



Methodological Guidance for the Design of More Informative (or Pragmatic) Pharmaceutical Clinical Trials

Expert Working Group Meeting Summary

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Admiral Fell Inn, Baltimore MD

Working Group Meeting Overview

Patients, clinicians, payers and policymakers are increasingly interested in understanding the comparative and “real world” effectiveness of pharmaceutical products, and often note that traditional clinical trials performed for regulatory approval may not address important questions about the full range of benefits and harms of new drugs under conditions of typical clinical use. Pharmaceutical Pragmatic Clinical Trials (PCTs) are prospective studies designed specifically with the objective of creating evidence to assist these decision-makers in making informed decisions about alternative therapies. Study protocols for PCTs are constructed to provide the type of evidence desired by patients, clinicians and payers when making decisions surrounding drug therapies and other health care technologies. In May 2009, CMTP convened an expert-stakeholder working group to characterize recurring gaps in evidence that are generally not addressed in regulatory trials, explore the reasons for those shortcomings, and to generate ideas for improved methods to make pharmaceutical Phase III/IIIb clinical trials more informative for patient choices, clinical decisions, practice guidelines, and reimbursement and coverage decisions. The working group included representatives from pharmaceutical companies and regulatory bodies, private and public payers, government, clinical researchers, academics, patients/consumers, and technology assessment organizations.

The goal of this initial meeting was to develop a conceptual, methodological, and policy framework to modify the design and implementation of Phase III/IIIb pharmaceutical trials to make them more informative to post-regulatory decision makers (i.e. “pragmatic”). In the process of developing recommendations, the working group sought to identify the regulatory, methodological/scientific, legal, economic, ethical, and other challenges that constrain the design and implementation of PCTs and discuss strategies for overcoming these barriers. The insight developed through the working group discussions provided the initial content for a Guidance Document to guide the design of Phase III/IIIb PCTs. Modeled on the approach and content of FDA guidance documents on trial design, the PCT Guidance Document will provide specific principles and recommendations for the design of these studies, addressing methodological issues, as well as feasibility, ethical, and regulatory considerations.

Themes that emerged from the working group’s morning discussion were:

1. There appears to be some common ground among payers with respect to the desirable features of Phase III/IIIb clinical trials that would make these trials more informative, and many of the payers were open to having discussions with pharmaceutical companies early in the life cycle of a drug about important information to consider incorporating into trial design. There was repeated emphasis on the importance of enrolling in trials patients who more closely reflect the range of patients likely to receive the drugs after regulatory approval. A second major topic was the importance of incorporating into trials a broader range of outcomes, with greater emphasis on functional status, quality of life, and longer-term impacts. There is an opportunity for making this dialog between payers and industry occur earlier in the development process and on a more consistent and coherent basis.
2. There is higher than anticipated consensus among the regulators and payers who participated in the working group that some features of trials that are desirable in a post-regulatory phase are also desirable and feasible to include in regulatory trials. FDA representatives stated that they are open to considering trial designs that would better meet the needs of post-regulatory audiences, and are particularly interested in trials being conducted in broader populations. In the area of cardiovascular disease, regulators already require more pragmatic features in trial design and there has been more useful information generated in Phase III/IIIb trials in this disease area as a result, highlighting the potential importance of regulatory decision makers in promoting pragmatism.
3. The optimal approach to pragmatic clinical trials may not involve incorporating all possible pragmatic features. The Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) wheel developed by Thorpe et al. (2009) is a tool that can help researchers systematically consider each domain of trial design that may influence the degree to which the trial is likely to meet the needs of decision makers to answer specific clinical questions. Some domains of pragmatism are more important to payers than others (e.g., generalizability of patient population rather than loosening controls on compliance), and any incremental movement towards a more pragmatic design may be valuable. Not all barriers appear insurmountable.

