Patient-Centered Outcomes Research Institute Board of Governors Meeting

December 7, 2015 – Meeting Minutes

Mayflower Hotel
1127 Connecticut Ave, NW
Washington, DC 20036
Tel: (202) 347-3000

Board Members Present:
Grayson Norquist, MD, MSPH, *Chairperson*; Debra Barksdale, PhD, RN; Kerry Barnett, JD, *Vice Chairperson*; Lawrence Becker; Allen Douma, MD; Alicia Fernandez, MD; Christine Goertz, DC, PhD; Leah Hole-Marshall, JD; Gail Hunt; Robert Jesse, MD, PhD; Richard Kronick, PhD; Harlan Krumholz, MD; Richard Kuntz, MD, MSc; Michael Lauer, MD (acting as designee for Francis Collins, MD, PhD); Sharon Levine, MD; Freda Lewis-Hall, MD; Steve Lipstein, MHA; Barbara McNeil, MD; Ellen Sigal, PhD; Harlan Weisman, MD; Robert Zwolak, MD, PhD

Board Member Absent:
None

Methodology Committee Member Present:
Robin Newhouse, PhD, RN, *Chair*

Staff:
Joe Selby, MD, MPH, *Executive Director*; Rachael Fleurence, PhD; Laura Forsythe, PhD, MPH; Lori Frank, PhD; Jason Gerson, PhD; Mary Hennessey, Esq.; David Hickam, MD; Susan Hildebrandt, MA; Michele Orza, ScD; Sue Sheridan, MBA, MIM; Bill Silberg; Jean Slutsky, PA, MSPH; Scott Solomon, MBA, MSE; Harold Sox, MD; Regina Yan, MA

AGENDA ITEM	OBJECTIVE
Chairperson's welcome, call to order *Grayson Norquist, MD, MSPH, Chairperson and Joe Selby, MD, MPH, Executive Director*	Dr. Grayson Norquist chaired and opened the meeting, welcomed all to the meeting of the PCORI Board of Governors and read the Chair Statement on Conflict of Interest. Dr. Joe Selby reviewed the agenda for today's meeting.
Approval of the November 17, 2015 Board Meeting Minutes *Grayson Norquist, MD, MSPH*	The following motion was made by Kerry Barnett and seconded by Sharon Levine: **Motion:** Approve the November 17, 2015 Board Meeting Minutes. *Approved by a majority vote of the Board by voice vote (no opposed; no abstentions)*
Engagement in PCORnet - *Jean Slutsky, PA, MSPH and Sue Sheridan, MIM, MBA, Sharon Terry, MA*	The presentation highlighted patient and stakeholder engagement within Phase II of PCORnet. Speakers addressed tools and strategies to ensure and evaluate meaningful engagement, along with other programs to develop a community that is skilled in Patient-Centered Outcomes Research. The presentation also included specific examples of patient engagement and highlighted the new PCORnet Engagement Committee.
Executive Director's Report and End-of-year Dashboard Review - *Joe Selby, MD, MPH and Michele Orza, ScD*	Dr. Selby presented the End of Year Dashboard for the Board's review, and encouraged members to suggest new items to track. The Q4 Dashboard demonstrated three yellow-flagged items (items that are off target by more than 10%): Funds Committed to Research, Projects Completed, and Expenditures. Dr. Selby discussed Funds Committed to Research, and reminded the Board that our budget shows the upper limit of funding. The Q4 Dashboard included no red-flagged items. Dr. Selby highlighted an intentional shift in the distribution of our portfolio, with more funding in targeted and pragmatic studies. He discussed priority topics in the Topic Prioritization Pathway, and highlights from the Portfolio Analysis presentation. He reviewed the Measures of Progress of Research Projects, categorizing green, yellow, orange or red status for projects. He explained that two projects have been terminated to date, as defined by issuance of the Notice of Termination. Dr. Selby shared the increased support for PCOR at Tulane University as an example of progress on Strategic Goal 3 of increasing PCORI influence. He shared several examples of the uptake of PCORI Methodology, including uptake into continuing medical education and university curricula. Board members expressed interest in further information on expected project end dates, on projects that received modifications, and on publications from PCORI-funded studies.

Portfolio Portrait/Analyses - *Lori Frank, PhD*	Dr. Lori Frank provided an update on the portfolio taxonomy, describing its development and its structure, and illustrated the structure with examples. The Board was invited to consider ways PCORI can leverage this tool. The two goals that led to development of the taxonomy were 1) to support the need to report to the Board and the public about PCORI's funding. 2) to support strategic decision making. This taxonomy enhances the level of detail we can use to describe PCORI's funding. Examples of views of the portfolio were shared, highlighting the ability the taxonomy provides to identify a set of projects based on specific criteria, then explore that set in greater detail. Board members asked various questions about the coding process and use of the taxonomy, which were answered. 1. care, with specification, as a comparator; an additional 16%
Stakeholder Perspectives Panel: Patients *Jean Slutsky, PA, MSPH and Sue Sheridan, MIM, MBA* - *Moderator Gail Hunt* *Marc Boutin, JD, CEO, National Health Council* *Donna Cryer, JD, President & CEO, Global Liver Institute* *Celeste Castillo Lee, Institute for Patient and Family-Centered Care*	Gail Hunt, board member, introduced and moderated the patient panel. The purpose of the patient panel was to offer the Board an opportunity to interact with representatives from the patient community and to hear various reflections and perspectives regarding the value of patient engagement in research and PCOR. Marc Boutin, CEO of the National Health Council, shared that the legacy of PCORI will be the usefulness of the research findings. He commented that PCORI has created a cultural "aha" moment by meaningfully engaging the patient and caregiver community in research and that it has had a dramatic impact not only in the research that PCORI funds but on other sectors of the healthcare eco-system such as drug development and the FDA. Going forward he encouraged PCORI to engage the patient community in collectively defining "a value model" aligning incentives based on outcomes that matter to patients. Donna Cryer, liver transplant survivor and President and CEO of the Global Liver Institute, shared that she "looks through the lens of a patient" when reflecting on PCORI and the importance of patients as partners in research. She highlighted examples how, from her point of view, PCORI is demonstrating authentic patient engagement including the composition of the Board, blogs authored by patients, the report on the 2012 Patient Engagement Workshop and the patient centeredness and patient engagement criteria. She commented that PCORI has been a fantastic demonstration of patient engagement and that the model should be transferred to the rest of the research ecosystem. Celeste Lee, patient advocate with a rare disease, patient partner on the Vasculitis PPRN and faculty of the Institute of Patient and Family Centered Care, shared her experience as a patient partner in research and her desire to be a public advocate to effect the lives of others. She emphasized the importance for PCORI to orient and train the patient community to more effectively engage in research as partners and to highlight the value proposition of sharing personal health data to generate new knowledge to better manage disease. She challenged

