

Author's response to reviews

Title: Human Subjects Protection Issues in QUERI Implementation Research

Authors:

Edmund Chaney (chaney@u.washington.edu)
Laura G. Rabuck (Laura.Rabuck@va.gov)
Jane Uman (Jane.Uman@va.gov)
Debbie Mittman (Debbie.Mittman@va.gov)
Carol Simons (Carol.Simons@va.gov)
Barbara Simon (Barbara.Simon@va.gov)
Mona Ritchie (RitchieMonaJ@uams.edu)
Marisue Cody (Marisue.Cody@va.gov)
Lisa V Rubenstein (lisar@rand.org)

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Author's response to reviews: see over

Edmund Chaney, Ph.D.
VA Puget Sound Health Care System
Seattle Division 116MHC
1660 S Columbian Way
Seattle, WA 98108
206-764-2815
FAX 206-764-2872
edmund.chaney@med.va.gov
chaney@u.washington.edu

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Martin Eccles
Ian Graham
Series Editors
Implementation Science

Re: MS ID 2717689201122955
Title: Human Subjects Protection Issues in QUERI Implementation Research
Journal: Implementation Science
Authors: Edmund Chaney, Laura G. Rabuck, Jane Uman, Debbie Mittman, Carol Simons, Barbara Simon, Mona Ritchie, Marisue Cody and Lisa V. Rubenstein

Dear Drs. Eccles and Graham:

Thank you for the opportunity to resubmit our revised manuscript. We have attempted to address the issues that were raised by each reviewer. Below, we have included the reviewers' comments to facilitate description of our responses, noted in italics. The revised manuscript includes 5,483 words, 4 tables, 35 references, and 7 additional files.

Extensive revisions have been made to the manuscript in order to fully address the reviewer comments. It would be cumbersome to copy and paste updated text into the response letter. Instead we have cited page/s where changes are located with detailed explanation of the changes.

Thanks once again to you and the reviewers for your feedback on our manuscript. We believe firmly that the revision represents a substantial improvement over the original and we look forward to additional correspondence with you about it.

Sincerely,

Edmund Chaney, Ph.D.
Corresponding Author

Reviewer 1's Comments (Richard Ashcroft)

Major Compulsory Revisions

None

Minor Essential Revisions

None

Discretionary Revisions

None

Reviewer 2's Comments (Lee Green)

Major Compulsory Revisions

The section "Learning to Communicate Implementation Specific Issues" is potentially very valuable, but unsatisfying in its present form due to its generality bordering upon vagueness. A concrete example (with identifying information removed, of course) involving interacting with two very different IRBs around the same project would help greatly.

This section no longer exists because the paper has been re-structured to comply with the Editor's comments. In general, we reviewed each new section and added concrete examples where possible. Examples can be found in the following pages of the text:

- *Pages 10-11: Section 1. Implementation Specific Issues b. Plan – Do – Study – Act (PDSA) Intervention Adaptation Cycles*
- *Pages 12 -13: Section 1. Implementation Specific Issues c. Risk Benefit Issues*
- *Pages 14-15: Section 1. Implementation Specific Issues d. Multiple Roles of Researchers/Facilitators & Multiple Subject/Participant Classes*
- *Page 16: Section 2. Multiple Health Care Systems/Sites a. Transparency of System/Researcher Ethical Responsibilities*
- *Page 21: Section 4 .Multiple IRBs b. Communications with IRB and R&D Administrators*
- *Page 23: Section 4 .Multiple IRBs d. Variable Adverse Event (AE) Definitions & Reporting Requirements*

The "Tools and Solutions" section to the "Local Differences" issue is also much too brief and general.

The "Tools and Solutions" section and "Local Differences" issue no longer exists. Tools, termed process aides, are now discussed in the context of the issues they are intended to aid.

Minor Essential Revisions

There are a few places where copyediting is needed; I have eschewed copyediting at present however.

We have thoroughly edited the manuscript for copyediting errors.

Discretionary Revisions

For a recent pertinent reference that involved the VA system, the authors may wish to consider: Green LA, Wyszewianski L, Kowalski C, Lowrey J. Impact of Institutional Review Board Practice Variation on Observational Health Services Research. *Health Serv Res* 41(1): 214-30, 2006.

We have included this reference (#20) on page 6 in the manuscript.

Reviewer 3's Comments (Martin Eccles and Ian Graham)

Major Compulsory Revisions

Throughout the article it would be helpful if you could think about the issues that are specific to implementation research (lack of IRB understanding) and those that are specific to your IRB system (workload from multiple IRBs). This will allow the reader to place what you describe within their own national context. You use such a structure in Table 2 but not in the text or as a framework for the background, experiences or discussion. Table 2 offers a helpful structure to guide the reader through the paper and I would suggest that you use a common structure for both the text and Table.