The afternoon session was comprised of discussions of specific key issues in study design including selecting appropriate comparators, relaxing intensity of monitoring and protocol-driven care, enhancing generalizability of patient populations, and dealing with heterogeneity of the patient population and study setting. In addition, the discussion addressed implementation barriers and potential solutions, including reducing cost and improving efficiency of PCTs, expanding research to community settings, regulatory barriers, and opposition to PCTs within the cultures of companies, regulatory agencies, and research institutions. Incorporating pragmatic features into Phase III/IIIb pharmaceutical trials may not require a completely new trial structure and likely will not be necessary for all new pharmaceutical products. Participants appeared to agree that a dialogue among stakeholders, such as occurred at this meeting and the development of guiding principles developed by a broad stakeholder group can help break down the communication barriers and support the incorporation of more pragmatic features into Phase III clinical trials.

Introduction: Meeting Goals and Objectives

A major goal of comparative effectiveness research (CER) is to provide health care decision makers, particularly patients, clinicians and payers, with better evidence for use in making informed health care decisions. To meet this goal, comparative effectiveness or patient-centered outcomes research must consider a comprehensive array of health-related outcomes across diverse patient populations. (Federal Coordinating Council, 2009) The concept of pragmatic clinical trials (PCTs) is closely associated with the goal of CER. (Luce et al., 2009) PCTs are prospective studies designed with the specific objective of producing information that will assist patients, clinicians and payers in making informed decisions about alternative drug and other health care therapies. In order to understand the barriers to conducting PCTs to gain regulatory approval for drugs and opportunities for increasing the use of PCTs at this phase of drug development, the Center for Medical Technology Policy (CMTTP) brought together a multi-stakeholder workgroup to characterize recurring gaps in evidence that are often not sufficiently addressed in regulatory trials, explore the reason for these gaps, and begin to elucidate potential solutions. This stakeholder meeting marked the start of a six-month project, which will culminate with the development of a Guidance Document. Modeled on the approach and content of FDA guidance documents on trial design, the PCT Guidance Document will lay out principles and recommendations for increasing the use of PCTs earlier in the lifecycle of a drug. This document summarizes the meeting discussion and recommends topics for inclusion in the Guidance Document, based on focused break-out group discussions.

Developing a Common Framework

The morning began with a quick interchange during which payer representatives were asked to highlight the types of information currently missing from clinical trials but necessary for informing coverage and, implicitly, treatment decisions. Payers indicated that they would like to see trials conducted in a population that is more reflective of the end users, comparing new products against those most likely to be replaced, and measuring clinically-meaningful patient outcomes. In addition, payers noted that they would like to see translation of evidence to guide where in the treatment spectrum (e.g., first line) a product is most appropriate. To illustrate the importance of broadening patient inclusion criteria, payers noted that in key pre-approval trials to generate evidence on the clinical efficacy and safety of Chantix®, an aid to smoking cessation treatment, smokers who reported receiving treatment for depression at trial initiation or within the previous 12 months and smokers who reported a past or present history of serious mental illness were excluded from the trial. Exclusion of such patient populations is standard in Phase III/IIIb clinical trials and was approved by the FDA. Nonetheless, it is known that there is a higher prevalence of smoking in people with serious mental illness, and the pre-approval trials did not establish the safety and efficacy of Chantix in such individuals. In post-marketing experience, serious neuropsychiatric symptoms, including suicidal ideation and suicide, have been reported in some patients taking Chantix, although, as noted in the

Box 1: *In order to gauge how trials can be designed to better address the evidence needs of post regulatory decision makers, the payer representatives attending the meeting were asked: “**What type of information that is necessary for making coverage decisions is currently missing from clinical trials?**” In general, responses centered around three key points:*

- 1. Generalizability of the patient population*
 - 2. Active comparators*
 - 3. Consistently-measured, relevant outcomes across therapeutic options*
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Presentation 1: Developing a Common PCT Framework

