

## Full Text of Standards and Recommendations

Changes since Version for Public Comment.

Key: Black = Text from Version for Public Comment; [Blue](#) = new text; ~~Strikethrough~~ = deletions

Standards for Formulating Research Questions	
3.1.0	<p><b>Identify Gaps in Evidence (formerly 5.1.1)</b></p> <p>Gap analysis and 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, (<a href="#">see Standard 6.1.1</a>) 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.</p>
3.1.1	<p><b>Develop a Formal Study Protocol</b></p> <p>In addition to the general study protocol standards, registry studies should include a formal study protocol specifying: at least one purpose of the registry (e.g., effectiveness, safety, natural history of disease, quality improvement, or other); data sources and linkage plans, if any; <a href="#">data feasibility and quality</a>, measure(s) of effect; and use of any standardized data dictionaries (nationally or internationally accepted).</p>
3.1.2	<p><b>Identify Specific Populations and Health Decision(s) Affected by the Research</b></p> <p>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.</p>
3.1.3	<p><b>Identify and Assess Participant Subgroups</b></p> <p>In designing studies, researchers should identify participant subgroups of interest and, where feasible, design the study with adequate precision and power to reach conclusions specific to these subgroups. In addition, subgroup information should be reported for later systematic reviews.</p>
3.1.4	<p><b>Select Appropriate Interventions and Comparators</b></p> <p>When evaluating an intervention, the comparator treatment(s) must be chosen to enable accurate evaluation of effectiveness or safety compared to other viable options for similar patients. Researchers should make explicit what the comparators are and how they were selected, focusing on clearly describing how the chosen comparator(s) define the causal</p>

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.

### 3.1.5

#### **Measure Outcomes that People in the Representing the Population of Interest Notice and Care About**

Identify and ~~select~~ **include** outcomes the population of interest notices and cares about (e.g., survival, function, 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 “~~clinically meaningful,~~” “patient-centered,” and “relevant to decision-makers,” such as patient and decision-maker input from meetings, ~~or~~ surveys, or published **studies** ~~literature relevant to the question of interest.~~ Select outcomes based on input directly elicited from patient informants, ~~persons~~ **people** representative of the population of interest, either in previous studies or in the proposed research.

## Standards Associated with Patient-Centeredness

### 4.1.1 **Engage ~~Patient Informants, Persons Representative of the Population of Interest,~~ people representing the population of interest and other relevant stakeholders in ways that are appropriate and necessary in a given research context.** ~~in All Phases of PCORI~~

~~Patient informants include~~ People representing the population of interest include individuals who have the condition or who are at risk of the condition, and as relevant, their surrogates or caregivers. Other relevant stakeholders may include clinicians, administrators, policy makers, or others involved in health care decision making. Stakeholders can be engaged in:

- 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
- ~~Taking part in disseminating results~~ Designing/suggesting dissemination and implementation activities.

When applicable research proposals should ~~1) describe how these stakeholders~~ people representing the population of interest ~~patient informants~~ will be: identified, recruited, and retained. If engagement is not necessary or appropriate in these processes, explain why.

~~involved in determining the study design and monitoring of its conduct; and involved in dissemination of research results, and 2) state how the research process will follow PCOR principles of trust, transparency, co-learning, respect, and partnership.~~

### 4.1.2 **Identify, Select, Recruit, and Retain Study Participants Representative of the Spectrum of the Population of Interest ~~Facing the Health Decision 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 health care research such as those with multiple disease conditions, low literacy, low socioeconomic status, or poor health care 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.

#### 4.1.3 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.](#)

#### 4.1.4 [Support dissemination and implementation of study results.](#)

[Support dissemination and implementation of study results by suggesting strategies, indicating clinical and policy implications, and working with patients or organizations to report results in a manner understandable to each target audience](#)

#### ~~Develop and Implement a Dissemination Assessment to Achieve Broad Awareness of Study Results~~

~~PCOR research proposals and protocols must include an assessment that describes how the project and the composition of the research team supports dissemination and the anticipated facilitators, barriers and potential strategies for dissemination to key stakeholder groups, including patients and individuals at risk of a condition, clinicians and other health care system staff, and policy leaders. Effective dissemination includes the reporting of results in a manner understandable to each target audience, information regarding the relevance of the results for decision-making (recognizing that research findings from a single study alone should not necessarily affect decision-making or practice), along with attention to how the results can be incorporated into health decision-making if applicable. The plan must specify how the dissemination strategy is expected to affect the identified~~



health decisions and how dissemination engages the study participants or the population of interest. Requiring research dissemination, as well as engagement of patients and other stakeholders at this stage of research, represents a cultural shift for many institutions and researchers.