	PCORI to develop new ways to train patients and to create a network of educated patient leaders.
Methodology Committee Update **Consider for Approval:** Release Revised and New Standards for Public Comment - *Robin Newhouse, PhD, RN*	Dr. Robin Newhouse provided the Board with an overview of the Methodology Committee's work on the Methodology Standards Review. She presented the process used to review the existing Standards and draft the new Designs Using Clusters Standards. Both processes involved staff working with MC members and conducting a number of revisions before final vote by the MC. Additionally development of the Designs Using Clusters Standards involved expert input and drafting. Of the original 47 Methodology Standards, 25 were revised, 12 were combined to form six, one was deleted, nine were unchanged, and three were added. Rationales for the revisions included to streamline and clarify the Standards, to align the Standards with other guidance, to reflect advances in methodology, and to synchronize concepts addressed in more than one Standard. With the five proposed new Standards in Designs Using Clusters, there are now a total of 48 proposed new and revised Methodology Standards *(Attachment A)*. Following potential approval by the Board to make these Standards available for public comment, next steps include reading, processing, and categorizing the comments and, if indicated, making revisions. The Methodology Committee also has plans to revise the Methodology Report and will seek Board approval to publish the updated Standards and accompanying Methodology Report at a later date. The expected timeline to complete these next steps is June 2016. The following motion was made by Barbara McNeil and seconded by Christine Goertz. **Motion:** Approve release for public comment the proposed new and revised Methodology Standards. *Approved by a majority vote of the Board by a show of hands: 21 in favor; 0 opposed; 0 abstentions*
Consider for Approval: Revised Selection Committee Charter - *Christine Goertz, DC, PhD*	Dr. Goertz presented to the Board a revised charter for the Selection Committee *(see Attachment B)*. The revisions are intended to enable more flexibility in recognition of the various cycles and needed expertise. While this charter maintains several core principles of the original charter, it is being revised to: (a) change the number of members from exactly 6 to between 3 and 10 – Board members must be the majority - to accommodate availability of Board and Methodology members; (b) no longer require the Chair of the SOC to serve on the Committee; (c) align the chair terms with those of other PCORI Committees; and (d) outline more clearly the primary responsibilities of the Selection Committee in the context of the larger

	process that includes the merit review process and scientific program staff review. The following motion was presented by Mike Lauer and seconded by Larry Becker. **Motion**: Approve the Revised Selection Committee Charter *Approved by a majority vote of the Board by a show of hands: 20 in favor; 0 opposed; 0 abstentions (Dr. Harlan Krumholz was not present for this vote).*
Evaluation Update: Merit Review Score Analysis - *Laura Forsythe, PhD, MPH and Lori Frank, PhD*	Dr. Laura Forsythe presented results from the Merit Review score analyses, which builds upon work led by Dr. Rachael Fleurence and published in Annals of Internal Medicine in 2014. The main questions considered in this presentation were: 1) What is the impact of in-person discussion on reviewer scores? Agreement between reviewers? 2) Which criteria contribute the most to prediction of funding decisions? Final review scores? The main findings were reported. In-person discussion has an impact on review scores: scientist, patient, and stakeholder reviewers scores converge from before to after the group discussion. Agreement across reviewer types is greater after discussion. While PCORI Merit Review brings together reviewers from a variety of perspectives, all reviewer types demonstrate agreement about which projects best meet PCORI criteria. Scientists, patients, and stakeholders all influence the final merit review scores and funding decisions. Scientist reviewers' ratings have a strong influence on scores, and technical merit is important to all reviewer types. Potential to improve healthcare and outcomes is critical to success in merit review, as is scientist reviewers' views of the technical merit and patient-centeredness of the research. The Board discussed the extent to which changes in scores through the discussion are desirable. Other avenues for considering these data and these relationships were suggested. Specifically, there is interest in comparing change in scores in PCORI Merit Review to those observed in reviews for other agencies such as AHRQ and NIH.
Workforce Training Proposal - *Joe Selby, MD, MPH and Freda Lewis-Hall, MD*	Dr. Selby laid out the concept of pursuing an investment in workforce training. Early 2014 meetings with the Institute of Medicine (IOM) established a need for researchers with skills to leverage health system data to improve clinical outcomes. The Research Transformation Committee (RTC) has discussed training programs in learning health systems for several months and have established mutual enthusiasm for the project with Board Member Dr. Richard Kronick and other representatives from the Agency for Healthcare Research and Quality (AHRQ). Dr. Selby updated the Board on current work of other organizations. AHRQ is organizing an expert panel for evidence gathering, Academy Health has a needs assessment meeting in early 2016, and the Robert

