the central IRB is significantly cut or eliminated, the NIH should ensure a procedure is in place to continue review, adverse event monitoring and consent changes for ongoing multi-site trials. Also, the NIH should clarify how central IRB designation is tied to the origin of funding. For example, if a grant supporting a multi-site trial is awarded to a principal investigator (PI) at one institution, and the PI moves to another institution, would the central IRB designation stay with the investigator or institution?

Finally, IDSA applauds the draft policy's measures to address local institution perspective on issues such as the adequacy of informed consent. IDSA believes in some cases, informed consent documents require local context for adequate participant understanding, which may complicate the establishment of a unified informed consent document. IDSA recommends the NIH establish clear guidelines for how and when local institutions can alter a central IRB informed consent document to fit local needs.

IDSA is committed to ensuring that critical research is performed as efficiently as possible while maintaining transparent, robust protection for research participants. We thank NIH for this draft policy, and look forward to working with you on additional mechanisms to provide greater efficiency. We hope these comments prove useful for the NIH as it moves forward with its draft policy. Should you have any questions or concerns about these comments, please feel free to contact Greg Frank, PhD, IDSA Program Officer for Science and Research Policy, at gfrank@idsociety.org or 703-299-1216.

Sincerely,

Stephen B. Calderwood, MD, FIDSA
IDSA President

Comment #125

Commenter:

Date of Comment:

Comment:

January 29, 2014

Sarah Carr, Acting Director
Office of Clinical Research and Bioethics Policy
Office of Science Policy, National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Re: NOT-OD-15-026, Draft Policy on Single IRB

Dear Acting Director Carr:

The Parkinson's Action Network (PAN) appreciates the opportunity to comment on NOT-OD-15-026, the NIH draft policy to promote the use of a single Institutional Review Board (IRB) of record for domestic sites of multi-site studies funded by the National Institutes of Health (NIH).

PAN is the unified voice of the Parkinson's community advocating for better treatments and a cure. In partnership with other Parkinson's organizations and our powerful grassroots network, PAN educates the public and government leaders on better policies for research and improved quality of life for the 500,000 to 1.5 million Americans living with Parkinson's disease. Parkinson's disease is a progressive, degenerative neurological disorder for which there are no treatments that slow or halt progression. Current treatments for Parkinson's are based on an over 50-year-old therapy, which treats only some symptoms for some people and eventually loses its effectiveness.

We recognize that IRBs are an integral part of a clinical trial process that has at times become stagnated by outmoded procedures and protocol with respect to design and reporting mechanisms. We support instituting a single IRB for multi-site studies for the application of more consistent and streamlined standards of trial development that strengthen study integrity, protection of participants, and open opportunities for meaningful discoveries with respect to Parkinson's and other chronic conditions. This proposal represents the simplest step to advance the speed of invaluable medical research and bring cures faster to patients.

We understand that the use of a single IRB for multi-site studies helps to create standardization for clinical trials. However, single IRBs may also raise ethical, safety, and liability questions, including review quality and the possible loss of the safety net of redundant review. In further development of the policy, we urge NIH to consider and address these potential concerns through a lens that always considers first what is in the best interests of the patients and participants.

Thank you again for this opportunity to comment on NOT-OD-15-026. Please feel free to contact me at tthompson@parkinsonsaction.org or Jennifer Sheridan Palute, director of policy, at jjalute@parkinsonsaction.org with any additional questions.

Sincerely,

Ted Thompson, J.D.
Chief Executive Officer Parkinson's Action Network

Comment #126

Commenter:

Date of Comment:

Comment:

January 29, 2015

Via Electronic Delivery

Office of Clinical Research and Bioethics Policy
Office of Science Policy
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Re: Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research (Notice No. NOT-OD-15-026)

To Whom It May Concern:

Northwestern University appreciates the opportunity to comment on the above-referenced draft NIH policy. As noted in footnote 11 of the Request for Comments, the 2011 Advanced Notice for Proposed Rulemaking (ANPRM) also sought comment on the use of a single IRB for domestic sites in multi-site studies. Northwestern's comments on the ANPRM supported this concept and we maintain our position on this matter. In 2011 we wrote:

Northwestern supports the concept of mandating use of a single IRB for domestic, multi-site studies. In the absence of a mandate it is likely many institutions will continue to require local IRB review due to concern for institutional liability. Having a central IRB is already an option used by some institutions under certain circumstances. By only "encouraging" use of a single IRB of record for multi-center trials, the complexity of managing the trials is likely to increase, which will increase the workload and cost for the trial's data or clinical coordinating center, and as a result the cost to sponsors. Differences in how participating sites handle IRB review will result in a situation that is unchanged from or worse than currently exists.

In the intervening years the use of single IRBs for multi-site studies has increased, and our experience with this approach, while overall positive, has highlighted some concerns, including with NIH-funded studies. The assumption that a single IRB will make the process more efficient is only partially true. While one institutional review of the protocol does eliminate duplicative effort at the front end, each institution is still conducting local context review of the informed consent and needs to review the protocol for post-approval monitoring and/or for-cause auditing purposes. Moreover, the involvement of multiple institutions with separate electronic systems makes data and document sharing challenging and inefficient. Additionally, the use of single IRBs has created a notable administrative burden for the staff supporting the IRB process. For example, for one NIH-funded study, our IRB administrative staff had to attend a two-day study start-up meeting in Washington, DC, multiple webinars and other meetings with no compensation for time and effort. Additionally, on another study, the establishment of a NIH-mandated single IRB is requiring considerable administrative time and effort for staff at all institutions participating in the project, without compensation. NIH should be mindful of the administrative burden associated with the establishment and use of single IRBs and allow institutions to direct charge extraordinary administrative expenses.

Although Northwestern appreciates NIH's desire to move forward in requiring the use of single IRBs for multi-site studies (under certain circumstances), the university research community would benefit from a more unified federal approach rather than agency-specific changes. Hence, the preferred course would be for HHS to take action on the 2011 ANPRM and implement revisions to the Common Rule.

Thank you again for the opportunity to comment.

Joseph T. Walsh
Vice President for Research
Professor of Biomedical Engineering

Comment #127

Commenter:

Date of Comment:

Comment:

January 29, 2015

Francis S. Collins, M.D., Ph.D., Director
National Institutes of Health
Office of Clinical Research and Bioethics Policy
Office of Science Policy
National Institutes of Health 6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Dear Dr. Collins:

The Cystic Fibrosis Foundation appreciates the opportunity to comment on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research. We commend the National Institutes of Health (NIH) for publishing and seeking comment on a policy that is intended to produce efficiencies in the clinical trials process while still protecting research participants. At a time when research resources are restrained, efforts to reduce redundancy and improve efficiency in research should be considered if they can be implemented without risk to research participants.

Trials evaluating CF therapies are multi-site trials that can be slowed by repetitive review by local institutional review boards (IRBs). Our comments below reflect the experience of the Cystic Fibrosis Foundation and CF investigators who are engaged in multi-site review.

Consideration of Local Issues

In the draft policy, NIH identifies strategies for consideration of local issues by a central review board. The policy suggests that local issues and issues related to vulnerable populations might be addressed by the use of consultants or ad hoc members of the central review board with special knowledge of these issues. We are pleased that the policy acknowledges the need to address such issues, and we agree that there are opportunities within the central review structure for considering these matters.

Exceptions to the Presumption of Central Review

The draft policy would permit exceptions to the general policy of central review. The policy states that "Exceptions will be allowed only if the designated single IRB is unable to meet the needs of specific populations or where local IRB review is required by federal, tribal, or state laws or regulations." As the draft policy is implemented through additional guidance and in grant and contract conditions, we recommend that the standards for permitting exceptions to central review be more specifically described.

Clarity about the standards for exceptions will help to ensure that exceptions are granted when central review is not adequate and will also protect against exceptions undermining the policy, which favors central review.

Respective Responsibilities of Central Review Board and Local Boards

According to the draft policy, the central review board will have responsibility for initial and continuing research review. The policy also states that, "All participating sites will be responsible for meeting other regulatory obligations, such as obtaining informed consent, overseeing the implementation of approved

protocols, and, reporting unanticipated problems and adverse events to the single IRB of record.” As the central review policy is implemented, we anticipate that additional clarification will be necessary regarding the “continuing research review” responsibilities of central review boards compared to the “other regulatory obligations” that will be retained by local boards. In order to avoid confusion and duplication of efforts, additional guidance related to ongoing oversight of studies and the respective responsibilities of the central and local review boards will be helpful.

We recommend that any additional guidance on this policy also address the liability concerns of research institutions. Some have voiced concerns about how liability issues will be addressed as they move toward utilization of single review boards.

NIH Leadership in Forming Central Review Boards

In the document outlining the draft policy on central review, NIH notes the successful experience with central review boards of the National Cancer Institute and the National Institute for Neurological Disorders and Stroke. As the NIH moves forward with a policy that encourages central review for NIH grantees, we urge the agency to consider undertaking additional efforts to convene and fund central review boards.

We appreciate the opportunity to comment on the central review policy and commend NIH for advancing policies intended to bring efficiencies to the research process.

Sincerely,

Robert J. Beall, Ph.D.
President and Chief Executive Officer

Comment #128

Commenter: Scott L. Rauch, M.D.

Date of Comment:

Comment:

January 28, 2015

To Whom it May Concern:

Thank you very much for providing the opportunity to comment on the NIH Draft Policy entitled: *Use of Single Institutional Review Board for Multi Site Research (Draft Policy)*. I am writing on behalf of McLean Hospital, an affiliate of the Massachusetts General Hospital and a member of the Partners HealthCare System. A major teaching facility of the Harvard Medical School, McLean maintains the largest program of research in neuroscience and psychiatry of any private psychiatric hospital in the U.S. In FY 14, McLean received approximately \$28million in research funding from the NIH. Thus, reform of policies pertaining to Institutional Review Boards is of critical importance to McLean's research enterprise.

As a participant in multiple single IRB (SIRB) arrangements, including as a Central IRB, we strongly support the development and facilitation of SIRB review. However, we believe that the Draft Policy as written is premature in its breadth and inflexibility and does not adequately acknowledge or address the gaps in current knowledge about the relative benefits and costs of SIRB systems. As indicated in our detailed comments below, we propose that more research be conducted before mandating SFRB review for all types of multi-site studies and that the initial policy focus on a more limited set of research.

Our comments are organized into three sections: 1) comments on the assumptions/assertions made in the introduction to the Draft Policy; 2) comments on the specific proposals of the Draft Policy and 3) suggestions for alternate approaches.

Introductory assumptions/assertions:

Use of an SIRB for domestic multi-site research is promoted as promising potential advantages of efficiency, decreased time to study start-up and consistency of review and even conduct of the research. However, there is currently little research or data to demonstrate that these potential benefits will materialize in particular types of multi- site research, that they can be realized with no accompanying decrease in human subject protections, or that they outweigh the significant costs and resource investments required to implement a single IRB system in which all parties can have confidence.

A few specific comments:

The Draft Policy presumes that there will be efficiency in the initiation/initial review of a study. In our experience with serving as the SIRB and relying on other SIRBs, the efficiency has not been in the initial review of the protocol, but rather in the addition of sites after initial protocol review as well as in the subsequent reviews through the life of the protocol; e.g., continuing review, unanticipated problems (UAPs).

The Draft Policy asserts that local IRB review is not needed for assessing local context. While we agree this is not an IRB regulatory requirement, we note that it is generally the local IRB or at least the local IRB office that is most knowledgeable about the local context and about the application of local rules and norms to the conduct of research. Therefore recognition of the practical reality of ongoing IRB office, if not IRB, involvement is necessary.

The Draft Policy casts use of a SIRB as more cost effective than local IRB review. More information is needed before this can be accepted as a benefit.

Details of the Draft Guidance:

Our comments on specific proposals or aspects of the Draft Policy are listed here. Discussion of each item immediately follows this list.

1. The broad scope of the mandate - all multi-site domestic research with NIH
2. funding - without regard to the type of research or number and type of sites and to the existence of central infrastructure to support the SIRB
3. The limited scope for exceptions
4. Lack of details and proposed financial support for management of the necessary research oversight processes at the reviewing SIRB and the relying sites, and for required communication between them
5. Lack of details regarding expectations when the local IRB elects to review a project subject to the policy
6. Absence of information about the selection/approval criteria for the SIRB, including whether the SIRB's willingness/ability to serve as a HIPAA Privacy Board will be a factor
7. Apparent lack of coordination with other proposed mandates and/or regulatory changes regarding the use of SIRBs, including the 2009 and 2011 ANPRMs referenced in the Draft Policy

1. The broad of the mandate:

The Draft Policy describes in general the requisite responsibilities for both the reviewing SIRB and the relying institutions. But it fails to recognize how different types of studies require vastly different logistics and resources for both the SIRB and the relying institution. Due to these differences, there are multi-site studies that fit more easily into an SIRB approach and there are others that do not.

In our experience, examples of factors to consider before deciding that SIRB review is appropriate include:

- **Number of institutions:** a study involving 2 sites versus one with 75 will have very different impact on coordination, workflow and resources needed.
- **Types of institutions:** The success of SIRBs is predicated on trust and mutually agreed-upon processes. The SIRB must have confidence that the sites relying on the SIRB have good HRPPs that can provide all of the institutional requirements. And the relying sites must trust that the SIRB is a quality IRB that will be accessible to the each site. This trust grows from various factors, including the sites' and SIRBs' level of experience conducting or reviewing the type of studies at issue, the size of the respective research programs, and familiarity with one another's state and local rules and culture. Mandating a SIRB arrangement among several academic medical centers in the same area that are frequent collaborators is very different than mandating SIRB review among these centers and small private physician practices in different states.
- **Types of studies:** Minimal risk studies generally have few ancillary committee reviews as well as few amendments and UAPs over the course of the study. In contrast, more than minimal risk studies generally have ancillary committee reviews as well as frequent amendments and UAPs that require IRB review. The logistics and resources needed for SIRB review vary as a function of the type of research; hence adequacy of infrastructure must be assessed for each study.
- **Types of study teams:** Multi-site studies require some level of study team coordination. However, the degree of coordination that is customary and readily achievable varies: robust research networks with clinical and data coordinating committees are vastly different from one-time affiliations of several colleagues with no existing infrastructure. The 'one-time-affiliations' often lack the skills as well as funding to coordinate with a SIRB.

- Resources for the SIRB: If an institution is expected to provide SIRB services as an 'add-on' with no additional resources, then its overall capacity will be severely limited. For example, a 50 site high risk interventional study would easily require a full-time liaison to simply handle communications between all sites for initial review, continuing review, adverse events, amendments, etc. In addition, information technology (IT) resources must be in place to accommodate handling the processes between the participating institutions. In many situations this requires either a new system or a work-around of an existing IT system.
- Resources for Investigators: teams will have to assume much of the coordination functions between the sites - this will require resources.

The Draft Policy does not currently allow for consideration of such heterogeneity. A minimal risk study conducted at 4 institutions that are members of an existing network defies comparison with an interventional high risk study conducted at 25 institutions that have been newly brought together for specific research, in terms of capabilities, comfort level, and resources needed.

2. The limited scope for exceptions is not adequate

The Draft Policy states that "exceptions will be allowed only if the designated SIRB is unable to meet the needs of specific populations or where local IRB review is required by federal, tribal, or state laws or regulations." For all of the reasons addressed above, if the final policy adopts the broad scope that is proposed, we believe that there are many other factors that should be considered as justification for an alternate approach or an exception, including the type of study, types and numbers of involved institutions, and type of study team. In addition, it is unclear what sorts of situations would constitute inability to meet the needs of specific populations or why this could not be assessed before any particular IRS is designated as the SIRS.

3. Lack of details and proposed financial resources to support the processes at both the reviewing SIRB as well as the relying sites

The default in any reliance arrangement is that the only task that is ceded is the IRB regulatory review; all institutional responsibilities generally remain with the local sites and some in fact cannot be ceded. Institutional responsibilities include, for example, HIPAA determinations related to the study, ancillary committee reviews, compliance with state laws, COI, CMS, and training of investigators. Tasks like ancillary committee reviews necessarily must remain with the local sites, as must ultimate responsibility for compliance with state laws. Hence in ceded review, the relying sites retain significant tasks. These are tasks that in many institutions are completed by the IRB (such as in the case of HIPAA) or otherwise by the IRB office and closely integrated into the overall review of a protocol. When IRB review is ceded, the relying institution must develop processes and systems (often new IT systems) by which they not only coordinate these institutional responsibilities but also communicate their determinations to the SIRB.

Providing SIRB capacity requires planning and process development including identification of resources needed for both setting up the SIRB as well as completing the protocol review. The tasks for setting up a SIRB include for example: negotiation of reliance agreements; performance of due diligence of the relying sites; development of SOPs that address processes for communication between the SIRS and all relying sites, processes for obtaining and considering relying site issues such as HIPAA authorizations or waiver of authorization determinations, ancillary committee reviews, COI, CMS, sign-off on PI training, processes for dealing with noncompliance and required reporting, etc. Once these systems are set up, the SIRB must then be able to conduct all regulatory reviews (initial, continuing, amendments, UAPs etc) after obtaining appropriate input from local sites.

As noted above, the level of resources needed for serving as a SIRB as well as relying on a SIRB will be

informed by the type of study; e.g., complexity of the study, number of sites, structure of the study team etc.

We (institutions, IRBs, sponsors, regulatory agencies) do not yet have accurate information on these costs. Without this information, it will be difficult for institutions to responsibly serve as a SIRS or agree to rely. This discussion is further complicated by the paucity of data regarding the cost of local IRB review. As noted above, most IRB offices are responsible for much more than the regulatory review and it may be difficult to disentangle the costs of that regulatory review from all of the other tasks that the IRB/IRB office performs.

Adding to the comments made above - is the fact that we are currently in a time of evolving and multiplying SIRB models. At present there are a number of different models which share some features, but which each have their own approach. IRBShare is an example of a "share model" in which IRB regulatory review is shared between the SIRB and local IRBs. In contrast are the "nonshare" models in which all regulatory review is completed by the SIRB; examples include systems used by the VA, NCI and NeuroNEXT. Mandating SIRB review at this time without review and analysis of the relative benefits and costs of each model or determination which is most appropriate for different types of NIH-funded research just adds another requirement to the explosion of different models and approaches. A single institution may be faced with serving as a SIRB for several completely different types of research as well relying on several other SIRBs, each of which has their own policies and procedures. If the Draft Policy is finalized as proposed, different SIRB systems would be developed. This would then require that relying institutions have the infrastructure and resources needed to maintain working interfaces with multiple somewhat different systems. This could in fact decrease the efficiency of protocol review.

The proposal states that if the identified central IRB is a for-fee IRB, then that cost can be included in the budget. IRBs based at academic centers are typically not fee based, at least not for all reviews they perform—yet they will have to assume significant increases in work, as well as development of systems to comply with this proposal. How will that be funded?

4. Suggestion of SIRB AND local IRB review

The Draft Policy allows for parallel reviews, as we agree is appropriate in the absence of any current regulatory mandate for SIRB review. However, the policy does not discuss the implications of a situation in which both a designated SIRB and a local IRB(s) perform a regulatory review of a study. From a regulatory perspective, we presume that NIH agrees that both IRBs would have authority, and as a practical matter, the result is that the most stringent (protective of human subjects) requirements must govern. How does NIH intend for this concurrent review scenario to work, and what communication will occur to ensure that the designated SIRB selected by NIH is aware of the other IRBs' reviews?

5. Selection criteria for the SIRB

The Draft Policy does not indicate what criteria will be used by NIH to evaluate and select the SIRS. Transparency around this determination is critical for institutions and IRBs participating in trials subject to the policy to understand NIH's expectations and to develop robust proposals if they are interested in being designated as the SIRB.

Without limiting this general comment, we note that the Draft Policy does not mention the requirements of the HIPAA Privacy Rule for use or disclosure of Protected Health Information for research. Depending on the type of study at issue, the researchers may request a waiver of authorization for use/disclosure of PHI. Under the HIPAA Privacy Rule, a Privacy Board must determine whether a waiver is appropriate for the study and document that determination. In practice, many IRBs serve as the Privacy Boards for their institutions. In our experience, including reliance arrangements

where NIH's IRBs are designated as the SIRB, the designated IRB is not always willing to serve as a Privacy Board for the relying institutions. In such situations, the relying institutions (and specifically, their IRBs) must then review the study sufficiently to be able to apply the HIPAA waiver criteria and make the waiver determination. When this occurs, the potential efficiencies of the SIRS review are diminished. Does NIH intend to require willingness to serve as a HIPAA Privacy Board in order for an IRB to be selected as the SIRB under this policy?

6. Lack of coordination with other proposed mandates and/or regulatory changes regarding the use of SJRBs

As noted in the Draft Policy, there are two outstanding ANPRMs, from 2009 and 2011, that contain proposals relevant to reliance arrangements and requirements for use of single IRBs. It is not clear to us whether HHS intends to proceed with proposed regulatory change as discussed in the 2009 ANPRM, that would clarify regulatory responsibilities of each of the parties in a reliance arrangement and establish direct regulatory liability of IRBs. It is also not clear to us whether single IRB review will be mandated as a result of the 2011 ANPRM, and if so, for what scope of studies. Establishing a funding policy mandating broad use of single IRBs in advance of the resolution of these two regulatory initiatives may create confusion or result in inconsistencies if and when regulatory changes are adopted. We believe that it makes more sense for NIH's focus at the present time to be on funding additional research examining the potential benefits and costs of single IRB use as suggested above.

Suggestions for alternate approaches:

As noted above, we strongly support the development and facilitation of SIRBs for some multi-site research. We also note that the use of external IRBs is not a new concept and there is an experience upon which to build. Most academic medical centers (AMC) have experience relying on an IRB at another AMC; these arrangements are often limited to no more than minimal risk research conducted at two or three sites. In addition, many AMCs have experience relying on commercial/independent IRBs for a select category of research - most often industry-sponsored and initiated, phase 3 and 1 multi-site research. What is new with the NIH Draft Policy is the inclusion of all NIH-funded multi-site research regardless of type of study or number of institutions.

Given the current evolution of SIRB models and the paucity of data regarding these models, we suggest a more tempered approach. Instead of broadly requiring a SIRB for any NIH-funded multi-site research, we propose refining the policy either to be limited (for now) to minimal risk research involving no more than several sites or, if it remains broad, to including a process whereby flexibility be built into the policy to account for various types of research and other specific factors more fully discussed above. In this way, use of a SIRB could be considered case-by-case before being required by NIH as a condition of funding.

We also suggest that NIH simultaneously fund research on existing SIRS models to evaluate potential benefits and costs for both the SIRS site as well as relying sites. This could include research focused at models that are currently reviewing NIH-funded research or NIH could also identify a cohort of clinical research for which the NIH will fund a SIRB and as a condition of grant award require research on the SIRB itself.

All of these approaches would inform the process going forward.

In addition, NIH could convene expert panels to focus on a number of SIRS-related issues; such as, developing criteria to identify research best reviewed by a SIRB; identifying the elements and resources needed to provide SIRB services within an AMC; and evaluating the pros and cons of various reliance models.

Finally, NII I could support the development of tools that could facilitate SIRB processes — this would include working with groups that have already begun to address some of these. Examples of tools include: Reliance Agreement templates, Standard Operating Procedures, approaches to HIPAA.

Thank you for the opportunity to provide comments on this draft guidance. Please contact us with any questions or requests for clarification. We are very interested in working with you to develop a successful future for SIRBs.

Sincerely,

Scott L. Rauch, M.D.

Comment #129

Commenter:

Date of Comment:

Comment:

January 28, 2015

Office of Clinical Research and Bioethics Policy Office of Science Policy
National Institutes of Health 6705 Rockledge Drive
Suite 750
Bethesda, MD 20892

RE: Single IRBs in Multi-Site Clinical Research Studies

Submitted electronically at: SingleIRBpolicy@mail.nih.gov

Cleveland Clinic is a not-for-profit, integrated healthcare system dedicated to patient care, teaching and research. Our health system is comprised of a main campus, eight community hospitals and 18 family health centers with over 3,000 salaried physicians and scientists. Last year, our system had nearly five million patient visits and over 157,000 hospital admissions. We appreciate the dedication of the Agency staff and believe it is important for hospitals to share information so the Agency staff has a better understanding of the challenges and practicalities faced by the hospitals regarding proposed changes which influence hospital activity. The following are the comments of Cleveland Clinic with respect to the captioned proposed rule.

NIH Proposal and Hypothesis

On December 3, 2013, the NIH released a draft policy to promote the use of a single IRB model for multi-site studies funded by NIH to reduce procedural inefficiencies without compromising ethical principles and protections. The goal stated by NIH is to avoid duplication and allow institutions that participate in multi-site studies to rely on the review of another qualified IRB. The basis of the proposed model is that review of a multi-site study by local IRBs involves significant administrative burden in terms of IRB staff and members' time to perform duplicative reviews. The model assumes that the process can take many months with significant delay to the initiation of research studies and that the use of a single IRB in multi-site studies may decrease approval times and may be more cost effective.

CC Comments

While this proposed model may benefit some IRBs, especially if they pose an administrative burden to their investigators, we are concerned that the implementation will require additional infrastructure at a considerable cost and time to both the lead site and the relying sites and may delay the initiation of research at some participating sites

1. When does an IRB represent a significant administrative burden?

There are many IRBs that are efficient and do not pose a significant administrative burden. Efficient IRBs meet weekly and conduct thoughtful and rigorous initial reviews by knowledgeable and experienced staff and members. They have an organizational culture of shared responsibility for human subjects protections supported by a well-designed infrastructure. Submissions are typically reviewed within 10 days with results being promptly communicated and an average time of approval within 30 days. An efficient IRB is not an administrative burden. Efficient IRBs use technology that serves as an integrated communication hub for all interactions with the research team, research compliance, education and training and other research support services. Reliance on a single IRB for the initial approval only

addresses one aspect of the IRB mission. Will IRBs that represent a significant administrative burden and then rely on a single IRB suddenly develop efficient processes to address the other aspects of IRB oversight including local context items, monitoring of protocols and consenting, and reporting unanticipated and adverse events to the lead IRB? The relying IRB will still need efficient and effective processes even if they choose to rely on a lead site. The NIH proposed policy does not address IRBs that are inefficient.

2. Will a single IRB review speed the initiation of studies?

The initiation of a research study is not solely dependent on IRB review. Approval by the IRB is only one aspect of actual study initiation by the research team. Several other required activities must be completed before a trial can begin. These include negotiation and execution of clinical trial agreements, study initiation meetings, account activity set-up with research administration, and various other institutional ancillary services must be in-place (pharmacy, laboratory, operating room, imaging, and patient care areas). These other requirements are significantly more time-consuming than the IRB approval process and are major factors impacting when a study actually begins. After IRB approval is obtained (an efficient IRB takes 30 days) it takes an additional 75 to 100 days to complete these other requirements that are initiated by the study team at the same time as the IRB submission. The NIH proposed policy does not address the delays in study initiation due to these other requirements for study start-up.

3. Will a single IRB review save money?

Creating a single IRB model requires establishing individual IRB authorization agreements with each of the relying sites and will take considerable time and effort to complete but more importantly, both the lead and the relying sites will need to modify or create new infrastructure and technology to implement this arrangement. The relying sites cannot abandon their regulatory obligations and ethical responsibilities for oversight, tracking and monitoring. The cost to upgrade staffing and technology will be very expensive and will take considerable time to implement. This cost is proposed to be charged as an additional direct NIH grant expense thus reducing direct project funding. The additional cost to serve as the single IRB could run around \$50,000-80,000 per project based on services provided by commercial IRBs. The cost of the NeuroNext IRB and the NCI IRB models were separately funded by NIH at a cost of millions of dollars.

4. How will the single IRB be selected?

The extramural applicant or intramural principal investigator will identify the single IRB with NIH approving the selected single IRB. The NIH proposed policy does not address what criteria would be used to determine whether the selected IRB has sufficient experience, resources and infrastructure to administer and collaborate with multiple sites. How will NIH determine if the lead site has a quality IRB that is efficient and will conduct continuing review and modifications in a timely manner? Would a commercial IRB that specializes in IRB review present a better option?

5. Proposed alternative model

NIH should consider creating a separate human subjects review group to complement the scientific review. This review would focus on the assessment of research risk and benefits and develop an informed consent document in accordance with IRB approval criteria. This information would then be provided to each of the multi-site IRBs to assist with their IRB review. Inconsistency in IRB reviews is often the result of Investigators giving inaccurate or inconsistent information. A central human subjects review would provide consistency that could streamline the site IRB process without dividing their responsibilities or degrading the existing comprehensive human subject protection program of efficient

IRBs. Ceding IRB review is contrary to developing an IRB culture of a shared responsibility working with Investigators and the Research team to protect research participants. IRBs that present significant administrative burden should be addressed by requiring specific corrective action plans to resolve their inefficiencies.