## Standards for Prioritizing Research

### 5.1.1 ~~Moved to 3.1.0 Use Systematic Reviews to Identify Gaps in Evidence~~

~~[Highlight reflects NEW proposed revisions]~~

~~Gap analysis and of systematic reviews should be used to support the need for a proposed study as part of the process of identifying and prioritizing research gaps to establish funding priorities by PCORI. If a systematic review is not available, a systematic review should be performed using accepted standards in the field, (see Standard 6.1.1) 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.~~

### 5.1.2 ~~Moved to Recommendations Protect Independence in Peer Review of Research Funding Proposals~~

~~Adopted methods of peer review should aim to safeguard independence between reviewers and those being reviewed.—Note: Moved to recommendations~~

### 5.1.3 ~~Moved to Recommendations Ensure Adequate Representation of Minorities and Disadvantaged Segments of the Population in Peer Review of Research Funding Proposals~~

~~Approaches to topic generation in PCOR should involve both consultative and collaborative functions.—Note: Moved to recommendations~~

## Standards for SYSTEMATIC REVIEWS

### 6.1.1

#### NEW STANDARD

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 AHRQ, vary somewhat in their recommended standards. The Institute of Medicine recently issued standards that draw broadly from available sources. ~~However not all standards are based on empiric evidence and reliable systematic reviews may use alternative approaches~~ The methodology committee endorses these standards but recognize that there can be flexibility in the application of some of standards without compromising the validity of the review, specifically: The Methodology Committee make the following qualifications to the IOM standards:

- 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.
- 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.)

## General and Crosscutting Methods For All PCOR

### 7.1.1 Assess Data Source Adequacy

In selecting variables for confounding adjustment, researchers should assess the suitability of the data source in terms of its ability to assure robust capture of needed covariates.

NEW

### 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, and (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

### 7.1.2 A priori, Specify Plans for Data Analysis that Correspond to Major Aims

Researchers should describe the analytic approaches that will be used to address the major research aims prior to data collection. These include definitions of key exposures, endpoints, and covariates. 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.

### 7.1.3 Document Validated Scales and Tests

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

### 7.1.4 Use Sensitivity Analyses to Determine the Impact of Key Assumptions

The results of these sensitivity analyses should be reflected in the interpretation of results.

### 7.1.5 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](http://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), and STROBE (for observational studies).

## Causal Inference Standards

### 7.2.1 Define Analysis Population Using Covariate Histories Information Available at Study Entry

Decisions about whether patients are included in an analysis should be based on information available at each patient's time of study entry ~~and not based on future information such as future changes in exposure~~ 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 the covariates history up to and not beyond those time points should be used as population descriptors.

### 7.2.2 Describe Population that Gave Rise to the Effect Estimate(s)

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).

### 7.2.3 Precisely Define the Timing of the Outcome Assessment Relative to the Initiation and Duration of Intervention-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 the timing of the outcome assessment relative to the initiation and duration of ~~the intervention~~ exposure.

### 7.2.4 Measure Confounders before Start of Exposure. Report data on 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 therapy (or therapies) 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.

### 7.2.5 ~~Assess~~ Report the assumptions underlying the construction of Propensity Scores balance and the comparability of the resulting groups in terms of the balance of covariates and overlap.

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

### 7.2.6 Assess the Validity of the Instrumental Variable (i.e. how the assumption are met) and report the balance of covariates in the groups created by the IV for all IV analyses. ~~Assess the validity of the IV (i.e. how the assumption are met) and report the~~

balance of covariates in the groups created by the IV. )if it meets the assumption, and

**An instrumental variable (IV) is an observed measurable variable that induces or is associated with use of an intervention.** **When** an IV approach is used, 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).

## Standards for Heterogeneity of Treatment Effect (HTE)

### 7.3.1 State the Goals of HTE Analyses

State the inferential goal of each HTE analysis specifying how it is related to the topic of the research, translate this into an analytic approach and highlight the linkages between the two. Identify each analysis as either hypothesis driven (sometimes denoted confirmatory) or hypothesis generating (sometimes denoted exploratory). confirmatory, descriptive, or exploratory. See Table 7.1 comparing the different types of HTE analyses.

### 7.3.2 For ~~all Confirmatory and Descriptive~~ HTE Analyses, Pre-specify the analysis plan Subgroups and Outcomes; for Hypothesis driven confirmatory HTE Analyses, Pre-specify Hypotheses for Each-Subgroup Effect.

