Appendix 5. IRB Protocol and Approval Letter

PARTNERS HEALTHCARE
FOUNDED BY BRIGHAM AND WOMEN'S HOSPITAL AND MASSACHUSETTS GENERAL HOSPITAL

Partners Human Research Committee
116 Huntington Avenue, Suite 1002
Boston, MA 02116
Tel: (617) 424-4100
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Initial Review: Notification of IRB Exemption
Protocol #: 2015P001946/BWH

Date: September 28, 2015

To: Joel Weissman, Ph.D
BWH
Surgery / General Surgery (General and GI)

From: Partners Human Research Committee
116 Huntington Avenue, Suite 1002
Boston, MA 02116

Title of Protocol:	Research Ethics in Patient-Centered Outcomes Research
Sponsor/Funding Support:	Patient Centered Outcomes Research Institute
IRB Review Type:	Expedited
IRB Review Date:	9/28/2015
IRB Review Action:	Exempt

The IRB has determined that this project meets the criteria for exemption 45 CFR 46.101(b) (3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior that is not exempt under paragraph (b) (2) of this section, if (i) The human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally information will be maintained throughout the research and thereafter.

Continuing review is not required.

Exempt survey/interview study

As Principal Investigator, you are responsible for the following:

1. Ensuring that this project is conducted in compliance with the exemption determination.
2. Ensuring that all study staff have completed the required human research education requirements through the Collaborative Institutional Training Initiative (CITI).
3. Submission of significant proposed changes to this project to ensure that the project continues to meet the criteria for exemption.

Questions related to this project may be directed to Fausta M Figueroa, FFIGUEROA@PARTNERS.ORG, 617-424-4119.

CC: Avni Gupta, BWH - Surgery - Surgery and Public Health, Research Coordinator/Manager

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PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR
Dr. Joel Weissman, PhD

PROTOCOL TITLE
Research Ethics in Patient-Centered Outcomes Research

FUNDING
Patient-Centered Outcomes Research Institute (PCORI)

VERSION DATE
12/29/2016

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

Hypothesis:

PCOR/CER research may pose certain novel ethical challenges that are relevant to the IRB oversight and human subject protections. IRBs may need support to resolve those issues; and PCOR/CER investigators and patient advisors may need guidance to design and conduct their projects in an ethically responsible manner.

Objectives:

The overall goals of this study are to understand the regulatory oversight challenges posed by PCOR and CER and to develop guidelines, policy and recommendations to address those challenges.

The specific aims of this research are:

Aim 1. Describe the human subject-related challenges posed by PCOR and CER and learn how, if at all, IRBs in major research institutions are responding to those challenges.

Aim 2. Develop guidelines and recommendations for IRBs, investigators, and patient advisors to employ when designing or reviewing human subject research aspects of PCOR and CER.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

BACKGROUND:

Human subjects research must be governed by ethical principles in order to be conducted in a responsible manner. In the US, these principles, as delineated in the Belmont Report, have been implemented through regulation, policies, and guidance intended to protect the rights, safety and well - being of research participants, and to ensure the integrity of the research process. However, existing regulations such as the Common Rule paint policy in broad brush strokes, often leaving the appropriateness of specific practices open to interpretation by investigators, sponsors, and institutional review boards (IRBs). The absence of specific guidance could lead in some situations to widely divergent practices and controversy.

There is a substantial gap in evidence regarding what novel challenges PCOR/CER pose that are relevant to IRB oversight and human subjects protections; specifically it is unclear to what extent those issues are ethically relevant beyond their potential to hinder the efficient and robust generation of as much patient-centered and comparative data as possible – data that is essential to helping patients and their caregivers make the best decisions.

Research is therefore warranted to identify the challenges to ethical oversight of PCOR/CER and to promote evidence-based policy development to guide IRB processes. Resolving that question is essential to understanding whether there is a methodological gap in how we plan for, review, and conduct PCOR/CER to account for ethical oversight concerns, and if so, which methodological approaches should be tested, analyzed, and implemented. We will engage with IRBs, investigators, patients, and other stakeholders to better understand the practical realities of PCOR/CER: what are the barriers, ethical decision points, regulatory challenges, and outstanding questions calling for resolution?

SIGNIFICANCE:

This project will generate evidence as to what unique issues arise in PCOR/CER research, if any; what support IRBs may need to resolve those issues; and what guidance PCOR/CER investigators and patient advisors need to design and conduct their projects in an ethically responsible manner. Once we have collected our evidence, we will develop appropriately

responsive guidelines and recommendations, based on a rigorous ethical analysis and set of principles.