Thank you for conducting a thoughtful process that allows us to provide input on such important issues and for your consideration of this information. Please do not hesitate to contact me if you need additional information.

Sincerely,

Daniel Beyer

Comment #130

Commenter: Janice Q

Date of comment: January 29, 2015

Comment:

This proposed policy ignores and minimizes the real benefits of a local IRB review. There are very good reasons why most institutions have “not taken advantage of” the opportunity to have a single IRB review of clinical trials. It is not always an advantage to have a central or single IRB review from our institution’s perspective.

A local IRB (especially one that is at a relatively small organization like ours) is very aware of the culture of the institution. As a small religious institution we have certain values and norms that a central IRB may not be aware of and even if they are aware of them would be unable to appropriately address without being part of that culture. We also know our investigators and may have regular contact with them at various levels. We are aware of their strengths and limitations. We are aware of the organizational structure and administrative support of research.

At the local level, we need to have a mechanism to be able to track research activities on campus, not only for internal statistical reporting purposes, but also for routine auditing purposes. We currently have a mechanism to do random audits of various departments. Without ready access to our local IRB files and the ability to have IRB enforce any necessary Corrective Action Plans, our internal review processes would suffer.

I believe that our local investigators actually prefer to use our local IRB rather than report to a central IRB, as stated in the proposed policy. This way they have someone in the office to consult during their time zone, instead of having to deal with an IRB three time zones away. They can walk over to our office to get clarification in person instead of telephonic or email correspondence that may not be clear. They can have a sidewalk consult with the IRB chair. Therefore, the overall assertion that investigators prefer a central IRB that was made in the proposed rule statement may be true for NIH intramural researchers but is not necessarily true for extramural researchers at the local level. My recommendation is to not make this a term and condition of the grant but to keep it voluntary and continue to allow institutions to make their own evaluation of their situation to see if they are comfortable allowing an outside entity to make decisions for what happens on our campus.

For instance, a central IRB issued a waiver of HIPAA authorization for a “study.” This particular waiver is not in harmony with our own internal policies and procedures for a waiver and we did not feel comfortable ceding those types of decisions to an outside entity. We are responsible for our own medical records and to allow another IRB to say that an unknown researcher should be given PHI is not in harmony with our current practices. Even though they are a well-known central IRB an email sent to them asking for clarifications was never acknowledged.

Currently we have the IRB approval process tied in to our entire system of checks and balances which is one of the reasons that local IRB approval can take longer than running something through a central IRB with faster approval processes. Once the IRB approval process has been completed we will not release the IRB approval and allow the researchers to start the research until all of the various institutional requirements have been met. This obviously takes time and will continue to be a requirement at our institution even with a single IRB review. We need to ensure that our policies and procedures for education and training, completion of contracts, conflict of interest (COI) reporting requirements, COI management plans, prior review by our clinical trial center for billing compliance and feasibility, clinicaltrials.gov registration requirements, biosafety and radiation safety review and any other

institutional requirements are completed prior to the initiation of the research. This proposal does not change any of those requirements so, in practicality, this proposal would not substantially decrease the time it takes to start an individual research project. We have found that much of the time required for the approval is actually waiting for other responses or requirements and not the actual IRB review time. Because the IRB approval is not released until those requirements are met, the IRB is blamed for long approval process times.

Currently our IRB and COI committees work together to ensure that the subjects are appropriately notified. Our COI policy conforms to the reporting thresholds established by NIH. Therefore, if there is only a single IRB review it seems it would bypass our controls for COI or necessitate more work on the part of the institution since we currently have a COI review process integrated into the IRB electronic system. That system is currently set up to put a hold on IRB studies where the research conflict of interest has not been cleared. Part of a management plan for COI may be to have a statement in the informed consent document that notifies potential subjects that the investigator may have an interest or relationship that could potentially pose a conflict and use disclosure as an acceptable management plan. A single IRB would add more complexity and less flexibility to our processes and potentially even be a hindrance to the continuation of the research.

Please continue to make this voluntary and not mandatory. Thank you for your consideration.

Comment #131

Commenter:

Date of Comment:

Comment:

January 29, 2015

Ms. Sarah Carr

Director, Office of Clinical Research and Bioethics Policy Office of Science Policy

National Institutes of Health

6705 Rockledge Drive, Suite 750

Bethesda, MD 20892

RE: Draft NIH Policy on the Use of a Single Institutional Review Board (IRB) for Multi-Site Research

Dear Director Carr:

On behalf of the American Academy of Orthopaedic Surgeons (AAOS) Research Development Committee and Board of Specialty Societies Research and Quality Committee, we thank you for the opportunity to comment on the proposed policy. The AAOS supports the use of a single IRB for multisite research and is in general supportive of initiatives facilitating multicenter studies. Multicenter studies have advantages of increased sample size and increased external validity (generalizability). The time required to complete multiple IRB iterations can be prohibitive and cumbersome. A single IRB for multicenter research initiatives would be efficient and a positive step forward in research collaborations, and requirements imposed on funding agencies to ensure its success are strategic.

Several potential issues will need to be addressed, including the decision of which institution will house the IRB for the study. Would the IRB from the primary investigator's institution be selected? What if there are multiple PIs? States vary in the way that informed consent for research is obtained, particularly for minimal risk and retrospective studies; how will this be addressed by the single IRB, for studies involving states which differ in this aspect? IRBs may not want to relinquish authority for approval. Another concern is if a question of liability arises, the research site will be held responsible under local law, not the law applicable at the site of the remote IRB. Different processes may therefore be needed for interstate as opposed to intrastate multisite studies. Workflow questions also arise; will the sponsoring institution send a notification of preapproval by their IRB to each site? Will the local IRBs be required to approve or monitor the research? The AAOS believes that any policy regarding a single IRB for multisite research should address such issues.

Once again, thank you for the opportunity to provide feedback. Should you have any questions or require any additional information, please contact Judi Buckalew, BSN, MPH, AAOS Senior Manager of Regulatory and Government Relations in our Washington office at Buckalew@aaos.org or 202-548-4148.

Respectfully submitted,

Peter Amadio, MD

Chair, AAOS Research Development Committee

John Kirkpatrick, MD

Chair, BOS Research and Quality Committee

Comment #132

Commenter: Vanderbilt University Medical Center Response

Date of comment: January 29, 2015

Comment:

NOT-OD-15-026

We applaud your effort to streamline the Institutional Review Board (IRB) review of NIH-funded multi-site studies. Greater efficiency is truly needed. However, a single IRB of record per study is not the only solution available. Further, given there is no current body of evidence indicating a precise path forward on which to base policy, mandating a single IRB of record as a solitary solution seems quite premature, ignores the valuable ongoing perspective and contribution of local IRBs, and might put human subjects at increased risk.

In addition, without clarifying definitions, mandating use of a single IRB of record per study leaves the proposed policy up for much interpretation and would potentially result in hundreds of different “single IRBs of record” with which institutions and investigators would have to interact. As described below, this scenario would ineffectually decrease study start up time since negotiating reliance contracts and establishing procedural operations on a study-by-study basis would likely delay rather than shorten IRB approval.

A “single IRB of record” can be accomplished in several ways including the use of independent or commercial IRBs, central IRBs (cIRBs) (e.g., NeuroNEXT, StrokeNet, and NCI CIRB), study-specific memorandums of understanding, and various types of institutional reliance agreements. Significant challenges limit each of these models. **First, a single IRB of record only streamlines one portion of the approval process: the IRB regulatory review.** Human subjects research also requires other institutional reviews that fall under the umbrella of Human Research Protection Programs (HRPP) such as PI training and eligibility and ancillary committee reviews. These ancillary reviews cannot be centralized; thus, the local HRPP must be involved in every study approval, regardless of the use of a single IRB of record. **Second, given that each local HRPP must be involved, it is difficult to justify ‘centralizing’ the local context review for each enrolling site, and many question whether an external IRB of record can ever adequately perform this review for each institution.** Furthermore, adding this burden to the “single IRB of record” has little benefit or efficiency. Local context review is not a simple read of, for example, an investigator’s curriculum vitae. See Table 1 for a list of local context issues, some of which require local review regardless of whether a single IRB of record is used. Additionally, other issues are critical in that they potentially require a review outside of what the IRB of record could gain from a local site’s submission of their local context. Each IRB is intimately familiar with their local investigators and local population’s cultural backgrounds, some of which may not come across on paper. Additionally, single IRB of record models, as they exist today, vary in the pieces of review each has adopted. For example, the NCI CIRB reviews local context that contains Investigator qualifications (what comes across on paper) and HIPAA, while StrokeNet reviews local context that contains HIPAA, but not Investigator qualifications. Each model varies slightly, leaving different portions to the local IRB to review. This only adds to the burden (and confusion) IRBs are *currently* experiencing as they struggle to manage various reliance agreements. **Third, use of a single IRB of record requires additional time to modify the operations and information technology (IT) systems at Reviewing and Relying IRBs as many study-related processes (e.g., billing) are linked together to provide research infrastructure.** Most institutions have spent years creating efficient IT systems to manage concurrent activities (contracts management) and reviews (e.g., COI, biosafety, radiation safety, pharmacy review). Transitioning to the use of an external IRB of record or, worse, multiple IRBs of record, will require

reworking of these systems, causing a major disruption and additional costs and time at each institution. **Fourth, ensuring local compliance at the Relying IRB institution—a responsibility of the IRB of record—is a complex process that does not have a simple solution at this time.** The exchange and review of documents is cumbersome (e.g., scanning and emailing, faxing, etc.) without a sophisticated IT system. Additionally, physically travelling to each relying institution for an audit is costly. **Fifth, single IRB models can be difficult for local investigators to navigate and may result in conflation of investigator responsibilities and obligations.** Being unfamiliar with the IRB of record’s processes, investigators often think they have ceded their research responsibilities to the investigator at the IRB of record institution. Additionally, the reporting of adverse events and unanticipated problems can be difficult to navigate as investigators are required to report to an external entity rather than their usual, local IRB. As a result, most investigators fail to realize this and at least initially submit the report to their local IRB. Any delay in the reporting of events could put subjects at increased risk. These and other factors immediately limit the broad adoption of existing single IRB of record models and raise widespread questions about sustainability.

Table 1. The critical role of <i>Local Context</i>	
IF REQUIRED FOR STUDY APPROVAL, THE LOCAL IRB HAS TO PERFORM	
	Radiation safety
	Institutional biosafety
	Research billing/Medicare qualifying review
REQUIRE CRITICAL KNOWLEDGE FROM LOCAL IRB	
	Review of storage, handling and dispensing drugs/biologics
	Review of storage, handling and use of devices
	HIPAA authorization
	State- and/or site-specific confidentiality requirements
	Conflict of Interest
	State-specific laws/community standards that may affect the research (e.g., data security, mandatory reporting, etc.) (For local documentation)
OTHER IMPORTANT GENERAL LOCAL CONTEXT ISSUES	
	Site investigator
	Participating institution/hospital
	Local and total accrual targets
	Costs language
	Adverse event/subject injury language
	Payments language
	Local contact information for questions or to report possible research-related injuries
	Contact information for the site’s IRB/HRPP
	State- or site-specific pregnancy and/or birth control language
	Consent form or waiver is acceptable for local population
	Consent versions are consistent with the age of majority and assent laws of the state

Table 1. The critical role of *Local Context*

Non-English Consent versions and/or short form(s) are in a language understandable to participants
State laws around Legally Authorized Representatives have been addressed

A suite of national solutions is clearly needed. One that currently exists in early implementation is called IRBShare – a unique configuration based on a systematic mass reliance model which promotes a **single IRB review** (as opposed to a single IRB of record). This program already has formal, written acknowledgement as an acceptable joint review model from the Office for Human Research Protections (OHRP) and Food and Drug Administration (FDA), and is supported by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). IRBShare is based on a **uniform national reliance agreement** (i.e., institutions share regulatory responsibility) that allows IRBs to rely on the review of another IRB for all phases of review (initial study, annual/continuing reviews, and reviews of amendments) of multi-site studies at any risk level. After the Lead IRB reviews the study for their institution and gives approval, its review is uploaded to the IRBshare web-based system where other institutions in the study can approve the study via the “Shared Review Process” using a subcommittee (at least one IRB member) that 1) verifies they agree with the determination of the Lead IRB and 2) reviews its local context issues. Thus, the relying institution completes the review by adding their local context and retains study oversight, including review of study-related events. At continuing review or for the review of a study-wide amendment, the Lead IRB would again perform the complete review for its institution, upload approval to IRBShare, and the relying IRBs would again use the subcommittee to give approval. **IRBShare offers a single IRB review, streamlining the only duplicative process of review—the IRB regulatory review—without adding the infrastructural and review burden inherent to cIRBs and reliance agreements. This allows local IRBs to conduct the local context review and maintain study oversight (IRB of record status) between the times of reliance upon the lead IRB reviews.** Under the current proposed language in NOT-OD-15-026, IRBShare—now adopted by over 50 major academic medical centers—would be prohibited. This would be a disservice for human subjects research oversight and the protection of human subjects.

Specific advantages of IRBshare over the central IRB approach:

1. Does not require lengthy contract negotiations or system development as they already exist using one single national master agreement for all studies going forward;
2. Does not add significant burden to the Lead IRBs;
3. Does not require database changes for relying IRBs;
4. Does not require the NIH to create new funding mechanisms or factor in support for use of central IRB review into grant awards, i.e., there is no increase in costs over the current system;
5. Eliminates duplicative reviews while allowing relying IRBs to maintain local control and assess their own local context;
6. Increases transparency between IRBs to stimulate improved review quality, more consistent determinations/fewer minor changes, and facilitate the sharing of best practices.

Table 2. IRBshare Membership and Use	
Participating Institutions	53 (36 CTSAs)
Pilot Phase Reliances (Mar 2013-Nov 2014)	14 Year 1: 4 reliances Year 2: 9 reliances
Submission to approval	20 days (median)
Review to approval	1 day (median)

IRBshare is supported by a single master agreement and informatics platform and is open to any institution with a Federal wide Assurance with OHRP. See Table 2 for utilization data to date. Membership and utilization are expected to continue to increase as they have in 2014 due to the expansion to include all phases of review (the pilot only allowed reliance at initial study review).

Table 3. IRBchoice Options	
Lead IRB Options	Relying IRB Options
1. Serve as “IRB of Record”: allow institutions to cede all regulatory responsibility for a given study	1. Cede regulatory responsibilities to Lead IRB 2. Use Shared Review Process to rely on Lead IRB’s review, but maintain local oversight
2. Serve as a “Sharing IRB”: allow institutions to rely on my review via Shared Review Process, but not cede all regulatory responsibility (current IRBshare model)	1. Use Shared Review Process to rely on Lead IRB’s review, but maintain local oversight (current IRBshare model)

As referenced in the announcement of the proposed policy, current models are underutilized and lack evidence of effectiveness. For this reason, we strongly **discourage mandating the use of any single model to streamline IRB review**. It is important to better understand the lack of utilization in order to improve current models and uptake. NIH showed support for this notion in early 2014 when they issued a FOA to encourage Research Project Grant applications to explore “timely issues of significance for policy development relevant to...the principles and characteristics for central Institutional Review Boards (IRBs)”. This FOA specifically called for “Empirical Research on Ethical Issues

Related to Central IRBs”, presumably to inform the proposed policy at hand. Vanderbilt’s submission was **funded by NHLBI as “Using real world decisions to develop a modified central IRB model”** and is informally known as IRBchoice (1R01HL126492-01). In IRBchoice, IRBs will have multiple reliance models (ceded and shared) within a single, state-of- the-art, web-based platform, which will be an extension of the current IRBshare System and Master Agreement. See Table 3 for the IRBchoice options. A core component of this project is a thorough scientific evaluation of rationale for model selection (Lead and Relying IRBs), ethical compliance/quality, cost, satisfaction, and efficiency.

In summary, we again laud your effort to streamline IRB review of multi-site studies. Existing streamlining

models will continue to be underutilized without more encouragement from funders. However, we encourage NIH to continue to support and engage in the information exchange and sharing of best practices that is just beginning to occur across streamlined IRB review models (cIRBs, reliance agreements, reciprocal reliances, and IRBshare). With more and more institutions beginning to use streamlining models, mandating one model would undermine institutional preferences and the lessons learned across each model. Instead NIH should foster an environment that capitalizes on the achievements of well-established models. Given the challenges of single IRB of record models, we would support NIH recommending use of **single IRB review for each multi-site study**, as was done in **RFA-TR-13-002** (“Specifically, applicants are strongly encouraged to consider models that will facilitate “shared review” such as IRBshare or a central IRB of record model”). The University of Miami is currently using IRBshare to support the first trial under this U54. This is evidence that encouragement of principles can be effective in achieving a goal of efficiency while still allowing flexibility which would be prohibited in a mandated process as currently described in NOT-OD-15- 026.

Fortunately, this can be addressed by modifying the proposed policy language. Please see below:

The purpose of this Policy is to increase the use of joint Institutional Review Board (IRB) review models as described in the OHRP and FDA regulations (45 CFR part 46.114 and 21 CFR part 56.114, respectively) for multi-site studies funded by the National Institutes of Health (NIH). Its goal is to enhance and streamline the process of IRB review and reduce inefficiencies so that research can proceed efficiently without compromising ethical principles and protections.

Scope

NIH generally expects all domestic sites of multi-site NIH-funded studies to use a streamlining IRB review model that encourages ONE (1) COMPLETE IRB review of each study completed by a “Lead IRB”, which is defined as follows:

“Any IRB that reviews and approves a multisite study and allows, via a joint review arrangement, other institutions to rely upon their institution (becoming the IRB of record for the study) or their review (as part of a shared reliance).”

The Policy applies to all domestic sites participating in NIH conducted or supported multi-site studies, whether supported through grants, contracts, or the NIH intramural program. While foreign sites in multi-site studies will not be expected to follow this Policy, they may elect to do so.

Responsibilities

All sites participating in a multi-site study will be expected to utilize a central or shared IRB review mechanism to carry out the functions that are required for institutional compliance with IRB review set forth in the HHS regulations for the Protection of Human Subjects. research. The mechanism used must be in compliance with the OHRP and FDA guidelines regarding joint review (listed above). All participating sites will be responsible for meeting other regulatory obligations, such as obtaining informed consent, overseeing the implementation of approved protocols, and, reporting unanticipated problems and adverse events to the single IRB of record.

Agreements between the participating sites will be needed in accordance with 45 CFR part 46. IRB Authorization Agreements will document the delegation and acceptance of the responsibilities of each participating site’s IRB. The awardee o lead site for an NIH-funded, multi-site study will be responsible for maintaining authorization agreements and should be prepared to provide copies of the authorization agreements and other necessary documentation to the NIH funding Institute or Center upon request. Duplicate IRB regulatory at a participating site would be counter to the intent and goal of the Policy, but

the Policy does not prohibit any participating site from carrying out its own IRB review. If this approach is taken, the participating site should expect to bear the cost of the additional review.

Identification of the IRB that will serve as the single IRB of record will be the responsibility of the extramural applicant or officer, or the intramural principal investigator. The funding NIH Institute or Center has final decisional authority for approving the Lead IRB. Reliance on the reviews of the Lead IRB will be a term and condition of award. If the agreed-upon single IRB is a fee-based IRB, these costs will be included in the Notice of Award as a direct cost.

Compliance with this Policy will be a term and condition in the Notice of Award and a contract requirement in the Contract Award.

Exceptions

Exceptions to the expectation to use a single IRB may be made with appropriate justification. Exceptions will be allowed only if the designated Lead IRB is unable to meet the needs of specific populations or where local IRB review is required by federal, tribal, or state laws or regulations.

Comment #133

Commenter:

Date of Comment:

Comment:

January 29, 2015

Office of Clinical Research and Bioethics Policy

Office of Science Policy

National Institutes of Health

6705 Rockledge Drive, Suite 750,

Bethesda, MD 20892,

RE: NOT-OD-15-026

To Whom It May Concern:

Attached please find comments from the University of Rochester on the NIH's Draft Policy on the Use of a Single Institutional Review Board for Multi-Site Research.

Yours sincerely,

Kelley A. O'Donoghue, MPH, CIP

Director, Office for Human Subject Protection

University of Rochester Comments on Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research (Notice Number: NOT-OD-15-026)

I appreciate the opportunity to offer comments on behalf of the University of Rochester to the National Institutes of Health (NIH) on the Draft Policy on the Use of a Single Institutional Review Board for Multi-Site Research (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-026.html>). The draft policy represents the current climate where review by a single IRB, rather than multiple, will increase the speed by which research gets approved, save time and resources, and not have an effect on human subject protections. While there are research studies and research groups where this may be appropriate, there are other situations where the requirement to use a single IRB may necessitate more time and resources than to have the study be individually reviewed by local IRBs. In addition, the failure of the policy to define the criteria needed to act as the single IRB is concerning and prevents the University of Rochester from fully supporting this policy. Unless the policy will be significantly revised to address the points below, the University of Rochester is unable to support the adoption of this policy.

Mandatory Nature

The University of Rochester supports the concept of relying on a single IRB for multi-site studies. For over 15 years we have contracted with an independent IRB to review industry-sponsored, industry-initiated multi-site clinical trials because we recognize that inefficiencies exist in multiple reviews of standardized and well-written protocols. Our concern is not with the concept of single IRB review, but rather with the mandatory nature as proposed in the NIH policy. Mandating an operational function in policy can cause more regulatory complexity and add burden on institutions and investigators. While there are studies where one IRB of record is reasonable, a central IRB for cooperative groups (e.g. NCI) or when a study group plans to conduct several studies within the same group (e.g. NeuroNext), to mandate this across all multi-site research is not beneficial and does not recognize the complexity and variation across NIH-funded multi-site studies. While we tend to think of multi-site biomedical clinical trials first and foremost, there are many other studies that would be considered multi-center with this

mandate: epidemiologic, anthropologic, psychology, education studies, etc. When a NIH grant includes 3 or 4 sites and requires an exempt or expedited review, it may be quicker and less burdensome for each institution to submit to their local IRB and obtain approval, rather than to set up the infrastructure required to run a central IRB (i.e., IRB Authorization Agreements and memorandums of understanding to ensure that each site is aware of their responsibilities).

Liability

While the University of Rochester understands the NIH's desire to streamline and reduce redundancy in IRB review, in order to facilitate the use of a single IRB for multi-site research there must be a federally recognized change in the accountability and regulatory liability of IRBs and institutions. The draft policy indicates that *"The single IRB will be accountable for compliance with regulatory requirements for IRBs specified under the HHS regulations at 45 CFR part 46, such as providing initial and continuing review of the research. All participating sites will be responsible for meeting other regulatory obligations, such as obtaining informed consent, overseeing the implementation of approved protocols, and, reporting unanticipated problems and adverse events to the single IRB of record."* What is stated here is not consistent with the Common Rule and the assurance regulations (section 103), which holds the IRB of record responsible for the site conduct. Before the NIH can implement a mandatory policy for single-IRB review for multi-center research, the NIH must first work with Office for Human Research Protections (OHRP) to make this change to the assurance regulations. Under the current regulation, there is the risk of losing or having a restriction placed the reviewing IRB's Federal wide Assurance (FWA) if a compliance problem occurs at another site due to subject safety issues, even if the reviewing IRB performed their responsibilities adequately.

Selection of Central IRB

The draft NIH policy provides very little insight as to the selection process for identifying the single IRB for each multi-center study, other than to say *"Identification of the IRB that will serve as the single IRB of record will be the responsibility of the extramural applicant or offerer, or the intramural principal investigator. The funding NIH Institute or Center has final decisional authority for approving the selected single IRB."* The University of Rochester believes that allowing an investigator to select the single IRB would risk a process of "IRB shopping," whereby more lenient or permissive IRBs are utilized. Speed is often the major determinant in selecting IRBs, and too often, speed varies inversely with review quality and thoroughness. Because it cannot be assumed that single IRBs are being chosen on the basis of quality, NIH should consider implementing a federal audit procedure or central tracking of selected IRBs of record to look for trends on which IRBs are selected. If a certain IRB is selected to be the IRB of record more often than what is expected, that IRB would be audited more often.

An absolute requirement, if the NIH mandated use of single-IRB review, would be setting a minimum standard of qualifications for an IRB to take on the role of reviewing IRB for multi-site studies. If standards are initiated, then the risk of "IRB shopping" would be minimized. A system of accreditation (e.g., the Association for the Accreditation of Human Research Protection Programs [AAHRPP]) or some type of federal certification should be required. For an IRB to adequately conduct the review of multiple sites in a multi-site study, it would need the resources to do this effectively, including extra IRB staff to manage the approval process, the continuing review—including collecting and assessing unanticipated problem reports and other required notices, and potentially increased oversight/auditing function to ensure that the research is conducted appropriately and human subjects are protected. IRBs that review for sites across state lines would need to be conversant with all those state laws, which would seem to require the operation of a regulatory division within the single IRB. This is no small task, and while the NIH draft policy does allow for direct costs to be added to the grant, that may cover the cost for the

reviews, but not for the initial infrastructure. The institution would either need to bear this financial responsibility itself or charge the grant for this set up costs, similar to the structure used in NeuroNext.

Without appropriate established selection criteria, IRBs who do not have the infrastructure to support a multi-center study may be pressured into becoming the IRB of record by institutional leadership or investigators, based on concerns other than appropriate protection of human subjects. These situations create an environment that puts human subjects at risk and cause delays because the IRB of record does not have the staff or resources to handle the volume.

Institutional Review

It should be noted that IRB review is just one step in the local review and approval process. The University of Rochester, like many research-intensive academic centers, has developed an accredited comprehensive Human Research Protection Program (HRPP) comprised of multiple components that apply across the institution. While the University's IRBs have a pivotal role, overall protections are provided to subjects through coordinated interaction with other regulatory review entities within the institution, e.g., the coordination between the IRBs and the research administration office in assuring consistency of compensation for injury payment language between the informed consent document and the clinical trial contract. IRBs receive information and feedback from other components of the HRPP that work in coordination with other human research protections (e.g., radiation safety reviews, contract negotiation, conflict of interest committees, investigational drug service, biosafety committee review, etc.). There is the potential for negative impact on established HRPPs, resulting in reduced ability for coordinated oversight and implementation of systems and safeguards to protect human subjects at the local level.

Although not impossible, it is difficult to achieve full integration when using a remote IRB, unless the single IRB has the infrastructure to account for this. The information that is provided by institutional review (e.g., compensation for injury, financial conflicts of interest, site specific training requirements, ancillary committees, etc.) adds to the information that an IRB needs to consider in granting final approval and should be conducted prior to the single-IRB review for that site. Unless that single IRB considers each institution's individual policies and standards of care, each institution will still need to review the protocol and consent form to ensure compliance. If this is not done there may be a risk to the individual subjects when these conflict. At the University of Rochester, many of the site-specific requested changes in multi-site studies relate to conflicts that arise between institutional policy and the protocol as drafted. For example, in a study of subjects with dementia, the Rochester site did not enroll into one of the study groups because of the University's policy that greater than minimal risk research without the prospect of direct benefit cannot be conducted with individuals who lack the capacity to consent for themselves. In another case, the time frame for randomization into the study was shortened (24 hours to 12 hours) because of the University's policy on administration of a specific treatment. These changes were, of course, accepted by the sponsor before they were approved by the IRB and implemented, but without the first-hand knowledge of institutional policy, these could have been easily overlooked to the detriment of subject rights and safety.

It has also been our experience that a significant number of local delays in approval are due to the sometimes poor quality of the consent forms that are distributed to the local IRBs for review by many of the cooperative groups and large study groups. While risk tables now include explanations and are improving, the University has received consent forms with lists of risks as reported in an adverse event reporting system, rather than communicating the risks in a manner that the subjects will understand what they may experience. Having several, individual, local IRBs remediate inadequate documents is indeed inefficient, but the source of the inefficiency is the documents, not the IRBs.

There is a potential loss of additional local considerations including investigator qualifications, facility limitations, investigator history (including previous compliance and corrective action plans), unique population or community concerns, etc. We know that some sites have subject populations and risks attendant to the research that are radically different, e.g., large immigrant minorities with cultural differences and language issues. The policy does state that this might qualify for exception, but it's possible that this information might not be readily apparent during the grant application procedure, and only during the local review of the protocol.

