Introduction

On July 23, 2012, the Patient-Centered Outcomes Research Institute (PCORI) announced a public comment period for its draft Methodology Report which proposes standards for the conduct of patient-centered outcomes research (PCOR). Comments are submitted through PCORI’s on-line comment and survey tool, found at http://www.pcori.org/survey/methodology-report/.

Shire Pharmaceuticals Inc is an interested stakeholder in how methods should be applied when conducting PCOR. Shire is a leading specialty biopharmaceutical company whose purpose is to enable people with life altering conditions to lead better lives.

The comments contained in this submission represent the views and recommendations of the three Shire business unit, Specialty Pharmaceuticals- which develops therapies for specialty conditions affecting larger numbers of people such as ADHD and ulcerative colitis.

Shire is committed to serving the needs of patients who suffer from rare and often life-threatening conditions that are generally treated by specialist physicians.

Shire Pharmaceuticals, Inc. (Shire) is submitting the following comments through PCORI’s on-line comment and survey tool, found at http://www.pcori.org/survey/methodology-report/.
ES1-2: “Over time, these reports, standards, translation tables, and public engagement forums are expected to produce better research methods, which in turn will provide information of benefit to all stakeholders—researchers planning an investigation, policy-makers weighing the value of healthcare interventions, and patients and their caregivers facing health decisions.”

1.) **Comment:** The term stakeholder(s) is used broadly throughout the document and has 2 definitions provided in Appendix F: Glossary that are exactly the same. PCOR Stakeholders and Stakeholders are both defined as “Anyone affected by health decisions. Stakeholders may include patients, clinicians, caregivers, policymakers.” (p 182 &185) This is not an inclusive list of the stakeholders that could be included when mentioned through the document. One example is the term “researchers” that is used in the excerpt above but not included in the definitions of stakeholders. This needs to be thought out more clearly. One suggestion is to be more inclusive in the general definition of stakeholders, including researchers, payers, industry, etc and then have several sub-definitions that are used more explicitly, such as PCOR stakeholders or research stakeholders – academia, industry, government funded, etc. We should think about all stakeholders that could benefit from this methods report, including the producers of the research that this is aimed at guiding, for the patients’ benefit.

2.) **Comment:** In order to produce better research methods in comparative effectiveness research (CER), other methods such as indirect treatment comparisons (ITC), meta-analysis, and mixed treatment comparisons (MTC) should be considered the starting point for all patient-centered research. This report begins with and focuses on improving and producing better research methods for CER, yet it skips over the initial stages where CER begins—the existing literature to inform the adaptive designs, registries and diagnostic testing designs which are called for later in chapter 8 of the report.

For example, recent advances in methods such as match-adjusted indirect comparisons (MAIC) have been created as a sub-type of ITC which can better inform decision making. We enclose a summary from a recent publication on the subject which was presented at the AHRQ symposium on novel CER methods in June 2011 and published inthe journal *Pharmacoepidemiology and Drug Safety* as a special edition focused on CER methods in 2012. There are 5 other publications in the recent literature available [Cite 4 Signorovitch et al publications] including ISPOR Good Research Practices on Interpreting Indirect Treatment Comparisons and Network Meta-Analysis for Health-Care Decision Making that state that “[O]btaining patient-level data for all RCTs in the network may be considered unrealistic. As an alternative, one could use patient-level data when available and aggregate-level data for studies in the network for which such data are not available, thereby improving parameter estimation over aggregate data—only models.”

An example excerpt describing MAIC and some of the benefits of it are described in appendix A.
Chapter 1, pg 1: “...how to best conduct research that had not been effectively disseminated.” MAIC and other ITC, MTC and meta-analytic methods have not been effectively conducted or disseminated and we encourage PCORI to consider to inform and disseminate such findings."

Chapter 1 pg 4: “...to develop and improve the science and methods of comparative clinical effectiveness.”

Chapter 2 pg 10: “...The goal was to propose methodological standards in important research domains that are representative of research issues in CER and that will eventually be covered more comprehensively.”