Development of evidence based policies to guide investigators, sponsors, institutions and IRBs in the conduct and review of PCOR/CER would likely reduce unnecessary variation in oversight practices, which has the potential to negatively impact research and the application of research results to patient care. Moreover, it will also improve protection of human subjects who participate in this socially valuable research. Our proposed research is intended to establish a foundation for such evidence-based policy development.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

Given the exploratory nature of the proposed research, we will employ a mixed methods approach. We will use qualitative methods (focus groups, individual interviews and case studies of research intensive institutions) to gather knowledge from IRB members and chairs, senior IRB administrators, human subjects thought leaders, and patient research partners, to understand the complex structures of IRBs, the behaviors of IRB members, and the research environments in which they exist.
We will use quantitative methods (a cross-sectional survey of IRB chairs in major research institutions) to gauge IRB policies and understand their perspectives on the challenges they face in overseeing PCOR and CER.
And we will use a Delphi consensus approach to develop a set of policy recommendations related to ethical regulation of PCOR and CER.

Anticipated Enrollment:-

A) **Focus groups**: 48 to 72 people
6 focus groups of 8-12 members each.

Following are the 6 groups with whom we will conduct focus groups:

1. IRB chairs and administrators/directors selected from among the PRIM&R (Public Responsibility in Medicine and Research) members
2. IRB members selected from among the PRIM&R members
3. PCORI investigators selected from the list of PCORI funded investigators and other PCOR/CER investigators selected from

among the senior authors identified through literature search of PCOR and CER publications
4. PCORI investigators selected from the list of PCORI funded investigators and other PCOR/CER investigators selected from among the senior authors identified through literature search of PCOR and CER publications
5. Patients from among the members of the Patient and Family Councils (PFACs)
6. Patients from another city and institute identified through contacts provided by stakeholder panel.

B) Individual interviews: 20 people

20 interviewees will be identified from among the thought leaders from our stakeholder panel, PCOR/CER investigators, Patient-Family Advisory Council advisors, and others (e.g., research ethicists).

C) Case Studies: 24 to 30 people

3 case studies with 8-10 individual interviews at each site
1 Public Health School, 1 Medical School and 1 independent research hospital will be selected for case studies.

Interview subjects will include the IRB chair(s), IRB members, a patient representative if one exists, investigators identified as doing PCOR or CER, and an executive from research management (e.g., a senior IRB administrator). We also will attempt to interview project directors who are responsible for submitting the protocols. We will conduct other interviews as appropriate based on the snowball method of qualitative sampling. For example, we will ask our case study contact to suggest other possible interviewees, e.g., persons at the institutional level who deal with Grants and Contracts.

D) Survey: Upto 500 people

Upto 500 chairs of IRBs registered with the Office for Human Research Protections (OHRP) at the Department of Health and Human Services will be identified from the 100 most research intensive medical schools, 15 most research intensive independent teaching hospitals, and 40 most research intensive schools of public health in the US.

E) Delphi Panel: 30 people

30 people will be selected from selected members of our stakeholder panel, PCOR/CER researchers, patient investigators, ethics experts, IRB members, and other thought leaders identified in the project up to the point we conduct Delphi Panel.

General Inclusion criteria for all subjects: English speaking.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

A) Focus Groups:

Purpose: The focus groups will serve several purposes: 1) to gather qualitative data about our topic of interest (IRB oversight challenges for PCOR/CER), in a setting that allows the investigators to test existing ideas based on the focus group participants' own words, thus avoiding technical jargon, misunderstanding, or missing elements which could occur in more structured methods like surveys; 2) to develop hypotheses and survey domains for further data collection; and 3) to test potential survey items (wording).

Plan: Altogether, we will conduct 6 focus group sessions of 8-12 members each. We will conduct separate focus groups of IRB members, IRB chairs and administrators, PCORI investigators, other PCOR/CER investigators, and two patient groups, in order to ensure that all concerns that could impact the research ethics issues are addressed. Each of these groups represents important stakeholders in the IRB oversight process.

Conduct: The PI (Dr. Weissman) will co-lead the focus groups with at least one of the other investigators. Focus Groups will be audio recorded as a back up to extensive notes. The focus group with investigators will also be video recorded as we will conduct it online to ensure that we can have a nationally representative sample of investigators.

Content: Focus Group Content and Domains will draw from the literature as well as consultation with patient research partners and members of our stake- holder panel. The actual focus group questions will be developed by Dr. Weissman and the rest of the members of the study team. We expect the questions and prompts for all or our qualitative pieces will evolve over time.
We will have different focus group discussion guides for IRB Chairs, IRB members, 2 groups of investigators and 2 groups of patients. They will be submitted to the Partners IRB for review and approval before being used.

B) Individual Interviews:

Purpose: Individual interviews are particularly useful for gathering the perceptions of thought leaders and those struggling with the practical

realities of these reviews, who will have opinions to lend, as well as others who are unwilling or unable to join group interviews.

