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AcademyHealth Feedback for Standards for the Individual Participant-Level Data Meta-Analysis (IPD-MA)

Below are descriptions for four new standards under consideration by the PCORI Methodology Committee. In response to an open request for comments on the standards, and on behalf of our members, AcademyHealth submitted the indented, blue comments on September 21, 2018. We wish to thank Dr. Kelly Devers and the members of the AcademyHealth Methods and Data Council for their assistance in compiling this response. Members with questions or comments on this response are invited to contact us at advocacy@academyhealth.org.

IPD-1: Specify the research question(s) that will be addressed through the IPD-MA and describe the specific information the IPD-MA will provide that other approaches would not.

Explain why the IPD-MA will address limitations of other potential approaches for answering the research question(s), including study-level meta-analysis.

AcademyHealth appreciates PCORI development of draft standards for individual participant-level meta-analysis (IPD-MA) and the opportunity to comment.

To strengthen and clarify the standard, AcademyHealth suggest that PCORI begins with a definition of individual participant-level data and specific examples of types of data they believe this includes. For example, is it IPD-MA clinical trial data only or could it include data from electronic health records, patient-reported outcome data, qualitative interview data, etc.? This definition and clear examples will ensure that all potential users of the standard are on the same page.

If primarily focused on clinical trial data, PCORI should consider referencing and encouraging use of the PICOTS framework developed by AHRQ's EPC program to specify the research question. Please see: https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHInnovation/UCM587380.pdf

On a more specific note, we recommend adding "or algorithms" after approaches, so the sentence would read: "….the IPD-MA will address the limitations of other potential approaches or algorithms…."

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IPD-2: Describe the proposed governance structure for the IPD-MA in the protocol and study reports.

The proposed governance structure should be designed to encourage investigator collaboration and improve the strength and quality of the research. The protocol and study reports should describe the following:

- Roles, relationships, and decision-making authority of the research team leading the IPD-MA, the trial investigators who have carried out the eligible studies, and the relevant stakeholders in the design, management, conduct, and interpretation of the IPD-MA
- Payment model to support investigator participation and data acquisition, as applicable
- Data use agreements, reflective of the IPD-MA study protocol and intended analyses, for each source of IPD requested and obtained

AcademyHealth recommends adding that the protocol and study reports should also describe the level and frequency of individual trial investigator involvement. For example, does the work necessitate in-person meeting and/or virtual meetings? If so, how often?

Additionally, AcademyHealth recommends that in addition to data use agreements, information be reported about IRB and protection of human subjects.

Finally, AcademyHealth recommends adding "clinical" in the first bullet, so the sentence reads: "Roles, relationships, and decision-making authority of the research team leading the IPD-MA, the *clinical* trial investigators…"

IPD-3: Use systematic, reproducible methods to identify studies for inclusion in the IPD-MA.

Describe the approach to ensuring that all relevant published, and unpublished studies are considered for inclusion. Record the number of studies and participants identified and screened, assessed for eligibility, and included in the IPD-MA. Document and explain the reasons for exclusion of studies.

AcademyHealth feels this standards is generally appropriate, but notes that the standard is not unique to IPD-MA. Rather, the standard is appropriate for most any systematic review and meta-analysis, regardless of whether it is an IPD-MA or a study-level aggregate MA. Is there anything more specific that could be added to this standard for IPD-MA meta-analysis?

AcademyHealth also suggests that PCORI consider including in the standard the creation of a PRISMA flow diagram to account for each step. Please see this site for further information. http://www.prisma-statement.org/

More specifically, AcademyHealth recommends adding "presented" and "excluded" in the text, so the sentences read:

"Describe the approach to ensuring that all relevant published**,** ***presented***, and unpublished studies are considered for inclusion."

"Record the number of studies and participants identified and screened, assessed for eligibility, and included *or excluded* in the IPD-MA."

IPD-4: Specify the design and planned analyses of the IPD-MA in a protocol, document any changes, and report significant amendments and modifications.

Develop a protocol and register it on PROSPERO prior to commencing work. In the study protocol, researchers should:

- Describe the data acquisition and management approaches used to maintain data integrity and protect personal health information (see IR-7). Data should be requested on all randomized participants eligible for the IPD-MA, even if they were not included in the final analyses of an original clinical trial.
- Document the processes used to check accuracy of data and to correct and harmonize data, including conferring with the original trial investigators.
- Describe the approach to assess the quality of the data, including assessing the potential risk of biases in individual studies.
- Describe the statistical analysis plan, which should include pre-specification and justification of the hypotheses within different types of participant subgroups, for example including whether these will be analyzed at the participant or study level; outcomes (and outcome measures), including whether these are main or additional analyses; and the analytical methods used.
- If the IPD-MA plans to include examination of unexplained between-trial heterogeneity, specify the intended factors to be explored; the evidence base supporting the factors' hypothesized role; and the proposed analytic approach, including dependent and independent variables.

All amendments and modifications to the protocol should be documented, and any significant changes (e.g., outcome definitions, analytic approaches, additional analyses) should be reported and amended in the publicly available protocol or statistical analysis plan.

AcademyHealth recommends being less specific about the place of public registration (i.e., PROSPERO), and allow for other mechanisms of publishing the protocol (e.g., government sponsored websites, or other publicly available sources). And, similar to our previous comments, many of these items are not particularly unique to an IPD-MA, they also apply to aggregate MAs. Is there anything more specific about IPD-MAs that PCORI might consider highlighting or emphasizing?

More specifically, AcademyHealth recommends the following additions or edits to the language shown in italics below:

- In the first bullet, last sentence, "Data should be requested on all randomized participants eligible for the IPD-MA, even if they were not included in the final analyses of an original *clinical* trial."
- In the second bullet, "Document the processes used to check accuracy of data and *to* correct and harmonize data, including conferring with the original trial investigators."
- In the third bullet, "Describe the approach to assess the quality of the data, including assessing the risks or *potential risks* of bias*es* in individual studies."
- In the fourth bullet, "Describe the statistical analysis plan, which should include pre-specification and justification of the hypotheses within different types of participant subgroups, *for example* including whether these will be analyzed at the participant or study level…"
- In the closing sentence, "All amendments and modifications to the protocol should be documented, and any significant changes (e.g., outcome definitions, analytic approaches, additional analyses) should be reported *and amended* in the publicly available protocol or *statistical analysis plan*."