Chapt 1, pg 1: “They can also help prevent the research agenda from employing flawed, out-of-date, or inappropriate methods to answer research questions, and may raise the bar for researchers, publishers, and industry as they try to inform decision-making.”

3.) Comment: See Comment 1 on stakeholders. Here the term research stakeholders may replace the term for “researchers, publishers, and industry”. Otherwise the examples are redundant and not all inclusive. Industry does much research, although there are also many other organizations/entities that do research and are not mentioned. Throughout the document, other stakeholders options could be “decision maker stakeholders, payer stakeholders, etc.”

Comments 1 & 3 can also be applied to (these are examples, not an exhaustive list)

Chapt 1, pg 2: “The purpose of PCORI is to provide the most reliable, relevant, and useful health-related evidence for decision makers, especially for patients and caregivers.”

Chapt 1, pg 8: “stakeholders—researchers planning an investigation, policy-makers weighing the value of healthcare interventions, and patients and their caregivers facing health decisions.”

Chapt 2, pg 10: “It is expected that the translation table will eventually include versions appropriate for use by different stakeholder groups”

Chapt 2, pg 11: “This includes engaging all stakeholders who might use the standards, creating reporting and surveillance opportunities, and developing enforcement functions over time.”

Chapt 6, pg 44: “Such study characteristics (see Box 6.1) need to be defined with stakeholder input as they will substantially influence the utility of the results for decision-making.”

Pg 2. “Given my personal characteristics, conditions, and preferences, what should I expect will happen to me?” and “What are my options and what are the potential benefits and harms of those options?”

4.) Comment: Patient Centered Medicine (PCM) approaches have been developed whereby regression modeling can be performed to predict who will be vs. who won’t be a responder across medications.

Comment 4 also applies to:

Chapter 3 pg 15. “One aim is to counter over generalization from studies in narrow populations or in highly controlled research settings to the broader range of people and settings in “real life.” (17, 18) But another aim, undoubtedly, is to learn more about how well the different treatment choices can work, and for whom they work best and are safest.”
“The next three years of Methodology Committee work will be a continual process of reconsidering, refining, and widening the scope of the standards to include the full spectrum of PCOR questions and approaches. Similarly, the translation table within this report will be expanded over time to include more examples, methodological issues, and approaches.”

5.) **Comment:** It is a good and fundamental place to start with the existing methods which can be improved with novel approaches as described above and that the report could be expanded now to incorporate PCM and ITC, MTC and meta-analytic methods into the PCORI methodology report.

“In 2008, the Institute of Medicine stated that methodological standards for the conduct of one type of research—systematic reviews—would help decisionmakers involved in PCOR “with respect to transparency, minimizing bias and conflict of interest, and clarity of reporting.” (15) In 2011, the Institute of Medicine published such standards. (16)"

6.) **Comment:** These guidelines don’t include novel methods such as MAIC or other advances in ITC, MTC, and meta-analytic methods which have become more readily utilized and standardly applied to more and more therapeutic area reviews for pharmacologic or device interventions.

**Chapter 3, Table 3.1, pg. 18** “Create conceptual framework Specify hypothesized mechanisms of effect, influences on outcomes, and clinical context of affected care processes to guide data collection and analysis plans”

7.) **Comment:** Patient perspective should be taken into account somewhere along the way, whether it is in the conceptual stages quoted above or in earlier stages of identifying the research questions.

“Because some standards apply only to certain types of studies, a portfolio of templates applicable to various study designs should be developed.”

8.) **Comment:** As before, a portfolio of novel methods should be considered such as PCM, MAIC, etc.

**Chapter 3, pg 20. “Standards for Formulating Research Questions” Box**

9.) **Comment:** A statistical analysis plan should be created and finalized (ie signed off) either in parallel or subsequent to the protocol. If it is not specified here, then it should be included in Section 7.