Differences in conflict of interest policies and related management strategies and the level of compensation for injury provided can vary by protocol, by institution, and by study. Ensuring that the subject is completely informed and that the IRB has reviewed and approved this information is important in ensuring that the subjects have all pertinent information to make an informed decision about participation in a study. Experiences with the "single IRB model" have been less than satisfactory when ensuring that subjects are presented with accurate institutional information, because of the single IRB's unfamiliarity with institutional policy.

Other Considerations

The NIH should consider, in the process of reviewing this draft policy, specifically seeking out opinions from the potential research subjects who would be affected by the policy. Research subjects may (or may not) value other characteristics of human subject protection more highly than efficiency and consistency.

If successful, an NIH policy that encourages the use of single IRBs may have the additional benefit of helping to develop a core contingent of university or other IRBs that could cultivate and adopt a new set of best practices for multi-site research review. Implemented properly, the policy may advance the field of human research protections significantly.

Conclusion

The University of Rochester agrees that it is inefficient for each site in a multi-site trial to reconsider all of the components of a complex interventional research trial. However, in order to properly centralize the research review process, there would need to be substantive changes in regulations, guidance, and enforcement in areas such as liability. It is also important to remember that variation does not necessarily mean that IRBs are not doing the job properly. Research is not simple; studies often are complex and nuanced. Perceived inefficiencies among local IRBs may, in some cases, be the result of appropriate scrutiny of substandard protocols, consent forms or other documents. It takes a significant amount of time from research personnel, IRB staff, and IRB members to make changes to the consent form to ensure the document is understandable and comprehensible.

The University of Rochester is supportive of moving toward a single-IRB review model for multi-center research, but the mandatory nature of the NIH's draft policy and the lack of clarity about the criteria required to be the IRB of record is unsettling. Human Research Protection Programs are just getting their feet wet with setting up the needed infrastructure to take on multi-site research and conduct institutional review. The NIH's policy is premature given the current regulatory climate. Unless the policy will be revised to address the points above, the University of Rochester is unable to support the adoption of this policy.

Comment #134

Commenter:

Date of Comment:

Comment:

January 29, 2015

Office of Clinical Research and Bioethics Policy
Office of Science Policy National Institutes of Health
6075 Rock ledge Drive, Suite 750
Bethesda, MD 20892

RE: Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research
Notice# NOT-OD- 15-026

Submitted electronically via singleIRBpolicy@mail.nih.gov

Indiana University is pleased to have the opportunity to comment on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research.

Indiana University supports the use of a single institutional review board (IRB) for multi-site research. Such use provides opportunity for increased efficiency, and decreases the time and resources spent on IRB review across all site and in total throughout the lifetime of a study. However, we also recognize that the logistics of implementing such a policy may cause unintended burdens on institutions, especially during the initial review period.

Our institution has participated in several multi-site research projects in past years in which a single academic center IRB was utilized by all sites. In our experience, academic institutions readily agree to a single IRB model; however, conducting and facilitating the initial review often takes a significant amount of time and effort from IRB administrators at individual sites. Local administrators ensure qualification of the reviewing IRB, review informed consent and HI PAA authorization language for local requirements, ensure local investigators are qualified and properly educated, and facilitate IRB authorization agreements. In addition, administrators often meet to discuss and agree upon policies and procedures for review of research, which can take months to years in some cases. Time savings are recouped as the study continues since annual IRB review and review of changes to research are not conducted by each and every site, but time to completion of review for all sites can be significant.

Given these considerations, Indiana University supports adoption of the policy, but encourages NIH to provide additional guidance for implementation of single IRB systems, especially in the following areas:

- NIH support of the IRB of record: We would support a policy which requires use of an NIH IRB for NIH-funded multi-site research, similar to the National Cancer Institute Central IRB initiative. Use of an NIH IRB would centralize policies and procedures and facilitate familiarity with the single IRB process, decreasing burden on local IRB administrators during initial review.
- Identification of the IRB of record: In absence of an NIH IRB, we would encourage NIH to provide guidance which helps to identify the IRB of record. For example, the policy might require that the grantee institution provide IRB services for all sites in absence of a compelling reason otherwise. Such a requirement would decrease uncertainty about the process and put institutions on notice of their IRB responsibilities early in the grant proposal process, allowing them to identify and handle logistical issues well before IRB approval is necessary.
- Model policies and procedures: In order to facilitate implementation of the policy, NIH could encourage or even coordinate creation of best practices and model policies and procedures for

single IRB review. These should address guidelines for communication among sites, local language for consent and HIPAA authorization, and review of adverse events and other unanticipated problems, among other issues. Such an initiative could be led by current consortiums and groups which have successfully implemented single IRB systems, such as NeuroNEXT.

- Evaluation: As discussed above, single IRB systems are expected to provide greater efficiency but practical experience may suggest otherwise. As such, we encourage NIH to sponsor pilot studies on implementation of single IRB systems in order to evaluate the impact of such systems. In addition, NIH should provide guidance regarding collection of IRB metrics, specifically measurement of turnaround times and cost of IRB review, to help quantify these impacts.

Thank you for consideration of these comments. Indiana University looks forward to the opportunity to enhance and streamline the IRB experience through collaboration and single IRB review.

Sincerely

John Baumann, PhD

Assistant Vice President, Research Compliance

Comment #135

Commenter:

Date of Comment:

Comment:

January 29, 2015

To whom it may concern:

On behalf of the leadership of the University of Michigan's (U-M's) Human Research Protections Program (HRPP), I am writing to comment on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research (NOT-OD-15-026). The U-M HRPP covers more than 6000 active protocols, with a large proportion of these projects funded by NIH.

Our main concern about the draft policy is that it proposes to require that studies fit into a single IRB of Record model without considering whether or not this is the best IRB review model for the specific project. By requiring researchers to identify a reviewing IRB at the time of proposal submission, this policy undermines the important role IRBs and HRPPs have to protect human subjects. We are concerned with the process of how and when a reviewing IRB is identified and about the impact to the institutional HRPP. The proposed policy has significant potential to adversely affect investigator timelines and to add burden in preparation of NIH funding proposals.

As an institution that strives to streamline regulatory burden for investigators, U-M is committed to avoiding duplicate IRB review whenever possible. We appreciate the value of the NCI central IRB model and routinely utilize it and several commercial IRBs. However, on a weekly basis, we review requests from our investigators to rely on other IRBs, and we find there is value in closely examining the proposed relationship to be sure that all research-related ethical, regulatory, and safety obligations and concerns have been considered, including but not limited to reviewing for potential conflicts of interest, ensuring HIPAA protections are in place, and looking at the need for data or specimen use agreements. While we find we can adjust our electronic approval system for ceding or accepting IRB of record responsibilities, this is not an easy or automatic process and is an added expense to the HRPP.

We support the adoption of the single IRB of record model for multi -site research projects when each site is required to follow the same protocol and deviations from that protocol would have a detrimental effect on research results. We note that research reviewed by the NCI CIRB fits these criteria, and we recommend that the NIH pilot the proposed policy on these same types of research projects.

At the same time, we urge NIH not to impose this process on other types of studies where it would be of little benefit or, in fact, a detriment to the study design. Large clinical trials and social and behavioral studies are often designed to partition major roles and responsibilities for the project among the sites according to the expertise of the researchers. A sole source of IRB review at a single institution external to these sites does not necessarily provide the board expertise best suited to evaluate the research given the varying nature of these specialized tasks.

Importantly, single IRB review can create a new cost burden to the reviewing institution. NIH proposed that the fee for review could be charged to the award, but for an institution like U-M, we already accommodate these costs in our indirect costs recovery. In our case, this would create an extra financial burden that could not be added to our already capped IDC administrative costs.

Oversight of multi-site research by a single IRB requires additional and substantive modifications to the procedures at the responsible institution. Specialized standard operating procedures are required to address regulatory requirements, workflows, and communication between the reviewing IRB and the

participating sites. A secure document portal is necessary to house and disseminate approved study documents. Monitoring of external sites requires additional personnel and effort. Importantly, a reliable, well-trained administrative core, overseen by the principal investigator and requiring additional funding, is essential for managing the information flow (such as adverse event reporting) into the reviewing IRB and providing a timely response back to the sites. Subject safety is dependent on the ability of the reviewing IRB to receive and respond to relevant information in a timely manner.

Likewise, the cost of overseeing research at the ceding site is not completely relieved by relying on another institution's IRB. Local IRBs or other institutional authorities must still maintain awareness and oversight of the research conducted at their sites in order to fulfill their many other research-related ethical, regulatory, and safety obligations. At many, if not most, institutions, mechanisms for such oversight have been integrated into the same infrastructure that serves their local IRB review. Thus, even if local IRB review of some multi-site research is ceded to another IRB of Record, the cost of fulfilling the remaining obligations is not eliminated. We do not expect that the significantly increased costs of serving as an IRB of Record for some multi-site research projects will be completely offset by the partial savings of ceding IRB review for others. The net result may very well be an overall increase in costs to research institutions.

Furthermore, not all IRBs, or associated HRPPs, are well positioned to take on these tasks. Inexperienced IRBs may have trouble scaling-up or responding to the influx of information necessary to address matters on a nationwide or international scale. Costs and necessary infrastructure may be prohibitive and not sustainable.

Finally, concerns about institutional liability remain unaddressed. Many IRB reliance agreements are silent on the matter, assuming institutions have appropriate insurance coverage. However, liability issues are necessarily magnified in a multi-institutional situation where reliance on the decision-making of a single institution is mandated as a condition of participation.

In summary, we urge you to consider that "mandating" single IRB review to the effective exclusion of other options is contrary to the statement in the proposed policy that "...too few institutions involved in multi-site studies are taking advantage of the option." Research institutions need options and flexibility, not mandates, so that they may make the best choices to foster the efficient and effective conduct of quality research conducted by their investigators. We believe that the public will be better served by sensible decisions based on circumstances and criteria, rather than by a one-size-fits-all mandate.

Thank you for your attention and consideration,

Sincerely,

Lois Brako, Ph.D.

Assistant Vice President for Research- Regulatory and Compliance Oversight & U-M HRPP Director

Comment #136

Commenter:

Date of Comment:

Comment:

January 29, 2015

Office of Clinical Research and Bioethics Policy

Office of Science Policy

National Institutes of Health

To Whom It May Concern,

This serves as a response to the Request for Comments as proposed by the draft NIH policy on the use of a single institutional review board for multi-site research. As the chair of the IRB Working Group for the Big Ten/CIC-Ivy League TBI Research Collaboration, I support the proposed use of single IRB for multi-site studies.

Launched in 2012, the TBI Research Collaboration represents a multi-institutional, cross-conference coalition with the potential to tap the time and talent of more than 500 investigators, 600 clinicians, and 17,000 student-athletes from 23 institutions. Individuals participating in the initiative represent Sports Medicine, Neurology, Neuropsychology, Physics, Engineering, and Biological Sciences. The purpose of the TBI Research Collaboration is to help develop science-based strategies for preventing, detecting, and treating TBI and sports-related concussion. To realize these outcomes, academic researchers and university Sports Medicine personnel contributing to the collaboration are partnering to standardize research approaches, establish appropriately-sized study populations, and develop evidence-based protocols.

Many of my colleagues have already or are in the process of submitting multi-site TBI research grants. A single IRB would expedite conducting this research with our various institutions as well as provide a model of fostering collaboration. Streamlining the process of IRB review is a crucial step in making the research process more efficient.

In short, it is my hope that this draft NIH policy becomes a reality and that the use of a single IRB for multi-site research is in effect in the near future.

Sincerely,

Andrew R. Peterson, MD MSPH FAAP Clinical Assistant Professor of Pediatrics
Director, University of Iowa Sport Concussion Program
Chair of IRB Working Group, Big Ten/CIC-Ivy League TBI Research Collaboration

Comment #137

Commenter:

Date of Comment:

Comment:

January 29, 2015

VL4 electronic mail

Office of Clinical Research and Bioethics Policy
Office of Science Policy, NIH
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

RE: Comments on Draft NIH Policy on Use of a Single IRB for Multi-Site Research; NOT-OD-15-026

Dear Sir or Madam:

On behalf of the University of Pittsburgh- Of the Commonwealth System of Higher Education ("University"), a state-related institution of higher learning, and its faculty and staff who conduct human subject research funded by the National Institutes of Health ("NIH"), please accept these comments in response to the above referenced NIH Draft Policy on the Use of a Single Institutional Review Board for Multi-Site Research. The University Institutional Review Board ("IRB") serves as the IRB of Record for all human subject research conducted by faculty, staff and students of the University of Pittsburgh, and also serves as the designated IRB of record for much of the human subject research conducted by employees of UPMC Health System at its domestic locations. While we understand the basic tenants for utilizing a single IRB for multicenter NIH-funded research, the Draft Policy lacks standards for the scope and/or responsibilities of both the reviewing and relying IRBs.

For the fiscal year ending June 30, 2014, the University IRB reviewed 1230 full board protocol submissions (including modifications and renewals), 7366 expedited protocols, and 1016 exempt projects. Given the need for our faculty to collaborate efficiently with peers at other institutions, the University currently participates in the National Cancer Institute's CIRB initiative, as well as the National Institute of Neurological Disorders and Stroke single IRB mechanisms (NeuroNEXT and StrokeNET). In addition, the University has multiple agreements in place with various institutions for single projects to reduce duplicative review. Each request is considered separately and is dependent on the nature of the research and on the commitment and resources of the other institutions.

As a threshold matter, the University respectfully notes that would be more appropriate for the NIH to work within HHS so that there is a common, regulatory approach to the use of central IRBs. Current reluctance of institutions to use central IRBs may well be related to the lack of federal clarity on payment for the costs and liability associated with either serving as, or using such central IRBs. It is worth noting that the Office of Human Research Protections (OHRP) has still not acted on issues identified in the 2009 ANPRM on the responsibilities of the IRB or the 20 11 ANPRM on the Common Rule. Each of these notices included recommendations for the use of a single IRB for multicenter trials. Action on these pending ANPRMs would allow harmonization of the regulatory and practical aspects of this initiative.

The Draft Policy, while instituting the requirement for the use of a single IRB, does not provide substantive information regarding the details of the implementation that should be taken by institutions that either agrees to serve as the IRB of record or that agree to accept the review of another institution's IRB. Should NIH require use of central IRBs, model agreements as well as standard

delegation of responsibility language should be provided by NIH in order to ensure that appropriate protections are in place for subjects participating in research as well as the institutions conducting the study. Without this type of roadmap, each designated Central IRB would be left to develop their own model, leading to duplicative efforts and inconsistencies across IRBs, essentially what the centralized effort is striving to eliminate. Furthermore, the Draft Policy, while indicating that the identification of a single IRB of record would be a term and condition of award, does not prohibit any of the participating sites from conducting its own review. Again, this would appear to be counter to the intent of reducing duplicative IRB reviews.

There is no requirement in the Draft Policy that a reviewing IRB has to be from an accredited organization. Although variation in IRB review arises from differences in local laws, or legitimate differences in risk assessment based on the qualifications and expertise of a particular investigator or institution, utilizing the accreditation standards as a basis for review helps to ensure consistency with respect to conformance with regulatory requirements. As such, the University does not and will not defer IRB review to a non-accredited organization, and we would recommend that this requirement be included as a base requirement in the Policy.

Academic institutions have limited funds to support and staff their IRBs and to pay for insurance to cover the liability associated with the oversight of research. It may be difficult for an academic institution to permit other parties to rely upon their IRB for large, multicenter trials without an exchange of funds for the addition of resources or at the very least, extensive re- allocation of current resources. In order to adequately discharge its obligation to ensure human subject protection, such IRBs may need to hire additional staff to 1) negotiate and manage the execution of agreements; 2) develop SOPs; 3) develop a notification system related to initial approval, amendments, and continuing review of studies under the IRB's purview; 4) review consent documents to ensure each site's local context requirements are met; 5) program electronic system to permit access by other sites; and 6) perform auditing and monitoring functions as required. Currently, IRB costs are paid for primarily through indirect cost recovery on grants. As the administrative portion of the federal indirect cost rate has been capped for some time, a new funding stream will have to be identified to account for additional costs.

The University of Pittsburgh IRB welcomes this opportunity to provide input on this Draft Policy. Protection of human research subjects is truly a shared responsibility, in which IRBs, researchers, regulators and grant making institutions all have a role to play. If the responsibility for IRB review is shifted to a system with a centralized IRB function, it is important that the protection of human subjects in research remain foremost.

Very truly yours,

Randy P. Juhl, PhD
Vice Chancellor Research Conduct and Compliance
Vice Chancellor and Distinguished Service Professor of Pharmacy

Comment #138

Commenter:

Date of Comment:

Comment:

January 29, 2015

Office of Clinical Research and Bioethics
Policy Office of Science Policy
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Submitted electronically via SingleIRBpolicy@mail.nih.gov

Re: NOT-OD-15-026: Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

To whom it may concern:

The American Society of Clinical Oncology (ASCO) and the Association of American Cancer Institutes (AACI) appreciate the opportunity to provide feedback to the National Institutes of Health on the use of a single institutional review board (IRB) for multi-site research. Founded in 1964, ASCO is the world's leading professional organization representing over 35,000 physicians and other healthcare professionals specializing in cancer treatment, diagnosis and prevention. ASCO is committed to improving cancer care through scientific meetings, research, educational programs, defining and measuring cancer quality, and publishing peer-reviewed journals. AACI comprises 93 leading cancer research centers in the United States. AACI's membership roster includes National Cancer Institute-designated centers and academic-based cancer research programs that receive NCI support. AACI is dedicated to reducing the burden of cancer by enhancing the impact of the nation's leading academic cancer centers. Our organizations value the chance to contribute to this discussion on behalf of our members.

Research and innovation are at the center of our organizations' missions, and our organizations are longtime advocates and supporters of clarifying, simplifying, and streamlining processes related to research, including IRB review. At the same time, we strongly believe that research participants must be well informed about the risks, benefits and alternatives of participation in research studies and we are committed to maintaining high standards for IRB review. We strongly support the proposed NIH Policy to increase and promote the use of single IRBs for NIH-funded multi-site studies. ASCO and AACI believe that using a single IRB in multi-site studies helps promote a consistent approach to research protections, heightens the influence an IRB can have, involves national experts in research review, and reduces administrative requirements and inefficiencies for all stakeholders in the research process.

As stated above, we agree with the proposal that all domestic sites in a NIH-funded multi-site study be required to rely on a single IRB as the IRB of record for the study. In cancer and many other life-threatening diseases, multi-site studies are growing in number and importance as we discover the biological basis for subpopulations of what were previously thought of as single disease types. In cancer clinical trials, we have significant experience with use of a single IRB to support multi-site cancer clinical trials in both the adult and pediatric settings, thanks to the National Cancer Institute's (NCI) investment and development of central institutional review boards (CIRBs).

The NCI CIRB Initiative has been implemented, refined, and well accepted in the National Clinical Trials Network (NCTN). The CIRB model has proven more efficient and provides cost savings over multiple local

IRB reviews. The CIRB began with a facilitated review model that involved ongoing review by local IRBs. As it turned out, this dual review was confusing and did not realize efficiencies and cost savings. The NCTN now relies on adult and pediatric central IRBs as the IRB of record to streamline review for NCI-funded studies, demonstrating the value and effectiveness of requiring a single IRB of record for multi-site research studies.

Acceptance of the NCI central IRBs has grown significantly over time, and it is now required that all NCTN sites participating in NCI-funded studies within the U.S. use the central IRB process. This requirement has helped ensure consistent protocols and consent processes across the NCTN and has resulted in cost savings to the system. More importantly, the use of a single IRB helps to ensure that all prospective study participants receive consistent and complete information about research studies regardless of the site of enrollment. As the NIH notes in its draft Policy announcement, a single IRB allows local IRBs to devote time to single-site studies. Other important site responsibilities (e.g., investigator competence and site suitability) can be accomplished through the overall human research protections program at the institution. The success of the NCI CIRB Initiative and an independent analysis of its performance^{1,2} points to the feasibility and benefits of this approach. Using a single IRB for multi-site studies will likely replicate these benefits in other diseases areas.

ASCO and AACI support the NIH proposal to expect all sites participating in a multi-site study to use a single IRB of record. Local IRBs are challenged by considerable workload and mustering sufficient resources. NIH-funded trials undergo significant scientific review through the grant-making process, so additional review by each institution involved is unwarranted and rarely results in substantive changes to the research protocol. ASCO and AACI encourage the NIH to allow very narrow exceptions to the requirement for a single IRB. Exceptions may be warranted with unique populations that pose specific concerns at the local level. With rare disease populations, however, a single IRB would provide more potential to involve people with the needed expertise—who are not directly involved in the study under review. The onus should be on the institution to provide evidence that a local IRB review is required to protect the interests of special populations and would benefit the study and contribute to its research—in a timely manner. If exceptions are widely granted, the effect of the requirement will be void.

The Policy should discuss what action would be taken if a local IRB review resulted in a requirement to change the protocol or consent. Such a situation may significantly delay the research process and result in protocol and consent differences that could influence the study, especially if multiple local IRB reviews take place. Therefore, we strongly encourage NIH to limit local IRB reviews as they are frequently duplicative and burdensome to the research process. Wider use of single IRB review in multi-site studies has the potential to obviate the need for local IRB review. As noted in ASCO's 2003 Policy Statement on Oversight of Clinical Research, "centralized review would provide for greater consistency across the trial sites to enable review boards and investigators to implement more quickly and consistently protocol and informed consent amendments."³ If an exception for local IRB review is granted by NIH, we recommend that any protocol or consent form changes associated with the review should be approved by the IRB of record before the study can proceed. In addition, deletion of content from the protocol or the consent should not be allowed.

The single IRB process will improve monitoring and assessment of adverse events, which has real potential to enhance trial participants' safety by giving local institutions more information on the overall trial and enabling them to devote more time to ongoing review of the trial onsite. For a single IRB review to work, the IRB of record must commit to open, regular communication with participating institutions to ensure all parties are kept informed of the progress of the study and any emerging safety concerns. Constraints on the single IRB of record should be taken into account, such as the workload of the IRB and its capacity to handle the reviews in a timely manner. With respect to how the single IRB of record might

be selected, a reasonable and perhaps cost- and time-efficient approach would be to use the IRB at the principal investigator's institution.

NIH should consider, along with this Policy, issuing guidance documents that provide clear examples of responsibilities that it considers specific to the IRB of record versus local institutional responsibilities for oversight of institutional researchers and research participants. In addition, NIH could release examples or best practices for agreements between institutions and external IRBs of record. NIH guidance on this topic would help institutions and external IRBs develop clear agreements that delineate responsibility for research review and oversight. NIH should also consider setting expectations that language and templates remain consistent across IRBs that may be facilitating multi-site research, thereby reducing variability, providing assistance to IRBs of record, and simplifying administrative duties.

Thank you again for the opportunity to provide this feedback. We would be pleased to provide additional information on these comments, or collaborate on developing these ideas further. If you have any questions in the future, please do not hesitate to contact Suanna Bruinooge, Director of Research Policy for ASCO at suanna.bruinooge@asco.org (571-483-1670).

Sincerely,

Peter P. Yu, MD, FACP, FASCO
ASCO President

George J. Weiner, MD
AACI President

Footnotes

- ¹ Hahn K. Measuring IRB efficiency: Comparing the use of the National Cancer Institute central IRB to local IRB methods. *SOCRA Source*. 2009 May; 49-52.
- ² Wagner TH, et al. Costs and benefits of the National Cancer Institute Central Institutional Review Board. *J Clin Oncol*. 2010 Feb 1; 28:662-666. Epub 2009 Oct 29.
- ³ American Society of Clinical Oncology Policy Statement: Oversight of Clinical Research. *J. Clin Oncol*. 2003 Jun 15; 21:2377-86. Epub 2003 Apr 29.

Comment #139

Commenter:

Date of Comment:

Comment:

January 29, 2015

Submitted by email to singleIRBpolicy@mail.nih.gov

Francis S. Collins, MD, PhD Director
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

RE: NOT-OD-15-026, Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research (*NIH Guide for Grants and Contracts*)

Dear Dr. Collins:

Public Responsibility in Medicine and Research (PRIM&R), a nonprofit educational and professional development organization, appreciates the opportunity to submit comments in response to the “Draft Policy on the Use of a Single Institutional Review Board for Multi-Site Research” published in the NIH Guide for Grants and Contracts on December 3, 2014, by the National Institutes of Health (NIH).

For 40 years, PRIM&R has been dedicated to advancing the highest ethical standards in the conduct of research. We accomplish this goal by serving the full array of individuals and organizations involved in biomedical, behavioral, and social science research, particularly the members and staff of human research protection programs (HRPPs) and institutional review boards (IRBs). Through conferences and other educational activities, PRIM&R provides balanced, thorough, and accurate information on a range of ethical and regulatory issues affecting research.

The biomedical research landscape has evolved dramatically since the publication of the federal regulations for the protection of human subjects in 1974. In particular, research with human subjects has become an increasingly complex endeavor in which multi-center rather than institution-based research is increasingly the norm. In light of this shift, it is sensible to consider whether an alternative structure for research review better safeguards the rights and welfare of research participants and lessens unnecessary administrative burden. To that end, we understand the NIH’s interest in reducing inefficiencies associated with multiple IRB review by mandating that studies involving multiple institutions rely on a single IRB for review.

However, while the use of a single IRB can be a beneficial approach for *some* multi-site studies, PRIM&R believes that it is premature and perhaps inappropriate to mandate single IRB review for *all* NIH-funded and conducted studies. Many factors influence whether the use of a single IRB serves the interests of greater efficiency, reduced costs, and stronger protections for subjects. Such factors include the number and types of institutions involved, the study design, the degree of risk created for subjects (e.g., minimal risk or greater than minimal risk), the nature of the study team, and the resources available for investigators and local sites.

Further, reliable empirical data on the various ways in which a single IRB can be used to provide ethical review of multi-site research, and on whether such review is better, from the perspective of subject protections, administrative costs, efficiency, and quality of review, than relying on local IRBs, are sparse to nonexistent. In the absence of sufficient evidence, we believe that a policy requiring the use of single

IRBs for all domestic sites of multi-site NIH-funded studies is premature and ill advised. As in medicine, innovations in policies should be preceded by research and supported by adequate data. We understand that the NIH is currently investing in research directed at answering some of the relevant empirical questions related to the use of a single IRB, as well as alternative models for improving IRB efficiency. Accordingly, it would seem prudent to await the results of these studies prior to promulgating such a policy.

The mandated use of a single IRB is associated with many as yet unanswered procedural questions and logistical challenges. For instance, institutions tasked with serving as the single IRB of record will need to have sufficient infrastructure to manage the network of participating institutions. The development of such an infrastructure is likely to involve considerable time, resources, and costs. It is unclear from the draft policy who would bear those costs. Similarly, while the use of a single IRB may be familiar to some institutions, it is likely to be unfamiliar to most. The field requires more time to conduct research on the use of a single IRB, to develop guidance, and to disseminate best practices before the use of a single IRB for multi-center studies is mandated.

As stated at the outset, we recognize the value of streamlined and efficient IRB review and the use of a single IRB for *some* multi-site research. However, instead of mandating single IRB review for all studies at this time, we urge the NIH to consider incentives to encourage voluntary adoption. The NIH and others should also promote the development of tools and resources to guide institutions through the process of both building the required infrastructure and crafting policies and procedures for managing or working through a single IRB. Finally, the NIH ought to support the conduct of empirical research on the costs and benefits associated with the use of the single IRB mechanism. PRIM&R believes that taken together, these are the most appropriate means for the NIH to foster the stated purposes of the draft policy, namely, “to increase the use of single IRBs for multi-site studies funded by the NIH.”

Below, then, are several examples of activities we encourage the NIH to consider in its effort to support the wider use of the single IRB mechanism for multi-site studies:

1. Convene an expert panel to host open meetings to develop criteria regarding the types of research that lend themselves to the single IRB model and those that do not;
2. Sponsor research on existing models of review by a single IRB for multi-site research to gather more evidence about both the quality and cost of review;
3. Create incentives (e.g., preferential treatment in the award process) that encourage and reward the use of, and require the collection of data on the use of, single IRB review and/or elements of single IRB review processes; and
4. Develop tools, guidance, and best practices to help facilitate the use of single IRB review mechanisms (e.g., model reliance agreements, standard operating procedures, etc.)

Finally, we wish to raise concerns about how the adoption of this policy may impact harmonization efforts. The provisions put forward in the NIH’s draft policy are in line with changes first proposed in the Department of Health and Human Services’ 2011 Advance Notice of Proposed Rulemaking (ANPRM), entitled *Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators*. That ANPRM sought to update the federal regulations for the protection of human subjects and strengthen harmonization amongst the regulatory agencies involved. However, with the status of DHHS’ proposed rule unclear, we are concerned that the NIH’s adoption of policies originally proposed under the framework of the ANPRM may worsen a piecemeal approach to regulatory change and undermine harmonization amongst regulatory requirements from different funding agencies, which may, in turn, cause confusion and, ultimately, weaken subjects protections.