Due to restructuring of the paper and the addition of the QUERI table, Table 2 is now Table 3. In compliance with the Editor's comments, we restructured the entire manuscript to align with Table 3, and used headers from Table 3 to introduce new sections of the manuscript. These changes can be found on pages 8-24 of the manuscript.

Throughout you tend to assert that your studies are typical of all implementation research – the examples of PSDA cycles and being unable to foresee all changes. You should, as appropriate link the issues back to your studies as there are studies of other interventions where the intervention is much more stable.

We have referenced our studies directly, so not to confuse readers. The changes relevant to PSDA cycles can be found on pages 9-11 Section 1. Implementation Specific Issues b. Plan – Do – Study – Act (PSDA) Intervention Adaptation Cycles

Prior to the section “THE IRB EXPERIENCE FOR TIDES-RELATED PROJECTS” it would be helpful for the reader if you could include two sections. The first should describe the principles of the IRB process that you had to contend with. This would be informative because it has influenced some (but not all) of the issues that you faced. Implementation Science has an international readership and other countries have different systems which would reduce some of the problems you faced. For example in the UK whilst there are local ethics committees that deal with research proposals conducted solely on their site, there are also Multiple Site Research Ethics Committees (operating through a central web-based system) set up to deal with studies that need to enroll three or more sites. What is the IRB system? Does each institution have its own IRB or is there a regional one? Do they need a university IRB as well?

We have added this information to the Methods section (pages 7-8) and have provided the manuscript material below.

“In 2001, we began a series of interrelated studies on implementing evidence based collaborative care for depression in VA primary care known by the acronyms TIDES, WAVES, and COVES for the initial studies and ReTIDES for the subsequent

regional rollout (Table 2). Our VA-funded multi-site projects required a two-step approach to obtain necessary IRB approval. Because our projects represent collaboration among four regional health services research centers with Principal or Co-Principal Investigators at each of these sites, protocols had to be approved by their respective IRBs on the basis of Investigator involvement. Then each local Site Principal Investigator (PI) participating in the implementation research submitted the protocol to their IRB with our assistance. The sites we work with are either covered by their own resident VA IRB or an affiliated University IRB. We have submitted a combined total of over 100 IRB applications, amendments, and renewals in the past six years for these four projects and in doing so have interacted with six resident VA IRBs and seven contractually affiliated University IRBs across the United States.

In Table 3, we present the four overarching IRB-related themes encountered throughout the implementation of our projects, including items specific to implementation research, operating within multiple health care systems/sites, coordinating with multiple local Site PIs, and managing differences among multiple IRBs. Within each issue, we identify key challenges and suggest approaches that have proven useful and may aid other researchers. Where applicable, we showcase process aids developed to assist in resolving a particular IRB challenge. These range from process guidelines through examples of explanatory material to a relational tracking database. Table 3 provides the structure and order for the paper. Many of these themes and challenges are interrelated and may overlap and/or complement each other among sections. As always, IRB review is a dynamic process that continues to change over time as new controversies present themselves and issues that were at one time problematic become routine both within individual IRBs and in the field of human subjects protection.”

The second should detail the overall activity from which your experiences are drawn. You begin to talk about these data on page 11 linked to Table 3 but it would be useful to the reader to have had the information earlier to inform their reading of the rest of the paper.

Due to restructuring of the paper and the addition of the QUERI table, Table 3 is now Table 4. The information specific to Table 4 can be found in the following paragraphs from pages 12 and 13 and is pasted below.

- *Page 12- “We have had some success in using an opinion letter process as an initial step in the application process. For example, one IRB (Table 4, Site I) considered a protocol to fall under Quality Improvement and be classified as “non-human” research not requiring IRB review. However, for the same protocol, another site required a full submission. Given the societal health benefits likely to be associated with researcher involvement with clinical systems and practices, and the known risks of poor quality care, the ethical issues of adding burden to the process of improving care should be considered in these determinations [32, 33].”*
- *Page 13-“Some systems provide expedited review for research judged to be minimal risk. For example, our protocols include evaluation through surveys, medical record reviews, and stakeholder interviews. However, these multiple activities may result in complex IRB decision-making and risk to the implementation activity timeline if after initial review the IRB decides that the study is inappropriate for expedited review and the study must be transferred to*

the full review mechanism. For example, one site (Table 4, IRB C) stated, “If the survey was the only thing that came to the IRB board, it could have been exempt or if the chart data had come to the IRB separately, it too, could have been expedited. But because it came all together, it would be hard to expedite it as a whole with all the different components presented.”