**Chapter 4 (Patient centeredness):**
10. **Comment:** This chapter is very process oriented, and broadly highlights the key issues and the thinking framework needed to think about “patient centeredness” to advance this field. These points should be further elaborated upon and described in greater detail in this chapter. The following is a suggested framework of thinking that could be proposed:

a. Define outcomes that are meaningful to patients that are measurable and concrete, especially in disease areas where outcomes have not been defined (this is mentioned but could be further elaborated upon). Who should be involved? How it should be done, etc...

b. Not only should meaningful outcomes be defined, but in order to be able to use this outcome to “personalize” care, this outcome variable should also be able to highlight and accentuate “heterogeneity” across different populations. For example: in attention deficit hyperactivity disorder (ADHD), a patient with the outcomes measure CGI-I score 1 to 2 is defined as a “responder” and those not reaching this threshold classified as “non-responders”. Obviously, this outcome is not that sensitive in picking out differences across the different patients and highlighting the potential heterogeneity across the different individuals, because there may be patients who move from a score of 7 to 4 in the CGI-I, but it this patient group is still going to be classified as “non-responder” whereas in reality they are actually responding but are not meeting the threshold of “response defined”. If there was a more sensitive outcome measure that could be used to categorize patients into the different levels of response and thus “break them into different” sub-groups based on this outcome, then treatment could be potentially tailored to these different subgroups depending on the care needs of each subgroups.

c. Suggestions to get to this point include looking at their genetics, coupled with their actual reported outcomes (i.e., PRO), or other patient specific characteristics. This was not mentioned or clearly elaborated in this chapter.

Additional suggestions include development of novel innovative methods to identify subgroups of patients who may be responding better to one therapy vs. another. One example in using personalized medicine methods is a paper that was recently accepted in Journal of Medical Economics by Erder et al.²

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**Chapter 5**

11. **Comment:** A key element in this report is the key focus on patient involvement and peer review process that has been stipulated. While VOI analysis is a useful tool, it should be supplemented with practical, real-world applications.

With regard to research priority factors/focus, these seem very broad and may not be meaningful enough unless further expanded upon. Suggestions to consider would be to focus on heterogeneity among patients and effective mechanisms for meaningful subgroup evaluations and analyses, consider predictive modeling research approaches that can lead to results tailored to patient differences, aim for practical design and outputs that can realistically effect change with prescribers in a patient-centered treatment approach, and aim to assess treatment outcomes of comparators (vs PBO) to identify high value products based on patient outcomes.
Chapter 6

12.) **Comment:** The Translational Framework & Decision Tree could be very useful tools as long as either all possible study scenarios are considered or the interpretation of them leaves room for unique or new situations. This is important so that studies are not automatically labeled as “wrong”, especially in grey areas. One way to do this would be to distinguish between minimum requirements and those characteristics that are important, but not required. The validation of this framework is very important to encourage future use and increase the level of confidence around the tool.

Chapt 7 pg 59. 7.1.2 “Researchers should describe the analytic approaches that will be used to address the major research aims prior to data collection”

13.) **Comment:** Instead of stating the above, it should state “Researchers should DOCUMENT the analytic approaches that will be used to address the major research aims prior to data collection”

Chapter 8

14.) **Comment:** This chapter seems to be focused on “adaptive RCT design” approaches vs. other non-RCT designs that could be adaptive and useful in PCORI approaches. There could also be consideration of other types of modeling used (MSM or prop score model approaches employed) and a trial could be adaptive with regard to sub-group analyses being pre-specified. Indirect modeling comparisons might also be useful for informing trial design, rationale of trial, and endpoint selection or study power.

The section on observational registries focused on the drawbacks and limitations of these registries and did not expand upon the benefits that could be achieved by using these methods, though they are briefly mentioned. The registry / real-world use approach is very likely to be applicable for collecting patient centered data and tracking outcomes of broader external generalizability.

Chapter 8 pg. 80-81 “Adaptive designs are particularly appealing for PCOR because they have the potential to maintain many of the advantages of randomized clinical trials while minimizing some of the disadvantages.” and “The flexibility and efficiency that are gained in adaptive trials have to be balanced with the risk that such trials typically require a longer design period and involve more logistical complexity.”