Plan: We will conduct approximately 20 semi-structured interviews with thought leaders from our stakeholder panel, PCOR/CER investigators, Patient-Family Advisory Council advisors, and others (e.g., research ethicists). A number we anticipate would be sufficient to reach saturation on relevant issues using the standardized qualitative methodology described below. We will make every attempt to obtain broad representation from different institutions, geographic location, and socio- demographic characteristics.

Conduct: Interviews will be facilitated by one or more investigators from the research team. Focus Groups will be audio recorded as a back up to extensive notes.

Content: The individual interview guide is attached with the application.

C) Case Studies:

Purpose: Case study research allows us to select a limited number of units representing the phenomenon to be studied and to examine the characteristics of those cases intensively. By comparing and contrasting cases, we can identify complex processes and relationships. The case studies will describe the perceptions, barriers, and facilitators to the review and oversight of PCOR and CER. The goal is to understand complex IRB behaviors in situ that would not be possible with a structured survey instrument. The advantage of the case studies over the focus groups is that we can dig deeper into the specific culture of the selected organizations to understand the context in which IRB review and oversight occurs.

Plan: We will conduct 3 case studies in major academic institutions, one in a medical school, one in a school of public health, and one in a research intensive independent hospital.

Conduct: Three members from the project team will visit each site. We expect to conduct approximately 8-10 interviews at each site. If a key participant is not available on the day of the visit due to scheduling difficulties, we will interview that person by phone. Interviews will be audio recorded to ensure accuracy and will be used as back-up to extensive notes. In addition to the interviews, site observation notes will be taken and the copies of important relevant documents for the IRB review process' policies and guidelines will be collected from each site.

Content: Development of the interview protocol will build upon focus groups, our conceptual framework, what is already known in the peer-reviewed and grey literature, as well as issues raised by the stakeholder panel. From this review we will identify specific domains of interest such as IRB chairs' and members' experiences, investigator experiences and institutional policies. Within each domain, we will explore examples of the unique human subjects related challenges associated with CER and PCOR research. For example, in the domain of IRB member experiences we will interview IRB members about the challenges they have experienced with review of PCOR and CER research, including definition of patient roles, and privacy concerns from data intensive projects.

After the interview guides are developed they will be submitted to the Partners IRB for review and approval before being used.

D) Surveys:

Purpose: One of the major sources of data for fulfilling the aims of this study is a mailed survey of a random sample of IRBs chairs at research intensive medical schools, teaching hospitals, and schools of public health.

Plan: We will mail survey questionnaire to upto 500 IRB chairs from research intensive institutions. We have planned for a survey instrument that should take no more than 15-20 minutes complete.

Conduct and Content: Instrument Development will be done in three phases.

Phase 1 (Content/Domains) - In Phase I, we will develop survey domains and potential questions within those domains. We will use a literature review and findings from the focus groups, individual interviews, case studies, and stakeholders and patient advisors, to direct the development of a draft instrument. We will ensure standardized survey response as described in the literature: (1) avoiding complex skip patterns; (2) having clear response categories, (3) preventing bias. We will not however, seek to ensure a grade school literacy level given the highly educated sample. The questionnaire will consist of closed ended questions but will contain up to 6 "other specify" responses and 1 open ended question. As an additional step, we will evaluate the survey questions using question appraisal methods in order to find and fix problems of clarity, respondent burden, and so on. Finally, before the questions "go into the field", we will finalize the instrument draft – including formulating

new questions based on cognitive interviews (see below), identifying relevant issues, question flow, and survey length.

In addition to the domains described in the section on focus groups, the final questionnaire will collect characteristics of the IRB, e.g., volume of PCOR/CER, and personal characteristics of IRB chairs, including respondents' gender, race/ethnicity, age, experience(s) as a research subject and the experiences of family and friends as a subject(s).

Phase 2 (Cognitive interviews and field pre-testing) - Phase 2 will involve cognitive interviews, which are a form of pre-testing where we ask a sample of likely respondents how they understood the questions we asked and compare their responses to the intent of the questions in order to identify any issues with formatting, comprehension, and acceptability. Nielsen (the survey firm) and/or the PI, Joel Weissman will recruit 8 IRB chairs from the survey sample (see above) or from members of PRIM&R by purposefully contacting the IRB chairs or ex-IRB chairs directly to invite them; and will conduct 30-minute cognitive interviews (via telephone). Prior to the interview, respondents will be sent the questionnaire and asked to complete it and return it to Nielsen. During the interview, select survey question will be reviewed and a series of related follow-up questions will be asked. The follow up questions will be designed to elicit respondents' understanding of the underlying concepts. The results of these interviews will ensure that the survey items are comprehended in a standard way, and as free from bias as possible.

Phase 3 (Pre-test) - In phase 3, after the cognitive interviews and prior to mailing questionnaire packets to the full sample, Nielsen will mail 10 questionnaire packets. The purpose of the pre-test mailing is to ensure that respondents receive the packets and that the completed questionnaires are sent to the correct address. (Please note that the pre-test will consist of only 1 postal contact, so it will not be possible to assess the response rate we may achieve at the end of the study. We anticipate we will receive 6-8 completed surveys from the pre-test.)