A description of the overall activities of our projects can be found in the methods section that has been pasted in to the response to the previous question (page 8).

A discussion of the differing role of implementation researcher from clinical (more detached) researcher (including the mixing of the role of implementation researcher and facilitator) could be expanded and linked back to the QUERI steps and phases and the different roles of implementation researchers throughout the framework.

This can be found under Multiple Roles of Researchers/Facilitators Section 1.d. page 13 & 14 and has been inserted below.

“Sometimes it is not the implementation research practice itself that is the risk, but ill-defined relationships among researchers and the system with which they are working that may add risk. Implementation researchers may best be understood as facilitators or consultants within their research projects, with no direct decision making authority in the intervention. Within our projects, researchers were available as consultants to local site champions who provided leadership for customizing and adapting the intervention to the sites. Researchers also functioned as consultants at the national level to encourage national rollout of improved depression care. These different roles (and risks) need to be clearly communicated with administrators and IRBs. For example, because our projects involved depression treatment, it was important to establish suicidality risk response protocols specifying activities of researchers and clinicians of which all parties were aware.

Subjects, more appropriately called “participants,” in implementation research have different relationships with researchers depending on their relationship to the health care system in which the implementation takes place. Participants may include providers, regional and/or medical center leadership, and/or patients. Patients, for example, may not encounter researchers, but have specific aspects of their medical records examined for evidence that is relevant to the implementation. Providers are crucial in the success of clinical improvement efforts, however their role as a “subject” must be carefully considered. If they see themselves as subjects from whom consent is required for their participation, their buy-in and interest in sustaining the improvement after the investigative phase is over is likely to be vitiated. All classes of participants or their representatives may be involved as decision makers in the specifics of the implementation. For example, our project start up meetings often included Nurse Depression Care Managers, Primary Care Physicians, Mental Health Practitioners, leadership/management personnel, and patient representatives. Clearly defining these different roles and the risk appropriate to each will enable the IRB to make an informed decision.”

Many of the IRB issues relate specifically to action research methodology (the researcher becoming a facilitator) as opposed to other implementation research generally (i.e. trials of effectiveness of different implementation/KT interventions) and this might be highlighted.

The intent of the paper reorganization has been to present issues like this one that apply to some but not all implementation research in a manner that assists the reader to decide whether the particular section is relevant to their concerns. We hope we have achieved this.

In the discussion, when you discuss the RE-AIM framework could you define the components at the start of the section, capitalize them when you are describing them and don't use underlining.

The section on the Stetler Model and the RE-AIM framework has been moved to Implementation Specific Issues a. External Validity Consideration on page 9. See below.

“Most IRBs tend to be much more familiar with the rationales for biomedical research procedures than with those for implementation research. Two conceptual models can be helpful in providing clear explanations for specific aspects of implementation research that promote external validity and also bear on human subjects' protection issues, the Stetler model of Research Utilization [26, 27] and the RE-AIM framework [28-30]. The models can be incorporated in IRB applications by researchers as appropriate to inform their interactions with IRBs, as they describe external validity considerations. While these frameworks came to our attention after we had put much thought into our approach to IRB issues, they may be helpful to other researchers. These two models are presented briefly in additional file 1: Implementation Evaluation Theory: Stetler Model of Research Utilization and RE-AIM.”

The extensive descriptions of both models have become additional file 1: Implementation Evaluation Theory: Stetler Model of Research Utilization and RE-AIM. We have defined the components of the RE-AIM framework at the start of the section in Additional File 1, and capitalized as requested.

In the discussion, given that you are writing for an international audience the final part of the discussion is less relevant and could be usefully be deleted.

We have reworked the discussion (found below and on pages24-25 of the manuscript) to apply to broader, international audience.

“Specific aspects of implementation research interact with variations in knowledge, procedures and regulatory interpretations across IRBs to impact the study of best methods to increase evidence-based practice. Through lack of unambiguous guidelines and local liability concerns, IRBs are at risk of applying both variable and inappropriate or unnecessary standards to implementation research that are not consistent with the spirit of the Belmont Report, a summary of the three basic ethical principles identified by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, and impede the conduct of evidence-based quality improvement research. However, there are promising developments in the IRB community. For instance, in November 2005, the Office for Human Research Protections (OHRP) sponsored a workshop on alternative models for IRB review, including Centralized IRBs, with a follow-up conference in 2006 [34, 35]. Efforts to accredit IRBs may increase uniformity and the IRB's ability to be a full partner in improving care. In the meantime, it is incumbent upon implementation researchers to interact with IRBs in a manner that assists appropriate risk/benefit determinations and

helps prevent the process from having a negative impact on efforts to reduce the lag in implementing best practices.”

Minor Essential Revisions

None

Discretionary Revisions

None