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AcademyHealth Comments on 2017 Additions to PCORI Methodology Standards

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A complex intervention has multiple components, which may act independently or interdependently to change patient outcomes. Health systems interventions, interventions intended to change knowledge or behaviors, and many non-pharmacological interventions often are complex. For patient-centered outcomes research studies, the intervention, the comparator, or both may be complex interventions. In general, a complex intervention will likely have one or more of the following characteristics (adapted from Craig et al. 2013 and Guise et al. 2017):

- Multiple components that interact
- Specified behaviors and activities carried out by healthcare staff
- Complex and/or multiple causal pathways
- Multiple entities or levels targeted by the intervention
- Adaptation or flexibility of the intervention
- Contextual factors associated with variation in outcomes

SCI-1: Fully describe the intervention and comparator and define their core functions

Researchers should provide a description of the intervention and comparator under study and clearly define any aspects related to core functions and forms. Core functions refer to the intended purpose(s) of the interventions. The form of the interventions includes the intended modes of delivery, providers involved, materials or tools required, dose, and frequency/intensity. The description should also explicitly indicate who the intervention is aimed at (i.e., patients and/or providers).

Do you have comments or edits to this standard? Enter them here.

Comments on the preamble:

It is not clear what "levels" are being referred to in "multiple entities or levels targeted by the intervention". Are you referring to the six levels of community, patient, provider, microsystem, mesosystem, and macrosystem. A clear definition should be provided.

Comments on the standard:

AcademyHealth recommends that just as researchers should fully describe the intervention(s) and comparator(s) being studied, they should also describe the intervention implementation strategy, or at least the planned implementation approach. When the comparator is the standard of care, this standard should be fully specified.

We also recommend that this standard include guidance for researchers to explain key contextual factors that may affect implementation outcomes, effectiveness, fidelity and variation across sites as well as a definition of the meaning of "levels".

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Further we recommend that researchers describe the extent of freedom that exists for implementers to vary core functions and forms of the intervention, that is, **how much variation in functions and forms** is allowed within the study context (see SC-3 for more detail). In some instances (e.g. adaptive designs), researchers may be further refining the intervention mode of delivery through iterative phases and if so, this should be specified.

Minor edit on the last sentence in the standard: the examples in parentheses are just that – examples and this should be edited to be an e.g. not an i.e.

SCI-2: Specify the hypothesized causal pathways and their theoretical basis

Researchers should clearly describe the hypothesized causal pathways by which the proposed complex intervention generates change (see CI-1). This description should depict how each intervention function generates the hypothesized effects on the prespecified patient outcome(s). Any contextual factors that may influence the impact of the intervention should be included in the causal model so that their hypothesized relationships are made explicit. The theoretical and/or empirical bases underlying the proposed interventions and their hypothesized effects should be described.

Do you have comments or edits to this standard? Enter them here.

AcademyHealth agrees that defining, in advance, the causal pathway and theoretical basis for change is necessary. To that end, the logic model should be supported by an established conceptual framework and appropriate citations provided. Logic models are linear and may fail to display the hypothesized interactions that are driven by context and complexity. Lack of a supporting conceptual model makes it difficult to see where the planned intervention fits in the larger context, as well as to visualize interactions.

Accounting and planning for context is critical as context inevitably has an impact on the dose of an intervention that is actually received, which could be seen as a mediator of outcomes. Thus, the context influences the actual intervention (forced modification of the intervention due to the context), the dose of the planned intervention that actually is received, the success of the planned activities in achieving planned outputs, change in process measures/behaviors, and outcomes. These dimensions should be mapped to the components of the logic model for clarity and not be limited to “prespecified patient outcomes(s)”.

In addition, to recognize the potential to ensure maximum learning from the implementation of the intervention, we recommend requiring both the documentation of the causal pathway in advance (prior to seeing the data) as well as any modifications made to the model after data analysis and the rationale for such changes. Retrospective analysis, and publication, of such discovered pathways and the rationale for the changes in the logic model will further contribute to the body of knowledge.

We further note a theory explaining how and why the proposed interventions will affect the outcomes is insufficient. Researchers should provide an explicit quantitative prediction of the attributable effect, along with the expected precision of this estimate (in the form of degree of

belief, prior probability, or confidence intervals). Too often failure to specify a target outcome is due to lack of good evidence regarding the likely attributable effect, failure to consider the low reliability of health systems in implementing core changes, and/or adequate consideration of bias and confounding. The hypothetical causal pathway and the implied attributable effect should be weighted in the light of the Bradford Hill or other epidemiological criteria/standards.[1]

Minor edit to the third sentence: it would be unrealistic to ask for "any" contextual factors. This should refer to "key" contextual factors.