The pre-test packet will consist of the Questionnaire packet, sent via priority mail, containing a cover letter (with fact sheet) explaining the nature of the survey and unique URL so that respondents can complete the survey online if preferred; $25 cash incentive; 8-page questionnaire booklet with a unique identifier printed on the back; Postage-paid return envelope.
To obtain a high response rate, we anticipate mailing upto 500 questionnaire packets to potential respondents. Up to three postal

contacts per respondent will be made. We will make follow-up phone calls to non-respondents after first and second mail contacts. Our definition for non-response will be about 2 weeks. After the first mail contact (we will have an option of taking the survey electronically by providing a URL in the mailed survey cover letter), we will begin to make follow-up phone calls to all non-responders (from whom we have not received the mail or the electronic survey back in about 2 weeks). We will make 6 attempts per person (only to non-responders from 1st mail contact). To maximize response, we also plan to follow-up via emails. Email to follow-up will only be done for those Non-responders whom we are not able to reach via phone after the 6 attempts and those whose voicemail says to send email instead of calling. They will only be sent email if during anytime they have not called/emailed back to indicate that they do not want to be contacted again. We will do 2 email contacts at a gap of about 3-7 days, i.e if we do not get reply back/returned phone call back in mean time, we will send another email after about 3-7 days. In both the situations- when we are not able to reach out to the person in 6 attempts and when we are able to reach out and they indicate sending the survey again, we will send another mail which will be our second mail contact. If someone indicates being emailed the survey URL, we will ask their email and forward them only the link to survey and not mail. If during anytime they call/email back to indicate that they do not want to be contacted again, no further contact will be made through any mode. After the 2nd mail contact, we will make another set of follow-up calls (6 calls/person) to the non-responders from 2nd mail contact (i.e we will call people from whom we have not received the mail back or have not received the electronic survey back in about 2 weeks after the second mail contact). If they indicate that survey should be emailed, we will email the URL for the survey. To maximize response, we will also follow-up via emails. Email to follow-up will only be done for those Non-responders from 2nd mail contact that we are not able to reach via phone after the 6 attempts and those whose voicemail says to send email instead of calling. They will only be sent email if during anytime they have not called/emailed back to indicate that they do not want to be contacted again. We will do 2 email contacts at a gap of about 3-7 days, i.e if we do not get reply back/returned phone call back in mean time, we will send another email after about 3-7 days. In both the situations- when we are not able to reach out to the person in 6 attempts and when we are able to reach out and they indicate sending the survey again, we will send another mail which will be our third mail contact.

Third mail contact will be the final contact. We will not make any further phone call or mail any further beyond these attempts. If someone indicates their unwillingness to participate at any point, they will not be contacted again either through mail or phone. We have

determined from our focus groups and case studies (as well as from our stakeholder panel) that we will keep the survey non-anonymous but confidential. We have decided to keep it non anonymous and we will ensure confidentiality of the data and confidential tracking of all non-responders. All packet mailings will be sent via USPS priority mail.

The final survey questionnaire is being submitted with this amendment to the Partners IRB for review and approval before being used.

E) Delphi Panel:

Purpose: The Delphi technique is a consensus method used to collect expert opinion systematically It has been used widely in healthcare research to set priorities and develop practices when obtaining high level scientific evidence is impractical. The technique provides a transparent and rigorous basis for assessing expert opinion, and involves asking a panel to take part in a series of rounds to identify, clarify, and refine thinking around particular topics. We will use a modified Delphi approach, which limits the number of rating rounds and relies to some extent on anonymity, feedback, and replication, so that individuals can express their opinion without being unduly influenced by others. Our goal will be to engage as many stakeholders as is practicably feasible, being sure to avoid a bias in the group by selecting participants that are diverse geographically, professionally, and socio-demographically.

Plan: We will send emails to invited participants and ask them to suggest other participants. The participants in this modified Delphi process will include up to 30 people, including selected members of our stakeholder panel, PCOR/CER researchers, patient investigators, ethics experts, IRB members, and other thought leaders identified up to that point in the project.

Conduct and Content: The process will consist of the following steps. Prior to convening the group, project staff will prepare a current literature review and a summary of the empirical work from this project (qualitative and quantitative results). Following this, we will hold four rounds: Round 1 - Participants will review a draft list of candidate recommendations and guidelines, comment on them, and suggest others to add to the list (2 week turnaround); Round 2 - Participants will rate each item on the list (2 weeks). The traditional 9 point scale will be used, where 1 = not important and 9 = most important. Results will be tabulated and distributed to all participants, with their own votes indicated so that they can determine where they fall with respect to other voters; Round 3 – a conference will be held, with some participants attending in person and others participating in a webinar. A webinar Delphi round has successfully been implemented

by RAND in other projects. Round 4 – approximately 4 weeks later, we will hold a Concluding Conference Call to give participants an opportunity to discuss the results of the webinar, and to offer ideas for dissemination or for additional research.