The study protocol should unambiguously pre-specify planned ~~confirmatory~~ HTE analyses. Pre-specification of hypothesis driven confirmatory HTE analyses should include a ~~public record with~~ a clear statement of the hypotheses the study will evaluate, including the definitions of subgroup variables and outcomes, and the direction of the expected treatment effects: how groups will be defined (e.g. by multivariate score or stratification) and outcome measures, and the direction of the expected treatment effects. The prespecified hypotheses should be based on prior evidence which should be described clearly in the study protocol and published paper. ~~be available for review and the study protocol should present this~~ The hypotheses for descriptive HTE need not be pre-specified; rather, specify the subgroups to be studied, as one goal is to facilitate future meta-analyses.

### 7.3.3 For ~~Hypothesis Testing~~ Confirmatory Analyses, Report ~~a priori~~ Statistical Power

Studies should calculate and report the power to detect treatment effects in each subgroup and to detect the interaction between the treatment and the subgrouping variable (i.e., the power to test whether the effects are statistically different between particular subgroups).

### 7.3.4 All HTE claims must be based on appropriate statistical contrasts among groups being compared, such as interaction tests or estimates of differences in treatment effect.

#### ~~For Any HTE Analysis, Perform an Interaction Test and Report Sufficient Information on Treatment Effect Estimates~~

A common error in HTE analyses is to claim differences in treatment effect when one group shows a statistically significant treatment effect and another does not. To claim differences in treatment effect among subgroups, appropriate statistical methods must be used to directly contrast them. Such contrasts 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. Within each subgroup level, studies should present the treatment effect estimates and measures of variability.

To detect differences in treatment effect between subgroups, use an interaction test (i.e., test whether the interaction between the treatment indicator and the subgroup variable is statistically significant). Within each subgroup level, studies should present the treatment effect estimates, standard errors, 95 percent confidence intervals, and appropriate statistic. Studies should also report result of the statistical test for the interaction (e.g. p-value or Bayes factor) interaction test for each subgrouping variable. For descriptive analyses, studies should also consider presenting a forest plot as a visual summary of the results, although such forest plots should not be used to infer HTE.

7.3.5

### **For Hypotheses generating Exploratory HTE Analyses, Discuss Findings in the Context of Study Design and Prior Evidence**

Hypothesis generating Exploratory HTE analyses should be presented in the context of whether they are consistent with prior evidence and how well the study design addresses the HTE question. These considerations are more important than P-values for inferences

7.3.6

### **For Any HTE Analysis, Report All Pre-specified Analyses and, at Minimum, the Number of Post-hoc Analyses, Including Number of 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, (e.g. by categorical predictors or continuous risk scores), and the effective number of subgroups and outcomes examined. If a non-prespecified stratum or subgroup is claimed to show a treatment effect that is different from others, methods should be used that account for the number of contrasts examined. 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).

Studies must report the results of all the HTE analyses that were pre-specified in the study protocol or grant application conducted regardless of their statistical significance or Bayes Factors. Reports of hypothesis testing HTE should account for multiple tests or the ensemble of estimates. HTE analyses that did not pre-specify subgroups should clearly report the number of subgroups and outcomes analyzed.

## Standards for Preventing and Handling Missing Data

### 7.4.1 Describe in Protocol Methods to Prevent and Monitor Missing Data

Investigators should explicitly anticipate potential problems of missing data. The study protocol should contain a section that addresses missing data issues and steps taken in study design and conduct to monitor and limit the impact of missing data. Missingness can occur from patient dropout, failure to provide data, and/or administrative or data management issues. As relevant, the protocol should include the anticipated amount of and reasons for missing data, as well as plans to follow up with participants. This standard applies to all study designs for any type of research question.

### 7.4.2 Describe Statistical Methods to Handle Missing Data in Protocol

Statistical methods for handling missing data should be pre-specified in study protocols. The reasons for missing data should be considered in the analysis. The plausibility of the assumptions associated with the approach should be assessed. A [discussion of the potential ramifications of the approach to missing data](#) ~~choice~~ [on the results](#) should be provided. ~~stated in a way that can be understood by stakeholders.~~ This standard applies to all study designs for any type of research question.