PRIM&R is grateful to the NIH for the opportunity to comment, and we hope that you and your colleagues will find our input on this matter useful as you finalize this policy. If you have any questions or require any further information, please feel free to contact me at (213) 740-2557 or PRIM&R's executive director, Elisa A. Hurley, PhD, at (617) 423-4112 or ehurley@primr.org.

Respectfully Submitted,

Alexander M. Capron Board Chair

cc: Board of Directors Executive Director

Comment #140

Commenter:

Date of Comment:

Comment:

Office of Clinical Research and Bioethics
Policy Office of Science Policy
National Institutes of Health
6750 Rockledge Drive; Suite 750
Bethesda, MD 20892

RE: Request for Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-site Research (NOT-OD-15-026)

Submitted via e-mail at SingleIRBPolicy@mail.nih.gov

Dear Ms. Carr:

The American Psychological Association (APA) appreciates the opportunity to comment on the National Institutes of Health (NIH) Draft Policy on the Use of a Single Institutional Review Board for Multi-Site Research (NOT-OD-15-026). The APA Committee on Human Research (CHR) has reviewed the draft policy and assessed the potential impact of the policy on the conduct of research. We believe that a single Institutional Review Board (IRB) review of multi-site studies would greatly facilitate scientific progress, by reducing the time required to launch research studies as well as reducing the substantial staff resources dedicated to IRB reviews at multiple universities for a single study – a concern that is exacerbated when each IRB requests different changes to the protocol or other study documents. Thus, we strongly support the draft NIH policy “to promote the use of a single Institutional Review Board of record for domestic sites of multi-site studies funded by the NIH.”

However, we would like to reemphasize some of the issues regarding the use of a single IRB of record that we outlined in our letter dated October 11, 2011 to Dr. Jerry Menikoff (Office for Human Research Protections), in response to the Advance Notice of Proposed Rulemaking on Human Subjects Research Protections. These specific considerations are delineated below.

Identifying the IRB of record: APA emphasizes the need to clearly specify a variety of mechanisms for determining the IRB of record for any particular multi-site study, and appreciates the Draft NIH Policy’s specifications: “Identification of the IRB that will serve as the single IRB of record will be the responsibility of the extramural applicant or offerer, or the intramural principal investigator. The funding NIH Institute or Center has final decisional authority for approving the selected single IRB. Use of the designated single IRB will be a term and condition of award.”

APA agrees with the importance of clear guidelines for identifying the IRB of record in funding announcements and prior to issuance of the award notice. This will allow researchers and institutions to consider carefully leadership roles and resource requirements, and it will prevent a scenario wherein “all sit on their hands” and no institution offers to take on the issues of accountability and legal responsibility (noted below) or the opposite. It will be important, however, to give consideration to the substantial resources and responsibility involved in “single IRB of record” oversight of research at multiple sites. One challenge of multi-site studies is the tremendous indirect costs associated with these studies and the trend for federal grant Requests for Applications (RFAs) to indicate total cost limits rather than total direct cost limits. APA believes that some consideration of the costs to the site with the single IRB of record is warranted.

Issues of accountability and legal responsibility: APA urges the need to specify clear guidelines regarding the oversight and enforcement of regulatory compliance. As one example, the single IRB of record may be the appropriate body to oversee and enforce certain types of compliance, such as involving a protocol deviation that occurs across sites (e.g., measure in IRB-approved study protocol is not included in study survey) or the failure to institute a serious adverse report mechanism across sites. The local IRBs may be the appropriate bodies to oversee and enforce other types of compliance (completion of informed consent documents for all subjects in study).

Understanding the local context of the research: APA agrees that “as necessary, mechanisms should be established to enable the single IRB of record to consider local context issues during its deliberations,” including issues such as institutional commitment, feasibility (number of competing studies being implemented, with limited participant pool), PI competence, and state and local laws and ordinances. Given the importance of some level of local/institutional oversight and regulatory responsibility, APA recommends that local IRBs (1) have awareness of the study being conducted, and (2) agree to specified areas of oversight and regulatory responsibility (e.g., local secure and confidential data storage, acquisition of informed consent). Similarly, APA recommends that one or more mechanisms be available to local institutions for providing input to the single IRB of record that is pertinent to local concerns such as feasibility (site and competing study considerations) and any local laws or ordinance that impact study implementation.

Communications: APA believes that the regulations need to clearly articulate mechanisms for communications between the IRB of record, local IRBs, and investigators. This is particularly important with regard to reporting of compliance incidents, adverse events, and unanticipated problems.

Exceptions: APA is opposed to any exception to the use a single IRB and strongly urges that the policy be mandatory. Including the option for individual sites to conduct their own internal review defeats the intent and goal of this draft policy (i.e., to reduce procedural inefficiencies so that human subjects research can proceed efficiently). Internal reviews would be just as time-consuming and result in the same kinds of conflicts and delays as is the case with the current practice of multiple reviews. Furthermore, if the local institution no longer has any regulatory status, this review would not provide additional protections for research participants, and would only be a waste of the IRB’s valuable time and limited resources. Finally, we are concerned that the examples of “appropriate justification” are vague. We re-emphasize our belief that a single IRB review of multi-site studies should be the norm and that some of the justifications listed may serve as criteria for identifying the IRB of record.

APA thanks NIH for this opportunity to share our comments on the draft policy on the use of a single IRB for multi-site studies. Any and all efforts that streamline the research process, without minimizing human research participant protections is in the best interest of public health. Thus, we strongly support a policy that mandates the use of a single IRB and explicitly proscribes multiple reviews at local research sites. If you have any questions, or if we can provide any further information, please feel free to contact me at 202-336-6000, or by email at hkurtzman@apa.org.

Sincerely,

Howard S. Kurtzman, PhD
Acting Executive Director for Science American Psychological Association

Comment #141

Commenter: Linda Halstead

Date of comment: January 29, 2015

Comment:

While we acknowledge the regulatory mandate of an Institutional Review Board, the IRB is inherently assigned to shoulder a broader ethical responsibility as a central player in the institution's Research Protection Program. This responsibility includes: serving as an ambassador for human subject protections locally, fostering public accountability on the part of the institution's research community, and balancing the interests of its scientists, the human subjects, and the advancement of science. Central review boards might be considered the most efficient way to advance science in limited circumstances, but an academic institution such as the one where I have worked for over 35 years seeks to preserve the role of the local IRB to achieve the objectives identified above. The founding purpose of the Institutional Review Board was built on the laudable concept of local, i.e., institutional responsibility. Indeed it is the local institution which relies on the good will of its community, and in the case of our institution its community is both geographic and cultural, being a lead research entity within the international religious organization which supports it. As is true for all institution-based IRBs, our IRB is the logical force for incorporating local culture and customs wherever our investigators conduct their research. Other examples of institutional concerns that are tied to the IRB process include conflict of interest management, HIPAA compliance, and investigator education. How a central IRB can either incorporate those responsibilities or divest itself from them is manifestly unclear. How can a central IRB maintain expediency without becoming rigid? In what way does this serve society's welfare at large and protect human subjects in particular?

At a practical level, our IRB is at the heart of an entire administrative system of checks and balances. Removing the IRB from that local system is not likely to shorten the time it takes for an institution to meet the network of local approvals which remain, even if IRB review is removed. In fact, extracting the IRB element from the local institution's review process in hopes of achieving a faster 'approval process' overlooks the fact that associated institutional responsibilities remain. Many of these responsibilities are imposed by unfunded regulatory burden which our institution has worked diligently to address with maximum efficiency. Remove those local institutional responsibilities and the perception emerges that the central IRB has a faster approval process. But it actually just distances IRB review from the local research administration processes which can result in a disjointed, possibly more complex solution. Central review has a place in the larger research community in select circumstances. An example is for national cancer trials by which much cancer treatment is provided. National coordination of immunization trials, which must act rapidly and in concert, is also a natural candidate for central review. Thus we do not argue wholesale against central review but request and support that central review boards continue to be a voluntary option.

Thank you for noting these concerns.

Submitted personally by an IRB Director at a mid-size healthcare academic institution.

Comment #142

Commenter:

Date of Comment:

Comment:

January 29, 2015

Office of Clinical Research and Bioethics
 Policy Office of Science Policy, NIH
 6705 Rockledge Drive, Suite 750
 Bethesda, MD 20892

In reference to docket number: **NOT-OD-15-026**

The Association of Clinical Research Professionals (ACRP) is the primary resource for clinical research professionals in the pharmaceutical, biotechnology and medical device industries, and those in hospital, academic medical centers and physician office settings. ACRP was founded in 1976 to address the educational and networking needs of research nurses and others who supported the work of clinical investigations. Almost 40 years later, ACRP is a global association comprised of individuals dedicated to clinical research and development. Our mission is “ACRP promotes excellence in clinical research.” The Academy of Physicians in Clinical Research (APCR) is an affiliate of ACRP and is the leading professional organization, exclusive to physicians, that supports and addresses these unique issues and challenges of all physicians involved in clinical research.

ACRP appreciates the opportunity to provide the NIH with our comments on the Policy on the Use of a Single Institutional Review Board for Multi-Site Research as this issue has a significant impact on our membership. It appears the policy has adequate allowances for various exceptions, and we agree that adequate human subject protections can be obtained through a single, competent IRB review body in most multi-center trials supported with NIH funds. This policy should be adjusted in response to the public comments and staff recommendations where feasible and activated with a generous period of notice to the NIH and investigator community. The attached document provides detailed comments, suggestions, and recommendations on specific sections of the draft guidance.

We applaud the NIH’s efforts on this important issue and hope that our feedback helps improve the final version of the document. Please let me know if you have any questions regarding our comments, or if we may otherwise serve as a resource on issues related to clinical research.

Sincerely,

Jim Thomasell, CPA Executive Director

NOT-OD-15-026: Policy on the Use of a Single Institutional Review Board for Multi-Site Research			
Page Number	Text Line	Reference (if applicable)	Comments
1	1	all	We encourage NIH to work with FDA to coordinate on policies about using a single IRB for each individual trial, and to work with FDA staff to update the existing FDA guidance (March 2006) in order to make the two policies more harmonious.
2	“Several extramural...”	CIRB	Consider the potential conflict of interest when apparently promoting the NIH NCI CIRB in this document, and provide in parallel an example of commercial IRB review that is also supported by an NIH-sponsored

NOT-OD-15-026: Policy on the Use of a Single Institutional Review Board for Multi-Site Research			
Page Number	Text Line	Reference (if applicable)	Comments
			awardee.
2	"The draft Policy..."		The policy should state by what criteria an IRB should be considered qualified to provide this service, and whether, e.g., active registration with OHRP and a current Federal Wide Assurance (FWA) for participating institutions linked to the IRB are together adequate for this qualification, or whether additional quality criteria should apply. We recommend that the policy should specify the minimum qualifications, and should further specify that the selecting institution/awardee should have a written procedure in place to assess and document the qualifications of the selected IRB in order to fulfill their selection responsibility. This should be no different than qualifying a vendor for other key activities that are a function of the research plan. When approving the selected single IRB, the funding NIH IC must be able to review both the selection criteria and the supporting evidence of qualification before making their decision.
3	"A duplicate IRB..."	Cost	When a second IRB exists by necessity at another location, how will discrepancies between approved protocols and Informed Consent materials from the Central IRB of record and Site IRB be managed by the Central IRB? How will different requirements for reporting safety and efficacy performance concerns be transmitted to the respective IRBs? How should necessary costs for differences in reporting or even continuing review frequency be addressed by the Central IRB and the awardee institution/investigator budget?
4-5	Ref 11	accountability	How will "diminished accountability for participating sites, and decreased consideration of local context..." be managed? We believe the guidance document should address this area of concern.
5	Ref 13	Example	While the word "local" appears in the cited example regarding US medical device laws, 21 USC 360j(g)(3)(A) may not be an appropriate example that restricts the application of this guidance within the US. It should be noted that this enabling legislation for IDEs presumes that each investigational site may have its own IRB. This is clearly not the case for many investigational sites in device trials (or drug trials, for that matter). Additionally, the cited language on IDEs indicates that the "local" IRBs, "established in accordance with regulations of the Secretary to supervise clinical testing of devices in the facilities where the proposed clinical testing is to be conducted," can be argued to apply to any IRB "established" at any location if the local institution/facility has agreed to that IRB's supervision. This is because the regulations derived from this part of the FD&C Act do not give any specific indication to suggest a "local" requirement exists in that regard. In support of this, the regulations for IRBs (in 21 CFR 56 and 45 CFR 46) never use the term "local" IRB, and the definition of an IRB (in 21 CFR 56.102(g)) is written as, "any board, committee, or other group formally designated by an institution to review, to approve..." etc., with no mention or implied use of the term, "local." This definition is echoed with similar wording in 21 CFR 50.3(i). There is not even an obligation of affiliation with the institution or facility, other than by the agreement to be designated as the IRB authorized to review, approve

NOT-OD-15-026: Policy on the Use of a Single Institutional Review Board for Multi-Site Research			
Page Number	Text Line	Reference (if applicable)	Comments
			and supervise the research activity. In addition, the regulation for IDEs in 21 CFR 812.40 et seq., while referencing 21 CFR 56, uses the term “reviewing IRB” as opposed to “local IRB,” which implies a wider opportunity for where the IRB might be located. The equivalent regulations for drugs under an IND have no reference to “local” IRBs either, and also use the term “reviewing IRB” in 21 CFR 312.23. Our experience with FDA oversight for numerous INDs and IDEs indicates there are no de facto restrictions with regard to requiring “local” IRB oversight, meaning from within each institution/facility conducting the research, for device studies or otherwise. FDA normally asks only for the contact information of the relevant reviewing IRB(s), however many or wherever there are. It may be better to cast possible exceptions as they may relate to state, local and tribal laws, regulations, or rules, and not US Federal laws or FDA regulations.

Comment #143

Commenter:

Date of Comment:

Comment:

January 29, 2015

Francis S. Collins, M.D., Ph.D. Director
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892

Submitted by email at SingleIRBpolicy@mail.nih.gov

Dear Dr. Collins:

The undersigned organizations representing cancer patient, health professionals, and researchers appreciate the opportunity to comment on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research. We commend the National Institutes of Health (NIH) for taking this step to reduce duplication and inefficiency in the initiation and oversight of multi-site research studies. This policy will provide appropriate protections for research participants while encouraging greater efficiency in initiation and oversight of research.

The National Cancer Institute (NCI) has been a leader in enhancing review of human subjects research, administering the NCI Central Institutional Review Board and fostering efficiencies in the review of multi-center clinical trials. Other institutes at NIH have also pioneered centralized review efforts. We are pleased that NIH is moving beyond these innovative efforts to set a standard for NIH-funded institutions to use a single institutional review board (IRB) of record for domestic sites of multi-site studies. A standard that applies to multi-site studies that are supported by NIH grants, contracts, or the NIH intramural program will begin to address the reluctance of many research institutions to utilize central IRBs. Whether the resistance to central review relates to institutional inertia, concerns about the management of local context, or concerns about regulatory liability in the case of non-compliance in a central review situation, the implementation of a clear NIH grant and contract policy will begin to address these reservations and concerns.

The draft policy provides for exceptions to the presumption that a single IRB will be used, if those exceptions are presented to NIH with appropriate justification. The draft policy states that, "Exceptions will be allowed only if the designated single IRB is unable to meet the needs of specific populations or where local IRB review is required by federal, tribal, or state laws or regulations." We anticipate that exceptions will be requested, perhaps somewhat routinely, by institutions asserting that local issues or the needs of specific populations can only be met by local IRB review. We urge NIH to develop clear policies for assessing local review issues or the needs of specific populations so that it can efficiently address requests for exceptions to single IRB review. Without clear standards for exceptions, the NIH policy favoring central IRB could be seriously undermined by the request for and grants of exceptions.

In the draft policy, NIH defines the responsibilities of the single IRB for a multi-site study and the responsibilities of individual sites. The draft policy notes that all participating sites "will be responsible for meeting other regulatory obligations, such as obtaining informed consent, overseeing the implementation of approved protocols, and reporting unanticipated problems and adverse events to the single IRB of record." In the final policy, any additional guidance, and in the terms and conditions that are included in the Notice of Award or the requirements in the Contract Award, the respective

responsibilities of the single IRB and the participating research sites should be reinforced. Because the single IRB policy represents a change in decades of research oversight and compliance practices, NIH should reinforce the new standards and provide clear guidance regarding implementation of the new standards.

In an era of restrained research resources, it is important that the research system embrace any opportunity to reduce duplication and enhance efficiency. We commend NIH for advancing a policy that encourages efficiency while still protecting those who participate in research.

We look forward to collaborating with NIH to publicize this new standard, when finalized, and to encourage research sites to adopt the use of a single IRB.

Sincerely,

Cancer Leadership Council

American Society of Clinical Oncology

CancerCare

Coalition of Cancer Cooperative Groups

Fight Colorectal Cancer

Hematology/Oncology Pharmacy Association

Kidney Cancer Association

The Leukemia & Lymphoma Society

LIVESTRONG Foundation

Lymphoma Research Foundation

Multiple Myeloma Research Foundation

National Coalition for Cancer Survivorship

National Patient Advocate Foundation

Ovarian Cancer National Alliance

Pancreatic Cancer Action Network

Prevent Cancer Foundation

Sarcoma Foundation of America

Us TOO International Prostate Cancer Education and Support Network

Comment #144

Commenter:

Date of Comment:

Comment:

January 29, 2015

Francis S. Collins, M.D., Ph.D. Director
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20892

Sent via email to SingleIRBpolicy@mail.nih.gov

Re: NOT-OD-15-026 - Request for Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

Dear Dr. Collins:

On behalf of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), we offer support for the draft National Institutes of Health (NIH) policy on the use of one Institutional Review Board (IRB) of record for multi-site research.

With more than 1,500 members, NASPGHAN is the leading society in the field of pediatric digestive diseases. NASPGHAN's mission is to improve quality of care and health outcomes for infants, children and adolescents with disorders of the gastrointestinal tract and the liver and with malnutrition by promoting advances in clinical care, research and education.

We believe by establishing the expectation that all facilities participating in a multi-site study will rely on a single IRB is particularly important for advancing research into rare diseases, including rare pediatric diseases of the digestive system, because inclusion of multiple centers is often needed to amass the required number of study subjects for meaningful research.

As referenced in the notice, while both the Food and Drug Administration and Office for Human Research Protections support the use of a single IRB, too few institutions involved in multi-site studies are taking advantage of the option. We believe a change in NIH policy to encourage greater use of a single IRB will lead to more institutions participating in multi-site studies because the administrative burden to individual center IRBs, which are often composed of volunteers, will be reduced while maintaining the integrity human subject protections.

The draft policy states "The funding NIH Institute or Center has final decisional authority for approving the selected single IRB." We want to emphasize that when studies include children, it will be important that the single IRB have expertise in pediatric research.

Public Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

We thank you for soliciting public comment on this important policy change. Should you have any questions or require further information from NASPGHAN, please contact Camille Bonta at (202) 320-3658 or cbonta@summithealthconsulting.com.

Sincerely,

Carlo Di Lorenzo, MD
President
NASPGHAN

Neera Gupta, MD, MAS
Chair
NASPGHAN Research Committee

Comment #145

Commenter:

Date of Comment:

Comment:

January 29, 2015

Office of Clinical Research and Bioethics Policy

Office of Science Policy

National Institutes of Health

SingleIRBpolicy@mail.nih.gov

Dear Comment Review Board:

The IRB Leadership and Enhancement Committee (ILEC), on behalf of the Virginia Commonwealth University (VCU) Human Research Protection Program (HRPP), is submitting comment regarding the *Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research* issued by the National Institutes of Health on December 3, 2014.

The VCU ILEC acknowledges that the draft policy is well intentioned and affords some potential advantages, such as greater expediency in IRB review. The draft policy does, however, raise some questions and concerns that should be given attention prior to issuing final policy:

Lacking Evidence of the Benefit of Central IRBs: The draft policy states, “Importantly, there is no evidence that multiple IRB reviews enhance protections for human subjects. In fact, the use of single IRBs may lead to enhanced protections for research participants...”. The current models of central IRB review predominantly in use today are either independent, fee-based central IRBs or central IRBs established to support a network of studies focused on a particular disease area. Even with these highly developed systems supported by robust infrastructure, substantiated evidence of enhanced protections is lacking. A central IRB model relying on traditional, institutionally based IRBs to serve as IRBs of record is even less likely to demonstrate enhanced protections. In this model, it seems probable that IRBs could be selected even though overall HRPP quality and experience with reviewing large multi-site studies have not been vetted; adequate administrative support is not available to manage a large, multi-site review; and substantial infrastructure is not in place to support seamless information sharing among sites. One could envision a situation such as this leading to administrative errors at best and mistakes that could compromise protections at worst.

Shift in Administrative Burden: The draft policy notes, “...proponents of the single IRB model maintain that review of a multi-site study by the IRB of each participating site involves significant administrative burden in terms of IRB staff and members’ time to perform duplicative reviews.” In our opinion, the administrative burden involved with reviewing a higher volume of studies will be replaced by equivalent or greater burden assumed by tasks such as negotiating authorization agreements with each site that describe the division of responsibilities, managing incoming submissions from numerous unfamiliar sites, collecting and applying local context information to the review of each site’s submission, ensuring continuing review submissions are submitted in a timely fashion to prevent expiration, and establishing systems for information sharing with the participating site investigators and research administration.

Need for Continued Local Research Oversight: Participating sites will not be relieved of all research oversight responsibilities under the proposed central IRB initiative. Numerous ancillary reviews will still be needed, such as pharmacy, biosafety, radiation safety, and conflict of interest reviews; as well as verifying principal investigator qualifications, adequate institutional resources, and HIPAA compliance.

The ceding institutions will need to develop a mechanism for sharing pertinent information from these reviews with the IRB of record. In some cases, a duplicative review may result if the IRB of record also wants to conduct some of these reviews, such as conflict of interest and HIPAA.

Need for Timely Authorization Agreements: The negotiation of authorization agreements specifying the division of responsibilities can be time consuming. The need to negotiate agreements at the time of notice of award and prior to a participating site submitting its materials to the IRB of record could delay IRB review of the site specific information, potentially negating any time savings associated with utilization of a central IRB. Alternatively, authorization agreements could be negotiated at the time of proposal; however, this may result in significant wasted effort and cost should the proposal not be funded.

Cost to the Local Institution: Participating sites will incur the additional burden of developing and staffing a research oversight system for considering and tracking research ceded to a central IRB.

Quality of the Central IRB and Participating Sites: As an AAHRPP accredited institution, some concerns arise regarding the quality of the HRPP at the sites to whom IRB review may be ceded. The draft policy indicates that selection of the IRB of record will be the responsibility of the extramural applicant or the intramural principal investigator. Participating sites must accept the IRB of record or lose the award. AAHRP accredited sites are responsible for ensuring that IRBs, on whom they rely, maintain equivalent standards with their human research protection program. Conducting a substantive review of the policies and procedures of the IRB of record to determine equivalency will involve additional administrative effort. Additionally, the mandate has the potential to result in a situation where the institutional administration must either accept reliance on an IRB that does not meet equivalent standards or risk losing an award if refusing to utilize the selected IRB of record.

This issue is even more troublesome if IRB review of non-accredited participating sites were to be ceded to our AAHRPP-accredited HRPP, for example, as the IRB of record. The Draft NIH Policy notes that “all participating sites will be responsible for meeting other regulatory obligations, such as obtaining informed consent, overseeing the implementation of approved protocols, and, reporting unanticipated problems and adverse events to the single IRB of record.” This single sentence is insufficient to insulate the central IRB of record from its overall responsibility of ensuring a high regard for the ethical and compliant conduct of the research among participating institutions whose HRPPs have not been otherwise vetted for quality.

Study Team Workload: The draft policy has the potential to result in significant additional responsibilities to principal investigators and research coordinators. When engaged as a participating site for multiple studies, research personnel will be required to adapt to varying IRB procedures and maintain regulatory documentation being distributed through numerous channels.

When engaged as the lead site responsible for coordination with the IRB of record, substantial effort may be needed to serve as a liaison between all of the participating sites and the IRB of record. Research dollars that otherwise would be utilized more specifically to carry out study procedures would need to be allocated to administrative, coordination efforts.

Exception from Informed Consent Research (EFIC): Reliance on a central IRB seems to run counter to the intent of the regulatory requirements for IRB approval of EFIC research. Much of the IRB’s responsibility involves assuring that adequate plans are in place to conduct community consultation and disclosure. Assessment of these plans by a central IRB; which is unfamiliar with local population, geography, and culture, would be quite difficult.

Local Communication and Education: When principal investigators and study staff routinely work with a

single IRB, they develop relationships that promote ongoing communication and education, ultimately leading to more compliant and ethically sound research conduct. Routine reliance on external IRBs could lead to erosion of that cohesive relationship between researchers and the administrative infrastructure at institutions, ultimately leading to more poorly prepared researchers and increased noncompliance.

Thank you for the opportunity to provide comment on this draft policy. We welcome any questions or feedback. Please direct correspondence to Dr. Michelle Stickler, mcstickler@vcu.edu.

Respectfully submitted,

IRB Leadership and Enhancement Committee Virginia Commonwealth University Richmond, VA

Comment #146

Commenter:

Date of Comment:

Comment:

January 30, 2015

By Email

Office of Clinical Research and Bioethics
Policy Office of Science Policy
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Submission of Comment on Announcement of a Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research - *Revised*

Dear Madam/Sir:

Pfizer Inc (Pfizer) welcomes the opportunity to submit comments on the National Institutes of Health (NIH) Announcement of a draft policy on the use of a single Institutional Review Board (IRB) for multi-site research, the notice of availability of which was published in the Federal Register on January 6, 2015 (80 FR 511-512).

Pfizer is a leading global biopharmaceutical company that is committed to applying science and our global resources to improve health and well-being at every stage of life. Pfizer's purpose is to innovate to bring therapies that significantly improve patients' lives. Research and Development is at the heart of fulfilling Pfizer's purpose as we work to translate advanced science and technologies into the therapies that matter most. Today our pipeline is comprised of over 80 innovative therapies including potentially first-in-class vaccines for two deadly hospital-acquired infections, new antibodies for lupus and high cholesterol and the next-generation of targeted therapies for cancer. We are committed to the safety of patients who take part in our trials, and uphold the highest ethical standards in all of our research initiatives.

As a bio-medical research company that sponsors over 250 studies a year, working with approximately 175 U.S IRBs, we often experience delays in the commencement of our trials due to complexities with multiple IRBs, including alignment on protocol/processes and unnecessary administrative variation across sites (e.g., informed consent documents). Therefore, as a stakeholder with the shared goal to bring safe innovations to patients in need, we welcome the NIH draft policy to promote the use of a single Institutional Review Board for multi-site studies. A single IRB process could greatly improve the quality and efficiency of the IRB review and promote consistency within the review process. However, we are mindful of the complexities in the adoption of a single IRB model and offer our thoughts on factors that may be considered for implementation.

Academic institutions currently have experience with the single IRB policies of the National Cancer Institute (NCI) and the National Institute of Neurological Disorders and Stroke (NINDS) but as currently drafted in this policy, adoption of single-IRB for multi-site research will likely be challenging and require significant resources for implementation. Many IRB systems differ in terms of standards and do not have the systems or processes to function as a centralized IRB. Therefore, we would recommend that the NIH clarify the timeframe for adoption and include appropriate incentives to promote the use of single-IRB for multi-site research. This would help to encourage and provide institutions with necessary time to

standardize and adopt centralized review processes.

In addition, while the use of single IRBs could greatly improve efficiency of the review process, it is important to note that local variations in ethics and institutional policies must continue to be recognized and accommodated.

Pfizer appreciates the opportunity to comment on this policy. If you have any questions about these comments, please contact Carol Haley at 212-733-4787 or by email at carol.haley@pfizer.com.

Sincerely,

Roslyn F. Schneider, MD, MSc, FACP, FCCP
Global Patient Affairs Lead

Comment #147

Commenter:

Date of Comment:

Comment:

January 29, 2015

Office of Clinical Research and Bioethics Policy Office of Science Policy
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

RE: Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research (Notice number NOT-OD-15-026)

The Association of American Medical Colleges (“AAMC”), a not-for-profit association representing all 141 accredited U.S. medical schools, nearly 400 major teaching hospitals and health systems, and 90 academic and scientific societies, appreciates the opportunity to submit comments on the draft policy on the use of a single Institutional Review Board (IRB) for multi-site research, released on December 3, 2014 by the National Institutes of Health (“NIH”). Through the AAMC’s member institutions and organizations, the AAMC represents 128,000 faculty members, 83,000 medical students, 110,000 resident physicians, and thousands of graduate students and post-doctoral trainees.