Round 3 and Round 4 discussions will be audio recorded as a back up to extensive notes.

All the documents that will be developed to share with Delphi panel participants will be submitted to the IRB for review and approval before being used.

F) Symposium

Purpose and Content: Toward the end of Year 3, we will hold a public symposium, co-hosted by the Law School and the Medical School, to launch our white paper and recommendations, which will be important as a communication and education tool. The symposium will take place at Harvard Law School over the course of one day, and will feature presentations of the empirical findings from the project, the ultimate recommendations, and collaborative thinking about next steps to improve dissemination and implementation of those recommendations.

Plan and Conduct: We anticipate that invitees/attendees will include: IRB chairs and members nationwide, as well as appropriate institutional officials; PCOR/CER investigators; patient groups; and other stakeholders, ideally including regulators and funders. We also plan to engage with Public Responsibility in Medicine and Research (PRIM&R), a leading human subjects research protection and IRB training organization, for this event. The Petrie-Flom Center hosts major public conferences on a routine basis, including a two-day conference in 2012 on human subjects research regulation. Because attendees at the symposium will not be selected in advance, we do not expect to change our findings or recommendations, but the event will be recorded and posted online for the benefit of further education, discussion, and dissemination.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

No laboratory tests, clinical interventions or use of medical records are included in this study. There are no expected physical risks to the study participants. There may be some risk of psychological discomfort (i.e.,

cognitive dissonance) if the survey brings to light inconsistencies in subjects' beliefs/value structure and their actual behavior. This is a risk that cannot be avoided when soliciting data regarding human behavior. In order to minimize this risk we will encourage participants to skip any question that that they find uncomfortable.

This study does not involve direct treatment or diagnosis. It involves gathering knowledge from IRB members and chairs, senior IRB administrators, human subjects thought leaders, and patient research partners, to understand the complex structures of IRBs, the behaviors of IRB members, and the research environments in which they exist.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

There are minimal risks in relation to this study. The only risk could be the risk to the rights and welfare of the subjects through disclosure of data. However, we will use following robust technical safeguards for our data throughout the project to ensure that no incidence of data disclosure occurs.

A) Focus groups: Focus groups will be audio recorded and that with investigators will also be video recorded, and extensive notes will be taken. As we aim to ensure broad representation of the groups in terms of their age, gender, race/ethnicity, geographical region and institution, we will collect these details from prospective participants. To achieve aims of the study we will also need to record names of the participants because we want to understand perspectives of people with different institutional representation and names will help us track the participant's institution. Audio recordings will be downloaded, and will be deleted from the audio recording device. All the data will be stored only in secure password protected computers managed by partners' healthcare security protocols at partner's site. No identifiable survey data will be stored on personal computers or any other device outside of BWH. Notes from focus groups will be stored in locked file cabinets. Only the research team will have access to the data. The data will be stored with the research team for a maximum of three years after completion of study.

B) Individual interviews: Interviews will be audio recorded and extensive notes will be taken. As we aim to ensure broad representation of the interviewees in terms of their age, gender, race/ethnicity, geographical region and institution, we will collect these details from participants. To achieve aims of the study we will

also need to record names of the participants because we want to understand different perspectives of people with varying roles and responsibilities and names will help us track these details of the participants. Audio recordings will be downloaded, and will be deleted from the audio recording device. All the data will be stored only in secure password protected computers managed by partners healthcare security protocols at partner's site. No identifiable survey data will be stored on personal computers or any other device outside of BWH. Notes will be stored in locked file cabinets. Only the research team will have access to the data. The data will be stored with the research team for a maximum of three years after completion of study.

C) Case Studies: Data from case studies will involve notes and audios from interviews, participant observation notes and copies of texts collected from the site. Audio recordings will be downloaded, and will be deleted from the audio recording device. All the data will be stored only in secure password protected computers managed by partners' healthcare security protocols at partner's site. No identifiable survey data will be stored on personal computers or any other device outside of BWH. Notes will be stored in locked file cabinets. Only the research team will have access to the data. The data will be stored with the research team for a maximum of three years after completion of study.