SCI-3: Specify how adaptations to the form of the intervention and comparator will be allowed and recorded

Researchers should specify any allowable adaptations in form and/or function, along with a description of how planned and unplanned adaptations will be managed, measured, and reported over time. Any planned adaptations should have a clear rationale, ideally be supported by theory, evidence, or experience and maintain fidelity to the core functions of the intervention. Upon conclusion of the study, researchers should provide guidance on allowable adaptations or unproductive adaptations (i.e., adaptations that may reduce the effectiveness of an intervention).

Do you have comments or edits to this standard? Enter them here.

Recognizing that an intervention will not be delivered 100 percent of the time to 100 percent of the patients or community members—and often for good reasons— AcademyHealth recommends that this standard not only detail specification of adaptations, but also the documentation of unplanned, *observed* adaptations that were not pre-specified, and the rationale, setting, and frequency of those adaptations.

The need to describe clearly the rationale for any adaptation goes beyond the desirability of comprehensiveness or completeness. In cases where an adaptation to an intervention may be chosen because the chooser knows or suspects that this particular adaptation will work better than any other in the specific setting, outcomes of the particular adaptation may be uniquely good in the setting in question, but not generalizable to other settings. Allowing for endogenous adaptations may itself be a characteristic of an intervention, but this needs to be appreciated and documented. Qualitative data is especially helpful in understanding whether an adaptation was chosen because it was known or suspected to be especially effective in a specific setting.

SCI-4: Describe planned data collection and analysis

Researchers should describe plans to test the hypothesized causal pathways and explain how the results will be used to draw inferences about both effectiveness (i.e., patient outcomes) and the processes of

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[1] http://qualitysafety.bmj.com/content/26/11?current-issue=y) (BMJ Qual Saf. 2017 Nov;26(11):933-937. doi: 10.1136/bmjqs-2017-006756. Epub 2017 Aug 2.How to attribute causality in quality improvement: lessons from epidemiology. Poots AJ1, Reed JE1, Woodcock T1, Bell D1, Goldmann D2,3.

care (i.e., process outcomes). Researchers should select valid and reliable patient outcome measures that are explicitly affected by the hypothesized causal pathway and the theoretical and/or empirical basis for the intervention.

The main process questions should be informed by the key uncertainties underlying the hypothesized causal model. Process evaluations should measure, document, analyze, and report: the fidelity of the delivery of the intervention (i.e., planned and unplanned adaptations); the quantity or dose of the intervention actually delivered; whether the intended audience received the delivered intervention (i.e., reach); the mechanisms of action (e.g., mediators, intermediate outcomes); and important contextual factors (e.g., moderators) at all levels where the intervention is aimed (e.g., patient, provider, hospital).

Researchers should select a combination of methods appropriate to the research questions identified and describe the timing and sources of data collection. These plans should include appropriate quantitative statistical methods that account for the nature of the functions defined by the causal pathway. When appropriate, mixed methods analyses may have value in supplementing the process evaluation. The design should be flexible enough to allow important questions that emerge to be addressed.

Researchers should describe the plans for integration of process and outcome data in advance of intervention delivery to determine whether and how outcomes and effects are influenced by implementation or contextual moderators.

Do you have comments or edits to this standard? Enter them here.

The wording of this standard raises a number of concerns. First, effectiveness can be measured by both process and outcomes. The term “process outcome” is confusing, however we recognize that in some instances, especially when true outcomes are hard to obtain, intermediate outcomes are used, and these can in fact be processes. We suggest editing the first sentence to: “draw inferences about the impact of the intervention on processes of care and patient outcomes”.

Second, we strongly support the use of valid and reliable patient outcome measures but only when they are appropriate to the patient, population, intervention and context. The standard should not encourage use of measures for a different patient population/setting that the researchers think are inappropriate for their study. This statement also should discuss the balance between process and outcome measures. When outcomes are rare, hard to capture, or in the distant future, an explicit case must be made for why process measures are reasonable proxies.

Third, the statement also appears to favor quantitative methods over qualitative ones. AcademyHealth suggests that for complex interventions qualitative and mixed methods should be more strongly suggested as quantitative methods alone are likely to be insufficient. In fact, some questions may only be analyzed with rigorous qualitative methods.

Fourth, specifying contextual factors at all levels of the targets of the intervention is certainly the ideal; however, depending upon the scope and budget of the project, it may be reasonable to target measures to selected levels or selected aspects of the process.

Fifth, Researchers should describe in detail how the subject/settings for study were identified and how intervention status was assigned. In many health services research studies of complex interventions the subjects may be a convenience sample and intervention assignment may be based on voluntary participation. In others, the data will be observational with or without a true natural experiment. In either instance, researchers should identify and describe potential sources of bias and, if possible, determine the likely direction of the bias. Researchers should also describe the methods used to minimize bias and to quantify its likely magnitude and direction.