In the draft policy, NIH has taken a sweeping approach to ensuring the increased use of single IRBs with the general rule that “all sites participating in a multi-site study will be expected to rely on a single IRB,” and that compliance with the policy “will be a term and condition in the Notice of Award and a contract requirement in the Contract Award.” The AAMC recognizes that increased use of single (or central) IRBs for certain multi-site trials has the potential to increase the efficiency of reviewing proposed and ongoing research and reducing burdens on institutions and investigators in what can be a redundant and inefficient process without commensurate increased protections to human subjects. As we expressed in our 2011 comments responding to the Department of Health and Human Services’ (HHS) advanced notice of proposed rulemaking (ANPRM)¹ that first suggested this approach:

The use of a single IRB of record for multi-site studies has the potential to decrease burden, standardize protections, and reduce delays in approval processes. The ANPRM proposes that a single IRB of record be mandated for all multi-site, domestic trials. AAMC supports the establishment of a regulatory framework that promotes and facilitates the adoption of single IRB review for multi-site studies. Regular use of a single IRB of record in large multi-site trials could accomplish both goals of the ANPRM if certain considerations, guidance, and clarifications are in place prior to the effective date of such a requirement.²

Despite our support for the increased use of single IRBs for multi-site trials, we believe that the implementation of this policy as drafted will not accomplish the NIH’s laudable goals, but may instead increase costs, shift administrative burdens, and encourage the development of “shadow” IRB reviews to fill in the gaps left by insufficient guidance on how to create many simultaneous reliance agreements and relationships. We concur with many academic medical centers and research institutions that have commented on this issue, both in response to this draft policy and to the related section in the 2011 ANPRM, providing valuable information about the concerns and increased responsibilities of sites that function as single IRBs as well as sites that rely on others. We commend these thoughtful letters to your attention as well.

In these comments, we identify the primary concerns with the scope and structure of the policy and offer NIH recommendations for addressing these problems and alternative approaches that could accomplish similar results without unintended negative consequences.

Creating an effective inter-institutional reliance is not a rapid or simple process. The successful examples of single IRBs for large, complex multi-site studies are often the result of expensive and time-consuming development and negotiations. These relationships evolve over time and require the establishment of trust, a familiarity with processes, procedures, and personnel, and clear designation of roles and responsibilities for all aspects of managing the trials. An institution that has never served as an IRB for other sites will need to build the requisite infrastructure and expertise to allow it to play this role.

A single IRB will not be equally beneficial for all multi-site trials. This policy would be strengthened if NIH could use the experiences of institutions across the country to create a set of criteria identifying which types of trials would be most likely to realize the goals of efficiency and adherence to ethical principles. These criteria might include trials of a certain size, number of sites, or level of risk, or inclusion of a site with infrastructure in place to act as a single IRB. Using these guideposts, the NIH could implement a policy that had a more limited scope or implement a tiered or phased approach as we recommend below.

Roles and responsibilities of all sites must be clearly and explicitly defined before institutions will be confident in their ability to cede or take on IRB review for all NIH-funded multi-site studies. The roles that the responsible and the reliant institutions need to consider in the context of a multi-site trial are numerous, and should be better enumerated in the policy or in related guidance. These would include issues related to cost, allocation of resources, liability, subject injury, investigator and subject records management, and the other institutional responsibilities now coordinated by many IRBs.

Institutions will need more guidance on how to choose a single IRB, and when this decision needs to be made. The draft policy indicates that NIH will have “final decisional authority for approving the selected single IRB,” but does not include further information on the attributes that such an IRB must have or whether the selection of the single IRB must occur prior to the Notice of Award. It is not clear whether the appropriateness of the applicant’s selection of the single IRB will affect the likelihood of a multi-site trial being funded. If the agreed-upon IRB must be identified at the time of application, applicants would need to have assurances that the selected IRB will meet established thresholds, such as accreditation by the Association for the Accreditation of Human Research Protection Programs (AAHRPP).

The exceptions to a mandate should be broader than currently proposed. If this policy is finalized with as expansive a scope as currently envisioned, the NIH should consider a policy of exceptions that goes beyond the inability of a designated single IRB “to meet the needs of specific populations or where local IRB review is required by federal, tribal, or state laws or regulations.” There will undoubtedly be times when circumstances will warrant the local review to ensure the protection of human subjects, and the NIH policy should provide institutions with a clear mechanism for addressing these concerns without the fear of penalty from the funding entity.

Research the NIH has already agreed to fund should be used to determine the most effective way to draft and implement this policy. In a recent notice of funding opportunity, NIH has specifically solicited applications for grants to “explore two timely issues of significance for policy development” including “the principles and characteristics for central Institutional Review Boards (IRBs).”³ As NIH states in the background to this notice, “the use of a single IRB for multi-site studies, which is permitted under current Federal human subjects research regulations (45 CFR part 46), was proposed as a requirement

for domestic, multi-site studies in the 2011 Advanced Notice of Proposed Rulemaking on the Common Rule. While central IRBs have been used effectively in some contexts, research and analysis could inform the move to broader use of central IRBs.” The application deadline for these grants is February 19, 2015, and we encourage NIH to consider how to promote “evidence-based policy” by using the information gained from this research to inform the current proposed move to a broader use of single IRBs.

NIH should consider alternatives to a broad mandate for all NIH-funded studies. There are many actions that the NIH could take in the interim to move toward the goal of increasing the use of single IRBs beyond simply reminding institutions of the mechanism for the use of single IRBs and encouraging their wider use. We recommend that the NIH instead take one or more of the following approaches:

- Run a pilot program with a select group of institutions and studies to measure the true costs, benefits, and consequences of greater adoption of single IRBs.
- Issue a policy with incentives for voluntary adoption.
- As discussed above, determine the attributes of studies that are most readily adaptable to single IRB review and either limit the policy to those studies or begin a phased-in implementation of a broader mandate starting with these studies.
- Create or fund resources and tools that facilitate collaboration, cooperation and greater efficiencies, perhaps allowing the central review of multi-site studies through an online platform.

In the AAMC’s comments to the 2011 HHS ANPRM, AAMC stated that “this is an area of great promise, but the process to move towards a mandated single IRB of record needs to be deliberate and thoughtful.” The AAMC is appreciative of NIH’s commitment to engaging the research community in ensuring that this policy is drafted and implemented in a manner that meets the NIH’s stated goal to “enhance and streamline the process of IRB review and reduce inefficiencies so that research can proceed efficiently without compromising ethical principles and protections” and is also deliberate and thoughtful. We would be happy to provide any further assistance in this process. Please feel free to contact me or Heather Pierce, Senior Director for Science Policy and Regulatory Counsel at hpierce@aamc.org or (202) 478-9926 with any questions.

Sincerely,

Ann C. Bonham, Ph.D. Chief Scientific Officer

Footnotes:

¹Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, (notice published July 26, 2011).

²AAMC Comment Letter, October 25, 2011, (available at <https://www.aamc.org/download/264544/data/aamccommentlettertohhsproposedhumansubjectsresearchregulation.pdf>).

³NIH Funding Opportunity: Empirical Research on Ethical Issues Related to Central IRBs and Consent for Research Using Clinical Records and Data, RFA-OD-15-002 (available at <http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-15-002.html>).

Comment #148

Commenter:

Date of Comment

Comment:

January 29, 2015

Office of Clinical Research and Bioethics Policy Office of Science Policy
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Re: Notice number NOT-OD-15-026, Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research, published on December 3, 2014.

The WIRB-Copernicus Group (WCG) is pleased to have this opportunity to comment on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research, issued by the National Institutes of Health (NIH).

General Comments

WCG thanks NIH for proposing a policy with the potential to enhance the protection of human subjects while simultaneously improving administrative efficiency, lessening regulatory burden, and reducing the costs of conducting research. The draft policy demonstrates an understanding of how the research landscape has changed over the course of the last several decades to an environment where a great deal of research is conducted across multiple collaborating institutions. In the current context, many large institutions and academic medical centers have ceded review of industry-sponsored multisite clinical trials to central IRBs, but have continued to insist on local IRB review for almost all other research even as the FDA and OHRP have routinely encouraged the broad use of central IRBs. Therefore WCG believes that this policy is critical to encourage those institutions that have been hesitant to move towards reliance on central IRBs for NIH sponsored multisite research.

Utilization of central IRBs provides an opportunity for enhanced human subject protections. With a single IRB there is better communication between the IRB and the sponsor, including the opportunity for more efficient discussion of protocol comments and concerns. In multisite research, a central site can serve as a single point of contact with a sponsor to ensure a consistent protocol across all sites, while also coordinating appropriate site-level changes, such as no enrollment of children at sites without appropriate expertise or allowance for ethical directives of faith-based organizations.

This avoids inconsistency in scientifically relevant procedures and greater uniformity in study conduct across sites. A central IRB is also better positioned to observe compliance trends and safety issues across sites. In addition, having one point of contact for subject concerns may help identify concerning trends during the course of the study.

There are also some potential areas of concern with the proposed policy. As written, the policy does not describe necessary characteristics of central IRBs. This may lead to an assumption that any local IRB can serve as a central IRB. However, local IRBs are generally not suited to serve as central IRBs, and generally lack necessary capacity, processes, flexibility, and technology to oversee research across multiple diverse sites. Indicators of effective central IRBs that address this concern are described below.

We believe that the policy should provide guidance on how institutions and investigators should choose an IRB that is most capable of providing effective IRB oversight. Rather than control the selection of an

IRB, the policy should instead focus on identifying the indicators of an appropriately-qualified IRB. To that end, we note that the DHHS Secretary's Advisory Committee on Human Research Protections (SACHRP) submitted recommendations in January 2013 outlining key considerations for central IRBs. We encourage NIH to consider the SACHRP recommendations as the draft policy is refined.

Indicators of Appropriate Central IRBs

Local Context

A primary concern for central IRBs is knowledge of local research context. Local research context covers four general domains: applicable law and local standards, institutional policies and resources, qualifications of the investigator and study staff, and community and subject considerations. Any IRB serving in a central role for multisite research must be equipped to address each of the four domains.

Central IRBs must have knowledge of state law relevant to human subject research and be aware of differences as they affect research conducted at sites in multiple states. IRBs serving in a central capacity need to establish and maintain an up-to-date database of state laws relevant to human subject research.

Central IRBs must also have systems and procedures for collecting information from investigator sites that allow them to ascertain whether or not sites have the capabilities and resources to execute research studies. Institutional capabilities include the resources to support the research such as space, equipment, and personnel.

Institutional commitments include policies on issues such as contraception, compensation for injury, or contacts for research subjects' questions. Central IRBs must have mechanisms for assessing institutional capacity in an efficient yet comprehensive manner.

In addition to validating institutional capabilities, the central IRB should have mechanisms in place that allow it to assess the experience and qualifications of site investigators. This includes an assessment of prior research non-compliance, criminal activities, and state board and other licensing issues. Other factors to be considered in this assessment include financial conflicts of interest, research workload, and training in research ethics and the responsible conduct of research.

The last domain of local context is the population of prospective research subjects. While information about the intended subject population can often be discerned through review of the research protocol and standard IRB application materials, there will be exceptions. Central IRBs must develop mechanisms for obtaining supplemental information when research will involve sensitive topics or when research requires the participation of discrete and insular communities. In some cases, the IRB may need community-level information and demographic data including, but not limited to, race/ethnicity, religious affiliation, and language.

Compliant Electronic Systems

Many IRBs currently utilize electronic systems for managing the submission of protocols as well as administrative operations. Most systems employed by IRBs that are not experienced serving in a central role are not well designed to support central IRB functions, particularly the ability to maintain separate records for each investigator conducting a given protocol, as discussed below. We also note that for FDA-regulated research, all electronic recordkeeping systems must meet the requirements of 21 CFR Part 11, and many NIH funded multi-site studies also fall under FDA jurisdiction. In general, IRBs that rely on paper recordkeeping are poorly situated to serve as a central IRB.

Administering Multisite Review

Managing multisite research can present several administrative challenges for IRBs. These

administrative challenges include the ability to manage continuing review cycles for multiple sites on a single research protocol, or having a process to harmonize those cycles. A central IRB also needs to have the ability to consider reports of potential noncompliance or unanticipated problems and suspend or terminate research at a single site or across all sites depending on the issue. Administrative processes must be flexible enough to accommodate the unique needs of each institution. For example, consent forms and other study materials will also need to reflect local differences including site- specific legal and institutional requirements.

Independent Accreditation

Accreditation of central IRBs by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) provides independent assurance that an IRB has policies and procedures in place to ensure that research is scientifically valid, ethically appropriate, and sensitive to local context issues. NIH should encourage the use of AAHRPP-accredited central IRBs for its multisite research.

Conclusion

WCG would like to thank NIH for this opportunity to comment on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research. We hope that the NIH finds our input useful as this important policy is further refined. We strongly endorse the implementation of a final policy on the part of NIH.

Respectfully Submitted,

The WIRB-Copernicus Group

Comment #149

Commenter:

Date of Comment:

Comment:

January 29, 2015

Office of Clinical Research and Bioethics Policy
Office of Science Policy, National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Human subject research presents challenges for all Native Peoples. These challenges are quite distinctive to every different tribal entity and cannot be met adequately by a single non-tribal IRB. Tribal IRB members have firsthand knowledge of local tribal customs, cultural values, and tribal sensitivities. If Tribal IRB members are not able to participate and provide the necessary level of local expertise during a review, and this review is conducted by individuals who have never visited tribal areas and have no knowledge of tribal customs and ways of life, our citizens are affected by persons who are not sensitive to their distinctive needs.

Tribal organizations are managed service delivery organizations which are responsible for delivering optimal health care to its citizens utilizing limited resources. Consequently, human subject research is not always a priority. When there are gaps in tribal knowledge of significant problems, tribes may determine tribal engagement in research activity has potential to significantly impact the wellbeing of tribal citizens and lead tribes either alone or in collaboration with research intensive partners to engage in human subject research. During such engagements, tribal IRB's work with researchers before research begins, during the ongoing project, and after research has concluded. Tribal IRS's ensure research is conducted in a community engaged manner and that research does not deplete or divert limited tribal resources away from direct patient care. In addition, tribal IRS's play a critical role in preventing irresponsible interpretation or publication of research data, thereby preserving tribal sovereignty and the rights of its citizens. Tribal IRS's also ensure that research findings are first shared with tribal leadership, tribal communities, and other key stake holders.

I firmly believe that a single IRB cannot adequately represent and protect the unique needs and interests of the Cherokee Nation and other Native Peoples in evaluating and approving studies involving human research. Therefore, I unequivocally support the idea of providing exemption to tribal nations from the requirement of "Single Institutional Review Board for the Multi-site Research". This idea has been recognized in the draft NIH policy as a possible exception and it is wholly supported by the Cherokee Nation.

Bill John Baker
Principal Chief
Cherokee Nation

Lacey Horn
Treasurer
Cherokee Nation

Comment #150

Commenter:

Date of Comment:

Comment:

January 29, 2015

TO: NIH Office of Science Policy

RE: Comments on the Draft NIH Policy—Use of a Single Institutional Review Board for Multi-Site Research

We are writing today on behalf of the 68 institutions and 197 clinicians and researchers who have joined together under the umbrella of the Pediatric Dermatology Research Alliance (PeDRA) to bring new solutions to the field of pediatric dermatology care. PeDRA provides the platform from which investigators can join together in multi-center collaborative research studies. Unified and working together in this manner has greater impact and brings results for patients, multiplying the power of each individual researcher. Since PeDRA's inception in 2012, enthusiastic engagement in this organizational concept has continued to escalate.

Given this mandate, the prospect of using a single Institutional Review Board (IRB) for multi-center studies is particularly exciting. In the current environment, having to coordinate 20 or more IRBs for a study is common and the burden increases greatly for longitudinal investigations. A central IRB improves efficiency, streamlines the work, minimizes overlap of effort, and encourages collaborative research.

We heartily agree with Dr. Sally Rocky that the "proposed policy is a step forward to reducing burdens associated with NIH-funded clinical research and enhancing the efficiency of the process while still ensuring protections of all the volunteers who generously participate in human subjects research for the betterment of us all." Having the NIH support a policy of use of single IRBs for multi-site studies not only facilitates NIH-funded research, but sets an example for multi-site studies funded from other sources as well.

Unmet needs in pediatric dermatology

Many pediatric skin diseases are so uncommon that meaningful study is difficult without collaborative effort. Conducting clinical trials in young children, even in common diseases, is also challenging. Recruitment of eligible subjects can be difficult, especially given the busy clinical practice, limited time, poor funding and lack of infrastructure for most pediatric dermatologists to perform high-quality research. These challenges mean that many – perhaps most – of our therapies for pediatric skin disease are based on anecdotal evidence, expert opinion, and precedent. There is a lack of accepted clinical guidelines for many dermatology conditions, including life-threatening skin disorders. Standardized treatment protocols that exist in pediatric oncology and pediatric rheumatology are sorely lacking in our field and, to date, scant NIH funds have been allotted to pediatric dermatology research. Better evidenced-based management for children with skin disorders requires well-designed, multi-center collaborative clinical trials that would be facilitated by working with a single IRB.

Creating a research alliance to meet needs

In 2012, pediatric dermatology leaders came together to plan a collaborative clinical and translational pediatric dermatology research network and PeDRA was born. Since that time, PeDRA has developed a leadership structure to drive the work, a seminal website, <http://pedraresearch.org>, and a free-standing annual conference, which NIH R13 funding supported in 2013 and 2014. These meetings were designed

to bring together clinicians, basic scientists, and patient advocates to enhance opportunities for translational research. Study groups have formed focused on specific research areas, drawing senior and junior investigators from diverse geographic regions into collaborative projects.

Through these early successes, PeDRA is well on its way to achieving the mission so well articulated by its founders: to promote and facilitate high quality collaborative clinical, translational, educational, and basic science research in pediatric dermatology. PeDRA's vision is to create sustainable collaborative research networks to better understand, prevent, treat and cure dermatologic diseases in children.

Barriers to successful research collaboration

Studies requiring research blood and tissue specimens are critical to investigation of genetic pathogenesis, biomarker development, and disease natural history. For rare disorders, procuring biological samples at one site is limited by population frequency, with some disorders present in fewer than one in 500,000 individuals. When samples must be obtained from more than one institution, it is frequently necessary to generate a local version of the study protocol at the clinical site, even if for just one patient, and materials transfer requirements are also often necessary. This places an administrative burden both on the investigator and on collaborating physicians, slowing the speed, and increasing the cost of research. The same cross-institutional barriers exist in the conduct of clinical and translational research, including clinical trials and studies of disease natural history.

In addition, private practice physicians are eager to participate in translational research but, unless associated with a university or hospital, do not have access to an IRB. Such individuals may be subject to liability/risk without IRB oversight, creating a barrier to participation by the large group of private practice dermatologists who could contribute meaningfully to research.

Ensuring a future for multi-center studies

Our PeDRA founding members and each of us have extensive experience in both translational basic science research and clinical trials. We strongly agree that eliminating redundant local IRB review will lead to enhanced protection for research participants and will expedite research, while reducing administrative burden and cost.

We support the proposed policy stating that central IRB utilization will be "expected" rather than optional, as this will lead to necessary changes in institutional culture, permitting broad adoption of central IRBs in intramural, extramural, and privately-funded studies.

The provision of direct costs in awards for fee-based IRBs recognizes the administrative costs that can be associated with large studies. By stating that "use of the designated single IRB will be a term and condition of award," this policy ensures its rapid implementation.

Recommendations and conclusion

Adoption of a policy for use of a single centralized IRB for multi-center studies would greatly facilitate research towards meeting the goals of our Pediatric Dermatology Research Alliance. We currently have several studies ready to benefit from this policy. Although we understand the draft policy to pertain to NIH-funded studies, enforcement of this policy by NIH will serve as an important precedent that others will obligatorily follow. We are committed to working with the NIH to enact this policy and offer the resources of PeDRA for further deliberation and discussion.

Sincerely,

Keith A. Choate, M.D., Ph.D., F.A.A.D.
Associate Professor
Dermatology, Genetics, and Pathology
Yale University School of Medicine

Lawrence F. Eichenfield, M.D.
PeDRA Co-Chair
Professor of Pediatrics and Dermatology
Chief, Pediatric & Adolescent Dermatology
University of California, San Diego and
Rady Children's Hospital, San Diego

Comment #151

Commenter:

Date of Comment:

Comment:

January 29, 2015

Sarah Carr, Acting Director
Office of Clinical Research and Bioethics Policy
Office of Science Policy
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892

Dear Director Carr,

The Association of American Universities (AAU) and the Association of Public and Land-grant Universities (APLU) welcome the opportunity to provide feedback to the National Institutes of Health (NIH) on the “Draft NIH Policy on the Use of a Single Institutional Review Board (IRB) for Multi-Site Research” (NOT-OD-15-026). AAU and APLU together represent most of the major public and private research universities in the United States, all of which are engaged in research involving human subjects affected by the proposed policy.

First and foremost, AAU and APLU applaud NIH’s effort to streamline regulations in order to improve efficiency without compromising the protection of human subjects. The administrative burden across the research enterprise has grown appreciably due to a significant increase in regulations and reporting obligations promulgated by Federal agencies and a lack of harmonization among those regulations. Policies and regulations related to human subjects protection are among the most frequently cited causes of the increased burden and cost associated with research, and certainly the inefficiencies caused by duplication of IRB review in multi-site trials is a substantial part of that.

In the absence of revision of the Common Rule, AAU and APLU appreciate NIH’s leadership in beginning to address these issues. We also welcome the opportunities created by NIH to receive substantive input on this policy, and we encourage the agency to consider additional fora – such as a workshop or symposium during which success stories and lessons learned from current models of central IRBs could be discussed – before enactment of a final policy. AAU and APLU note that the administration of human subjects protections involves multiple entities on a university campus, ranging from senior research officers to compliance officers to general counsels, who may have different perspectives on the impact of this policy, depending on their responsibilities related to human subjects research.

AAU and APLU, in principle, support the movement towards the use of a single IRB for multi-site research studies. Many of our research institutions have embraced this model or participated in central IRB initiatives. That being said, we think NIH needs to move in a cautious, deliberative fashion in mandating the use of single IRBs, and we offer some principles below to consider. For the adoption of a single IRB model for multi-site studies to be successful, implementation of the policy must carefully take into account potential unintended, negative consequences. Because our member institutions have extensive experience with setting up and participating in central IRBs, and many are submitting detailed comments based on their own experiences, we encourage NIH to strongly consider the lessons that may be gleaned from those comments.

Principles to consider:

1. Creating a glide-path towards a mandate:

As a practical matter, sometimes mandating change is the best way to make progress with systems that have been in place for a long period of time. As such, AAU and APLU hesitate to suggest that the use of single IRBs not be mandated, but rather be optional and incentivized. We agree with NIH's finding that the use of single IRBs for multi-site studies is currently under-utilized. However, we are concerned that the proposed policy would be too disruptive and costly if implemented at a rapid rate without giving institutions time to transition. As noted below, the movement towards a single IRB can take a substantial amount of time and resources. As such, NIH should consider some sort of phased-in approach to an ultimate mandatory policy, perhaps by starting with lower-risk studies or offering incentives for earlier, voluntary adoption. Another possibility would be by expanding the use of the NCI CIRB as a pilot before implementing the policy on a larger scale.

2. Formation of a central IRB is not an overnight event:

It takes time to set up and smoothly administer a central IRB. The most successful models of a single IRB for multi-site trials, such as those developed by the University of California system or the NCI CIRB, took time to establish. It requires a tremendous amount of trust for institutions to rely on another IRB's review and that trusting relationship takes time to develop. The authorization agreements described by the draft policy will take a substantial amount of time to negotiate and are likely to evolve over time, as institutions become accustomed to new relationships and joint processes or procedures. We are concerned that the policy does not recognize the time and effort this endeavor will entail, and presents an overly simplified view of establishing a single IRB of record.

3. Infrastructure to support this effort must not be an unfunded mandate:

In discussing the NIH policy with our institutions, AAU and APLU have found that while the use of a single IRB for multi-site studies has the potential for cost savings and reduction of burden when implemented well, reaching that point requires a substantial investment in supporting infrastructure. Establishing and maintaining a central IRB requires costly investment, including but not limited to the creation of electronic management systems that are interoperable between institutions, the adaptation of automated processes to multiple institutions, the communications tools necessary to link investigators and IRBs, the staff time necessary to develop agreements, consensus documents or standard operating procedures, and the interaction necessary to build and maintain trusting relationships between institutional officials. Even if an institution is not serving as the IRB of record, the infrastructure necessary to adapt existing human research protection programs software systems and protocols to participate in the centralized process has real financial implications. While the draft policy allows for IRB fees to be charged as part of the direct cost of the grant, institutions will have no way to recoup the costs of setting up the infrastructure necessary to administer participating in a central IRB. AAU and APLU urge NIH to avoid shifting this cost onto institutions that are already struggling with the considerable costs of research compliance. For example, could the agency create electronic tools or template documents that could ease the cost burden of participating institutions?

4. Reconsidering flexibility for local review:

AAU and APLU acknowledge that there are a variety of reasons for why an institution might strongly support the need for local review. We agree that some of these issues could probably be addressed, as described by the draft policy, through the use of ad hoc consultants or submission of additional information, and that others, such as how to deal with liability concerns related to subject injury, could be clarified in the details on the policy. However, there may be situations where a local IRB review is relevant and should allow for an exemption from the policy beyond the current exemption

scope described. Examples could include well-documented local sensitivities to specific research or differing interpretations on ethical issues between partnering institutions. We do not expect that these would be frequent occurrences, but we do believe it is important that the policy leaves flexibility for exemption in the unique circumstances that will inevitably arise in a research enterprise as large and diverse as that supported by NIH.

5. The policy should not result in a multitude of central IRBs:

The policy should explicitly state that its purpose is not to create a more complex system by promulgating a unique single IRB for every multi-site study. Managing multiple IRBs – as many as a different one for every multi-site study would present a far greater cost and administrative burden for institutions and would seem to run counter to the intent of the policy.

6. Timing is everything:

The policy needs to provide clarity in regards to the timing of IRB selection and approval relative to grant application and approval. AAU and APLU urge NIH to carefully think through the sequence of events in which investigators identify the IRB of record and the award is issued to prevent delaying the initiation of research.

Currently, the draft policy is light on the details related to implementation, such as how one defines a multi-site study, and definitions of responsibilities between the participating institutions. While this lack of detail may provide some welcome flexibility for some institutions, we are concerned that ambiguity may raise additional concerns, and we again strongly urge NIH to pay careful attention to comments submitted by institutions on this point. AAU and APLU appreciate the opportunity to provide some feedback on the draft NIH policy, and look forward to continuing to work with the agency as the final policy is developed.

Sincerely,

Hunter R. Rawlings III
President
Association of American Universities

Peter McPherson
President
Association of Public and Land-grant Universities

Comment #152

Commenter:

Date of Comment:

Comment:

January 29, 2015

Via email: SingleIRBpolctcy@mail.nih.gov

Office of Clinical Research and Bioethics Policy

Office of Science Policy

National Institutes of Health

6705 Rockledge Drive, Suite 750

Bethesda, MD 20892

Re: Comments on Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research, Notice No. NOT-OD-15-026

Dear NIH:

The Consortium of Independent Review Boards ("CIRB") is pleased to provide comments on the National Institutes of Health (NIH) Draft Policy on the Use of a Single Institutional Review Board for Multi-Site Research ("NIH Draft Policy"). CIRB is a professional organization that was founded in 1993 and since that time it has served as the only professional trade association representing the independent institutional review board ("IRB") community. CIRB is a consortium of independent institutional review boards ("IRBs") that provide services to institutions external to their individual member institutions. All of CIRB's members are accredited by the Association for the Accreditation of Human Research Protection Programs, Inc. ("AAHRPP"). Additionally, all of the members of CIRB have either served as a central IRB on some research studies and/or as a single IRB on some studies. Accordingly, CIRB feels that it is in a unique position to provide comments on the NIH Draft Policy.