	Wood Johnson Foundation (RWJF) has a new clinical scholars program, which emphasizes interdisciplinary collaboration and leadership. The Board of Governors reaffirmed the need for bringing training to where care is delivered, expanding expertise in data science, and leveraging large data sets to change clinical practice. RWJF's departure from training traditional researchers may leave an opportunity for PCORI to fill this vital need. Board members expressed their sense that collaborating through AHRQ would be a favorable course of action. Board members encouraged PCORI to determine what specific contributions are needed and how we can re-direct training programs to include patient engagement and comparative effective methodologies in the training. Board members expressed general enthusiasm and support, but agreed that clarity is needed on program specifics.
Progress on Open Science - *Joe Selby, MD, MPH and Jason Gerson, PhD*	Dr. Jason Gerson presented an update to the Board on the efforts of the Open Science Work Group. The update focused on three sets of current activities: (1) consultation with national experts, (2) Open Science plenary session at the 2015 PCORI Annual Meeting, and (3) revisions to the Draft PCORI Open Science Policy. Dr. Gerson also discussed envisioned activities for 2016. These include working with a subset of PCORI awardees on a pilot, addressing governance protocols for reviewing data access requests, and convening a group of experts to guide PCORI on how to best operationalize data sharing. Board members expressed support and enthusiasm for these efforts. Discussion focused in part on the challenges with the current advancement and promotion system in academia and the need to think about how researchers' commitment to open science should be recognized in this system. There was also some discussion about the technical challenges related to linking data from multiple data sources and health systems in order to answer important research questions.
Public Comment - *Sue Sheridan, MIM, MBA*	There were no requests for public comment.
Wrap-up and Adjournment *Grayson Norquist, MD, MSPH*	Dr. Norquist thanked all who joined the meeting and reminded attendees that PCORI welcomes any feedback. The meeting adjourned at 4:51 pm.

See Attachment A for <u>Revised and New Methodology Standards for Public Comment</u>

See Attachment B for <u>Revised Selection Committee Charter</u>

Approved by the PCORI Board of Governors 01-26-2016

Proposed Revised Methodology Standards

Contents

Cross-Cutting Standards for PCOR

1: Standards for Formulating Research Questions

RQ-1: Identify gaps in evidence

Analysis of gaps in the evidence based on systematic reviews should be used to support the need for a proposed study. If a systematic review is not available, a systematic review should be performed using accepted standards in the field (see standard SR-1), or a strong rationale should be presented for proceeding without a systematic review. In the case where a systematic review is not possible, the methods used to review the literature should be explained and justified.

RQ-2: Develop a formal study protocol

Studies should include a formal protocol specifying at least one purpose for which the data were collected (e.g., effectiveness, safety, natural history of disease, quality improvement); data sources and linkage plans, if any; data feasibility and quality, measure(s) of effect; and use of any standardized data dictionaries (nationally or internationally accepted).

RQ-3: Identify specific populations and health decision(s) affected by the research

To produce information that is meaningful and useful to people when making specific health decisions, research proposals and protocols should describe: 1) the specific health decision the research is intended to inform; 2) the specific population for whom the health decision is pertinent; and 3) how study results will inform the health decision.

RQ-4: Identify and assess participant subgroups

In designing studies, researchers should identify participant subgroups and explain why they are of interest, preferably based on prior data. Where feasible, the study should have adequate precision and power to reach conclusions specific to these subgroups.

RQ-5: Select appropriate interventions and comparators

The interventions and comparators should correspond to the actual health care options for patients who would face the clinical decision. The clinical decision should be vital and consequential, and one in which current evidence is insufficient to inform the tradeoffs of benefits versus harms associated with the different options. Researchers should make explicit what the comparators are and why they were selected, focusing on clearly describing how the chosen comparator(s) define the causal question, reduce the potential for biases, and allow direct comparisons. Generally, non-use (or no specific treatment) comparator groups should be avoided unless no specific treatment is a likely option in standard care.

RQ-6: Measure outcomes that people representing the population of interest notice and care about

Identify and include outcomes the population of interest notices and cares about (e.g., survival, functioning, symptoms, health-related quality of life) and that inform an identified health decision. Define outcomes clearly, especially for complex conditions or outcomes that may not have established clinical criteria. Provide information that supports the selection of outcomes as meeting the criteria of "patient-centered" and "relevant to decision makers," such as patient and decision-maker input from

meetings, surveys, or published studies. Select outcomes that reflect both beneficial and harmful effects, based on input from patient informants and people representative of the population of interest.

2: Standards Associated with Patient-Centeredness

PC-1: Engage people representing the population of interest and other relevant stakeholders in ways that are appropriate and necessary in a given research context

Include individuals affected by the condition and, as relevant, their surrogates and/or caregivers. Other relevant stakeholders may include clinicians, purchasers, payers, industry, hospitals, and health systems, policy makers and training institutions. These stakeholders may be end users of the research, or, be involved in healthcare decision making.

Examples of processes in which patients, caregivers, clinicians, and other healthcare stakeholders can be involved include but are not limited to:

- Formulating research questions;
- Defining essential characteristics of study participants, comparators, and outcomes;
- Identifying and selecting outcomes that the population of interest notices and cares about (e.g., survival, function, symptoms, health-related quality of life) and that inform decision making relevant to the research topic;
- Monitoring study conduct and progress; and
- Designing/suggesting plans for dissemination and implementation activities.

PCORI's Engagement Rubric provides further guidance.

When applicable, research proposals should describe how these stakeholders will be identified, recruited, and retained. If engagement is not necessary or appropriate in these processes, explain why.

PC-2: Identify, select, recruit, and retain study participants representative of the spectrum of the population of interest and ensure that data are collected thoroughly and systematically from all study participants

Research proposals and subsequent study reports should describe: 1) the plan to ensure representativeness of participants; 2) how participants are identified, selected, recruited, enrolled, and retained in the study to reduce or address the potential impact of selection bias; 3) efforts employed to maximize adherence to agreed-on enrollment practices; and 4) methods used to ensure unbiased and systematic data collection from all participants.

If the population of interest includes people who are more difficult to identify, recruit, and/or retain than other study populations (for example, individuals historically underrepresented in healthcare research such as those with multiple disease conditions, low literacy, low socioeconomic status, or poor healthcare access, as well as racial and ethnic minority groups and people living in rural areas), then specify plans to address population-unique issues for participant identification, recruitment, and retention.

PC-3: Use patient-reported outcomes when patients or people at risk of a condition are the best source of information

When patients or people at risk of a condition are the best source of information regarding outcomes of interest, then the study should employ patient-reported outcome (PRO) measures in lieu of, or in addition to, measures derived from other sources. Proposals should describe: 1) the concept(s) underlying each PRO measure (e.g., symptom or impairment) and how it is meaningful to, and noticed by, patients in the population of interest; 2) how the concept relates to the health decisions the study is designed to inform; 3) how the PRO measure was developed, including how patients were involved in the development; and 4) evidence of measurement properties including content validity, construct validity, reliability, responsiveness to change over time, and score interpretability, including meaningfulness of score changes in the population of interest with consideration of important subgroups. If these measurement properties are not known, a plan for establishing the properties must be provided. Caregiver reports may be appropriate if the patient cannot self-report the outcomes of interest. If PROs are not planned for use in the study, justification must be provided.

