Overview of the Methodology Committee's Response to Public Comments

Purpose

This brief provides the PCORI Board a short summary of the Methodology Committee's response to public comments. First, we discuss the broad themes identified in the report titled *Public Comment Analysis and Revision Recommendations: PCORI Methodology Report*, prepared by American Institutes of Research. Then, we discuss our responses to the public comments and revisions of specific groups of methodological standards. This brief also will summarize the process for revising the *PCORI Methodology Report.*

Background

Over 120 individuals and organizations commented on the *PCORI Draft Methodology Report*[1] via the online public comment tool. In addition, PCORI solicited comments in Webinar polls held on August 3 and14, 2012.

PCORI engaged a contractor, American Institutes for Research (AIR), to identify, code, and analyze these comments. They found that the majority of commenters thought the proposed standards and recommended actions were consistent with PCORI's mission and could be useful to inform PCORI policy regarding research funding decisions.

The AIR report noted that "There was very little disagreement expressed about the specific standards themselves, and very few submissions provided specific revision recommendations for individual or groups of standards." Instead, most comments focused on five areas (Table 1).

Table 1. Five themes across the public comments.

1.	Requests for additional detail concerning how the standards could be implemented.
2.	Concerns regarding the feasibility of the standards to produce patient-centered research findings.
3.	Potential gaps in the Report (occasionally expressed as gaps in the standards) concerning missing patient populations, patient interests, research methods, and stakeholder representation, limited discussion of dissemination of research findings, and missing standards regarding the use of research to affect clinical practice, shared decision making, and healthcare delivery.
4.	Concerns regarding the use of standards in general and standards in determining research funding.
5.	Concerns about the length, complexity, focus or voice of the document, particularly for non-researcher audiences.

[1] pcori.org/assets/MethodologyReport-Comment.pdf

In the past two months, the Methodology Committee has focused on revising the standards and recommendations based on comments received from the public. We held committee-wide conference calls to address overarching issues. In addition, subgroups of committee members were assigned to review and respond to the comments that concerned specific standards or groups of standards and recommended actions (Table 2). They re-examined each standard in light of the public's comments and proposed revisions, additions, or deletions. In some instances, expertise outside the MC was solicited. In particular, we sought outside advice for the Heterogeneity Standards, Research Prioritization Standards, Adaptive Trials Standards, and the Diagnostic Test Standards. Several experts participated in conference calls with the specific work groups to provide advice and recommendations regarding standard modification. Finally, we held an all-day meeting on October 31 to finalize and approve the revised standards and recommended actions. The Methodology Committee reached consensus on the final set of standards and recommendations to be delivered to the Board.

Table 2. Groups of standards

Causal Inference	Heterogeneity	Systematic Reviews	Data Networks
Adaptive Trials	Missing Data	Patient Centeredness	Research Prioritization
Registries	Dissemination	Diagnostic Tests	

These efforts have generated a large body of materials. In addition to the AIR report, these include a 197-page table of the Methodology Committee's responses to specific comments about the standards and recommended actions and a spreadsheet with details of the Committee's responses to comments from PCORI Board members about an earlier version of the standards (May 2012). Over the next few months, the Methodology Committee will use these materials to revise the *PCORI Methodology Report*. A detailed response to comments will be published along with the final report.

Response to Overarching Themes (Table 1)

Many commenters requested additional details of how the standards could be implemented (Theme 1) or more evidence and explanation on how the standards can be feasibly adopted and realized (Theme 2). Commenters also had important concerns about how the standards would be interpreted and used by review panels (Theme 4). The Methodology Committee shares these concerns. We recognize that, once the standards are adopted, their success in achieving the goals of valid, patient-centered research will depend on how they are implemented and whether researchers can apply them effectively.
We agree that the report needs more text about how we want the standards to be used. Some of the recommended actions call on PCORI to create materials that would illustrate how the standards might be realized or provide criteria for research teams to determine if a standard was indeed being met. In other cases, though, the report was silent about implementation. The reason is that, as some commenters noted, the state of the science underlying each standard varies. Some standards can be interpreted as "standards for conduct" but, in other cases, they are standards in the sense of having "moral standards" —standards for direction and goal, which are not prescribing a specific approach.

In the latter case, it is less clear how one would adhere to the standards, and some would describe these as "guidelines" rather than "standards." Our intent is that (in funding decisions, for example) no one will be held to a set of fine details for this type of standard, but that the standards will allow the research community to offer creative ways to achieve the direction and goals we have set out. We have revised some of the standards that provoked the most concern to make this distinction clearer.

Once the standards are adopted, the PCORI Board will play a role in implementing them in a way that recognizes this distinction. We expect that the Board and PCORI Staff will work with the Methodology Committee, who can provide a link between the intent of each standard and the best ways to implement them and hold researchers accountable for them.