CIRB applauds NIH's Draft Policy to require the use of a single IRB for NIH conducted or supported multi-site studies ("NIH research"). CIRB agrees that the Draft Policy will result in significant benefits and time savings for NIH research. The benefits will include the following: (1) the empowerment of the Single IRB to provide a thorough and substantive IRB review which can improve the protection of human subjects; (2) the consistency of initial and continuing IRB review; and (3) the time savings and elimination of delays created by the prevention of numerous lengthy and duplicative IRB reviews of the same research.

As an illustration, under the IRB review system proposed by NIH, the designated single IRB will be able to decide during initial and/or continuing review if the research is approvable. Accordingly, the decisions of the single IRB will have a substantive impact on the research and must be considered by the sponsor or the research cannot begin. Additionally, the single IRB will have initial and continuing safety and other relevant data which will position it to determine if additional protections are necessary for the research. In contrast, under the current duplicative IRB review system, IRBs frequently feel that their reviews have little or no impact on the research since it has generally already been approved by other IRBs. In other words, their IRB review decision is often limited to either approving the research as submitted or preventing the research from being conducted at their institution.

It is well documented that duplicative IRB reviews of multi-site research add costs and delays but do not meaningfully add to enhanced human subject protection. In the recent article, The Harvard Catalyst Common Reciprocal IRS Reliance Agreement: An Innovative Approach to Multisite IRB Review and

Oversight, the authors noted the following: "In multi-site studies, review by several IRBs is burdensome and the burden and expense of conducting multiple and duplicative ethics reviews at several institutions has been cited as a major barrier to research, manifest in delays in research conduct in the absence of demonstrable enhanced human subjects protections."¹ The lack of value of duplicative IRB review was also highlighted in an article several years ago by Dr. Jerry Menikoff and Dr. Joseph Miliam as follows: "... different IRBs mandate different, often minor, changes to consent documents or the protocol and researchers go back and forth...."² Menikoff and Miliam also noted another problem stemming from wasteful duplicative IRB reviews. They stated as follows: "... there are always constraints on IRBs' time and resources. Time spent reviewing one protocol takes away time from reviewing others." Ibid.

Accordingly, CIRB believes that NIH Policy for Single IRB review will add efficiencies to the IRB process and help reduce burdens on the local IRB and delays in the conduct of research.

Additionally, the NIH Draft Policy expressly states that it will not relieve research sites from their traditional regulatory obligations for such things as obtaining informed consent and reporting unanticipated problems and adverse events to the single IRB of record. The reporting of these events from all research sites to a single IRB of record also enhances the likelihood of a consistent IRB review since the single IRB will receive all of the unanticipated problems and safety information and will be much better positioned to make informed review decisions than under today's piecemeal approach. This approach will also eliminate duplicative IRB review of the same adverse events and unanticipated problems and thus reduce the burden on institutions and their IRBs who rely on the single IRB.

Lastly, if there are truly local issues which are relevant to the research such as applicable local laws or regulations, the Draft Policy allows for one of two approaches. In the first approach, the research site can notify the single IRB of these relevant local issues so they can be considered by the IRB. The second approach allows for an exception to the single IRB review but only where local IRB review is, required by federal, tribal, or state laws or regulations."

In conclusion, CIRB submits that the Draft NIH Policy on Use of a Single Institutional Review Board for Multi-Site Research is very beneficial as it provides significant efficiencies and cost savings and reduces the burdens and delays of duplicative IRB review of multi-site research.

CIRB has circulated these comments to additional IRBs and is pleased to attach additional letters of support from those IRBs.

CIRB thanks the NIH for issuing this Draft Policy and for the opportunity to submit comments. CIRB looks forward to additional opportunities to provide NIH with its collective experience in advancing the protection and welfare of human subjects involved in clinical research.

Sincerely,

Matt Baker, Chair
Consortium of Independent Review Boards
Attachments

Footnotes

¹Winkler, S.J., Witte, E, Bierer, B.E., The Harvard Catalyst Common Reciprocal/IRB Reliance Agreement: An Innovative Approach to Multisite IRB Review and Oversight. *Clinical and Translational Science*. 2014;1D.III/cts.I220.

² Miliam, J., Menikoff, J., *Streamlining Ethical Review*, *Annals of Internal Medicine*. 2010;153 (10):655-657.

Comment #153

Commenter:

Date of Comment:

Comment:

Notice No. NOT-OD-15-026

Comments on Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

DUNS: 096360284 NAICS Codes: 541711/541712

Submitted to: National Institutes of Health

Office of Science Policy

Office of Clinical Research and Bioethics Policy 6705 Rockledge Dr. / Suite 750

Bethesda, MD 20892

EMAIL SingleIRBpolicy@mail.nih.gov

401 N. Washington St. / Suite 700 Rockville, MD 20850

January 29, 2015

Submitted by:

Emmes Point of Contact: Anne Lindblad, PhD TITLE President

TEL 301 251 1161 EXT 105

FAX 301 251 5745

EMAIL alindblad@emmes.com

EMMES' COMMENTS ON DRAFT NIH POLICY ON THE USE OF A SINGLE INSTITUTIONAL REVIEW BOARD FOR MULTI-SITE RESEARCH

In 1999, the National Cancer Institute (NCI) established its Central Institutional Review Board (CIRB) Initiative. In the past 15 years, the CIRB Initiative has transformed and grown from a single Institutional Review Board (IRB) for review of phase 3 Adult Cooperative Group trials to four separate IRBs responsible for review of the bulk of the Cancer Therapy Evaluation Program's portfolio. The newest of the four CIRBs was established in December 2014 to review studies sponsored by NCI's Division of Cancer Prevention. The CIRB Initiative is not the only success the National Institutes of Health (NIH) has experienced on the front of centralization of IRB reviews—NICHD's Central IRB and NINDS' NeuroNEXT Central IRB have been developed in recent years. In fact, support for central IRBs seems to be growing to the extent that the Office for Human Research Protections (OHRP) has issued an Advance Notice of Proposed Rule-Making that includes a requirement to utilize a central IRB for multi-site research.^{1,2,3,4} Thus, the proposed NIH policy on the use of a single IRB for multi-site research is well-timed.

The EMMES Corporation (Emmes) is a woman-owned small business of approximately 400 full-time employees located in Rockville, Maryland. For over 35 years, Emmes has devoted its efforts exclusively to providing Contract Research Organization support for clinical and research programs. Historically, a significant proportion of Emmes' revenue has come from NIH. In 2007, Emmes took over as the contractor responsible for operations of NCI's CIRB Initiative. Emmes currently holds a contract with NCI to support operations of the CIRB Initiative for the Cancer Therapy Evaluation Program and the Division of Cancer Prevention through 2019. The EMMES Corporation offers the comments below in light of this experience operating a federally funded central IRB.

There are several factors NIH may wish to consider as it plans to implement a requirement for use of a single IRB for multi-site research studies. These concerns fall into three key categories:

1. Choice of IRB and Model for Centralization
2. Local Context
3. Vulnerable Populations

Choice of IRB and Model for Centralization

In centralizing IRB review, there are several options, each with its own advantages and disadvantages:

- Creating a dedicated central IRB
- Leveraging existing local IRBs to serve as a central IRB
- Using “commercial” IRBs to serve as a central IRB

Creating a dedicated central IRB

Creating a dedicated central IRB such as those created by NINDS, NICHD, and NCI comes with a significant cost for the institution, but doing so also allows for the creation of specialty IRBs with expertise in the areas of research funded by the institute. Such an approach also allows for the central IRB to develop policies and procedures that integrate with the institute’s programs, to develop an understanding of the institute’s broader research program, and to serve as the IRB for all extramural research sponsored by that institute. Providing funding for centralized IRB review on a project-by-project basis seems antithetic to the idea of centralized review. Thus, NIH should carefully consider whether using a series of IRBs on a grant-by-grant basis for centralized IRB review is an advantageous approach, or whether it might be more efficient in terms of IRB review, costs, and protection of subjects to create its own central IRBs by institute or by research program. Creating a central IRB dedicated to the review of an institute’s extramural research may be a more effective use of funds in the long term. An additional advantage is that IRBs created as central IRBs can be designed with adaptability in mind to accommodate variations in research practices at participating institutions.

Leveraging existing local IRBs to serve as a central IRB

Creating a Central IRB to serve a program, as in the case of the NCI CIRB Initiative and NICHD’s Central IRB, anticipates interacting with many participating sites by allowing for adaptability. Local IRBs are created within and operate under the auspices of individual institutions. Leveraging existing local IRBs to serve as a central IRB, as in the case of the NeuroNEXT Central IRB, takes advantage of existing infrastructure within an institution and, as a result, may carry a lower cost burden and may yet involve modifications to IRB policies and procedures in order to serve as a central IRB. NIH should carefully consider the experience of the IRB proposed to serve as a central IRB for a study particularly if participating research sites are in multiple jurisdictions with different local context considerations.

Using “commercial” IRBs to serve as a central IRB

Existing “commercial” IRBs represent a third option. Commercial IRBs provide an advantage in that they, as in the case of the local IRB, have existing infrastructure that can be leveraged to support a multi-site study. In the case of commercial IRBs, however, the onus is on the research program to adapt to the IRB’s business model in a sort of “one-size-fits-all” mentality. This approach may not adequately address the uniqueness of the research and, as such, NIH should carefully consider whether the IRB is sufficiently capable of adapting to the individual needs of individual research programs.

In addition to the selection of an appropriate IRB, NIH should consider carefully the model of IRB review. The taxonomy of IRB review ranges from “local IRB only” to “shared responsibility” models all the way through “central only” models. There are advantages and drawbacks to any of these models to be considered.

The “local only” model is precisely what the draft NIH policy aims to replace with centralized review for funded research, and will not be addressed here.

The “shared responsibilities” model is the first step toward centralization. NCI established its CIRB Initiative as a “shared responsibilities model,” as described in retired OHRP guidance, “IRB Knowledge of Local Research Context.”⁵ NCI referred to this model as a facilitated review (FR) model. In this FR model, a central IRB and local IRB shared responsibility for oversight of the conduct of research. The central IRB was responsible for review and approval of the protocol and a model consent form, while the local IRB was responsible, for example, for determining the appropriateness of the PI to conduct the research, adapting the model consent form to local standards, and providing for ongoing local oversight of the conduct of the research. In Emmes’ experience operating the FR model from 2007-2013, the FR model left institutions and investigators confused as to the regulatory responsibilities and liabilities under the common rule. This confusion and concern regarding regulatory responsibility and liability in using an external IRB is evidenced in the exchange between OHRP and Carolinas Healthcare System in April 2010.⁶ In pursuit of accreditation by the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP) and in an effort to bolster usage of the CIRB, NCI opted to shift the entire CIRB Initiative to an “independent model” similar to those operated by other independent commercial IRBs, where the NCI CIRB is solely responsible for IRB review with no shared efforts with local IRBs. This represents a shift toward the “central only” model when accompanied by a mandate for utilization of the CIRB in the NCI’s guidelines for the newly formed National Clinical Trials Network (NCTN) and Experimental Therapeutics Clinical Trials Network (ETCTN).⁷ While this shift lends clarity to the regulatory questions spurred by the FR model, it may or may not lead to greater protection of research subjects, or greater overall efficiency.

As we understand it, the NeuroNEXT Central IRB follows an approach similar to NCI’s independent model and can be categorized as a “central only” model. Similarly, most commercial IRBs will function under a “central only” approach.

The NICHD’s Central IRB follows a “federated model,” which can best be described as a model that operates each of the three categories (“local only,” “shared responsibility,” and “central only”) as options for participating research sites. In this model, individual institutions select the level at which they participate in centralized IRB review. While NICHD’s model has enjoyed some success,⁸ regulatory clarity in the IRB model is essential if each NIH-funded research study is to use centralized IRB review.

Local Context

Regardless of the IRB or the model chosen to review NIH-funded multi-site research, the IRB must be able to account for local context. The Common Rule requires that the IRB be knowledgeable not only regarding the research to be conducted but also the broader contextual considerations regarding where the research will be conducted and specific needs and concerns of the potential subject pool.⁹ Knowledge of local context is still meaningful even in multi-site research. In Emmes’ experience with the NCI CIRB, local context varies from state to state, community to community, and even between institutions serving the same community. A central IRB will need to be able to accommodate a wide variety of state and local laws should multi-site research be carried out across state lines – something many existing local IRBs may be ill-prepared to do. Similarly, the same IRB will need to be able to accommodate variability in the research practices of each participating site; though the protocol may be the same, the actual conduct of the research in practice may vary across sites. Beyond variability in research practices, and perhaps more important than those practices, is variability in the community served. Even within a single community, two sites may serve very different populations, and accommodations must be able to be made for this variability in the IRB review process. In short, multi-

site research still takes place at individual sites, situated within individual communities and states, each with its own unique local context. In centralizing IRB review, NIH should be careful not to lose the trees for the forest.

Vulnerable Populations

Consideration of local context naturally brings about discussion of vulnerable populations. The Common Rule defines vulnerable populations as inclusive of children, prisoners, pregnant women, or handicapped or mentally disabled persons.¹⁰ In fact, the Common Rule even goes so far as to include regulations specific to three vulnerable populations (pregnant women/ neonates, prisoners, and children). Though the regulations go far in defining vulnerable populations, the list provided is not exhaustive nor is it static.

The common rule recognizes core vulnerable populations in US society whose vulnerability is assumed as part of the prevailing social order; however, other populations may become vulnerable in the context of research. The NICHD IRB is tasked with reviewing studies including children, a population considered vulnerable because of their diminished or developing autonomy. The NeuroNEXT Central IRB reviews research that may include individuals who suffer from impaired decision-making capacity as a result of their health conditions. The NCI CIRB reviews research involving cancer patients who, though not recognized as a vulnerable population in the Common Rule, may be considered vulnerable due to the high-stakes nature of certain cancer treatments and diagnoses. Adequate understanding of local context, particularly of populations that may be vulnerable unto themselves or vulnerable in the context of the proposed research, is critical to ensure appropriate protections of human subjects. Failures to adequately address the vulnerability of populations in the research context is not a thing of the past.¹¹ NIH must give significant consideration to the suitability of the selected IRB to review the proposed research with particular attention to the populations served by the various research sites who may not be *prima facie* vulnerable, but who in the context of the proposed research may become vulnerable.

Footnotes

- ¹ Flynn KE, Han CL, Kramer JM, Check D, Dombeck CB, Bang Soo, Perlmutter J, Khin-Maung-Gyi FA, Weinfurt KP. "Using Central IRBs for Multicenter Clinical Trials in the United States." PLoS One 2013 8:e54999 [PMCID: PMC3559741].
- ² Menikoff J. "The Paradoxical Problem with Multiple-IRB Review." N Engl J Med 2010 363:1591-1593
- ³ Silverman H, Chandros Hull S, Sugarman J. "Variability Among Institutional Review Boards' Decisions Within the Context of a Multicenter Trial." Crit Care Med 2001 29:235-241
- ⁴ "Advance notice of proposed rulemaking," 76 Federal Register 143 (06 July 2011), pp. 44512-44531. (available online at: <http://www.gpo.gov/fdsys/pkg/FR-2011-07-26/html/2011-18792.htm>)
- ⁵ OPRR, "IRB Knowledge of Local Research Context" August 27, 1998 [Updated July 21, 2000; Archived August 2, 2012].
- ⁶ OHRP Correspondence: <http://www.hhs.gov/ohrp/policy/Correspondence/mcdeavitt20100430letter.html>, accessed 1/25/2015.
- ⁷ NCTN Program Guidelines: http://ctep.cancer.gov/initiativesPrograms/docs/NCTN_Program_Guidelines.pdf and ETCTN Program Guidelines: http://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_Program_Guidelines.pdf
- ⁸ See: Slutsman, J. and Hirschfeld, S. "A Federated Model of IRB Review for Multisite Studies: A Report on the National Children's Study Federated IRB Initiative" in IRB Ethics and Human Research, November – December 2014 (Volume 36: No. 6)
- ⁹ See 45 CFR 46.107(a)
- ¹⁰ See 45 CFR 46.107(a)
- ¹¹ Notably, Arizona State University researchers used genetic data from the Havasupai Indians (obtained in the 1990s for a study of diabetes within the population) to study mental health and origins of the Havasupai Indians – research to which the subjects had not consented and which significantly undermines their cultural beliefs. See "Indian Tribe Wins Fight to Limit Research of Its DNA" The New York Times, April 21, 2010, http://www.nytimes.com/2010/04/22/us/22dna.html?pagewanted=all&_r=0 (accessed 1/25/2015).

Comment #154

Commenter:

Date of Comment:

Comment:

January 29, 2015

Office of Clinical Research and Bioethics Policy
Office of Science Policy, NIH
6705 Rockledge Drive, Suite 750
Bethesda MD 20892

Submitted electronically to: SingleIRBpolicy@mail.nih.gov

RE: Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

Dear Sir or Madam:

Kaiser Permanente offers the following comments on the *Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research* (“Draft Guidance”), published on December 3, 2014, in the NIH Guide. We appreciate the opportunity to provide our feedback on the Draft Guidance.

The Kaiser Permanente Medical Care Program is the largest private integrated healthcare delivery system in the U.S., with nearly 9.5 million members in eight states and the District of Columbia.¹ Kaiser Permanente is committed to providing high-quality, affordable health care services and improving the health of our members and the communities we serve.

Kaiser Permanente also conducts and supports a broad agenda of health services research through its various research entities.² As a result, the broad range of our constituencies that are focused on research, including the directors and investigators in our seven research centers, our IRB leadership, and those involved in research compliance have participated in the development of this response.

General Comments

Kaiser Permanente offers qualified support for using a single IRB for multi-site studies as an important regulatory change that may improve and streamline the research approval and oversight processes as long as the primary purpose remains protecting human subjects rights and privacy. There may be real advantages in having one IRB for multi-site studies, such as: consistent application of policies and procedures across sites; centralized oversight; reduced costs; and reduced variation in documentation and process. However, these advantages must be balanced by mechanisms and policies that limit any negative impact on the protection of human research subjects, and permit consideration of local standards of research conduct.

We offer several comments to highlight the importance of ensuring that this policy does not have a negative impact on the ability to protect research participants:

- Although using a single IRB could streamline some of the current oversight functions of local IRBs, it does not reduce the participating institutions’ responsibilities to protect their research participants. Local institutions will still be bound by ethical and fiduciary duties to members/patients/participants.
- NIH should provide clear guidance for how the IRB of record in a multi-site trial should respond to local institutional concerns about the risk profile of the specific research study under consideration. Guidance should support a formal mechanism for communication between local sites and the IRB of record about additional safeguards to ensure that participants are adequately protected from

investigational and informational risks. A local IRB may desire enhanced protection beyond what the IRB of record requires; for example, unaddressed concerns about whether sensitive participant information will be appropriately sought or shared. In such a case, the local IRB might want to request that an investigator obtain a Certificate of Confidentiality. If the IRB of record does not agree, the local site's only option would be to opt out of the use of the single IRB and provide its own IRB review and oversight, but at its own expense. Thus we recommend that final guidance develop a mechanism for ensuring that the centralized IRB responds to requests for information or for enhanced protection.

- While having a single IRB of record may be highly advantageous to research sponsors, this approach could be problematic for local institutions. A local IRB that relies on an IRB of record to thoroughly review the risks to subjects has no assurance of the quality or comprehensiveness of the review done by the IRB of record. We would therefore favor guidance that ensures quality through the use of best practices in all IRBs that serve as the IRB of record for multi-site studies. The notion of accepting another IRB's determination is acceptable in principle, but more attention should be focused on how to gauge the abilities of various IRBs and support communication between local institutions and the IRB of record. One possibility would be to require IRBs that serve as the single IRB of record for multi-site trials to be accredited, as accreditation subjects IRBs to routine external review and scrutiny. Another strategy would be to require that the IRB of record be subject to regular random audits, perhaps tiered based on performance, that would provide the opportunity for routine evaluation.
- Even with one IRB of record, duplication of effort could persist. It would not be likely that a single IRB of record would be able to meet the requirements for HIPAA/privacy protection review under all applicable law. In addition, some local institutional policies and procedures may still require internal committees to review and approve various aspects of research (e.g., scientific review, resource review, feasibility, institutional congruence, etc.). Informed consent processes may be different in each location, based on state law or organizational requirements which derive from the institution's experience with its specific research populations. The local review processes may become more complicated and confusing. We recommend that guidance addresses ways to mitigate potential confusion.
- Research studies frequently require consideration of state and local laws and regulations, which may have broader scope than human subject protections. For instance, states may restrict the use or disclosure of HIV or mental health data; state regulations may use different definitions of legally authorized representatives for informed consent to research; and laws or regulations regarding genetic privacy may vary by state. NIH should provide clear guidance on how state and local laws will be considered in the context of a single IRB of record.
- NIH guidance should clearly delineate the roles and responsibilities of the IRB of record and the local site. In the Common Rule, the IRB's authority is limited to approve, disapprove, or require modification to protocols. The local site has authority over their employees. Thus, if issues arise, the IRB will have to rely on the local site to address them. Similarly, the site will still be responsible for providing training for and oversight of its staff and their research activities. Clear understanding and documentation of the division of responsibilities, including communication pathways, will be essential.

- Recent draft guidance from OHRP would require a new approach to standard of care research, which by their nature will require local review and therefore may pose serious challenges to the use of a single IRB of record for multi-site comparative effectiveness studies.

We appreciate your willingness to consider our comments. Please feel free to contact me (510-625-4764; karen.m.emmons@kp.org) with any questions or concerns.

Sincerely,

Karen M. Emmons, PhD Vice President, Research
Director, Kaiser Foundation Research Institute

Footnotes

¹ Kaiser Permanente comprises Kaiser Foundation Health Plan, Inc., the nation's largest not-for-profit health plan, and its health plan subsidiaries outside California and Hawaii; the not-for-profit Kaiser Foundation Hospitals, which operates 38 hospitals and over 600 other clinical facilities; and the Permanente Medical Groups, independent physician group practices that contract with Kaiser Foundation Health Plan to meet the health needs of Kaiser Permanente's members.

² Research has long been a hallmark of Kaiser Permanente and is one of the ways the organization demonstrates its benefit to the communities it serves. Kaiser Permanente conducts research in all of its regions, both within research centers and in medical centers and other health care delivery venues. In addition to health services research, Kaiser Permanente also conducts many studies involving FDA-regulated drugs, devices, and biologics.

Comment #155

Commenter:

Date of Comment:

Comment:

January 29, 2015

Office of Clinical Research and Bioethics Policy

Office of Science Policy

National Institutes of Health

6705 Rockledge Drive, Suite 750, Bethesda, MD 20892

Re: Draft NIH Policy on the Use of Single Institutional Review Board for Multi-site Research (Notice OD-15-026)

The Society for Women's Health Research (SWHR®) appreciates the opportunity to submit comments in response to the National Institutes of Health (NIH) Office of the Director's Draft NIH Policy on the Use of Single Institutional Review Board (IRBs) for Multi-site Research (Notice OD-15-026).

SWHR is dedicated to transforming women's health through research, advocacy and education. We are a national non-profit organization based in Washington, D.C. and are widely recognized as the thought leader in promoting research on sex differences in all stages of medical research. For the past 25 years, we have actively advocated for inclusion of women and minorities in all phases of clinical trials and medical research. Due to SWHR's advocacy efforts, women are now routinely included in most major medical research studies and scientists are considering sex and gender as a variable in their research.

SWHR recognizes that NIH wishes to utilize single IRBs to speed the initiation of clinical trial research. We recommend that a single IRB review process take into account inclusion of both sexes in dual-sex clinical trials and that other demographic subgroups (such as race, age, ethnicity) are adequately represented and included where appropriate. We believe this will optimize clinical research to achieve greater efficiency in the initiation of studies across NIH's entire research portfolio.

Recently, NIH established policy changes regarding the inclusion of both sexes in preclinical research. Ensuring that both sexes are included in dual-sex clinical studies during the review by single IRB would provide appropriate framework for translation of preclinical research into clinical research, thereby facilitating efficiency of clinical trials. We further encourage that the clinical protocols provide detail in how subgroup populations will be appropriately analyzed to ensure that the clinical trials are well designed before their initiation.

Exception to the policy: If exceptions to the use of a single IRBs is made and the use of a local IRB review is necessary to meet the needs of specific populations, SWHR recommends that NIH have appropriate policies and guidelines in place that would ensure appropriate subgroups inclusion and analysis is done.

Further, local IRBs should adhere to the same review standards and requirements as the single IRB. SWHR believes that it is critical that IRBs, multi-center or single, have a critical role to play in ensuring that there is a consistent standardization in collecting and analyzing demographic subgroup data.

Public Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

We appreciate the opportunity to provide comments on this important policy change. Please feel free to contact us should you need additional information or have questions. We can be reached at 202-223-8224 or by email at monica@swhr.org.

Sincerely,

Monica P. Mallampalli, PhD
Director, Science Programs

Martha Nolan, JD
Vice President, Public Policy

Leslie Ritter, MA
Director, Government Affairs

Comment #156

Commenter: Rodavita

Date of comment: January 29, 2015

Comment:

The following are needed clarification/questions on the specific NIH single IRB proposal:

- Will this apply to new studies only or ongoing studies as well? Recommend only new studies.
- Recommend allowing local changes to a standard consent form as needed (within reason).
- Recommend allowing local review for conflict of interest and retaining local privacy board review.
- Clarify what documents will the relying site need to have on hand (in their regulatory binder) from the main IRB review.
- The guidance indicates that the NIH will approve which IRB will serve as the Central IRB for each study. Clarify how that approval will be obtained.
- If there are multiple sites that fall under the IRB of record for one protocol, can the extent of the reliance vary between sites or must it be uniform?
- We recommend that the IRB of Record retain the ability to formally report specific findings or issues to the local site IRB if they feel appropriate.
- Clarify which IRB's SOPs will be applied, the local IRB or the Central IRB.
- Most IRB use electronic review systems which are not designed typically to function as a central IRB without major upgrades to the system.
- The use of local eIRB systems to maintain document, track HSP certification, COI means that even with the use of a central IRB, the local IRB needs to perform a pass through review in order to get the documents into the system to use locally.

We encourage efforts to streamline the regulatory requirements for multisite research. We hope that any final policy would contain sufficient details to prevent confusion or ambiguity amongst the varying site interpretations.

Comment #157

Commenter:

Date of Comment:

Comment:

January 29, 2015

TO: Office of Clinical Research and Bioethics Policy, Office of Science Policy

SingleIRBpolicy@mail.nih.gov

FROM:

Al Richmond, Community---Campus Partnerships for Health, Raleigh, NC Paige Castro,
Community---Campus Partnerships for Health, Seattle, WA
John Cooks, Galveston Island Community Research Advisory Committee, Galveston, TX
Kelly Edwards, The Graduate School, University of Washington, Seattle, WA
Elmer Freeman, Center for Community Health Education Research and Service, Boston, MA Mei-
--Ling Isaacs, Formerly of Papa Ola Lokahi IRB, Honolulu, HI
Phil Lowenthal, Attorney at Law, Wailuku, HI
Lola Santos, Guam Communications Network, Long Beach, CA
Sarena D. Seifer, Community---Campus Partnerships for Health, Seattle, WA Nancy Shore,
University of New England School of Social Work, Seattle, WA Eric Wat, Special Service for
Groups IRB, Los Angeles, CA

RE: NOT-OD-15-026 Request for Comments on the Draft NIH Policy on the Use of a Single
Institutional Review Board (IRB) for Multi-Site Research [http://grants.nih.gov/grants/guide/notice-
files/NOT-OD-15-026.html](http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-026.html)

Thank you for the opportunity to comment on the draft NIH policy to promote the use of a single IRB of
record for domestic sites of multi-site studies funded by the NIH.

While we applaud NIH for seeking “to reduce procedural inefficiencies so that human subjects research
can proceed efficiently without compromising ethical principles and protections,” we are concerned that
the draft policy could inadvertently compromise research ethics. Specifically, we are concerned that the
draft policy will undermine the ability of communities involved in and/or impacted by the research being
reviewed to not only contribute to its ethical analysis, but to even be aware that a study has been
proposed. Utilizing a central IRB for a multi-site study could in effect shield the proposed study from local
community review for the sites not routinely served by the central IRB.

It is well documented in the literature on research ethics and community-engaged research that
institutional IRBs do not adequately assess the community and cultural ethical implications of the
research they review.¹⁻⁻⁹ A number of factors contribute to this situation, including the questions
typically asked on institutional IRB applications, the membership composition of institutional IRBs and
the lack of institutional IRB member understanding of community-engaged research. These could be
amplified by the use of a central IRB that is even further removed from the communities in which the
study sites are located.