PC-4: Support dissemination and implementation of study results

For study results that are appropriate for dissemination and implementation, involve patients and relevant stakeholders: a) in planning for dissemination from the start of the research study; b) in creating a dissemination plan for the study indicating clinical implications; c) in working with patients or organizations to report results in a manner understandable to and usable by each target audience; and d) in identifying successful strategies for adoption and distribution of study findings to targeted patient and clinical audiences.

3: Standards for Data Integrity and Rigorous Analysis

IR-1: A priori, specify plans for quantitative data analysis that correspond to major aims

Researchers should describe the analytic approaches that will be used to address the major research aims before analysis is undertaken. These include definitions of key exposures, endpoints, and covariates. Also identify patient subgroups of interest, plans (if any) for how new subgroups of interest will be identified or how analysis plans may be adapted based on changing needs and scientific advances, and plans for how missing data will be handled.

IR-2: Assess data source adequacy

In selecting data sources, researchers should ensure robust capture of exposure, outcome, and relevant covariates. When statistically adjusting for covariates or confounding factors, measurement properties of the important covariates must be considered to allow adequate adjustment.

IR-3: Describe data linkage plans, if applicable

For studies involving linkage of patient data from two or more sources (including registries, data networks, and others), describe 1) each data source and its appropriateness, value, and limitations for addressing specific research aims; 2) any additional requirements that may influence successful linkage, such as information needed to match patients, selection of data elements, and definitions used; and 3)

the procedures and algorithm(s) employed in matching patients, including the success, limitations, and any validation of the matching algorithm.

IR-4 Document validated scales and tests

Studies should include documentation of the names of the scales and tests selected, reference(s), characteristics of the scale, and psychometric properties.

IR-5: Provide sufficient information in reports to allow for assessments of the study's internal and external validity

Reporting guidelines for specific designs can be found at the EQUATOR Network website (www.equator-network.org). This website has brought together all reporting guidelines that have been developed using formal approaches, many of which have been adopted by journals, such as CONSORT (for randomized clinical trials), STARD (for diagnostic tests), STROBE (for observational studies) and SRQR and/or COREQ (studies using qualitative research). Researchers should register their studies with the appropriate registry (e.g. clinicaltrials.gov for clinical studies or observational outcomes studies) and provide complete and accurate responses to the information requested (e.g., enter the required and optional data elements for clinicaltrials.gov).

New IR-6: Masking should be used when feasible

Masking of evaluation staff should be implemented, especially in situations for which study participant and investigator masking are not feasible. When masking is not feasible, the impact of lack of masking on the results should be discussed.

4: Standards for Preventing and Handling Missing Data

MD-1: Describe methods to prevent and monitor missing data

Investigators should explicitly state potential reasons that study data may be missing. Missing data can occur from patient dropout, nonresponse, data collection problems, incomplete data sources, and/or administrative issues. As relevant, the protocol should include the anticipated amount of and reasons for missing data, plans to prevent missing data, and plans to follow up with study participants. The study protocol should contain a section that addresses steps taken in study design and conduct to monitor and limit the impact of missing data. This standard applies to all study designs for any type of research question.

MD-2: Use valid statistical methods to deal with missing data that properly account for statistical uncertainty due to missingness

Valid statistical methods for handling missing data should be pre-specified in study protocols. The reasons for missing data should be considered in the analysis. A discussion of the potential ramifications of the statistical approach to missing data on the results should be provided. The plausibility of the assumptions associated with the approach should be assessed.

Statistical inference of intervention effects or measures of association should account for statistical uncertainty attributable to missing data. This means that methods used for imputing missing data

should produce valid confidence intervals and should permit unbiased inferences based on statistical hypothesis tests. Bayesian methods, multiple imputation, and various likelihood-based methods are valid statistical methods to deal with missing data. Single imputation methods like last observation carried forward, baseline observation carried forward, and mean value imputation are discouraged as the primary approach for handling missing data in the analysis. If investigators do use single-based imputation methods, they must provide a compelling scientific rationale as to why the method is appropriate. This standard applies to all study designs for any type of research question.

MD-3: Record and report all reasons for dropout and missing data, and account for all patients in reports

Whenever a participant drops out of a research study, the investigator should document the following: 1) the specific reason for dropout, in as much detail as possible; 2) who decided that the participant would drop out; and 3) whether the dropout involves some or all types of participation. Investigators should attempt to continue to collect information on key outcomes for participants unless consent is withdrawn. All participants included in the study should be accounted for in the report, whether or not they are included in the analyses. Describe and justify any planned reasons for excluding participants from analysis. In addition, missing data due to other mechanisms (such as nonresponse and data entry/collection) should also be well documented and handled appropriately in the analyses.

MD-4: Examine sensitivity of inferences to missing data methods and assumptions, and incorporate into interpretation

Examining sensitivity to the assumptions about the missing data mechanism (i.e., sensitivity analysis) should be a mandatory component of the study protocol, analysis, and reporting. This standard applies to all study designs for any type of research question. Statistical summaries should be used to describe missing data in studies, including a comparison of baseline characteristics of units (e.g., patients, questions, or clinics) with and without missing data. These quantitative results should be incorporated into the interpretation of the study and reflected in the discussion section and possibly the abstract.

5: Standards for Heterogeneity of Treatment Effects

HT-1: State the goals of HTE analyses, including hypotheses and the supporting evidence base

State the inferential goal of each HTE analysis, and explain how it is related to the topic of the research. Specify whether the HTE analysis is hypothesis driven (sometime denoted confirmatory), or hypothesis generating (sometime denoted exploratory). Hypothesis-driven HTE analyses should be pre-specified, based on prior evidence (described clearly in the study protocol and published paper), and supported by a clear statement of the hypotheses the study will evaluate, including how subgroups will be defined (e.g., by multivariate score or stratification), outcome measures, and the direction of the expected treatment effects.