### 7.4.3 Use Validated Methods to Deal with Missing Data that Properly Account for Statistical Uncertainty Due to Missingness, ~~Such as Multiple Imputation; All Forms of Single Imputation Is Discouraged~~ [Highlight reflects NEW proposed revisions]

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 have valid type I error rates and that confidence intervals should have the nominal coverage properties. This standard applies to all study designs for any type of research question. [Bayesian imputation methods and frequentist methods such as multiple imputation](#) satisfy this condition, along with various likelihood-based and other validated methods. Single imputation methods like last observation carried forward and baseline observation carried forward 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 why the method is appropriate.](#)

### 7.4.4 Record and Report All Reasons for Dropout and Missing Data, and Account for All Patients in Reports

Whenever a participant [drops out of](#) ~~discontinues some or all types of participation in a~~ research study, the investigator should document the following: 1) the [specific](#) reason for [drop out is continuation in as much detail as possible](#); 2) who [decided](#) that the participant would [dropout](#) and 3) whether the ~~discontinuation~~ [drop out](#) involves some or

all types of participation. Investigators should **attempt to** continue to collect information on key outcomes for participants **unless consent is withdrawn** who ~~discontinue their protocol-specified intervention~~. This standard applies to all prospective study designs that aim to assess intervention effectiveness. All participants **included in** who ~~enter~~ the study should be accounted for in the report, whether or not they are included in the analysis. Describe and justify any planned reasons for excluding participants from analysis. ~~This standard applies to all study designs for any type of research question.~~

#### 7.4.5 **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** ~~Tables 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.** ~~Potential bias resulting from imperfect definitions should be discussed with an estimate of the change in the direction and magnitude of the effect due to bias.~~ These quantitative results should be incorporated into the interpretation of the study and reflected in the discussion section and possibly the abstract. ~~If there are big effects, help the user further understand the reason for the missing data and the effect of the missingness on the findings.~~

## Standards for Data Networks

### DATA Networks Standards are Reorganized

#### 7.5.1 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 assure appropriate privacy, confidentiality, and intellectual property protections:

#### 7.5.1 **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 either a) transform and standardize data elements prior to analysis or b) 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.

#### 7.5.2 **B. Risk Assessment Strategy**

Data custodians should ~~assess the uniqueness of records (i.e., no other records have the same values) of patient records~~ to measure risk of re-identification risk of data and apply algorithms to ensure that the desired level of confidentiality is achieved to meet the need of the particular PCOR application.

#### 7.5.3 **C. Identity Management and Authentication of Individual Researchers**

Develop a reliable process for verifying credentials of researchers who are granted access to a distributed research network and authenticating them.

#### 7.5.4 **D. Intellectual Property Policies** [**Recommend PCORI legal counsel review wording**]

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 and (2) making the fruits of research widely accessible, particularly to the people who need them the most.

#### 7.5.5 **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 the party using the data.

#### 7.5.6 **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. A data element is the entity and its property described with a given data. A data element is defined with a set of metadata.

7.5.7

### **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.

7.5.2

### **Standard 7.5.2: Standards for Selection and Use of Data Networks**

Researchers planning PCOR studies relying on data networks must assure that these networks meet the requirements contained in Standard 7.5.1, and 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 7.5.1.

## Standards for Adaptive and Bayesian Trial Designs

### 8.1.1 Specify Planned Adaptations and Primary Analysis

The adaptive clinical trial design should be prospectively planned and the design clearly documented, including:

- All potential adaptations, including timing;
- Trial results and populations that will be used in determining each adaptation;
- Statistical models to be used; and
- Planned analysis of the primary endpoint(s).

The description of the design should be sufficiently detailed that it could be implemented from the description of procedures. The specification of the design should be completed and documented in the trial protocol before enrollment begins. This specification should include, in all but the simplest designs, a Statistical Analysis Plan (SAP) that is separate from the trial protocol in which all necessary detail is provided regarding planned interim and final analyses. Prior specification is a prerequisite for valid and meaningful evaluation of an adaptive design.

### 8.1.2 Evaluate Statistical Properties of Adaptive Design

While not necessary for simple designs, the statistical properties of complex 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. Additional performance metrics may also be evaluated (e.g., the frequency with which specific adaptations occur, the likelihood of substantial covariate imbalance, the likely adequacy of final data for subgroup and safety analyses).

The programming code used to create the simulations should be retained with version control. The programming code and software used should be made available to stakeholders who have a need to know, including reviewing agencies.

### 8.1.3 Specify 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. Utility functions, if employed, should be defined and their source should be described. 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.

#### 8.1.4 **Ensure Clinical Trial Infrastructure Is Adequate to Support Planned Adaptation(s)**

The clinical trial infrastructure, including centralized randomization, data collection related to the assessment and recording of key outcomes, data transmission procedures, and processes for implementing the adaptation (e.g., centralized, web-based randomization), must be able to support the planned trial. In simple adaptive trials, qualitative verification of the capabilities of the proposed trial infrastructure may be adequate. 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. [The study plan should 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 by an analytical group that is 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.](#)

#### 8.1.5 **Use the CONSORT statement, with Modifications, to Report Adaptive Randomized Clinical Trials**

The following sections of the 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.