To ensure the ethics and integrity of the research in which they and their communities are engaged, a
growing number of community groups and Tribes have developed their own research ethics review
processes that operate independently or in conjunction with institution-based IRBs.^{1,9--15} We have been
studying these review processes since 2009 and thus believe we are uniquely positioned to comment on
the draft NIH policy in light of our study findings.^{1,3,4,15--18}

In 2009, we completed the first national systematic study of community-based processes for research ethics review.¹⁶ The study, supported by a grant from the Greenwall Foundation, identified and described 109 community-based processes in 31 states, the District of Columbia and Puerto Rico that fall primarily into one of three categories: federally recognized community or tribal IRBs, research review committees hosted by community organizations, and research review committees hosted by academic institutions. We found that communities develop these review processes to (a) enhance community protections in research by assuring that community risks and benefits are considered, (b) encourage community participation in and ownership of the review process, and (c) respond to dissatisfaction with institution-based IRB processes that historically have either not taken their concerns into account or actively ignored them. Further, we found that community-based processes for research ethics review routinely consider research ethics and integrity issues that institutional IRBs normally do not, such as culturally appropriate recruitment strategies, opportunities for community capacity building, shared power and resources among study partners, and plans to share findings with involved communities. In 2012, supported by an NIHR21 grant, we conducted in-depth case studies of five community-based processes for research ethics review, including two community IRBs.¹⁸ We found that community review processes can enhance the ethical review of research and improve research rigor and feasibility by addressing community concerns, risks and benefits. Research findings and national recommendations point to a likely increase in the number of community-based processes for research ethics review in the future.¹⁹⁻⁻²²

NOT-OD-15-026 observes that some commenters responding to the 2011 request for public comments on the Advance Notice of Proposed Rulemaking expressed concern that “the use of a single IRB could lead to decreased consideration of local context” and we concur (indeed, Community-Campus Partnerships for Health was among the commenters raising that concern). In situations in which an institution-based researcher is collaborating with community partners that either operate or have access to a community IRB, mandating a single IRB of record would likely result in an institutional IRB being designated. Our research has demonstrated that community IRBs are not duplicative of institutional IRBs.¹⁵⁻⁻¹⁸ While both assess individual study participant risks and benefits, community IRBs also assess community and cultural considerations of proposed studies that institutional IRBs do not normally consider.⁶ Having a single IRB of record removed from the communities involved in a proposed multi-site study would make it unlikely for that IRB to adequately assess local community risks and benefits and to consider local community perspectives

NOT-OD-15-026 asserts that “With regard to assuring that local perspectives are addressed, the assessment of a study’s risks and benefits and the adequacy of the informed consent should not generally require the perspective of a local IRB. Local contextual issues relevant to most studies (e.g., investigator competence and site suitability) can be addressed through mechanisms other than local IRB review, such as the involvement of ad hoc members or consultants with the necessary specialized knowledge or expertise or by submission of information by the individual site(s). Even when certain vulnerable populations are targeted for recruitment, such alternative approaches may be appropriate.” NOT-OD-15-026 further states that “As necessary, mechanisms should be established to enable the single IRB of record to consider local context issues during its deliberations.” Although investigator competence and site suitability are certainly local contextual issues relevant to most studies, we are especially concerned about local contextual issues that pertain to specific communities that will be involved in or impacted by the proposed research. For the most part, institutional IRBs do not adequately consider local community and cultural contexts of the research they currently review.⁶ We believe alternative approaches are needed to assure they are considered (both for single site and multi-site research) and must be documented prior to the approval of a plan for a central IRB. These alternative approaches could include:

- Specifying a community IRB of record in addition to an institutional IRB of record. The community IRB of record would be responsible for assessing the ethics of the proposal study from the perspectives of the involved and/or impacted communities. Review and approval by both IRBs would be needed prior to initiating a study.
- Requiring that each study site submit to the central IRB evidence of local community review and support for the study, along with any expressed concerns or recommendations (this could include review and approval by a local community IRB or other community-based research review process). The central IRB would be required to consider and respond to this information in its review.
- Forming a study-wide community research advisory committee comprised of representatives of the involved and/or impacted communities from each study site. Review and approval of the proposed study by the committee and the institutional IRB would be required prior to initiating a study.

NOT-OD-15-026 indicates that “Exceptions to the expectation to use a single IRB may be made with appropriate justification. Exceptions will be allowed only if the designated single IRB is unable to meet the needs of specific populations or where local IRB review is required by federal, tribal, or state laws or regulations.” It is unclear what entity is responsible for making and monitoring this decision. The designated single IRB, for example, may believe it is able to meet the needs of specific populations, but if those specific populations have not been consulted or involved in reviewing the ethics of the proposed study, how would it know?

In closing, we note that NOT-OD-15-026 points out that federal research ethics regulations already allow institutions to voluntarily enter into some sort of central review process, but that “too few institutions involved in multi-site studies are taking advantage of the option.” Rather than risk compromising the ability of communities involved in and/or affected by the proposed research to contribute to the ethics review of the research by mandating the use of a central IRB, we recommend that NIH increase its efforts to publicize and promote the ability of institutions to voluntarily enter into a central review process. We also urge NIH to adopt language that requires any proposed central IRB to articulate a thorough plan for assuring that vulnerable populations at each study site will be protected and that community level risks and benefits pertaining to each site will be assessed and addressed.

Thank you again for the opportunity to voice our concerns about the draft NIH policy. If you have any follow-up questions or comments, you may reach us through Al Richmond at executivedirector@ccph.info.

Citations

- ¹ Grignon J, Wong K, Seifer SD (2008). Ensuring Community---Level Research Protections. Seattle, WA: Community---Campus Partnerships for Health. Available at <http://ccph.info>
- ² Kelley A, Belcourt---Dittloff A, Belcourt C, Belcourt G. Research Ethics and Indigenous Communities. (2013). *American Journal of Public Health*. 103(12):2146---2152.
- ³ Shore N, Wong K, Seifer SD, Grignon J, Gamble VN. (2008). Advancing the Ethics of Community-Based Participatory Research. *Journal of Empirical Research on Human Research Ethics*. 3(2), 1---4.
- ⁴ Shore N. (2006). Re---conceptualizing the Belmont Report: A community---based participatory research perspective. *Journal of Community Practice*, 14(4): 5---26.
- ⁵ Ross LR, Loup A, Nelson RM, Botkin JR, Kost R, Smith GR, Gehlert S. (2010) Human Subject Protections in Community---Engaged Research: A Research Ethics Framework. *Journal of Empirical Research on Human Research Ethics*. 5(1):5---18.
- ⁶ Flicker S, Travers, et al. (2007) Ethical dilemmas in community---based participatory research: Recommendations for Institutional Review Boards. *Journal of Urban Health*, 84(4)
- ⁷ Brydon---Miller, M., and Greenwood, D. (2006). Are---examination of the relationship between action research and human subjects review processes. *Action Research*, 4(1), 117---128
- ⁸ Mikesell L, Bromley E, Khodyakov D. (2013). Ethical community---engaged research: a literature review. *Am J Public Health*. 103(12):e7---e14.
- ⁹ Casado J. (2013). Ethical Engagement of Communities, Institutions, and Providers in Research: Lessons From the Community. *Progress in Community Health Partnerships: Research, Education, and Action* 7(3):353---355.
- ¹⁰ Martin del Campo F, Casado J, Spencer P, Strelnick H. (2013). The development of the Bronx community research review board: a pilot feasibility project for a model of community consultation. *Pro Community Health Partnersh*. 7(3):341-52.
- ¹¹ Quinn, S., Kass, N. and Thomas, S. (2013) Building Trust for Engagement of Minorities in Human Subjects Research: Is the Glass Half Full, Half

Public Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

- Empty or the Wrong Size? *American Journal of Public Health*. 103(12): 2119-21.
- ¹² Ford AF, Reddick K, Browne MC, Robins A, Thomas SB, Quinn SC. (2009) Beyond the Cathedral: Building Trust to Engage the African American Community in Health Promotion and Disease Prevention. *Health Promot Pract* 10: 485-489.
- ¹³ Blumenthal DS. (2006). A community coalition board creates a set of values for community-based research. *Prevention of Chronic Disease*, 3(1): A16.
- ¹⁴ Watkins BX, Shepard PM, and Corbin-Mark CD. (2009) Completing the Circle: A Model for Effective Community Review of Environmental Health Research. *American Journal of Public Health*. 99(S3): S567-S577.
- ¹⁵ Community IRBs and Research Review Boards: Shaping the Future of Community-Engaged Research. Albert Einstein College of Medicine, The Bronx Health Link and Community-Campus Partnerships for Health, 2012. Available at <http://ccph.info> and in the Appendix to this application
- ¹⁶ Shore N, Brazauskas R, Drew E, Wong KA, Moy L, Baden AC, Cyr K, Ulevicus J, Seifer SD. (2010) Understanding Community-Based Processes for Research Ethics Review: A National Study. *American Journal of Public Health*. 101 (S1): S359-364.
- ¹⁷ Shore N, Drew E, Brazauskas R, Seifer SD. (2011) Relationships Between Community-Based Processes for Research Ethics Review and Institution-Based IRBs: A National Study. *Journal of Empirical Research on Human Research Ethics*. 6(2):13-21.
- ¹⁸ Shore N, Park A, Castro P, Wat E, Sablan-Santos L, Isaacs ML, Freeman E, Cooks JM, Drew E, Seifer SD. Redefining Research Ethics Review: Case Studies of Five Community-Led Models. Seattle, WA: Community-Campus Partnerships for Health, 2014. Available at <http://ccph.info>
- ¹⁹ Community Network for Research Equity and Impact. Community Leaders from Across the U.S. Call for Health Research Equity and Impact. Seattle, WA: Community-Campus Partnerships for Health, 2013. Available at <http://ccph.info>
- ²⁰ Likumahwa S, Song H, Singal R, Weir RC, Crane H, Muench J, Sim SC, DeVoe JE. (2013). Buildin research infrastructure in community health centers: a Community Health Applied Research Network (CHARN) report. *J Am Board Fam Med*. 26(5):579-87.
- ²¹ Cook WK, Weir RC, Ro M, Ko KL, Panapasa S, Bautista R, Asato L, Corina C, Cabllero J, Islam N. (2012). Improving Asian American, Native Hawaiian, and Pacific Islander health: national organization leading community research initiatives. *Prog Community Health Partnersh*. 6(1):33-41.
- ²² Proser M, Aaron KF, Meyers D, Cornell C. (2007) Building a research agenda for community health centers and the medically underserved: meeting proceedings. *Prog Community Health Partnersh*. 1(1):67-73.

Comment #158

Commenter:

Date of Comment:

Comment:

JANUARY 27, 2015

Thank you very much for providing the opportunity to comment on the NIH Draft Policy entitled: Use of Single Institutional Review Board for Multi Site Research (Draft Policy). I am writing on behalf of the Brigham and Women's Hospital (Brigham), a principal teaching affiliate of Harvard Medical School.

The Brigham was founded in 1980 with the merger of three of Boston's oldest and most prestigious Harvard teaching hospitals: the Peter Bent Brigham Hospital, the Robert Breck Brigham Hospital, and the Boston Hospital for Women. A founding member of Partners HealthCare System, the Brigham is known for its clinical, translational, bench and population-based research and is consistently ranked among the top two hospital recipients of NIH funding. In FY 14, Brigham received approximately \$323 million in research funding from the NIH. Thus, reform of policies pertaining to Institutional Review Boards is of critical importance to the Brigham research enterprise.

As a participant in multiple single IRB (sIRB) arrangements, including as a Central IRB, we strongly support the development and facilitation of sIRB review. However, we believe that the Draft Policy as written is premature in its breadth and inflexibility and does not adequately acknowledge or address the gaps in current knowledge about the relative benefits and costs of sIRB systems. As indicated in our detailed comments below, we propose that more research be conducted before mandating sIRB review for all types of multi-site studies and that the initial policy focus on a more limited set of research.

Our comments are organized into three sections: 1) comments on the assumptions/assertions made in the introduction to the Draft Policy; 2) comments on the specific proposals of the Draft Policy and 3) suggestions for alternate approaches.

Introductory assumptions/assertions:

Use of an sIRB for domestic multi-site research is promoted as promising potential advantages of efficiency, decreased time to study start-up and consistency of review and even conduct of the research. However, there is currently little research or data to demonstrate that these potential benefits will materialize in particular types of multi-site research, that they can be realized with no accompanying decrease in human subject protections, or that they outweigh the significant costs and resource investments required to implement a single IRB system in which all parties can have confidence.

A few specific comments:

The Draft Policy presumes that there will be efficiency in the initiation/initial review of a study. In our experience with serving as the sIRB and relying on other sIRBs, the efficiency has not been in the initial review of the protocol, but rather in the addition of sites after initial protocol review as well as in the subsequent reviews through the life of the protocol; e.g., continuing review, unanticipated problems (UAPs).

The Draft Policy asserts that local IRB review is not needed for assessing local context. While we agree this is not an IRB regulatory requirement, we note that it is generally the local IRB or at least the local IRB office that is most knowledgeable about the local context and about the application of local rules and norms to the conduct of research. Therefore recognition of the practical reality of ongoing IRB office, if not IRB, involvement is necessary.

The Draft Policy casts use of a SIRB as more cost effective than local IRB review. More information is needed before this can be accepted as a benefit.

Details of the Draft Guidance:

Our comments on specific proposals or aspects of the Draft Policy are listed here. Discussion of each item immediately follows this list.

1. The broad scope of the mandate- all multi-site domestic research with NIH funding - without regard to the type of research or number and type of sites and to the existence of central infrastructure to support the SIRB
2. The limited scope for exceptions
3. Lack of details and proposed financial support for management of the necessary research oversight processes at the reviewing SIRB and the relying sites, and for required communication between them
4. Lack of details regarding expectations when the local IRB elects to review a project subject to the policy
5. Absence of information about the selection/approval criteria for the SIRB, including whether the SIRB's willingness/ability to serve as a HIPAA Privacy Board will be a factor
6. Apparent lack of coordination with other proposed mandates and/or regulatory changes regarding the use of SIRBs, including the 2009 and 2011 ANPRMs referenced in the Draft Policy

1. The broad scope of the mandate:

The Draft Policy describes in general the requisite responsibilities for both the reviewing SIRB and the relying institutions. But it fails to recognize how different types of studies require vastly different logistics and resources for both the SIRB and the relying institution. Due to these differences, there are multi-site studies that fit more easily into an SIRB approach and there are others that do not.

In our experience, examples of factors to consider before deciding that SIRB review is appropriate include:

- **Number of institutions:** a study involving 2 sites versus one with 75 will have very different impact on coordination, workflow and resources needed.
- **Types of institutions:** The success of SIRBs is predicated on trust and mutually agreed-upon processes. The SIRB must have confidence that the sites relying on the SIRB have good HRPPs that can provide all of the institutional requirements. And the relying sites must trust that the SIRB is a quality IRB that will be accessible to the each site. This trust grows from various factors, including the sites' and SIRBs' level of experience conducting or reviewing the type of studies at issue, the size of the respective research programs, and familiarity with one another's state and local rules and culture. Mandating a SIRB arrangement among several academic medical centers in the same area that are frequent collaborators is very different than mandating SIRB review among these centers and small private physician practices in different states.
- **Types of studies:** Minimal risk studies generally have few ancillary committee reviews as well as few amendments and UAPs over the course of the study. In contrast, more than minimal risk studies generally have ancillary committee reviews as well as frequent amendments and UAPs that require IRB review. The logistics and resources needed for SIRB review vary as a function of the type of research; hence adequacy of infrastructure must be assessed for each study.
- **Types of study teams:** Multi-site studies require some level of study team coordination. However, the degree of coordination that is customary and readily achievable varies: robust research

networks with clinical and data coordinating committees are vastly different from one-time affiliations of several colleagues with no existing infrastructure. The 'one-time-affiliations' often lack the skills as well as funding to coordinate with a SIRB.

- Resources for the SIRB system: If an institution is expected to provide SIRB services as an 'add-on' with no additional resources, then its overall capacity will be severely limited. For example, a 50 site high risk interventional study would easily require a full-time liaison to simply handle communications between all sites for initial review, continuing review, adverse events, amendments, etc. In addition, information technology (IT) resources must be in place to accommodate handling the processes between the participating institutions. In many situations this requires either a new system or a work-around of an existing IT system.
- Resources for investigators: Study teams will have to assume much of the coordination functions between the sites- this will require resources.

The Draft Policy does not currently allow for consideration of such heterogeneity. A minimal risk study conducted at 4 institutions that are members of an existing network defies comparison with an interventional high risk study conducted at 25 institutions that have been newly brought together for specific research, in terms of capabilities, comfort level, and resources needed.

2. The limited scope for exceptions is not adequate

The Draft Policy states that "exceptions will be allowed only if the designated SIRB is unable to meet the needs of specific populations or where local IRB review is required by federal, tribal, or state laws or regulations." For all other reasons addressed above, if the final policy adopts the broad scope that is proposed, we believe that there are many other factors that should be considered as justification for an alternate approach or an exception, including the type of study, types and numbers of involved institutions, and type of study team. In addition, it is unclear what sorts of situations would constitute inability to meet the needs of specific populations or why this could not be assessed before any particular IRB is designated as the SIRB.

3. Lack of details and proposed financial resources to support the processes at both the reviewing SIRB as well as the relying sites

The default in any reliance arrangement is that the only task that is ceded is the IRB regulatory review; all institutional responsibilities generally remain with the local sites and some in fact cannot be ceded. Institutional responsibilities include, for example, HIPAA determinations related to the study, ancillary committee reviews, compliance with state laws, COI, CMS, and training of investigators. Tasks like ancillary committee reviews necessarily *must* remain with the local sites, as must ultimate responsibility for compliance with state laws. Hence in ceded review, the relying sites retain significant tasks. These are tasks that in many institutions are completed by the IRB (such as in the case of HIPAA) or otherwise by the IRB office and closely integrated into the overall review of a protocol. When IRB review is ceded, the relying institution must develop processes and systems (often new IT systems) by which they not only coordinate these institutional responsibilities but also communicate their determinations to the SIRB.

Providing SIRB capacity requires planning and process development including identification of resources needed for both setting up the SIRB as well as completing the protocol review. The tasks for setting up a SIRB include for example: negotiation of reliance agreements; performance of due diligence of the relying sites; development of SOPs that address processes for communication between the SIRB and all relying sites, processes for obtaining and considering relying site issues such as HIPAA authorizations or waiver of authorization determinations, ancillary committee reviews, COI, CMS, sign-off on PI training, processes for dealing with noncompliance and required reporting, etc.

Once these systems are set up, the SIRB must then be able to conduct all regulatory reviews (initial, continuing, amendments, UAPs etc) after obtaining appropriate input from local sites.

As noted above, the level of resources needed for serving as a SIRB as well as relying on a SIRB will be informed by the type of study; e.g., complexity of the study, number of sites, structure of the study team etc.

We (institutions, IRBs, sponsors, regulatory agencies) do not yet have accurate information on these costs. Without this information, it will be difficult for institutions to responsibly serve as a SIRB or agree to rely. This discussion is further complicated by the paucity of data regarding the cost of local IRB review. As noted above, most IRB offices are responsible for much more than the regulatory review and it may be difficult to disentangle the costs of that regulatory review from all of the other tasks that the IRB/IRB office performs.

Adding to the comments made above - is the fact that we are currently in a time of evolving and multiplying SIRB models. At present there are a number of different models which share some features, but which each have their own approach. IRBShare is an example of a "share model" in which IRB regulatory review is shared between the SIRB and local IRBs. In contrast are the "nonshare" models in which all regulatory review is completed by the SIRB; examples include systems used by the VA, NCI and NeuroNEXT. Mandating SIRB review at this time without review and analysis of the relative benefits and costs of each model or determination which is most appropriate for different types of NIH-funded research just adds another requirement to the explosion of different models and approaches. A single institution may be faced with serving as a SIRB for several completely different types of research as well as relying on several other SIRBs, each of which has their own policies and procedures. If the Draft Policy is finalized as proposed, different SIRB systems would be developed. This would then require that relying institutions have the infrastructure and resources needed to maintain working interfaces with multiple somewhat different systems. This could in fact decrease the efficiency of protocol review.

The proposal states that if the identified central IRB is a for-fee IRB, then that cost can be included in the budget. IRBs based at academic centers are typically not fee based, at least not for all reviews they perform - yet they will have to assume significant increases in work, as well as development of systems to comply with this proposal. How will that be funded?

4. Suggestion of SIRB AND local IRB review

The Draft Policy allows for parallel reviews, as we agree is appropriate in the absence of any current regulatory mandate for SIRB review. However, the policy does not discuss the implications of a situation in which both a designated SIRB and a local IRB(s) perform a regulatory review of a study. From a regulatory perspective, we presume that NIH agrees that both IRBs would have authority, and as a practical matter, the result is that the most stringent (protective of human subjects) requirements must govern. How does NIH intend for this concurrent review scenario to work, and what communication will occur to ensure that the designated SIRB selected by NIH is aware of the other IRBs' reviews?

5. Selection criteria for the SIRB

The Draft Policy does not indicate what criteria will be used by NIH to evaluate and select the SIRB. Transparency around this determination is critical for institutions and IRBs participating in trials subject to the policy to understand NIH's expectations and to develop robust proposals if they are interested in being designated as the SIRB.

Without limiting this general comment, we note that the Draft Policy does not mention the requirements of the HIPAA Privacy Rule for use or disclosure of Protected Health Information for research. Depending on the type of study at issue, the researchers may request a waiver of

authorization for use/disclosure of PHI. Under the HIPAA Privacy Rule, a Privacy Board must determine whether a waiver is appropriate for the study and document that determination. In practice, many IRBs serve as the Privacy Boards for their institutions. In our experience, including reliance arrangements where NIH's IRBs are designated as the SIRB, the designated IRB is not always willing to serve as a Privacy Board for the relying institutions. In such situations, the relying institutions (and specifically, their IRBs) must then review the study sufficiently to be able to apply the HIPAA waiver criteria and make the waiver determination. When this occurs, the potential efficiencies of the SIRB review are diminished. Does NIH intend to require willingness to serve as a HIPAA Privacy Board in order for an IRB to be selected as the SIRB under this policy?

6. Lack of coordination with other proposed mandates and/or regulatory changes regarding the use of SIRBs

As noted in the Draft Policy, there are two outstanding ANPRMs, from 2009 and 2011, that contain proposals relevant to reliance arrangements and requirements for use of single IRBs. It is not clear to us whether HHS intends to proceed with proposed regulatory change as discussed in the 2009 ANPRM, that would clarify regulatory responsibilities of each of the parties in a reliance arrangement and establish direct regulatory liability of IRBs. It is also not clear to us whether single IRB review will be mandated as a result of the 2011 ANPRM, and if so, for what scope of studies. Establishing a funding policy mandating broad use of single IRBs in advance of the resolution of these two regulatory initiatives may create confusion or result in inconsistencies if and when regulatory changes are adopted. We believe that it makes more sense for NIH's focus at the present time to be on funding additional research examining the potential benefits and costs of single IRB use as suggested above.

Suggestions for alternate approaches:

As noted above, we strongly support the development and facilitation of SIRBs for some multi-site research. We also note that the use of external IRBs is not a new concept and there is an experience upon which to build. Most academic medical centers (AMC) have experience relying on an IRB at another AMC; these arrangements are often limited to no more than minimal risk research conducted at two or three sites. In addition, many AMCs have experience relying on commercial/independent IRBs for a select category of research- most often industry-sponsored and initiated, phase 3 and 4 multi-site research.

What is new with the NTH Draft Policy is the inclusion of all NTH-funded multi-site research regardless of type of study or number of institutions.

Given the current evolution of SIRB models and the paucity of data regarding these models, we suggest a more tempered approach. Instead of broadly requiring a SIRB for any NIH-funded multi-site research, we propose refining the policy either to be limited (for now) to minimal risk research involving no more than several sites or, if it remains broad, to including a process whereby flexibility be built into the policy to account for various types of research and other specific factors more fully discussed above. In this way, use of an SIRB could be considered case-by-case before being required by NIH as a condition of funding.

We also suggest that NIH simultaneously fund research on existing SIRB models to evaluate potential benefits and costs for both the SIRB site as well as relying sites. This could include research focused at models that are currently reviewing NIH-funded research or NIH could also identify a cohort of clinical research for which the NIH will fund a SIRB and as a condition of grant award require research on the SIRB itself.

All of these approaches would inform the process going forward.

In addition, NIH could convene expert panels to focus on a number of SJRB-related issues; such as, developing criteria to identify research best reviewed by a SIRB; identifying the elements and resources needed to provide SIRB services within an AMC; and evaluating the pros and cons of various reliance models.

Finally, NIH could support the development of tools that could facilitate SIRB processes -this would include working with groups that have already begun to address some of these. Examples of tools include: Reliance Agreement templates, Standard Operating Procedures, approaches to HIPAA.

Thank you for the opportunity to provide comments on this draft guidance. Please contact us with any questions or requests for clarification. We are very interested in working with you to develop a successful future for SIRBs.

Sincerely,

Paul J. Anderson, MD, PhD
Chief Academic Officer
Senior Vice President of Research

Comment #159

Commenter: Katherine E. Hartmann, MD, PhD

Date of comment: January 30, 2015

Comment:

We are writing as experienced, federally-funded senior investigators. We also serve on the Steering Committee of the NIH Pelvic Floor Disorders Network (PFDN), an eight site surgical research network that is based in the Gynecologic Health and Disease Branch of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. We welcome the opportunity to comment on the draft NIH Policy on the Use of a Single Institutional Review Board (IRB) for Multi-Site Research. Many of us have experience with using single or central IRB's. Our comments reflect our experiences with single IRB structures and also draw on observations about what related factors have made the PFDN both productive and effective. The views expressed are our personal observations and do not reflect the opinions of the PFDN or its other collaborating investigators, or our institutions

We would like to provide some context to support our observations. As a network, not utilizing a central IRB structure, the PFDN has achieved an uncommonly high level of productivity. Over the past 13 years, the Network has completed a dozen major clinical trials and epidemiologic studies that have had a major impact on the treatment of women with pelvic floor disorders. Currently the Network has six major randomized controlled clinical trials in the field that include more than 1600 participants. Five of these have major translational supplementary sub-studies that will provide substantial understanding of the mechanisms of pelvic floor disorders.

The proposed policy to mandate use of a single IRB of record for all funded multi-site studies reflects the importance of the need for efficiency in Institutional Review Board (IRB) oversight of multi-site studies. However we have concerns that requiring new single IRB centralization could be costly, diverting funds from research, and would not definitively accelerate study launches or improve oversight. Effective networks have both a collaborative common ground and internal incentives (such as capitation based on achievement of subject milestones) that promote timely review. Furthermore, many experienced clinical trial investigators with long-standing participation in collaborative research networks such as ours, have built close working relationships with local IRB's that generally improve the speed and comprehensiveness of review and communication for Network trials. These relationships would have to be sacrificed or rebuilt. Consequently, a more flexible approach than the approach proposed in the draft Policy that utilizes these relationships to enhance approval processes may achieve the goals of the policy within alternative frameworks. Our network also has multiple sites that participate voluntarily in IRBshare, which may provide just such a flexible model.

IRBshare provides a unique configuration based on a systematic mass reliance model which promotes a single IRB review (as opposed to a single IRB of record). This program has formal, written acknowledgement as an acceptable joint review model from the Office for Human Research Protections (OHRP) and Food and Drug Administration (FDA), and is supported by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). IRBshare is based on a uniform national reliance agreement (i.e., institutions share regulatory responsibility) that allows IRBs to rely on the review of another IRB for all phases of review (initial study, annual/continuing reviews, and reviews of amendments) of multi-site studies at any risk level. After the Lead IRB reviews the study for their institution and gives approval, its review is uploaded to the IRBshare web-based system where other institutions in the study can approve the study via the "Shared Review Process" using a subcommittee (at least one IRB member) that 1) verifies they agree with the determination of the Lead IRB and 2) reviews its local context issues. Sites in our network have accomplished study approvals in as little as

three days using this mechanism.

This process has the additional attractive feature that the relying institution completes the review by adding their local context, thus retaining study oversight, including review of study-related events. At continuing review or for the review of a study-wide amendment, the Lead IRB again performs the complete review for its institution, uploads approval to IRBshare, and the relying IRBs again use the subcommittee to give approval. IRBshare offers a single IRB review, streamlining the only duplicative process of review—the IRB regulatory review—without adding the infrastructural and review burden inherent to conventional models of central IRBs and reliance agreements. This allows local IRBs to conduct the local context review and maintain study oversight (IRB of record status) between the times of reliance upon the lead IRB reviews. Under the current proposed language in NOT-OD-15-026, IRBshare—now adopted by over 50 major academic medical centers—would be prohibited. We find eliminating this option short-sighted and undesirable.