D) Survey: Final questionnaire will collect characteristics of the IRB, e.g., volume of PCOR/CER, and personal characteristics of IRB chairs, including respondents' gender, race/ethnicity, age, experience(s) as a research subject and the experiences of family and friends as a subject(s) We will keep all personally identifiable information including paper survey documents and sampling lists stored in secure environments. Mailed survey responses received from participants will be stored in locked file cabinets until the data is transferred to computers. Electronic data will be stored on secure computers protected by the Partners healthcare security protocols. No identifiable survey data will be stored on personal computers or any other device outside of BWH. Only the research team will have access to the data. The data will be stored with the research team for a maximum of three years after completion of study

E) Delphi Panel: As we aim to ensure broad representation of the interviewees in terms of their age, gender, race/ethnicity, geographical region and institution, we will collect these details from participants. Round 3 and 4 discussions will be audio recorded

and notes will be taken. All documents developed and data collected will be stored in secure environments. Audio recordings will be downloaded, and will be deleted from the audio recording device. All the data will be stored only in secure password protected computers managed by partners' healthcare security protocols at partner's site. No identifiable survey data will be stored on personal computers or any other device outside of BWH. Notes will be stored in locked file cabinets. Only the research team will have access to the data. The data will be stored with the research team for a maximum of three years after completion of study.

All data will be used entirely within Partners laptop and desktop computer systems on the Partners network, where appropriate technical safeguards (including authentication, security and virus protection) are in place. We will work with IS and RICS to ensure that any locations where data are stored are secure such as Shared File Areas (SFA). Only study personnel will have access to the project SFA. All information from individuals or entities in the course of this study that identifies an individual or entity will be treated as confidential. The importance of confidentiality will be stressed to all members of the study team. We will make each subject aware of our efforts to maintain confidentiality. Specifically, we will inform them of how identifiable data will be kept confidential, accessible only to study staff and used only for study purposes.

There are no physical risks to the participants in this study.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

The principal investigator will oversee the conduct of all study activities. Any incidents or concerns at any stage of research project will be immediately addressed by the research staff.

Our study involves 3 patient advisors as part of the research team because we are addressing issues that affect patients who participate as investigators in PCOR/CER research. The insights of our patient advisors will be particularly important to address the distinction between patient research partners pursuing scientific inquiry vs patients participating as research subjects within a scientific study. We need to learn more about what roles they play as researchers, including access to identifiable data, as well as their views as patients around the privacy and consent issues that arise around the use of medical records for research. Study will ensure that their rights as investigators are well protected and their voices are treated equal to other investigators by ensuring their participation in the project meetings

and giving equal weight to their suggestions as well as feedback. Our patient advisors are members of the PFAC and are actively involved in other research projects. They have experience in the development, interpretation and dissemination of prior PCORI research, and also represent minority community views.

The patient advisors and stakeholders are key contributors to this work and they will be invited to attend the regular co-investigator meetings. These meetings will provide all stakeholders an opportunity to receive updates and provide input. At least one of these meetings annually will occur in person (rather than by call) permitting all stakeholders with an opportunity to interact with each other and the team more intensively than is possible over the phone and to suggest enhancements in study protocols.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

The only foreseeable risk associated with participation in this research would be the effects of an unforeseen and unintentional breach of confidentiality of data. However, this event is highly unlikely as we will employ stringent data protection measures as mentioned above.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

This study will provide the first empirical data on the nature, extent and approaches of the human subject-related issues related to research ethics in PCOR/CER. While there will be virtually no risks to subjects, there will not be any direct benefit to the subjects for participating in this study. However, the results of this study may assist institutions, individual IRBs, investigators, and patient research partners in the development of new policies and procedures to manage the regulatory and ethical aspects associated with the review and approval of PCOR/CER.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children,

and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

The subjects for this study will be a) members and chairs of IRBs at medical schools, teaching hospitals and schools of public health registered with the Office of Human Research Protection at the Department of Health and Human Services; b) PCOR/CER investigators; and c) patient partners in research. No individual meeting these criteria will be automatically excluded from participating in the primary research activities which include focus group interviews, case studies, and a mailed survey. However, we will make no additional efforts, beyond the proposed sampling procedures to include special classes of potential subjects such as fetuses, children, prisoners and institutionalized individuals since members of these groups are unlikely to serve on IRBs. Pregnant women, who are considered a special class of subject by the federal government, will be included to the extent that they are represented in the study population. Because pregnancy status is likely to be unrelated to the focus of the study we will not collect data on this or make a special effort to recruit pregnant participants.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

We expect that all IRB staff and members, investigators and patients will speak English.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Non-English_Speaking_Subjects.1.10.pdf

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

A) Focus Groups:

IRB Members and Chairs: Subjects for focus groups of IRB members and IRB chairs and administrators will be drawn from attendees at

the 2015 annual meeting of Public Responsibility in Medicine and Research (PRIM&R). They will be recruited through the support of the PRIM&R leadership, who has offered to work with us on this task. Using PRIM&R's distribution lists, we will recruit participants in our focus groups via email, paying special attention to attain broad representation from types of IRB parent institutions and geographic location, and member characteristics (gender, race-ethnicity, role). Recruitment email that will be sent out is attached with the application. When participants contact us to express interest, we will follow up with individual potential participants to make a final determination. Any screening questionnaire or criteria to be used will be submitted to the IRB for review and approval.