## Standards for Data Registries

### 8.2.1 ~~Describe Data Linkage Plans, if Applicable~~ [This has been moved after 7.1.1](#)

#### Standards were reorganized to be similar to Data Networks

~~For studies involving linkage of registry data with another data source, describe the other data source and its appropriateness and limitations for addressing specific hypotheses. Consider any additional requirements that may influence successful linkage, such as information needed to match patients, selection of data elements, and definitions used.~~

### 8.2.1 [Requirements for the Design and Features of Registries](#)

[Registries established for conducting PCOR must have the following characteristics to facilitate the collection and aggregation of usable data, to assure appropriate privacy and confidentiality, to document changes to the registry protocol and all robust analyses that includes important confounders.](#)

### 8.2.2 ~~Plan Follow-up Based on the Registry Objective(s)~~

#### A. Patient Follow-up

The objective(s) of the registry should determine the type, extent, and length of patient follow-up. Describe what triggers the follow-up, the follow-up measures, and the last contact with the patient. Ensure that the planned follow-up time is adequate to address the main objective and that planned patient-retention efforts are suitable to the target population and anticipated challenges. Describe expected loss to follow-up and potential effect on the results, including possible biases resulting from differential loss.

### 8.2.3 ~~Describe~~ B. Data Safety and Security

Research proposals and protocols should [provide transparency for institutional review boards by describing](#) ~~describe~~ data use agreements, informed consent, data security, and approaches to protecting security including risk of re-identification of patients. If using previously collected data, describe how these address the risk of re-identification of patients and the actual use of data compared with the originally designed and consented use of the data.

### 8.2.4 ~~Take Appropriate Steps to Ensure~~ C. Data Quality Assurance

~~Create a~~ [A quality assurance plan for registries should that](#) addresses: 1) structured training tools for data abstractors; 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 [and validation statistics](#) focused on the key exposure and outcome variables and covariates for which sites may be especially challenged. A risk-based approach to quality assurance is advisable, focused on variables of greatest importance.

### 8.2.5 D. Document and Explain Any Modifications to the Protocol

Modifications to a registry protocol may be necessary for a variety of reasons. When modifications are necessary, document and explain any modifications to the formal study protocol.

#### 8.2.6 **E. ~~Collect Data Consistently~~ Data Collection**

~~Provide~~ Clear, operational definitions of data elements [should be provided](#). Create and distribute standard instructions to data collectors. Use standardized data element definitions and/or data dictionaries whenever possible. When creating a new registry, researchers should review published literature to identify existing, widely-used definitions before drafting new definitions.

#### 8.2.7 **F. Systematic Patient Enrollment and Follow-up Patients Systematically**

Enroll patients systematically and follow them in as unbiased a manner as possible, using similar procedures at all participating sites. Describe how patients and providers were recruited into the study to allow the impact of selection bias to be clearly understood [for example, by explaining whether the sampling was population-based or otherwise](#) and any efforts employed to confirm the quality of adherence to agreed-on enrollment practices.

#### 8.2.8 **G. Monitor and ~~Take Actions to Keep Loss to Follow-up to an Acceptable~~ Minimize Loss to Follow-up**

Monitor loss to follow-up to ensure that follow-up is reasonably complete for the main objective. Minimizing loss to follow-up requires having a target and advance planning for what actions will be employed in the event that this target is in jeopardy. At the outset of the registry, develop a patient retention plan that documents when a patient will be considered lost to follow-up and what actions will be taken to minimize such loss. At the enrollment visit, consider collecting multiple types of contact information (e.g., telephone, mailing address, and e-mail address) for the patient, as well as collecting contact information for an alternate contact if the patient cannot be reached directly. Verify contact information at each subsequent visit and update as needed. When a patient misses a visit, contact the patient following a standard protocol (e.g., phone call one day after missed visit, email one week after missed visit). If the patient withdraws from the registry, attempt to document the reason for withdrawal so that issues can be identified and addressed (e.g., overly burdensome patient-reported outcome measures). Efforts at minimizing loss to follow-up should be tempered by considerations and sensitivity to repeated intrusions on patients and to the health conditions and interventions under study. Consider collecting enough information to permit accurate linkage with other data sources, such as the National Death Index, for long-term follow-up.