HT-2: For all HTE analyses, provide an analysis plan, including the use of appropriate statistical methods

The study protocol should unambiguously pre-specify planned HTE analyses. Appropriate methods include, but are not limited to, interaction tests, differences in treatment effect estimates with standard

errors, or a variety of approaches to adjusting the estimated subgroup effect, such as Bayesian shrinkage estimates. Appropriate methods should be used to account for the consequences of multiple comparisons; these methods include, but are not limited to, p-value adjustment, false discovery rates, Bayesian shrinkage estimates, adjusted confidence intervals, or validation methods (internal or external). A common error in HTE analyses is to claim differences in treatment effect when one subgroup shows a statistically significant treatment effect and another does not.

HT-3: Report all pre-specified HTE analyses and, at minimum, the number of post-hoc HTE analyses, including all subgroups and outcomes analyzed

Protocols and study reports must report the exact procedures used to explore HTE, including data mining or any automatic regression approaches. HTE analyses should clearly report the procedures by which subgroups were defined, and the effective number of subgroups and outcomes examined. Within each subgroup level, studies should present the treatment effect estimates and measures of variability. Pre-specified HTE analyses (hypothesis-driven) should be clearly distinguished from post-hoc HTE analyses (hypothesis-generating). Statistical power for all analyses should be reported.

Standards for Specific Study Designs and Methods

6: Standards for Data Registries

DR-1: Requirements for the design of registries

A. Registry Purpose and Protocol

The purpose of the registry should be clearly defined to guide the design of key registry features including but not limited to: the target population, the research question/s to be addressed, the data source utilized, the data elements collected, data sharing policies, and the stakeholders involved in the development and use of the registry. Participants and other key stakeholders should be engaged in registry and protocol development. Registries should aim to be user-oriented in design and function.

B. Data Safety and Security

Registry custodians should comply with IRB requirements, local and national laws, and where applicable, HIPAA. Registries should provide information describing type of data collection (primary or secondary source data), data use agreements, informed consent documents, data security protections, plans for maintaining data protection if the registry ends, and approaches to protecting security including risk and/or process for re-identification of participants, especially for medical or claims records.

C. Data Elements and Quality

Standardized data element definitions and/or data dictionaries should be used whenever possible. When creating a new registry, published literature should be reviewed to identify existing, widely used definitions of outcomes, exposure, and confounders before drafting new definitions.

When collecting primary data, conduct multi-stakeholder engagement with potential participants and data users to prioritize data collection needs. When participants support their face validity, utilize validated instruments or patient reported outcome measures when available. If secondary data sources (e.g. electronic medical records, claims data) are utilized, describe the original purpose of the secondary data and verify the accuracy and completeness of the data, as well as the approach to and validity of the linkages performed between the primary and secondary sources.

The specifics of the quality assurance plan will depend on the type of data (primary or secondary) collected by the registry. In general, the plan should address: 1) structured training tools for data abstractors/curators; 2) use of data quality checks for ranges and logical consistency for key exposure and outcome variables and covariates; and 3) data review and verification procedures, including source data verification plans (where feasible and appropriate), and validation statistics focused on data quality for the key exposure and outcome variables and key covariates. A risk-based approach to quality assurance is advisable, focused on variables of greatest importance.

D. Confounding

Registries should identify important potential confounders pertinent to the purpose and scope of the research during the planning phase and collect reasonably sufficient data on these potential confounders to facilitate the use of appropriate statistical techniques during the analysis phase. When conducting analysis, refer to PCORI Methodology Standards for Data Integrity and Rigorous Analyses Standards for Causal Inference Methods.

E. Systematic Participant Recruitment and Enrollment

Develop a sampling plan (population-based or otherwise) of the target population and identify recruitment strategies for participants that minimize the impact of selection bias. Participants should be enrolled systematically, with similar procedures implemented at all participating sites and for each intervention of interest. Confirm adherence to agreed-upon enrollment practices.

F. Participant Follow-up

The objective(s) of the registry should determine the type, extent, and length of participant follow-up.

Describe the frequency with which follow-up measures will be ascertained, consider linkage with other data sources such as the National Death Index to enhance long-term follow-up, and identify the date of last contact with the participant in existing registries, where appropriate. Ensure that the participants are followed in as unbiased a manner as possible, using similar procedures at all participating sites.

Monitor loss to follow-up to ensure best efforts are used to achieve follow-up time that is adequate to address the main objective. At the outset of the registry, develop a retention plan that documents when a participant will be considered lost to follow-up and what actions will be taken to minimize loss of pertinent data. Retention efforts should be developed with

stakeholders to ensure the efforts are suitable for the target population and anticipated challenges are addressed appropriately.

DR-2: Documentation and reporting requirements of registry materials, characteristics and bias

Clearly describe, document with full citations where appropriate, and make publically available registry materials including but not limited to registry protocols; data sharing policies; operational definitions of data elements; survey instruments utilized and patient-reported outcomes captured.

Modifications to any documents or data collection instruments should be clearly described and made available for registry users and participants.

Characteristics of the participants in the registry should be described. Identify how the participants may differ from the target population to help assess potential selection biases. Document loss to follow-up and describe impact on the results, utilizing sensitivity analyses (pre-specified where possible) to quantify possible biases. Report the extent of bias clearly to stakeholders who may want to utilize the registry resource.

DR-3 Adapting Established Registries for PCORI Research

Established registries that intend to support PCORI research but may not have been guided by the PCORI standards during the registry development should engage key stakeholders, including registry participants, to ensure:

a. Informed consent documents are appropriately tailored to participant needs, characteristics and conditions
b. Data elements are meaningful and useful to researchers and participants
c. Recruitment and retention strategies are feasible and effective
d. Registry policies are patient-centered and the use of registry data is transparent to participants
e. Dissemination practices of PCORI-funded research using registry data are appropriate and effective at reaching the communities from which the data are collected
f. Opportunities for bi-directional benefit between participants and researchers.
g. Registry materials, described in DR-2, and informed consent forms are publically available in accessible formats

DR-4: Documentation requirements when using registry data

Researchers planning PCOR studies relying on registries must ensure that these meet the requirements contained in Standards DR-1 and DR-2 and must document each required feature of the registry(s) to be used (e.g., in an appendix to the funding application or study protocol). Deviations from the requirements with Standards DR-1 and DR-2 should be well documented and limitations of research related to the deviations from requirements should be addressed along with study findings.