We are eager to strongly recommend that rather than restricting to a conventional central IRB model, IRBshare be included as an acceptable strategy to enhance multi-site IRB review effectiveness and speed.

Sincerely,

Lily Arya, MD, MS
Associate Professor, Obstetrics & Gynecology
University of Pennsylvania

Matthew Barber, MD, MHS
Professor of Surgery
Cleveland Clinic Lerner College of Medicine at Case Western Reserve

Katherine E. Hartmann, MD, PhD
Lucius Burch Professor, Obstetrics & Gynecology and Medicine
Vanderbilt University

Charles W. Nager, MD
Professor and Chairman, Department of Reproductive Medicine
UC San Diego Health System

Holly E. Richter, PhD, MD
J. Marion Sims Professor, Obstetrics and Gynecology
University of Alabama at Birmingham

Rebecca G. Rogers, MD
Regent's Professor, Obstetrics and Gynecology
University of New Mexico

Vivian Sung, MD, MPH
Assistant Professor, Obstetrics and Gynecology
Warren Alpert Medical School of Brown University

Anthony G. Visco, MD
Professor, Obstetrics and Gynecology
Duke University

Dennis Wallace, PhD
Senior Research Statistician
RTI International

Halina Zycznski, MD
Associate Professor, Obstetrics, Gynecology and Reproductive Sciences
University of Pittsburgh

Comment #160

Commenter: Pepin Andrew Tuma, Esq.

Date of comment: February 2, 2015

Comment:

The Academy of Nutrition and Dietetics had hoped to offer support and comment to your Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research, but recognize the published deadline of January 29, 2015 just passed. Is it possible by chance that we could forward our comments to you today in the hope they still may be helpful to you, even after the deadline

Comment #161

Commenter: Dea Papajorgji-Taylor

Date of comment: February 2, 2015

Comment:

I am writing in support of the proposal to encourage use of a single IRB for multisite trials. This IRB model would serve as more efficient than utilizing multiple local IRBs at academic, medical centers that would require their own modifications using their own respective consent form templates. The required changes proposed by our local IRB don't always improve the safety of study subjects or ensure that subjects are not being coerced or influenced unjustly. From my experience, local IRBs can add additional time and financial restraints to the startup process of a new clinical trial. Being able to utilize a central IRB model would streamline the general IRB review process and provide more efficiency. In our experience, there have been times when the study sponsor believed that the local IRB review process, compounded by the amount of time the sponsor's legal team requires to review our local IRB templates, did not justify our site as being selected to participate in a new trial. Such decisions affect our Center's research funding, ability to conduct more clinical trials, and ultimately lead to limiting our research efforts aimed to improve clinical care.

Thank you for your attempt to improve this aspect of conducting multisite trials.

Comment #162

Commenter:

Date of Comment:

Comment:

February 3, 2015

Ms. Sarah Carr

Director, Office of Clinical Research and Bioethics Policy

Office of Science Policy

National Institutes of Health 6705 Rockledge Drive, Suite 750

Bethesda, MD 20892

Dear Director Carr:

The Pediatric Orthopaedic Society of North America (POSNA) and the Scoliosis Research Society (SRS), fully support the NIH proposal on the use of single institutional review board for multi-site research. POSNA and SRS represent over 2,000 Board-certified orthopaedic surgeons who care for conditions affecting the health and function of the musculoskeletal system in children and young adults.

The pediatric population remains underserved with regard to the availability of drugs and devices specific for treating musculoskeletal pathology. Regulatory, clinical, economic, and legal issues continue to limit research and the development of innovative treatments for orthopaedic conditions affecting children and young adults. It is our contention that the adaption of a single, universal institutional review board for multi-site research will expedite the review process for studies in children and facilitate important breakthrough discoveries. The Department of Health and Human Services requires IRBs to review all studies involving human subjects to protect study participants from unethical or unsafe research activities. However the mandate does not specify how this process should be accomplished and as such each local IRB has interpreted this mandate differently, especially with regard to children. In some instances in addition to enforcing state and/or local regulations, the local IRB has evolved to become the instrument of the hospital or sponsoring institution to exercise control over research activities and to enforce institutional policies as they relate to medical-legal issues and intellectual property. Variability in the interpretation of this government mandate by local IRBs becomes problematic when conducting multi-center studies in children, which increasingly are being proposed to generate "big data" for relatively rare conditions or as part of FDA required phase I or II studies for IDE/HDE designated devices. Currently all investigators participating in a multi-center NIH sponsored grant or FDA mandated study to evaluate the safety and/or efficacy of a medical device are required to get approval from each local IRB. However the process of getting IRB approval from each of the participating institutions can be onerous as each local IRB attempts to satisfy its perceived charge, often demanding changes to the design of the study (inclusion/exclusion criteria, measurement process, outcome metrics and/or statistical analysis of the data) which in aggregate interferes with the uniform implementation of the study across all participating institutions. The process of achieving IRB approval from all participating institutions takes considerable time and effort; delay in getting IRB approval interrupts initiation of the study, squandering valuable human resources allocated to conduct the study, culminating in wasted research dollars.

As an example, the five year funded, NIH/NIAMS sponsored, multi-center U01 BRAIST study to investigate the utility and efficacy of brace treatment for adolescent idiopathic scoliosis in children required nearly two years to obtain approval from all of the IRBs of the participating institutions, significantly delaying initiation of the study at a cost of hundreds of thousands of precious research

dollars. While there is a mechanism for participating IRBs to cede control to the IRB of the sponsoring institution, often (as was the case for the BrAIST study) the sponsoring institution does NOT want to accept the responsibility of oversight of participating investigators not specifically associated with that institution. Another example where review by multiple IRB's stymied the performance of important clinical research was the implementation of the prospective multi-center study to evaluate the safety and efficacy of the vertical expandable prosthetic titanium rib (VEPTR) for the treatment of rare, life-threatening birth defects of the spine and thorax that induce thoracic insufficiency syndrome. The multi-center phase of the clinical trial, supported by limited funding from the FDA office of orphan products, was significantly delayed by the need to respond to often contradictory critiques by multiple local IRB's, even though the overall study design was developed in collaboration with the FDA to accumulate evidence required by the agency to support approval for the device. It took nearly 4 years to obtain approval at one study site and overall 14 years to accrue enough patients to complete the study.

Changes in the economics of the medical device industry and stricter interpretation of compliance standards threaten the availability of drugs and devices for children. Even though the FDA regulates the indications and intended use of drugs and devices, the FDA does not regulate the practice of medicine. Physicians and surgeons may prescribe medical products that they believe to be in the best interest of the patient. However, critical evaluation of the efficacy of these physician directed interventions on a large scale by carefully controlled, prospective scientific *study is often thwarted by local IRB reviews who do not believe they have the mandate to evaluate the "off-label" use of drugs and/or devices approved for use in adults with similar conditions or approved for use in conditions other than that being treated. This proposal presents an opportunity to develop a mechanism to conduct innovative research on a large scale that balances patient safety with the unmet needs of these at risk pediatric patients that.* In particular POSNA/SRS welcome involvement in the process where a framework could be developed to evaluate the safety and effectiveness of physician-directed uses of drugs or medical devices in children based on a systematic review of published biomechanical, animal and clinical studies to ascertain that the performance of a drug or device in children is equivalent to its approved use in adults or by using meta-analysis of existing published data as valid scientific evidence for a pediatric indication. Additionally, a new pediatric pathway could be created for very small pediatric populations with rare conditions similar to that developed for orphan drugs that include the use of objective performance criteria or historical controls to demonstrate effectiveness.

Based on the experience of the BrAIST study, where the sponsoring institution was unwilling to accept the responsibility of oversight for ALL participating investigators and institutions, we propose the creation of an NIH or FDA sponsored IRB committee comprised of a “blue ribbon” panel with appropriate expertise to evaluate the ethics, safety and scientific integrity specific to the NIH or FDA sponsored multi-institutional study being reviewed (much like an NIH study section) to which all other institutional IRBs would cede to. Participating sites will be responsible for implementing the regulatory obligations directed by the universal IRB including oversight and implementation of approved protocols, informed consent and the reporting unanticipated problems and adverse events. It is the contention of POSNA and SRS that such a stream-lined process will facilitate efficient, predictable IRB reviews for studies involving children and young adults and accelerate the development of innovative treatments for pediatric musculoskeletal pathologies.

Respectfully submitted,

Gregory A. Mencio, MD
POSNA President

John P. Dormans, MD
SRS President

cc: Brian Snyder, MD-BOS Research Committee

Comment #163

Commenter:

Date of Comment:

Comment:

February 4, 2015

Dr. Sarah Carr

Acting Director,

Office of Clinical Research and Bioethics Policy

Office of Science Policy, Office of the Director,

National Institutes of Health, Rockledge 1, Suite 750

6705 Rockledge Drive

Bethesda, MD 20817

Dear Dr. Carr:

The National Science Board (NSB) shares the commitment to reducing procedural inefficiencies that do not enhance protection of human subjects that underpins your *Draft Policy on the Use of a Single Institutional Review Board for Multi-Site Research* (NOT-OD-15-026). Last year, we issued a report on *Reducing Investigators' Administrative Workload for Federally Funded Research* (NSB-14-18). That report recommended, among other things, that steps be taken to encourage use of a single IRB for multi-site studies. This was one of a set of recommendations seeking to ensure that agencies try to reduce work that does not enhance meaningful protections for subjects.

We received comments from nearly 4,000 scientists and science administrators as we examined administrative workloads for our report. IRB strictures were listed among the most cumbersome for investigators and the problems associated with clearing multiple IRB committees for a single project was singled out as a challenge with significant costs and little or no benefit. When more than one committee reviews the same work, our scientific commenters reported they often have to undertake additional work in order to master different forms and procedures, they can experience nontrivial delays due to incompatible deadlines, and they can encounter inconsistencies in interpretation or application of IRB rules that can lead to compromises in research design that do not add to and may even reduce the value of the research itself.

Our examination of this issue led us to conclude that for a policy for single IRBs to be highly effective it should include clear guidance on the respective responsibilities and compliance requirements of the institution housing the IRB of record and the institutions where the protocols will be implemented. Your proposed policy goes a long way toward clarity in the first paragraph under "Responsibilities." However, the "such as" clauses may leave the research community and their institutions uncertain about their responsibilities. Greater specificity about compliance and oversight requirements could reduce liability concerns -which can vary by state - and make implementation of your new policy more successful.

It may be helpful to note that National Science Foundation (NSF) Primary Investigators designate one IRB for their multi-site studies with some regularity, though not universally. The paperwork can be simple, lead institutions have been willing to accept review responsibilities, and agreements apparently have been reached in many instances without significant difficulty or delay. While NSF's research community is not identical to NIH's, it is still relevant to consider that there are contexts in which single IRB review is currently viable.

One additional thought we would offer is that your policy does not mention variation in the work

conducted at different sites as a possible justification for exemption from single IRB. If survey work is to be completed on one site and experiments on another, it could be more sensible and efficient to clear the survey at one institution and the experiment at the other. Similarly, if there is human subjects work at one campus but only outreach at another, it could be more efficient to allow full IRB review at the first site and IRB exemption at the second.

We applaud and support your proposed policy and the open comment process you are using to improve and finalize it. We anticipate that you will receive many helpful and supportive comments and we look forward to a successful revision and implementation . If the NSB can be of further assistance, please do not hesitate to be in touch. Our ad hoc Working Group on Administrative Burdens is actively working on this topic. Dr. Arthur Bienenstock, who has led this activity, is particularly knowledgeable and available to assist you.

Sincerely,

Dan E. Arvizu
Chairman

Comment #164

Commenter:

Date of comment: February 6, 2015

Comment:

On behalf of the Indian Health Service (IHS) National Institutional Review Board (NIRB), I would like to provide the following comments on the Draft NIH Policy. As you know, all human participant research conducted in IHS facilities or with IHS staff or resources must be approved by an IHS Institutional Review Board (IRB). This includes all research in Tribally managed or Urban facilities since they fall under the IHS federal-wide assurance (FWA) 00008894. Urban or Tribally managed facilities, however, may obtain their own independent FWA with the Office of Human Research Protections (OHRP). In these cases, the urban or Tribal facility may use their own IRB or use the IHS IRB if they so choose. The IHS encourages Tribally managed health programs engaging in research to obtain independent FWAs to insure local authority over research within their territory and research activities affecting Tribal members. The aim here is to insure that local political, social, cultural, and spiritual considerations are taken into account when research is conducted in "Indian Country" (defined at 18 USC § 1151). Local Tribal control over research conducted within their jurisdiction is necessary to prevent instances of human subject protections failures. Tribal leaders and researchers report numerous examples of "helicopter research" occurring within Tribal territories historically and there are also more recent examples of misunderstandings between researchers and Tribes that illustrate this point quite well (i.e., *Havasupai v. Arizona State University*; for discussion, see *N Engl J Med.* 2010 Jul 15;363(3):204-7 and *Virtual Mentor.* 2011 Feb;13(2): 113-117).

Although we understand the "significant administrative burden" to perform duplicate reviews and the need to "avoid duplication of effort", investigations occurring in Indian Country receive special consideration for a number of reasons, not the least of which is the government-to-government relationship between the United States and Indian Tribes (Article I, Section 8 of the Constitution, given form and substance by numerous treaties, laws, Supreme Court decisions, and Executive Orders). Although the Request for Comments asserts that there is "no evidence that multiple IRB reviews enhance protections for human subjects", to my knowledge this has not been addressed in Indian Country. Indeed, we know that non-IHS and non-Tribal IRB review has been associated with significant harm to American Indian and Alaska Native (AI/AN) research participants. Furthermore, the statement "the assessment of a study's risks and benefits and the adequacy of the informed consent should not generally require the perspective of a local IRB" may be generally true for the overall population; however this policy begs for an exception for AI/AN communities, where Community-Based Participatory Research has become the gold standard in conducting research.

Regarding the statement, "contextual issues relevant to most studies can be addressed through mechanisms other than local IRB, such as the involvement of ad hoc members or consultants with the necessary specialized knowledge or experience or by submission of information by the individual site(s)", it is unclear what is meant by "contextual issues" but this should not include the important considerations of social, cultural, and spiritual considerations in communicating risk and benefits of participation in research studies among and with Tribal members. Moreover, the "involvement of ad hoc members or consultants" could be interpreted to require that only 1 member of any Tribe, regardless of his or her affiliation with any one of the 566 federally-recognized Tribes or level of understanding of the cultural milieu of the population(s) under study, would be needed to satisfy this requirement. As you know, Tribes are very different in many respects and only local Tribal IRB review can ensure compliance with 45 CFR Part 46.

For the above reasons, among others, we recommend that an exemption be made in the draft NIH policy for studies conducted within the jurisdiction of AI/AN Tribes. Multi-site studies with central IRB approval should nonetheless seek IHS or Tribal IRB approval, as appropriate, for research conducted within the jurisdiction of federally recognized AI/AN Tribes.

Thank you for your consideration.

Comment #165

Commenter: Elizabeth Ledger, CCRP

Date of comment: February 11, 2015

Comment:

I am definitely in favor of a single IRB policy for all NIH-funded multi-site studies conducted in the United States.

Comment #166

Commenter: Michael Van Scott

Date of comment: February 18, 2015

Comment:

East Carolina University (ECU) appreciates the opportunity to comment on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research (NOT-OD-15-026). It is our understanding that the proposal involves the use of a single IRB review for multiple institutions implementing a single protocol.

The idea of a single IRB review has been proposed many times over the past ten years. In theory, the concept would reduce regulatory burden. However, applying that concept would mean a great deal more work for the institutions implementing federally-funded research.

Most institutions have some form of electronic systems to manage IRB submissions, grants, contracts, and ancillary reviews. In order to accommodate a single IRB review, these electronic systems would all have to be reprogrammed to permit opportunity for these peripheral but critically important reviews to occur. This type of reprogramming would not only be very expensive but would require additional burden on the investigators since they would need to apply through two systems.

Furthermore, it is not clear from the NIH Draft Policy how Inter-Institutional Agreements would be negotiated, whether a new Agreement would be needed for each study, and how those Agreements would alleviate the “home” institution from liability. Each IRB has its own procedures, SOPs and policies. Would NIH have a set of SOPs that would be followed by all institutions? If so, the expense of doing business with two sets of policies and procedures would not be efficient and would cause great confusion for investigators, IRB members, and IRB staff.

Most institutions, including ECU, struggle to provide an infrastructure for the “home” IRB. Having two systems would require additional burden on existing IRB offices with no real financial incentive for those offices to expand.

ECU has an electronic system for managing all protocols involving humans, including all ancillary reviews, IRB reviews and oversight actions. That system provides opportunity for our affiliates to review proposed research, including that funded by NIH, for feasibility, accessibility, and appropriateness. To make changes to this system for a small number of protocols would involve extreme expense and would require setting up a different process system. ECU also has several Affiliate institutions that rely upon the University’s IRB and these Affiliates have expressed that they will not rely upon another IRB which means for investigators who utilize the Affiliates facilities they would have to go through two IRB reviews.

Therefore, it is our opinion that this proposed method of reducing regulatory burden would, in fact, increase such burden. Furthermore, ECU and its Affiliates have a unique population from which participants are drawn and this requires expertise in local customs and cultures. Finally, it seems that it would be more prudent to wait to initiate any changes until such time that the Advanced Notice of Proposed Rule Making is clarified since it would be fiscally challenging for ECU to implement system changes only to have to do so again when the final changes to the regulations are issued.

Again, we thank you for the opportunity to submit comments.

Comment #167

Commenter: SACHRP

Date of Comment:

Comment:

Comments of the Secretary's Advisory Committee on Human Research Protections In response to the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

The National Institutes of Health issued a draft policy on December 3, 2014 promoting the use of a single Institutional Review Board Review. The draft guidance would mandate the use of a single IRB in any NIH-funded/supported multi-site study for sites located within a U.S. jurisdiction. The proposal assumes the mandatory use of single IRBs will increase efficiency of IRB review, prevent duplication of effort, and prevent disparities among protocols and informed consent forms in multi-site studies that often have reviews by multiple local IRBs.

The draft policy proposes limited exceptions to use of a single IRB. Exceptions would only be permitted if: (1) the designated single IRB is unable to meet the needs of specific populations; or (2) where local IRB review is required by federal, tribal or state laws or regulations.

Improving the efficiency of the system for the review, approval and oversight of research involving human subjects is a laudable goal. Efficiency issues in the pre-approval review process likely include much more than just the IRB process. There are many research focused committees, departments and offices that play a role in the pre-approval review of human subjects' research. These include, but are not limited to radiation safety, pathology, pharmacy, nursing, institutional bio-safety, billing, grants and contracts. Mandating single IRB review for domestic multi-site studies is not the appropriate solution to improve turn-around time for human subject's research.

While the use of single IRBs may be effective and efficient in some circumstances, SACHRP believes that it is premature at this time to mandate single IRB use in NIH funded domestic multi-center trials. Requiring a single IRB to review a multi-site research protocol may well, as described below, result in new procedures and policies being created by the relying institutions (those institutions relying on another institution to conduct the IRB review) and the reviewing institution (the institution responsible for serving as the single IRB of record) that will undermine the goals of this policy change and create a host of new challenges for research institutions.

Summary of Recommendations

SACHRP recommends that:

- NIH fund research evaluating the advantages and disadvantages of single IRB use in domestic IRB multi-site research;
- NIH collect and disseminate data regarding its own experience with the use of single IRBs for grants that have been mandated to use a single IRB (e.g., the NeuroNEXT multicenter trial) or for those grants where it was voluntarily utilized;
- NIH support meetings with the research community where issues regarding the use of a single IRB can be discussed in a public forum;
- NIH evaluate the cost issues and provide a proposal that would cover the cost of *both* single IRB review and local review without reducing dollars to the researcher;

- Until data is available, rather than mandating review by a single IRB, NIH find mechanisms to encourage investigators and institutions to *voluntarily* utilize single IRBs as part of their grant submissions. This could be accomplished by providing incentives such as additional dollars to those grants that agree to utilize single IRB arrangements.

Need for More Data

More data should be developed and provided to the research community prior to imposing such a requirement on U.S. research efforts. Notably, the policy only identifies one paper dating back to 2010 in support of the statement that single IRB use in multi-site studies is more cost effective¹, and that paper concerns a national central IRB, not the ceding of review by multiple institutions to another institution's IRB. Comprehensive data is needed to assess: (1) the advantages and disadvantage of single IRB review on the reviewing IRB; (2) the advantages and disadvantages of single IRB review on the relying institution; (3) the categories of research that are most appropriate for single IRB review; (4) the impact on local review concerns; and (5) the cost of a single IRB system on the various institutions.

In general, SACHRP supports the voluntary increased use of a single IRB for multi-site studies, where appropriate, as such use may, in some circumstances, decrease differences, some of which may be arbitrary and some of which may be principled, among site implementation of protocols. Data might show that this could bring about a more rapid and efficient IRB review and continuing review processes; could increase predictability for researchers, all of whom would be operating under the same approved protocol and consent documents; and could make IRB review of unanticipated problems in the course of a study more meaningful and accurate, thus potentially better protecting the welfare of subjects.

We recommend a careful and well thought-out evaluation of what has been frequently discussed as the potential benefits of a single IRB review. The NIH draft policy focuses on "efficiency" as a key reason for requiring and justifying mandatory single IRB review. However, substantial experience suggests that the IRB review contributes only modest if any to the delays between project inception and subject recruitment. Further, improved efficiency from the perspective of the study sponsor and/or investigators may entail substantial changes in institutional policies, procedures, and tools, such as software platforms. Incremental gains in one domain may create substantial costs in others.

Evaluation of Impact on Relying and Reviewing Institutions

Mandatory single IRB review could serve to create increased burdens on all institutions. Most institutions have systems that are not necessarily designed for the purpose of managing multi-site research and thus service as a central IRB would require substantial resources, increased cost and re-tooling of processes for the site that serves as the IRB of record.

A significant barrier to institutional adoption of a single IRB for multi-site research is the information technology required to ensure adequate review, communication, and oversight. Systems currently serving IRBs and institutional human research protection programs differ from one another, are complex and expensive, and are not interoperable. Institutions incur significant expense to build technical solutions customized and appropriate to the needs of their institution. Changing existing technology to incorporate communication and management of research being conducted at numerous outside sites is a considerable obstacle that has to be acknowledged and addressed.

The reviewing site will need systems to ensure on-going communication with the other sites, as well as a system for managing and tracking agreements and protocol related issues. The relying sites will have to create other processes to manage reviews that are frequently linked to the local IRB review such as management of HIPAA requirements, radiation safety, as well as budgeting among other such internal committees and departments. Investigator conflicts of interest and institutional conflicts of interest are

two significant reviews that are often tied to the IRB review because conflicts of interest may well result in IRB determinations regarding: (1) additional information that should be included in the consent; (2) additional monitoring by an independent DMC or DSMB; or (3) removal of an individual as the primary investigator of a research study.

Consideration of local and regional variations in some circumstances and for some studies will be critical to assuring the welfare of subjects in research. In addition to widely different subject populations, other factors with significant variations among sites would include:

- State laws governing human subjects and/ research data (e.g., genetic testing, genetic privacy, health information laws that go beyond HIPAA, mental health information, mental retardation and developmental disabilities information, surrogate consent, inclusion of children in research, age of majority, age of consent to certain medical treatment such as for substance abuse, investigator licensing requirements, etc.);
- “Emergency research” undertaken without subject consent, for which the FDA requires local community consultation;
- Disparate cultural norms among populations targeted for recruitment;
- Varying investigator and research team experience, which may require more or less oversight during the conduct of the research; and,
- Varying institutional policies regarding availability of compensation for subject injury.

Qualifications of the Reviewing IRB

The method of selection of a single IRB in a specific study is critical; the IRB selected should have the appropriate expertise for the research being reviewed, and the capacity to act as coordinator, receiver and dispenser of critical study-related data to the sites, their research teams, their IRBs and their institutions.

Consideration also should be given to a process for qualifying a single IRB. SACHRP has identified the following issues as points to consider for IRBs serving in a central capacity. These are only some of the numerous issues that need to be addressed:

- Adequate record keeping systems and written standard operating procedures for tracking each site independently, including the ability to manage site-specific emergency care, conflicts of interest, sub-studies, unique consent forms, subject complaints, compliance issues, and unanticipated problems;
- Process to adequately obtain knowledge of state laws where the single IRB reviews sites in other states in order to assure compliance;
- Written SOPs describing how local cultural and resource context information will be gathered, both at initial and continuing review;
- Capacity to conduct site visits, as necessary;
- Written SOPs describing how the single IRB and institutions will coordinate issues such as review by other committees (IBC, Radiation, etc.) and unique institutional policies;
- Accreditation of its human research protection program; and
- Appropriate oversight by OHRP and FDA.

Evaluation of Costs of Single IRB Review

Costs of review and legal responsibilities for monitoring research and assuring its appropriate conduct would need to be allocated among a central IRB, local sites, their local IRBs, or other designated study reviewers. A cost allocation cannot be a categorical decision to fund a single IRB but not provide resources for the local reviews.

Finally costs to support the single IRB review and the local relying institutions should not be dollars that will reduce the amount of money that would otherwise be available to conduct the research. Budgets for grants should increase where single IRB review is an integral part of the proposal and take into consideration the additional costs to both the reviewing and relying institutions.

Importance of Consistent and Uniform Reliance Agreements

Any discussion of use of a single IRB would have to include consideration of the mechanics of implementing such processes for the reviewing IRBs and the relying institutions as well as the cost incurred by both. Reliance arrangements require complex coordination and communication to manage such issues as how the single IRB would interact on an ongoing basis with local IRBs or designated ethics reviewers in regard to, for example, the emergence of risks that might be unique to a site, the local investigator or its study population, and the implementation of uniform or site-specific measures to mitigate those risks. Single IRBs in multi-site studies should be expected, as part of their initial review and approval, to establish formal written standard operating procedures for accomplishing this in an ongoing way during the course of the approved studies. Yet this may be so complicated that without careful planning and implementation, such a system coupling local review with a single IRB would, in the end, be less efficient than the current practice of each IRB performing its own separate review.

A significant challenge to single IRB systems is the development and management of inter-institutional agreements and processes. Whether single IRB review is mandated or voluntary, tools need to be provided to the research community to ensure consistent and reasonable approaches. NIH needs to evaluate and work with institutions and the larger research community to fully develop a single IRB review model that addresses the issues faced by all of the involved parties. Central IRBs are operating now in many NIH-funded and industry-sponsored studies. They can provide the data on which evaluations can be made as to issues arising regarding legal responsibility, IRB and institutional liabilities, as well as general advantages and disadvantages of such systems. Institutions that defer to one another in a central IRB process need inter-institutional agreements, by which central IRBs and institutions engaged in research can more specifically describe what each party would do in a functioning central IRB model. Without more specific guidance on these points, it would likely not be possible for the entire research community to establish template inter-institutional agreements, while issuance of such specific guidance likely would ease and speed the emergence of templates.

Evaluation of Data on Prior Experiences

Given the various complexities discussed above, it is not surprising that adopting a central IRB model, when tried, has presented some tough challenges. Anecdotally SAHRP understands that the VA has experienced difficulties in implementing a single IRB system. For example, it has been difficult to develop information technology systems across sites to track studies and study reporting, and to coordinate communication among investigators, local facilities, and the VA Central IRB members and staff. Other challenges include considering and accommodating unique local conditions and affiliation arrangements, establishing methods for collecting, analyzing and then reporting back to local sites regarding unanticipated problems, and coordinating study monitoring that is necessarily done by the VA facility sites. If these issues have occurred within the VA system, then one would expect the problems to be more serious, complex, and acute if a mandate for single IRBs for all domestic multi-site studies were simply imposed by regulation or policy.

The NCI CIRB model has itself caused delays in the review process when investigators are asked repeatedly to re-format documents; fix hyperlinks; change margins; and, institutions are not advised of how to integrate reviews such as radiation safety reviews that have a direct impact on the language contained in the research informed consent document.

SACHRP strongly maintains at this time that a uniform mandate of single IRB review for all domestic multi-site studies is premature. SACHRP instead takes the position that a more measured and careful process of *encouraging* single IRB use, accompanied in a step-wise way by issuing guidance on critical issues involved in the use of single IRB review, would result in less disruption of the research enterprise and eventual improvements in a single IRB process that is anchored in deep collective experience.

Footnotes

¹Wagner, TH, et al, Costs and Benefits of the National Cancer Institute Central Institutional Review Board J. Clin Oncol 2010; 28:662-666.