#### 8.2.9 **H. Use ~~Appropriate Statistical Techniques~~ [Collect Data](#) to Address Confounding**

Registries should identify important potential confounders 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. ~~For registries that are intended~~

to evaluate the comparative effectiveness or safety of interventions, investigators should select an approach for adjusting for known and measured confounders, such as multivariable regression analysis or propensity scores to create matched comparison groups or an instrumental variable analysis if a valid instrument is available. It is also desirable to examine the robustness of the results through sensitivity analyses focused on testing key assumptions and evaluating the likely impact of unmeasured confounders. The rationale for using selected techniques, any assumptions made, and the strengths and limitations of the techniques should be described in reports of the study findings to allow for informed interpretation of the results. [Moved to below](#)

### 8.2.2

#### **Standards for Selection and Use of Registries**

Researchers planning PCOR studies relying on Registries must assure that these meet the requirements contained in Standard 8.2.1 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 should be justified by explaining why a required feature is not feasible or not necessary to achieve the overall goals of Standard 8.2.1

### 8.2.3

#### **Robust Analysis of Confounding Factors**

~~For registries that are intended~~ [In studies that use registries](#) to evaluate the comparative effectiveness or safety of interventions, investigators should select an approach for adjusting for known and measured confounders, such as multivariable regression analysis or propensity scores to create matched comparison groups or an instrumental variable analysis if a valid instrument is available. It is also desirable to examine the robustness of the results through sensitivity analyses focused on testing key assumptions and evaluating the likely impact of unmeasured confounders. The rationale for using selected techniques, any assumptions made, and the strengths and limitations of the techniques should be described in reports of the study findings to allow for informed interpretation of the results.

## Standards for Studies of Diagnostic Tests

### 8.3.1 Specify Clinical Context and Key Elements of Diagnostic Test Study Design

A comparative evaluation of diagnostic tests should specify each of the following items and provide rationale in support of the particular choices: (a) 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; (b) the goal of the comparison; (c) the technical specifications of the tests as implemented in the study; (d) the approach to test interpretation; (e) the sources and process for obtaining reference standard information, when applicable; and (f) the procedures for obtaining follow-up information and determining patient outcomes, when applicable. 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.

### 8.3.2 Study Design Should be Informed by Investigations of the Clinical Context of Testing

Design of comparative effectiveness studies should outline clinical pathways involving the tests and the anticipated implications of test use on downstream processes of care and patient outcomes. In the written research methods and study protocol, investigators should give examples of clinical pathways to demonstrate thorough understanding of the clinical context.

### 8.3.3 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.

### 8.3.4 Structured Reporting of Diagnostic Comparative Effectiveness Study Results

Broadly accepted checklists for reporting studies and assessing study quality, such as CONSORT, STARD, and QUADAS, should be consulted and utilized. Consult the CONSORT 2010 checklist for reporting randomized controlled trials. Consult the STARD checklist for reporting diagnostic accuracy studies. Consult the QUADAS-2 (updated in 2011) for additional guidance on reporting information that would be more useful to systematic reviews of diagnostic accuracy studies.

### 8.3.5 ~~Give Preference to Randomized Designs of Studies of Test Outcomes~~

[Focus studies of diagnostic tests on patient centered outcomes, using rigorous study designs with preference for randomized controlled trials](#)



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

## Recommended Actions

Topic	Action
Standards for Formulating Research Questions	<ul style="list-style-type: none"> <li>• The Methodology Committee recommends that PCORI develop policies to encourage public registration of all PCORI studies and the sharing of study protocols, statistical code, and data.</li> <li>• Form a standing committee within PCORI to recommend appropriate methods for data sharing and to ensure that proper scientific credit is given to those sharing protocols, code, and data.</li> <li>• To speed implementation of standards in funding announcements, peer review, and other internal processes, PCORI staff should develop or have developed templates for the preparation and review of proposals that incorporate the key elements of the standards. Because some standards apply only to certain types of studies, a portfolio of templates applicable to various study designs should be developed.</li> </ul>
Patient Centeredness	<ul style="list-style-type: none"> <li>• Support training in patient engagement methods for investigators <del>and patient informants.</del></li> <li>• Develop a sample patient engagement plan to demonstrate the key elements required for patient engagement in the research process. The sample plan should illustrate engagement of both patient <u>representatives</u> and study participants <u>to facilitate investigator adherence to PCORI standards.</u></li> <li>• <u>Develop PCORI infrastructure and services to support and facilitate investigators' engagement activities. These services might include support for identification and recruitment of patient representatives, support for the selected representatives' (and other stakeholders') involvement in PCORI-funded research, and other activities.</u></li> <li>• Improve the patient-reported outcomes (PRO) evidence base by supporting research on methods for assessing measurement properties (based on qualitative and quantitative evaluations), score interpretability, meaningfulness of score changes, and strategies for minimizing and interpreting missing PRO data in PCOR.</li> <li>• Evaluate patient dissemination activities and require incorporation in future research of relevant learnings from this evaluation.</li> <li>• <del>Create an infrastructure to support research on patient engagement. To facilitate this, PCORI should:</del></li> <li>• <del>Systematically collect information about patient engagement methods from PCORI-sponsored studies.</del></li> <li>• <del>Evaluate the effectiveness of patient informant engagement.</del></li> <li>• <del>Synthesize results across studies.</del></li> </ul>