Many commenters noted "gaps" in the standards (Table 1, Theme 3). There is no question that, because of the timeline specified in the legislation, the Methodology Committee had to make choices about what methodologies to address in the first report. The Committee has developed a list of topics—including, for example, cluster randomized trials, incorporating preferences into trial methodology, shared decision making— that we need to address in the future. Additionally, in many of the responses to public comments we mention additional work that needs to be done within the areas listed in Table 2.

Others perceived gaps in the sense that the report did not mention all relevant patient populations or patient and stakeholder interests. It is important to note that the methodology report is not the only policy standard that guides PCORI's work. The PCORI research portfolio, along with activities in engagement and dissemination around that agenda, will represent the true scope of PCORI. That is, PCORI's research portfolio can and should be assessed in the light of concerns about representation (for example, studies of children, parents and families, those with rare diseases or conditions, and rural and vulnerable communities). The scope of the Methodology Committee is more limited—it will address methods for conducting PCOR to the extent that there are scientifically important issues related to specific populations and contexts, but cannot seek to represent all relevant populations and stakeholder groups.

There were many helpful comments about the length, complexity, focus or voice of the document (Theme 5). We will take them into consideration when we make plans for revising the full report.

Responses to Comments about the Standards and Recommended Actions

Our aim was to select minimal standards that would raise the quality of research for PCORI and help ensure that the research was consistent with PCORI's aims. It is important to understand that in deciding whether or not to adopt a standard, the Methodology Committee *weighed* six criteria (Table 2.1 of the *PCORI Draft Methodology Report*[2], p14):

[2] pcori.org/assets/MethodologyReport-Comment.pdf

1. Contribution to patient-centeredness
2. Contribution to scientific rigor
3. Contribution to transparency
4. Empirical evidence and theoretical basis
5. Degree of controversy about use of the standards
6. Other considerations, including feasibility and barriers to implementation

By "weighing" we mean that, if we believed that adoption of a standard would make a strong contribution to patient centeredness, scientific rigor, or transparency, we might require less empirical evidence, or give less consideration to concerns about feasibility or implementation.

Many of the public comments can be viewed as disagreement with how the Methodology Committee weighed these six considerations. As noted above, many comments concerned feasibility and implementation. Several comments raised questions about the strength of empirical evidence underlying some of the standards. Other comments mentioned considerations such as transparency or feasibility in arguing for changes in particular standards.

Comments like these often led to revisions of a standard. At the same time, in some cases it was clear that the commenter placed greater weight on one of the criteria than we did, or did not place as much value on another criterion as we did. In making these judgments, we also took into account that PCORI can take actions that increase feasibility or remove barriers to implementation, and incorporated those considerations into recommendations for action.

Detailed Responses

We made detailed responses to comments about each group of standards in Table 2. Below, we offer executive summaries of those responses for five of the groups of standards.

Systematic Reviews

In the original public draft of the report, only a single non-specific standard was included on systematic reviews. The major theme of the public comments was criticism for not including specific methodological standards on the conduct of systematic reviews. Several commenters referred to the recently published Institute of Medicine (IOM) standards on systematic reviews, and some commenters referred to standards disseminated by the Agency for Healthcare Research and Quality (AHRQ). Some specific issues were also brought up, including the applicability of standards on systematic reviews to reviews on delivery system interventions (as opposed to reviews on specific medical/surgical interventions). There also were comments on limitations related to the original single standard on using systematic reviews to guide research gap analyses, pointing to the need also to use information from stakeholders and sources other than the published literature.

To meet these concerns, we have added a standard that endorses a set of standards for conducting systematic reviews of clinical effectiveness. This standard adheres to the standards developed by the IOM, with a few specific exceptions.

Heterogeneity of Treatment Effects

The comments on the heterogeneity standards virtually all emphasized the importance of this particular topic to the mission of PCORI. A number of comments related to the category of "descriptive" heterogeneity analyses. We agreed that this was not a standard designation, and this terminology was dropped from the standards. Another set of comments expressed the feeling that there was overemphasis on statistical "testing," and we agreed. This was addressed by changing the language from "hypothesis testing analyses" to "hypothesis driven analyses." In addition, a number of standards specific to testing were modified or dropped, like the standard that required the calculation of power for all prespecified subgroup analyses. We also widened the array of statistical approaches to characterizing heterogeneity to go beyond just testing for interactions and including both estimation and Bayesian approaches.

Another important set of comments focused on the standards' previous focus exclusively on subgroup effects defined by various baseline covariates. It was pointed out accurately that many HTE analyses will be done using multivariate scores or classification rules, and this language was added to the standards.

Comments deferred for possible future work included specifying baseline variables that are particularly important for HTE, providing more specific guidance regarding biomarkers in genetic testing as a basis for HTE analyses, specifying the level of evidence needed to claim HTE, possible development of a "checklist" for HTE analyses, incorporation of information from individual crossover and n-of-1 studies, the incorporation of HTE analyses into systematic reviews, and the extension of standards to design features rather than mainly analysis features. Some commenters wanted explicit discussion of quantitative versus qualitative interactions, and another wanted emphasis on simulation and graphical methods.

