American Association for Cancer Research

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Margaret Foti, Ph.D., M.D. (h.c.)
Chief Executive Officer

September 14, 2012

Joe V. Selby, M.D., M.P.H.
Executive Director
Patient Centered Outcomes Institute
1701 Pennsylvania Ave., NW, Suite 300
Washington, DC 20006

Sherine Gabriel, MD, MSc
Chair, Methodology Committee
Patient Centered Outcomes Institute
1701 Pennsylvania Ave., NW, Suite 300
Washington, DC 20006

Dear Drs. Selby and Gabriel:

The American Association for Cancer Research (AACR) is pleased to offer comments regarding the Patient-Centered Outcomes Research Institute's (PCORI's) draft Methodology Report (Report). As the world's largest and oldest organization dedicated to cancer research, our 33,000 members span the range of researchers from basic scientists to clinical practitioners and include cancer survivors and advocates. The AACR is very supportive of PCORI's mission, which is quite closely aligned with the AACR's own mission to prevent and cure cancer through research, education, communication, and collaboration. Improved patient outcomes are a driving force behind both organizations, and our comments are intended to help strengthen the foundation of PCORI's vitally important work.

Cancer is second-leading cause of death in the United States, and while cancer is often discussed as if it were one single disease, it is really a constellation of over 200 diseases, each made unique by a given disease's location and genetic underpinnings. With improved genetic screening technology, the ability to further classify cancers into smaller subclasses of cancer continues to grow, and with it, the drive to create therapies individualized to each cancer and each patient. Cancer research and treatment, however, is not just about the disease. The cancer research field is a leader in considering patient reported outcomes (PROs), supporting patient education, and fostering advocacy. For these reasons, the cancer community is already leading the way in Patient Centered Outcomes Research (PCOR), and our community's experiences can inform the growth of PCOR more widely. The AACR is encouraged by PCORI's work to bring increased attention and rigor to the search for patient-specific solutions, and is pleased to provide feedback on PCORI's Methodology Report.

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Specific Points for Consideration

Below you will find specific comments regarding individual standards and recommended actions contained within the Report, as well as more general comments on the Report as a whole.

Patient engagement

One of the hallmarks of PCOR is the focus on the patient. This focus is to be applauded, especially the Report's recommendation to include Patient-Reported Outcomes (PROs) wherever possible. Patient engagement, however, represents a new paradigm for many researchers, and more assistance in this area is therefore needed. The AACR endorses the recommendation within the Report calling for training in patient engagement and the creation and dissemination of a sample patient engagement plan designed to help researchers better execute this critical step of PCOR. More research into patient engagement is also needed along with creating benchmarks for successes.

Lack of clarity/harmony on standards

The Committee defines a standard as a *"..process…that is deemed essential…*" and further clarified that in order to be included in the Report that standards be developed by a professional group, be specific, unambiguous, and clear. These criteria combined imply a high level of specificity as well as presenting a de minimus requirement for research, but the level of detail varies greatly among the 60 standards from very specific language that references external standards to standards that might be described as design goals or aspirations. While widely varying standards (specificity and required adherence) are not necessarily problematic on the surface, the report is unclear about how researchers should interpret these differences. This uncertainty may leave researchers without important direction regarding the incorporation of the standards into their work. The Committee seems to recognize this contradiction in the closing section of the Report by including the following as one of the "Next Steps" for the Committee to address:

> *"2. Distinguish between standards that are minimum requirements and those that may be aspirational or best practice but are not required."*

Ideally, standards, and the Report as a whole, should remove subjectivity and ambiguity, to the degree possible, from the evaluation of what constitutes high-quality PCOR. The report makes an important step forward, but still leaves a significant level of ambiguity that will undoubtedly be addressed over time. The AACR suggests that it would be helpful for PCORI to more explicitly address the variations in specificity and degree to which standards are required now, rather than later. This can be accomplished either by attempting to harmonize the tone and specificity of the standards to the degree possible, by providing a timeline for further fine tuning, or by more explicitly acknowledging the differences with a discussion of any implied expectations behind the differences at the outset of the Report rather than as an implicit acknowledgement of the ambiguity at the end of the Report.

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Power versus Representation

There are slightly competing goals expressed in the Report of having representational participation in studies, but also of having adequate statistical power in these subgroups to draw conclusions. Complete representation with accompanying statistical power would only be possible with rather large studies. Trade-offs between power and representation are necessary and inevitable in order to facilitate all scales of research from community-level to national. Better clarity could be provided on PCORI's views regarding the trade-off between these conflicting goals and the ability for researchers to intentionally sacrifice one for the other in study design.