- ~~Disseminate findings to improve patient engagement in PCOR.~~

## Dissemination

The following actions are recommended for PCORI to adopt, in collaboration and partnership with AHRQ, in order to better achieve and enable effective dissemination of study results:

- Support training in research dissemination methods for investigators.
- Develop a sample dissemination plan to demonstrate the desired features of a dissemination assessment plus sample guidance for dissemination and implementation activities.
- Develop PCORI/AHRQ infrastructure and services to achieve and support effective dissemination of PCORI-funded research. These services might include a PCORI website and dissemination team responsible for posting (a) summaries of study findings written in lay language suitable for consumers and other stakeholders plus (b) listings and links to presentations and publications reporting study results; established communication channels with relevant media and the development of press releases and other dissemination activities for particularly significant findings; support and partnership with investigators to identify and contact key stakeholder groups likely to be interested in study results; and other activities that will achieve efficient, effective, standardized dissemination of PCORI-funded research in a manner that optimizes PCORI and AHRQ resources and capabilities and recognizes the efficiency inherent in centralized dissemination as well as limitations in researchers' capacity and ability to disseminate findings to the full range of relevant stakeholders.

## Research Prioritization

Work closely with the Methodology Committee to build on previous work and implement the framework efficiently.

- Approaches to topic generation in PCOR should involve both a process by which the public is encouraged to provide perspectives on topics (consultative) and a process by which the public is empowered to become active partners with other stakeholders in developing topics (collaborative) functions
  - Base all PCORI targeted funding opportunity announcements on evidence gap analysis.
  - Require that applicants demonstrate how their proposed research fills a research gap for non-targeted funding opportunity announcements.
  - Support education and training activities to broaden the base of individuals prepared to apply and evaluate VOI.
  - Maintain peer review processes that avoid interference of participants

General and Crosscutting Methods for All PCOR

Design-specific Methods – TAB H

and stakeholders with potential conflicts of interest. Peer review should incorporate patient perspectives.

- [Protect independence in peer review of research funding proposals. Methods of peer review should be adopted to safeguard independence between reviewers and those being reviewed.](#)
- [Ensure adequate representation of minorities and disadvantaged segments of the population in peer review of research funding proposals.](#)
- Sponsor randomized trials alongside registry studies to compare the validity of different methods for reducing confounding and bias.
- Develop and disseminate software needed for sensitivity analyses and approaches to evaluating the assumptions underlying complex analyses such as instrumental variable analyses.
- Develop education and training for consumers of research on various research methodologies with a focus on newer methods used to control for confounding.
- [Identify or support the development and distribution of software to reduce barriers that inhibit the use of more rigorous methods for handling missing data.](#)
- Provide training in methods for the following as they specifically relate to PCOR
  - systematic reviews,
  - modeling,
  - addressing missing data.
- Promote accumulation of evidence to supplement common practices as guidance for future development of data network structures.
- [Develop detailed guidance for best practices in the design and management of data networks to meet the requirements contained in Standard 7.5.1.](#)
- [Develop guidance and tools for researchers to use in assessing the features of a data network and for determining and documenting adherence to Standard 7.5.1.](#)
- [Identify and promote use of approaches to privacy protection in data networks that also consider how to enhance data utility](#)
- [Identify best practices and develop guidance for data network developers to overcome challenges to linking patient-level data derived from different sources.](#)
- Support development and use of software for adaptive trials that can simulate complex designs.
- Broaden experience with adaptive trials for PCOR, perhaps through funding of a cohort of adaptive trials on priority topic areas.
- Mentor investigators and develop a “how to” guide and a forum to share experiences with adaptive trials.