PCORI investigators and other PCOR/CER investigators: Nielsen/Harris Interactive will contact recruited investigators (recruited by us) to schedule the time for one focus group and Nielsen will conduct this focus group online. We will contact and schedule focus group session for the other focus group online. Study staff will prepare a list of funded investigators from PCORI, as well PIs from the literature using a scan of PCOR and CER publications and identifying senior authors.

B)

Patient Groups: One patient focus group members will be recruited by Maureen Fagan, DNP, MHA, the Executive Director of the Brigham and Women's Hospital (BWH) Center for Patients and Families and Coordinator of the Patient and Family Councils (PFACs). She will identify members of the PFACs who have or are serving as research partners in PCOR/CER projects throughout Harvard and Partners HealthCare System and invite them to participate. Assuming that the invited group is larger than the number needed for a focus group (approximately 12), we will select members to assure broad representation in terms of sex, race-ethnicity, educational level, and research experience. A second patient focus group will be conducted at a different institution in a different city, and will be recruited using a similar approach with contacts provided by members of our stakeholder panel. All screening questions and criteria will be submitted to the IRB for review and approval.

B) Individual Interviews

We will select 20 people from among thought leaders from our stakeholder panel, PCOR/CER investigators, Patient-Family Advisory Council advisors, and others (e.g., research ethicists) as recommended to us and will strive to obtain broad representation from different institutions, geographic location,

and socio- demographic characteristics. Experts in IRBs and research ethics will be identified via the snowball sampling approach, that is, each time we interview an expert we will ask for additional suggestions of names. Any screening and selection criteria will be submitted to the IRB for review and approval.

C) Case Studies

We will select sites based on research intensity and PCORI funding. This can be achieved by examining the NIH Rank for medical schools and for public health schools with the list of PCORI funded projects. NIH rank is based on the annual amount of NIH funding and is published on an annual basis by the NIH. Once we see where the top intersection of these lists lies, we will solicit 1-2 public health schools, 1-2 medical schools and 1-2 independent hospitals. To the extent possible we will try to obtain a reasonable distribution of public/private and geographic diversity (East, Midwest, South, and West). We do not expect to have difficulty recruiting sites for our case studies, since members of our stakeholder panel are well known in the research and IRB community and have offered to provide introductions where needed.

Institutions will be solicited to participate by Dr. Weissman. Initially a letter will be sent to the senior IRB official at each institution explaining the nature of the study and asking if the institution would be willing to participate. If after a week we have not heard back, Dr. Weissman will call each of the non-responding IRB officials to solicit participation. Once an institution's IRB chair (or other sponsor/champion) agrees to participate, we will ask the institution to identify a case study contact to facilitate the site visit.

Our case study site contact will work with us to identify and recruit interview subjects. Interview subjects will include the IRB chair(s), IRB members, a patient representative if one exists, investigators identified as doing PCOR or CER, and an executive from research management (e.g., a senior IRB administrator). We also will attempt to interview project directors. We will conduct other interviews as appropriate based on the snowball method of qualitative sampling.

D) Surveys

The sample will be drawn from chairs of IRBs registered with the Office for Human Research Protections (OHRP) at the Department of Health and Human Services. Because we are primarily interested in the phenomena of large funded PCOR and CER, our subjects will be from IRBs in medical schools, research intensive independent hospitals, and

schools of public health. We expect the sample to include the 100 most research intensive medical schools, 15 most research intensive independent teaching hospitals, and 40 most research intensive schools of public health in the US (total 155). The sample of IRB chairs will be drawn in a multi-step process.

First, we will identify the 100 medical schools that receive the most funding from the NIH in 2013— the most recent year complete data is available. . Then we will identify the 40 public health schools that received the most funding from the NIH in 2103. To this list we will add the top 15 independent hospitals that received the most funding from the NIH. This step is intended to identify the most research intensive medical schools, schools of public health and independent hospitals.

Second, using publicly available data from the Office of Human Research Protections at the Department of Health and Human Services we will identify all registered IRBs at each of the institutions.

Third, for each of the selected institutions we will obtain from the OHRP the listing of all IRB chairs. From this list we will select a random sample of 500 chairs. If there are 500 or fewer chairs on the list, we will survey the universe. We will aim to reach a sample as close to 500 as possible. So we will consider expanding to more institutions in the list, if we fail to reach 500 chairs in our list of 155 institutions.

Fourth, since this survey will be sent by mail it is imperative that we obtain accurate mailing addresses for each subject. Since chairs IRB will be employees of the institution or known to the IRB staff we will contact the institution directly to confirm addresses of each of the members. In cases where the individual address of an IRB chair is unavailable, IRB staff will be contacted and asked to forward the survey to the subject.