15.) **Comment:** There are a fair number of challenges in adaptive trials which need to be mentioned in the document in order to ensure clarity of decision making by the researchers considering utilizing them. First, adaptive clinical trials should model initially to predict the sample properly. This is not clear in the report. If it is not modeled appropriately, the sample may need to be re-
forecast up or down and enrollment adjusted after the “adaptive” part of the trial is completed. This could actually mean that they could be longer or require more sample than conducting a RCT directly. It could be more efficient to simulate or model out trial results in lieu of an adaptive trial and be more time-saving. It could also mean that adaptive trials are more expensive than other RCT trials. Worse, when checking that whatever the primary measure of effect is in the adaptive trial at the interim analysis stage, it could be found that the required sample to complete the adaptive trial is so large that funding for such a trial is not available, especially since the majority of the costs for a study are typically at study start-up (e.g. enrolling sites, patient incentives, etc). Lastly, because the interim sample and analysis are often less powered than the full trial, one could power the remainder of the trial based upon the initial interim analysis which could be incorrect simply due to study changes or low power. In medical device and diagnostic studies, this is particularly problematic since there is an operator learning that must be taken into account. The results for most human-operated devices or diagnostics initially will have more variation than later on when they become experienced users. The effect can cause great variation in the reliability and estimates for powering the remainder of the study.

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Chapter 8 pg. 82 section 8.1.3 “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).”

16.) Comment: when there is the possibility for multiple cut-offs or probabilistic approaches via Bayesian approach, sensitivities should be explored and modeled out to understand the potential impact of the extreme assumptions at the very least. Selection of which prior probabilities to use can cause the greatest variation in Bayesian adaptive trials.

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Chapter 8 pg. 83 “For example, these studies typically require simulations in the design phase in order to define the error rates, and descriptions of the design both in protocols and published papers must include more elements than a non-adaptive trial. Good adaptive trial design requires pre-planning and specification of procedures at the outset.”

17.) Comment: We agree with the comment above, but just to clarify and suggest: the MAIC approach is an appropriate method which could be used for this tool as well. It can “simulate” a trial outcome by matching patients within current trials. It gives the prior probability for an outcome of interest as long as that is the same outcome of interest that is sought for the adaptive approach, it can be very useful. The same applies to pg. 94- “Support development and use of software for adaptive trials that can simulate complex designs.” The MAIC approach can be a method that could be modeled out in the future using such software.

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Chapt 8 pg. 85 “Standards for Data Registries”
18.) **Comment:** Systematic literature review and synthesis of some kind is required as the first step before any registry can be planned to know what has previously been collected and what hasn’t been collected, but should be in the registry (in the interest of the patients).

Chapt 9, pg 96. This includes engaging all stakeholders who might use the standards.

19.) **Comment:** See previous comments 1 & 3. It is important to think about and refine the definitions around stakeholders. One suggestion is to provide a broad definition of all potential stakeholders and then have specific groups of stakeholders and specify that throughout the document when using the term (i.e., PCOR stakeholders).

References:

5. Signorovitch, JE; Wu, EQ; Yu, AP; Gerrits, CM.; Kantor, E; Bao, Y; Gupta, SR.; Mulani, PM. Comparative Effectiveness Without Head-to-Head Trials: A Method for Matching-Adjusted Indirect Comparisons Applied to Psoriasis Treatment with Adalimumab or Etanercept Pharmacoeconomics. Oct 1, 2010. 28(10):935-945.,

Appendix A: Excerpt Describing MAIC method from Signorovitch et al from Pharmacoepidemiol Drug Saf. 2012:

“Comparative effectiveness research requires the comparison of alternative therapies in a timely fashion, often in the absence of direct head-to-head randomized trials. For example, healthcare payers may wish to compare drug A versus drug B when randomized trials have only compared each with drug C (e.g., placebo). A traditional method for indirect comparison in this setting is the adjusted indirect comparison.2–6 This method uses the common comparator drug
Matching-adjusted indirect comparison is a recently developed method that can use IPD from trials for only one comparator to adjust for cross-trial differences in baseline characteristics. This method works by re-weighting patients with IPD such that their average baseline characteristics match those reported for trials without available IPD (i.e., with summary statistics only). Treatment outcomes can then be compared between balanced populations.”