Restrictions to variables at study entry

Two specific standards, 7.2.1, and 7.2.4 (listed below) deal with the timing and use of measured variables to group patients and analyze outcomes. Both standards suggest that patient grouping should occur based only on information about the patient available at the outset of a study and that changes during the study should be ignored. Tobacco use has been proven to have significant negative health effects related to wound healing, adverse treatment reactions, and secondary complications in patients. When testing the effectiveness of therapies, tobacco intake is therefore an extremely critical variable that must be measured longitudinally and not at a single time point. In other words, the tobacco intake that patients are subject to during treatment (e.g. whether they continue use, quit or relapse) is as relevant, if not more, than their tobacco use status at the initiation of treatment. The AACR suggests that PCORI revisit these standards to account for tobacco usage and other similar other modifiable risk factors/confounders like alcohol, drug use, etc.

> *7.2.1 Define Analysis Population Using 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.*
>
> *7.2.4 Measure Confounders before Start of Exposure*
> *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.*

Electronic Medical Record (EMR) Use

The Methodology Committee has recognized the role of EMRs in PCOR, but has thus far declined to create any standards or recommendations relative to EMR usage. Given the focus on EMRs in the broader healthcare community, it is not necessary for PCORI to create new initiatives or even lead in this area, but they should actively lend their voice to reinforce the needs of researchers as standards (such as Meaningful Use Criteria) are being developed, lest the standards focus on care delivery to the exclusion of secondary data use.

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Data sharing

The AACR is pleased by the recommendations presented in Chapter 3 of the Report, calling for PCORI to develop mechanisms for sharing findings, tools, and data. The typical dissemination route for research findings is through journals; however the information presented in journal articles can be influenced by length, style and editorial restrictions outside of the control of a given researcher. For this reason it is important to develop other dissemination outlets, and the AACR encourages swift action on PCORI's part on any efforts to create a repository or sharing network.

Data Networks

The AACR concurs with the Report that robust networks to systematically collect, store and distribute data in a standardized, ethical, and secure manner will be critical to advancing CER. While many of the standards listed in the Report represent good research practices that ensure reliable and applicable results, a select few deal with legal or ethical issues. A specific example includes standard 7.5.2, which deals with risk assessment and potential re-identification of data. To ensure compliance with these standards, PCORI may want to consider not only a request that researchers prepare a plan, but PCORI could also consider including language in the terms and conditions of grants that will create added protection, for example by expressly prohibiting researchers from reidentifying de-identified patient data. While reidentification is considered unethical, it is not expressly illegal. Likewise, it is not clear whether researchers will be expected to follow the Common Rule, and it would be useful to have additional clarification in this regard.

Specificity of research agenda

In previous comments on PCORI's Draft Research Agenda the AACR, along with other organizations, recommended that the Research Agenda be more specific. While the Methodology Report focuses on methods and standards, rather than the specific Agenda, the Report does include recommendations calling for specificity and prioritization of the Agenda. The AACR would like to take this opportunity to repeat our recommendation to be more specific in the Research Agenda, and we also endorse the recommendation contained within the Report to build off of existing agenda-setting processes such as those developed by the IOM and AHRQ.

Software development by PCORI

A number of the "Recommended Actions" presented in the MR, include calls for PCORI to create tools, especially with respect to software for data analysis. The AACR urges PCORI to carefully consider its investment in tools (especially software) and evaluate whether such tools are better created organically by grantees as a part of funded project as opposed to separately as stand-alone projects by PCORI. The National Cancer Institute (NCI) initiative known as "caBIG" is an example of the creation of stand-alone software by a funding agency that was meant to foster research, but instead ended up creating a number of expensive tools that did not see wide adoption by the research community.

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Transparency

Vital to the success of PCORI is the collaborative support of all relevant stakeholders: patients, providers, researchers, and the public. PCORI has sought input from stakeholders in the past, notably on the National Priorities and Research Agenda. What PCORI does with such stakeholder input, however, is unclear. Despite strong common themes expressed in public comments from past input opportunities, there appears to have been little change in the documents that were open for comment. The AACR encourages PCORI to be very open and transparent about the comments it receives and how it either addresses or dismisses the specific concerns expressed in those comments. A truly collaborative relationship requires not only asking for input, but a willingness to respond to it as well.

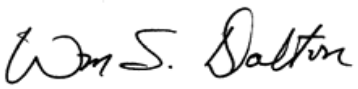
Summary

In its short existence PCORI has been given an enormous task. It has been charged with both catalyzing and focusing the move toward a relatively new way of thinking about medical research. As a new organization, PCORI has the wonderful opportunity of approaching research in a manner unconstrained by institutional inertia, but with that freedom also comes a significant workload to create new systems and standards nearly from scratch that will chart the direction for PCOR over the coming decade. It is imperative that PCORI capitalize on this formative period to align the efforts of the many researchers who may be engaging in PCOR for the first time. To be successful, PCORI must create very clear expectations about the research it sponsors, this clarity must be created quickly, and the only way to do so will be to genuinely listen and respond to the input of the patient, advocate and research communities.

In addition to the comments offered above, the AACR stands ready to provide any further assistance to PCORI as additional guidance is developed. If you have questions, please feel free to contact the AACR through Mark Fleury, Ph.D., associate director for science policy, at 215-446-7147 or mark.fleury@aacr.org.

Thank you for your consideration of AACR's comments.

Sincerely,



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