E) Delphi panel

Our goal will be to engage as many stakeholders as is practicably feasible, being sure to avoid a bias in the group by selecting participants that are diverse geographically, professionally, and socio-demographically. We will send emails to invited participants and ask them to suggest other participants. The participants in this modified Delphi process will include up to 30 people, including selected members of our stakeholder panel, PCOR/CER researchers, patient investigators, ethics experts, IRB members, and other thought leaders identified up to that point in the project.

Any recruitment email/mail that will be sent out to prospective participants for any of the above recruitments, or if any screening questionnaire will be developed to finalize subjects, and that has not been attached at this time of submission, will all be submitted to the IRB for approval before being used.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

A) Focus Groups: Reimbursement of $150 will be provided to all focus group participants.

B) Surveys: During instrument development and testing, to facilitate recruitment and to reimburse participants for their time, each IRB chair will be given $150 for his or her participation in the phase 2 of instrument development (Cognitive interview and pre-test).

In Phase 3, when we pre-test mailing of the questionnaire packet, we will mail $25 as an incentive to complete the questionnaire and mail it back.

When the final survey is sent out to upto 500 IRB Chairs, $25 will be mailed with the questionnaire packet.

C) Delphi Panel: Reimbursement of $200 will be provided to all Delphi Panel experts.

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Recruitment_Of_Research_Subjects.pdf

Guidelines for Advertisements for Recruiting Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Guidelines_For_Advertisements.1.11.pdf

Remuneration for Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Remuneration_for_Research_Subjects.pdf

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Case Study Interviews and Individual Interviews. Subjects who are willing to participate and are finalized to be a part of the study will be sent the interview protocol at least one week prior to the meeting. This procedure will allow sufficient time for subjects to reconsider participation and to prepare their responses. The interview protocol will be approved by the IRB at the Partners HealthCare prior to distribution to subjects. All interviewees will receive information about the elements of informed consent, and we will obtain and document verbal informed consent. Similar information will be provided verbally by Dr. Weissman at the beginning of each interview. We will apply for a Waiver of Documentation of Informed Consent (no signed forms will be used).

Focus Groups: The focus group protocol will be approved by the IRB at the Partners HealthCare prior to conduct. All focus group subjects who are willing to participate and are finalized to be a part of the study will receive information about the elements of informed consent and we will obtain and document verbal informed consent. This information also will be provided verbally by Dr. Weissman at the beginning of each focus group. We will apply for a Waiver of Documentation of Informed Consent (no signed forms will be used).

Survey: Subjects for the survey will be contacted by mail and asked to complete a questionnaire. The letter requesting participation will include a brief description of the aims of the study, the study staff, how the results of the survey will be used and the procedures taken to ensure subject anonymity. As is common practice in survey research, we assume that completion of the survey implies the informed consent of the respondent. Subjects who fail to complete the questionnaire will be re-contacted and encouraged to participate. Any subject who indicates that they are unwilling to complete the survey will be considered a persistent non-respondent and not contacted again.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research

and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects:
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Informed_Consent_of_Research_Subjects.pdf

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

Privacy and confidentiality will be protected as detailed above. Because there is minimal risk to the participants, we do not plan to employ a Data Safety Monitoring Board. All study staff that have access to study data will be required to have completed the necessary CITI and HIPAA training and will be approved by the IRB.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

Investigators will report any adverse events associated with this project to the IRB as specified by the Adverse Event Reporting guidelines.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

The Principal Investigator will be responsible for monitoring all aspects of data collection and ensuring that it is conducted in accordance with the IRB-approved protocol. The Shared File Area (SFA) will be accessible only to Partners study staff involved in this study and files contained within this SFA will be password protected. Access to data by Partners personnel will be authorized and managed by the project manager.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/DSMP_in_Human_Subjects_Research.pdf

Reporting Unanticipated Problems (including Adverse Events)
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Reporting_Unanticipated_Problems_including_Adverse_Events.pdf

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

All information from individuals or entities in the course of this study that identifies an individual or entity will be treated as confidential and will be used only by the study investigators for study purposes. Data collection will occur on encrypted desktops or laptops that are locked securely when not in use, and all data will be moved onto Partners servers regularly. Participants

may decline to answer any of the questions we ask, and may also withdraw their participation at any time.

Any paper files will be kept in locked cabinets, and any data stored in computer databases will be password protected and limited to study staff. Data will be analyzed and presented in aggregate form only. All study staff that have access to study data will be required to have completed the necessary CITI and HIPAA training and will be approved by the IRB.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

Data will only be shared with the IRB approved study staff outside of Partners. They will only be members of the study team. The consent process for all recruitments will duly inform the subjects about it and they will be assured that all measures will be taken to ensure that data is kept confidential and in secure environments only accessible to study team.

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

Data collected will not be stored at collaborating sites outside of Partners for future use.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

Nielsen is a vendor in our project and they will conduct the survey on behalf of the PI. They will send the collected data confidentially and securely to the research team members at Partners. Nielsen will not store any data with themselves after it has been sent to the research team here.