- Develop coursework and other training opportunities for statisticians and other methodologists interested in developing expertise in adaptive trials.
- [Encourage a program of research that examines whether using adaptation in clinical trials biases the results of those trials and the effectiveness of methods to ameliorate such biases.](#)
- Sponsor an Institute of Medicine committee to develop standards for research on medical tests.
- Encourage and actively seek alternatives to prospective randomized study designs for studying clinical outcomes after diagnostic testing

## Research Recommendations

Topic	Research Recommendations
Patient Centeredness	<ul style="list-style-type: none"> <li>• <del>Support research to develop a standardized nomenclature for patient engagement methods.</del></li> <li>• <a href="#"><u>Support and facilitate research on patient engagement by systematically collecting and funding the analysis of information about patient engagement methods from PCORI-sponsored studies.</u></a></li> <li>• <a href="#"><u>Support and facilitate research on methods for, and impacts of, engaging people representative of the population of interest during design and conduct of PCOR.</u></a></li> <li>• Disseminate findings <a href="#"><u>from these research activities</u></a> to improve patient engagement in PCOR.</li> <li>• <a href="#"><u>Support research to improve the patient-reported outcomes (PRO) evidence base, by supporting including research on methods for assessing measurement properties (based on qualitative and quantitative evaluations), score interpretability, meaningfulness of score changes, and strategies for minimizing and interpreting missing PRO data in PCOR.</u></a></li> </ul>
Dissemination	<ul style="list-style-type: none"> <li>• <a href="#"><u>Support and facilitate research on research dissemination by systematically collecting and funding the analysis of data measuring the impacts and effectiveness of PCORI/AHRQ dissemination activities.</u></a></li> <li>• <a href="#"><u>Support health-related dissemination and implementation research to better understand barriers, facilitators and effective strategies for disseminating and facilitating the implementation of PCOR and CER, including dissemination and implementation by consumers and patients, clinicians and other healthcare and public health professionals and organizations, policy and regulatory agencies, and other stakeholders.</u></a></li> <li>• <a href="#"><u>Disseminate findings from these research activities to improve PCOR and</u></a></li> </ul>

## Research Prioritization

### CER dissemination and implementation effectiveness.

- Encourage intra- and extramural research in the development and practical application of VOI methods for PCOR, including through studies that examine the contribution of VOI methods to research prioritization when used in conjunction with other approaches to research prioritization.
- Support empirical research to assess and improve research prioritization methods for use by PCORI.
- Support extra- and/or intramural research to establish a best practice approach to consultative and collaborative patient engagement in topic generation that is suitable for the heterogeneity of the US patient population.
- Study the employment of research gap analysis to continue to develop the empirical evidence on its use.
- Encourage studies, ideally with experimental designs, that assess different methods for engaging patients with diverse views and preferences and funneling their input into the peer review process in a consultative manner.

## General and Crosscutting Methods

- Fund research on innovative ways to identify and recruit new users of treatment for research studies.
  - Fund research on ways to identify and include reasonable treatment alternative comparators.
  - Further dDevelop and disseminate templates for describing who is in each analysis and the potential sources of selection bias.
  - Develop and disseminate methods for adequate analysis of data in cases where the treatment/exposure varies over time and it is not possible to adhere to these standards.
  - Incorporate evolving new technology, such as the use of cloud and mobile technology, into ongoing work in the design of networks.
  - Fund research on the best way to harmonize data elements across sources.
  - ~~Develop methods guidance for HTE analyses for HTE in observational studies.~~
  - Evaluate the impact of the IOM standards, (endorsed by the Methodology Committee) on the resources needed to conduct systematic reviews and on review quality.
- 
- Develop methods guidance for HTE analyses in observational studies and comparative effectiveness trials; ~~the literature on HTE almost exclusively discusses use in placebo-controlled trials~~

- Develop methods guidance on the use of Bayesian methods in HTE analyses and appropriate outcome scale for HTE analysis (e.g., risk difference, risk ratio, log of odds-ratio).
- Support the development of both analytic approaches and guidance for predictive approaches and applications of modeling to HTE as well as for SGA with a focus on their use for PCOR.
- ~~Develop the concept of Descriptive HTE and explore how it could be used to promote PCOR~~

For registry studies:

- Develop analytic techniques for addressing measured and unmeasured confounding.
- Develop analytic techniques for handling missing data when linking multiple sources such as EMRs, claims and survey data ~~that can be used in registry studies.~~
- Develop improved strategies for linking data while maintaining privacy protections and assuring that link data do not lead to re-identification in de-identified data.
- Develop innovative ways to reduce loss to follow-up as registries encompass longer time periods.
- Encourage the development of a variety of research methods, including designs other than randomized trials, that can be use in assessing clinical outcomes resulting from diagnostic testing