We felt that there were no comments unworthy of consideration, but those that veered into suggesting that we set stricter rules for evidential and interpretation and subgroup importance are unlikely to be put forward in the future, as they are prescriptive in ways that would inhibit analyses or methodological innovation.

Adaptive Trial Standards

There were many comments related to the standards on adaptive clinical trial designs —more than any other set of standards—but almost none resulted in a modification of the standards. This is because the comments were quite far ranging, and did not directly pertain in most cases to the restricted subject area of the standards. This is in some ways a reflection of the reason that this area was chosen to develop standards, i.e., that many researchers as well as PCORI reviewers are likely to be unfamiliar with them, even though they may become an important feature of RCTs done in this area.

The comments included discussing the values of RCTs in general versus observational studies, clinical trial designs that were not covered (e.g., cluster randomized trials), issues surrounding placebo-controlled trials, elicitation of pretrial treatment or outcome preferences, quasi-experimental designs, how to choose outcome measures, preference trials, cultural competency and trial ethics, how interventions adapt to local contexts, the relevance of RCTs to implementation science, the role of

modeling as an alternative to trials, and the need to expand the range of designs covered by the standards. While many of these comments were valid points, few of them directly pertained to the scope or substance of the standards themselves. The only modification made to the standards on the basis of the comments was in the standard on infrastructure, stating that the analytic group should be independent of trial investigators, and that investigators should not be apprised of the randomization probabilities, which encode information on treatment effectiveness or safety.

Missing Data

Reviewing the comments revealed five themes:

1. ***Lack of clarity: PCORI Board Member.*** Board Member Epstein referred to the section as 'a bit cryptic.' Board Member Lipstein called for the standard to meet a higher bar, in particular requiring a more comprehensive discussion of why certain approaches to handle missing data were chosen and the effect of these choices on the interpretation of the results.
    - We revised the text to improve clarity and to highlight aspirational goals as well as minimum standards. We revised 7.4.2 to include the need to specify how the chosen approaches to addressing missing data might affect interpretation of results.

2. ***Too restrictive***. The original standard stated that all forms of single imputation are 'discouraged', implied that the standard applied only to clinical trials, and did not mention the use of Bayesian alternatives to missing data imputation. Many commented that the standard should allow for more approaches to address missingness, depending on the study circumstances and the nature of the missing data (i.e., MAR, MCAR, MNAR).
    - We revised 7.4.5 to indicate that a broad range of valid approaches are possible and it is up to the investigator to use and justify any specific approach. The text of the report will also be also revised to explain the various categories of missing data.

3. ***Inadequate recognition of the analytic and technical complexity of solutions for missing data***. Developing and disseminating software is outside of the core competencies of the PCORI board and methodology committee and will require partnering with IT or software firms to develop such tools.
    - We revised the recommendation to acknowledge this.

4. ***Missing data analyses must be linked to the study objective/hypothesis.***
    - 7.4.5 was modified to incorporate this suggestion

5. ***Link between patient engagement and handling missing data was absent.*** Including patients as members of the team should help identify why research participants may have dropped out.
    - The text will be revised to clarify the link between effectively minimizing missing data and patient engagement.

In addition there were many comments regarding the chapter text (i.e., softening the tone so that it reads less like a statistical text, correcting some incorrect or outdated references in the sidebars, and emphasizing the link with patient engagement). These comments will be addressed in the final version of the report.

Data Networks

Comments received from members of the Board of Governors and via the public comment process generally fell into the following three themes:

1. ***A lack of clarity as to why this section was not joined to the chapter on data registries.*** Some commenters felt that the use of data was similar between these two categories, and standards for data networks could be covered within the set of standards for registries.
2. ***Integration of the data network standards with emerging standards for electronic health records (EHRs) and the meaningful use of EHRs.***
3. ***Endorsement by PCORI of data network standards developed by other societies.***

To meet these concerns, the original seven standards on data networks were consolidated into two standards. The revised standards related to Data Networks recognize that valid, high-quality, patient-centered research relying on data networks requires that minimum standards be met in (1) the design and creation of data networks, and in (2) individual studies relying on data networks. We also decided to drop one recommendation related to data networks (the recommendation addressing "accumulation of evidence"). Many of the comments were felt to be issues that were outside of the scope of the report. This indicates a need to review relevant text in the report to ensure that its scope is sufficiently explained.

In response to the comments regarding other organizations' standards, we concluded that it is not the role of the report to endorse such standards. However, such endorsement occurs in other sections of the report (specifically, the sections on systematic reviews and clinical trials). This issue will be addressed in making final revisions to the report. Other comments are acknowledged to be important but will be deferred to the next edition of the report. Among these issues was the relationship of standards about data networks to standards about EHRs.