7: Standards for Data Networks as Research-Facilitating Structures

DN-1: Requirements for the design and features of data networks

Data networks established for conducting PCOR must have the following characteristics to facilitate valid, useable data and to ensure appropriate privacy, confidentiality, and intellectual property protections:

A. **Data Integration Strategy**—In order for equivalent data elements from different sources to be harmonized (treated as equivalent), processes should be created and documented that describe the quality and completeness of the data integration. Processes should also be created and documented that either 1) transform data elements prior to analysis or 2) make transformation logic available that can be executed when data are extracted. The selected approach should be based on an understanding of the research domain of interest.
B. **Risk Assessment Strategy**—If data are exchanged between data partners, data custodians should develop policies for the management of the risk of use of the data other than the agreed upon use. This should include agreements for how data will be handled and how time limits on the data will be enforced.
C. **Identity Management and Authentication of Individual Researchers**—Develop reliable processes for verifying credentials of researchers who are granted access to a distributed research network and for authenticating them.
D. **Intellectual Property Policies**—A research network should develop policies for the handling and dissemination of intellectual property (IP); networks should also have an ongoing process for reviewing and refreshing those policies. IP can include data, research databases, papers, reports, patents, and/or products resulting from research using the network. Guidelines should balance 1) minimizing impediments to innovation in research processes, 2) determining whether or how IP belongs to the patients or research participants, and 3) making the results of research widely accessible, particularly to the people who need them the most.
E. **Standardized Terminology Encoding of Data Content**—The data contents should be represented with standardized terminology systems to ensure that their meaning is unambiguously and consistently understood by parties using the data.
F. **Metadata Annotation of Data Content**—Semantic and administrative aspects of data contents should be annotated with a set of metadata items. Metadata annotation helps to correctly identify the intended meaning of a data element and facilitates an automated compatibility check among data elements.
G. **Common Data Model**—Individual data items should be assembled into a contextual environment that shows close or distant association among data. A common data model (CDM) specifies necessary data items that need to be collected and shared across participating institutes, clearly represents these associations and relationships among data elements, and promotes correct interpretation of the data content.

DN-2: Selection and use of data networks

Researchers planning PCOR studies relying on data networks must ensure that these networks meet the requirements contained in Standard DN-1, and they must document each required feature of the data network(s) to be used (e.g., in an appendix to the funding application or study protocol). Deviations

from the requirements should be justified by explaining why a required feature is not feasible or not necessary to achieve the overall goals of Standard DN-1.

8: Standards for Causal Inference Methods

CI-1: CI-Model: Specify the causal model underlying the research question

Researchers should describe the causal model relevant to the research question, which should be informed by the PICOTS framework: populations, interventions, comparators, outcomes, timing, and settings. The causal model represents the key variables; the known or hypothesized relationships among them, including the potential mechanisms of effect; and the conditions under which the hypotheses are to be tested. Researchers should use the causal model to determine whether and how the study can handle bias and confounding and the extent to which valid estimates of the effects of an intervention can be generated based on the particular data source, hypothesis, and study design.

CI-2: Define and appropriately characterize analysis population used to generate effect estimates

Decisions about whether patients are included in an analysis should be based on information available at each patient's time of study entry in prospective studies or on information from a defined time period prior to the exposure in retrospective studies. For time-varying treatment or exposure regimes, specific time points should be clearly specified and relevant variables measured at baseline and up to but not beyond those time points should be used as population descriptors. When conducting analyses that in some way exclude patients from the original study population, researchers should describe the final analysis population that gave rise to the effect estimate(s).

CI-3: Define with the appropriate precision the timing of the outcome assessment relative to the initiation and duration of exposure

To ensure that an estimate of an exposure or intervention effect corresponds to the question that researchers seek to answer, the researchers must precisely define, to the extent possible, the timing of the outcome assessment relative to the initiation and duration of the exposure.

CI-4: Measure potential confounders before start of exposure and report data on potential confounders with study results

In general, variables for use in confounding adjustment (either in the design or analysis) should be ascertained and measured prior to the first exposure to the interventions (or intervention) under study. If confounders are time varying, specific time points for the analysis of the exposure effect should be clearly specified and the confounder history up to and not beyond those time points should be used in that analysis.

CI-5: Report the assumptions underlying the construction of propensity scores and the comparability of the resulting groups in terms of the balance of covariates and overlap

When conducting analyses that use propensity scores to adjust for measured confounding, researchers should assess the overlap and balance achieved across compared groups with respect to potential confounding variables.

CI-6: Assess the validity of the instrumental variable (i.e., how the assumptions are met) and report the balance of covariates in the groups created by the instrumental variable

When an instrumental variable (IV) approach is used to address potential unmeasured confounding, empirical evidence should be presented describing how the variable chosen as an IV satisfies the three key properties of a valid instrument: 1) the IV influences choice of the intervention or is associated with a particular intervention because both have a common cause; 2) the IV is unrelated to patient characteristics that are associated with the outcome; and 3) the IV is not otherwise related to the outcome under study (i.e., it does not have a direct effect on the outcome apart from its effect through exposure).

9: Standards for Adaptive Trial Designs

AT-1: Specify planned adaptations, decisional thresholds, and statistical properties of those adaptations

The adaptive clinical trial design must be prospectively planned and the design must be clearly documented in the study protocol before trial enrollment begins, including at a minimum:

- All potential adaptations, including timing;
- Interim trial findings that will be used in determining each adaptation;
- Statistical models and decisional thresholds to be used; and
- Planned analyses of the trial endpoint(s).

The description of the design should be sufficiently detailed that it could be implemented from the description of procedures. This specification should include a statistical analysis plan (SAP) in which all necessary detail is provided regarding planned interim and final analyses.