Additional points include:

- It would be helpful to define the expected duration of the intervention as well as the expected timeline for effects to appear for various outcomes and processes. This may well differ for different settings, patients, and populations and researchers should describe how this will be determined. Effects may appear at different times for different outcomes and processes. In complex interventions, it may take a considerable amount of time for the program to become fully effective—researchers should specify that for each outcome or group of outcomes and the basis for their assumptions.
- The definition of data collection tools and sources should be documented and additional implementation outcomes (acceptability, reach) and strategy outcomes (speed, quality, reach) should be considered. An assessment of the strength of evidence for the anticipated impact on outcomes is also necessary.
- It would be wise to consider collecting data on the potential costs and budget impact of the intervention and its implementation, including ongoing maintenance and opportunity costs of the intervention. Expending significant effort to develop and test a complex intervention that has little to no likelihood of adoption because of its cost is not ideal.

Do you have general feedback on the *Standards for Studies of Complex Interventions* (SCI)? Please add below.

AcademyHealth believes the pre-definition and documentation of planned analyses, data sources, and data collection tools as outlined in these standards is highly desirable, and will support the overall integrity of the research. We also acknowledge that doing so requires a significant investment of time and budget. Successful adherence to these standards may be difficult or unrealistic for a study with a limited budget, and considerations for this work should be made in the grant process.

To the degree possible, we also recommend simplification of the language and word choice in each standard to ensure both specificity and understanding across settings and disciplines.

Finally, it is not clear whether this guidance has been cross-walked with the published guidance in SQUIRE and STaRI and a crosswalk would be a helpful table, and if there are gaps in these guidelines or in SQUIRE and STaRI, they should be addressed.

Comments on the Proposed Standard (IR-7): Data Integrity and Rigorous Analyses

IR-7: In the study protocol, specify a data management plan that addresses, at a minimum, the following elements: collecting data, organizing data, handling data, describing data, preserving data, and sharing data.

Data management is a critical phase in clinical research that contributes to the generation of high-quality, reliable, and statistically sound data from clinical trials and observational studies. The underlying motivation for good data management practice is to ensure that the data are accessible, sustainable, and reproducible, both for future investigators who may want to use it, and (importantly) for the original research team as well. This standard applies to both the quantitative and qualitative data collected in a study.

A data management plan (DMP) is a document that describes the data to be generated by a research study, how that data will be managed and stored, who will have access, what documentation and metadata will be created with the data, how the data will be preserved, as well as how the data will be shared in support of future scientific inquiries. DMPs are distinct from statistical analysis plans, which articulate the planned statistical analyses associated with the study (e.g., statistical tests to be used to analyze the data, how missing data will be accounted for in the analysis).

The study investigators should self-monitor their data management procedures in order to ensure quality control. This includes checks to ensure manually entered subject numbers conform to study-defined site/subject number format rules and real-time review of data to verify their accuracy and validity.

DMPs should include language that, at a minimum, addresses each of the following considerations:

- Collecting data: Based on the hypotheses and sampling plan, describe the data that will be generated, and how it will be collected. Provide descriptive documentation of the data collection rationale and methods, and any relevant contextual information.
- Organizing data: Decide and document how data will be organized within a file, what file formats will be used, and the types of data products that will be generated.
- Handling data: Describe and document who is responsible for managing the data, how version control will be managed, the data handling rules, the method and frequency for backing up the data, and how confidentiality and personal privacy will be protected.
- Describing data: Describe how a data dictionary and metadata record will be produced (metadata standard and tools that will be used).
- Storing and preserving data: Implement a data storage and preservation plan that ensures that both the raw data and analytic files can be recovered in the event of file loss. The data storage

and preservation plan, including the approach to data recovery (e.g., storing data routinely in different locations), should be documented.

- Maintaining data: Develop a plan for maintaining the data in a data repository, consistent with PCORI's policy on Data Access and Data Sharing.
- Sharing data: Develop a plan for sharing data with the project team, with other collaborators, and with the broader scientific community, consistent with PCORI's policy on Data Access and Data Sharing.

Consistent with the Guideline for Good Clinical Practice (GCP), the investigator/institution should maintain adequate and accurate source documents, including the DMP. The DMP should be attributable, contemporaneous, original, accurate, and complete. Changes to the DMP should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

Do you have general feedback the Standards for Data Integrity and Rigorous Analyses?

Overall, the standards are quite useful and appear consistent with extant high quality data management approaches. However, for many implementation studies, it often is extremely difficult to conform to the high standards of a DMP as described. Therefore, the data collection and quality plan needs to be tested in the real setting in which it will be deployed. This should be done in advance so that problems can be foreseen and mitigated. Nowhere is this more important than in community based participatory research and other types of field research in low resource settings.

Additionally, funders should acknowledge that adhering to these standards often requires substantial resources of time and money that should be allowed for in proposals.