Additionally, the statistical properties of adaptive clinical trial designs should be thoroughly investigated over the relevant range of important parameters or clinical scenarios (e.g., treatment effects, accrual rates, delays in the availability of outcome data, dropout rates, missing data, drift in participant characteristics over time, subgroup-treatment interactions, or violations of distributional assumptions). Statistical properties to be evaluated should include Type I error, power, and sample size distributions, as well as the precision and bias in the estimation of treatment effects.

AT-2: Specify the structure and analysis plan for Bayesian adaptive randomized clinical trial designs

If a Bayesian adaptive design is proposed, the Bayesian structure and analysis plan for the trial must be clearly and completely specified. This should include any statistical models used either during the conduct of the trial or for the final analysis, prior probability distributions and their basis, utility functions associated with the trial's goals, and assumptions regarding exchangeability (of participants, of trials, and of other levels). Specific details should be provided as to how the prior distribution was determined and if an informative or non-informative prior was chosen. When an informative prior is used, the source of the information should be described. If the prior used during the design phase is different from the one used in the final analysis, then the rationale for this approach should be indicated. Computational issues, such as the choice of software, the creation and testing of custom

software, and software validation, should be addressed as well. Software used for Bayesian calculations during trial design, trial execution, and final analysis must be functionally equivalent. When feasible, software or programs should be made available to relevant stakeholders for evaluation and validation.

AT-3: Ensure that clinical trial infrastructure is adequate to support planned adaptation(s) and independent interim analyses

The infrastructure and processes for trial implementation must be able to support the planned adaptation. The study plan must clarify who will perform the analyses to inform adaptation while the study is ongoing and who will have access to the results. The interim analyses should be performed and reviewed independent from the investigators who are conducting the trial. Trial investigators should remain blinded to changes in treatment allocation rates as this information provides data regarding treatment success. Trials with more complicated requirements, such as frequent interim analyses, require thorough testing prior to trial initiation. Such testing should involve the trial's data collection and data management procedures, the implementation of the adaptive algorithm, and methods for implementing the resulting adaptation(s). The impact on the trial's operating characteristics of delays in collecting and analyzing available outcome data should be assessed.

AT-4: When reporting adaptive randomized clinical trials, use the CONSORT statement, with modifications

The following sections of the 2010 CONSORT statement can be used to report key dimensions of adaptation:

- Adaptation of randomization probabilities (sections 8b and 13a);
- Dropping or adding study arms (sections 7b and 13a);
- Interim stopping for futility and superiority (sections 7b and 14b);
- Sample size re-estimation (sections 7a and 7b);
- Transitioning of stages (e.g., seamless Phase II/III designs) (sections 3a, 7a, 7b, and 16); and
- Modification of inclusion and exclusion criterion (sections 4a and 13a).

CONSORT sections 16, 20, and 21 may also be expanded to report additional aspects of an adaptive trial.

If the trial incorporates adaptations other than those listed above, the authors should use their judgment as to where in the CONSORT structure to include both design details and the associated results. All possible adaptations included in the prospective design, even if they did not occur, should be included in the report.

10: Standards for Studies of Diagnostic Tests

DT-1: Specify clinical context and key elements of the diagnostic test

A comparative evaluation of diagnostic tests should specify each of the following items and provide rationale in support of the particular choices: 1) the intended use of the test and the corresponding clinical context, including referral for additional testing, referral for additional treatments, and modification of current treatment and target populations; 2) the goal of the comparison; 3) the technical specifications of the tests as implemented in the study; 4) the approach to test interpretation; 5) the

sources and process for obtaining reference standard information, when applicable; 6) the procedures for obtaining follow-up information and determining patient outcomes, when applicable; and 7) the clinical pathways involving the tests and the anticipated implications of test use on downstream processes of care and patient outcomes. These items ought to be specified for all designs, including observational designs (e.g., those using medical records or registries). If these items are not available directly, validated approaches to approximating these study elements from available data should be used.

DT-2: Assess the effect of factors known to affect diagnostic performance and outcomes

Studies of diagnostic tests should include an assessment of the effect of important factors known to affect test performance and outcomes, including the threshold for declaring a "positive" test result, the technical characteristics of the test and the interpreter, and the setting of care.

DT-3: Focus studies of diagnostic tests on patient-centered outcomes, using rigorous study designs with preference for randomized controlled trials

Studies related to diagnostic and therapeutic outcomes of diagnostic testing should use a prospective randomized study design when possible. If a non-randomized design is proposed, a rationale for using an observational study (or modeling and simulation) should be provided, and efforts to minimize confounding documented.

11: Standards for Systematic Reviews

SR-1 Adopt the Institute of Medicine (IOM) standards for systematic reviews of comparative effectiveness research, with some qualifications

Systematic reviews are used to answer questions based on comprehensive consideration of all the pertinent evidence, and can also identify the gaps in evidence and how they might be resolved. Standards for systematic reviews are currently in use, but credible authorities, such as Cochrane and the Agency for Healthcare Research and Quality (AHRQ), vary somewhat in their recommended standards. The IOM recently issued standards that draw broadly from available sources. The PCORI Methodology Committee endorses these standards but recognizes that there can be flexibility in the application of some standards without compromising the validity of the review, specifically:

- Searches for studies reported in languages other than English are not routinely recommended, but may be appropriate to some topics;
- Dual screening and data abstraction are desirable, but fact-checking may be sufficient. Quality control procedures are more important than dual review per se; and
- Independent librarian peer review of the search strategy is not required; internal review by experienced researchers is sufficient.

IOM (Institute of Medicine). Finding What Works in Health Care: Standards for Systematic Reviews. Washington, DC: The National Academies Press, 2011.

12: Standards on Research Designs Using Clusters

RC-1: Specify whether the study objectives, the interventions, and the primary outcomes pertain to the cluster level or individual level

a. Describe the target population of clusters and individuals to which the study findings will be generalizable.

b. Describe the clusters to be randomized and the subjects to be enrolled in the trial.

RC-2: Justify the choice of cluster randomization

Describe the benefits and disadvantages of cluster randomization versus individual-level randomization for the proposed research. Cluster randomization should be substantiated by a sound theoretical and conceptual framework that describes the hypothesized causal pathway. Cluster randomization generally is applicable when*:

a. An intervention is delivered at the cluster level

b. An intervention changes the physical or social environment

c. An intervention involves group processes, or

d. An intervention cannot be delivered without a serious risk of contamination

*Logistical considerations can also justify cluster randomization, for example to reduce costs or to improve participation, adherence, or administrative feasibility.

RC-3: Power and sample size estimates must use appropriate methods to account for the dependence of observations within clusters, and the degrees of freedom available at the cluster level

The methods used to reflect dependence should be clearly described. Sources should be provided for the methods and for the data used to estimate the degree of dependence. Sensitivity analyses incorporating different degrees of dependence must be reported.

a. For simpler designs, the dependence in the data can be reflected in the intraclass correlation.

b. Dependence can also be reflected in variance components.

c. Other factors that affect the power calculation include: the design of the study, the magnitude of the hypothesized intervention effect, the pre-specified primary analysis, and the desired Type I error rate.

RC-4: Data analyses must account for the dependence of observations within clusters regardless of its magnitude

Data analyses must also reflect the degrees of freedom available at the cluster level. Investigators must propose appropriate methods for data analyses with citations and sufficient detail to reproduce the analyses.

RC-5: Because cluster randomization trials often involve a limited number of groups or clusters, stratified randomization is recommended

Non-randomized intervention trials often involve a limited number of groups or clusters, and efforts should be made to balance treatment or study conditions on potential confounders.

a. The recommended stratification factors are those that are expected to be strongly correlated with the outcome or with the implementation of the intervention, such as:

   i. Baseline value of the outcome variable

   ii. Cluster size

   iii. Geographic area

Attachment B to the Minutes of the December 7, 2015 PCORI Board of Governors Meeting

Draft as of December 7, 2015

Charter for Selection Committees

Selection Committee(s) of the Patient-Centered Outcomes Research Institute (PCORI) shall advise the Board of Governors and PCORI by reviewing individual awards or slates of awards proposed for funding by PCORI staff after the merit review process is completed. The Committee(s) will prepare funding recommendations to the Board of Governors for approval. Selection Committee(s) shall serve as advisory committee(s) and shall not have delegated authority of the Board.

It is expected that there will be one Standing Selection Committee charged with making recommendations on slates of awards that result from PCORI's funding announcements, including Broad PFAs, Targeted PFAs, and pragmatic clinical studies funding announcements. However, at any given time, due to the volume of award decisions or the timing of award cycles, the need for specialized expertise, special circumstances, or other factors, the Board Chairperson may appoint one or more additional ad-hoc member(s) to serve on the Standing Selection Committee or additional Special Selection Committees may be established other than the Standing Selection Committee.

This Charter establishes the framework for establishing the Standing Selection Committee and any additional Special Selection Committees (each, "a Selection Committee") as well as the responsibilities of any Selection Committee. Each Selection Committee shall operate consistently with this Charter.

Establishment of a Selection Committee and Membership
The Chairperson of the Board shall be charged with establishing any Selection Committee and appointing its members and the Chair (and a Vice-Chair if desired), in consultation with the Chair of the Science Oversight Committee and the Executive Director. The Chairperson of the Board shall inform the Board of the establishment of any Selection Committee.

A Selection Committee shall consist of at least three (3) members. Membership of a Selection Committee shall be composed of no more than ten (10) Board members and may include one or more members of the Methodology Committee. Board members of a Selection Committee shall constitute the majority of the Selection Committee's members. The members of a Selection Committee shall include the Chair and any Vice-Chair of the Selection Committee.

The Chair of the Science Oversight Committee may be one of the Standing Selection Committee members, but, if appointed, need not serve as the Standing Selection Committee Chair.

The Chair of the Standing Selection Committee shall serve a term of one (1) year and can serve as Chair for no more than four (4) consecutive terms. If a Vice-Chair for the Standing Selection Committee is appointed, the Vice-Chair shall serve a term of one (1) year and can serve no more than four (4) consecutive terms as Vice-Chair.

Standing Members of the Standing Selection Committee will serve a term of one (1) year and may be reappointed to any number of additional one-year terms by the Chairperson of the Board, in consultation with the Chair of the Science Oversight Committee and the Executive Director. Any ad-hoc members appointed to the Standing Selection Committee shall serve for such time as determined by the Chairperson of the Board, in consultation with the Chair of the Science Oversight Committee and the Executive Director.

The Chair, any Vice-Chair, and the members of a Special Selection Committee shall serve a term as determined by the Board Chairperson, in consultation with the Chair of the Science Oversight Committee and the Executive Director, taking into account the purpose of the Special Selection Committee.

Quorum and Voting
A quorum shall consist of a majority of a Selection Committee. The act of a majority of the members present at a meeting at which a quorum is present shall be the act of a Selection Committee.

Selection Committee Operations
A Selection Committee shall meet upon the call of the Standing Selection Committee Chair, generally aligned with the timing of cycles and processes for merit review and selection of research funding applications, or upon the call of the Board Chairperson, provided that reasonable notice has been provided to all the Selection Committee members.

Meetings may be held in person, by teleconference, or by other electronic means that allow appropriate participation by all members present at the meeting. A Selection Committee shall be staffed by the Science program staff and by such other staff as the Chief Science Officer, with the counsel of the applicable Selection Committee, deems appropriate.

Selection Committee Responsibilities
A Selection Committee shall have responsibilities on the following matters, as well as any other responsibilities reasonably related to its purposes or assigned by the Chairperson of the Board or the Board of Governors:

- Advise the Board of Governors and PCORI by recommending slates of awards for Board approval, considering the following: scoring by merit review panels, scientific program staff recommendations, programmatic fit, portfolio balance, consistency with applicable funding announcement, possible duplication of previously funded research and/or methodological concerns, as appropriate; and,
- Operate consistently with applicable Conflict of Interest policies, procedures, and guidelines.

The Standing Selection Committee will annually review the Selection Committee Charter and the Selection Committee's performance and make appropriate recommendations to the Board.

History:
Approved by the PCORI Board of Governors July 29, 2014