Jodi Segal, MD, MPH

Dr. Jodi Segal provided an overview of Pharmaceutical Pragmatic Clinical Trials (PCTs), explaining that PCTs are prospective studies designed specifically with the objective of informing patients, clinicians and payers, when making decisions about drug therapies. She stated that interest in PCTs has increased with greater attention from payers and policy makers to the need for more reliable evidence of comparative effectiveness in typical practice settings among diverse patient populations. Dr. Segal noted that different decision-makers have different needs. Regulators, like the Food and Drug Administration (FDA) need evidence that a drug is likely to be safe in much of the population, evidence about its efficacy, and demonstration of any dose-response relationship. Pharmaceutical companies need information about the drug's efficacy and safety as well as pharmacoeconomic information. They also need comparative effectiveness data for marketing and reimbursement purposes. Clinicians and patients need information on an individual level about a drug's effectiveness and safety, when used in their respective clinical settings. Finally, payers need information about a drug's effectiveness and safety relative to comparators for coverage decisions.

Dr. Segal posited that PCTs may be well suited to address the needs of these multiple decision makers. They yield practical information about a heterogeneous group of patients receiving care in their usual setting; allow flexibility in the treatment regimen, including in ancillary care; and can provide more comprehensive, patient-oriented outcomes. The PRACTiHC project, a Canadian and European Union initiative, encourages investigators to regard pragmatic trials as existing on a continuum with more traditional explanatory trials.

Dr. Segal also pointed out some of the challenges of conducting PCTs, which include the responsibility to minimize exposure of large numbers of patients to potentially harmful or ineffective drugs. Therefore, in order to meet the needs of both regulators and the decision makers who need this information after approval, innovative methodologies need to be developed that maintain the internal validity of these trials, assure generalizability, and make sure that the questions being asked and the outcomes being measured are the right ones.

Dr. Segal prepared a background paper for this meeting laying out the definition, history, and specific design features of pragmatic clinical trials. A copy of this background paper is available on the CMTP website at: <http://www.cmtmpnet.org/>

Chantix label, such reports do not establish a causal relationship between these events and the medication. Expanding research into a broader population needs to be balanced with ethical considerations.

From the perspective of some stakeholders, payers create major barriers to conducting PCTs. Specifically, these stakeholders feel that payers are often uncommunicative about the evidence they need. Even when payers are explicit up front there is less assurance as to how health authorities and payers will embrace these trials once they are completed. Industry is concerned that data from pragmatic trials will be discounted due to concerns about internal validity and confounding.

Following this discussion, Jodi Segal from Johns Hopkins University presented a background paper she prepared that defined the concept of PCTs, and provided historical context as to why the current clinical trials framework often fails to meet the evidentiary needs of post-regulatory decision makers. She also described several recently completed PCTs, and briefly reviewed some of the barriers to conducting PCTs. The presentation was meant to ensure that meeting participants had a shared understanding of the concept of a pragmatic trial and to introduce those study design features (expanding research to the community setting, minimizing protocol-driven care and inclusion/exclusion criteria, and incorporating active comparators) that researchers should consider when planning and implementing PCTs. For a summary of this presentation, please refer to the **Presentation 1** text box.

Next, Marc Berger from Eli Lilly presented findings from a literature review conducted by Eli Lilly and United BioSource of all PCTs completed between 1996 and 2008. A search of the published literature using MeSH terms

including comparative effectiveness, naturalistic trials, pragmatic, and 'real world' identified only 23 PCTs of pharmaceutical products, nearly all of which were completed during the post-market phase

(Phase IV). Although one might contest their search strategy, and whether they identified the universe of PCTs, the authors' main conclusion was that published pharmaceutical-company sponsored PCTs are uncommon. Of the three PCTs sponsored by Eli Lilly, none showed a significant clinical advantage for their drug, highlighting one of the reasons pharmaceutical companies may be reluctant to sponsor or publish trials of this type. The lessons learned from this experience were that "usual care" is not a stable comparator and participation in such trials tends to result in generally improved care in the comparison arm. As a result, it is harder to find a statistically significant therapeutic improvement in these trials. Intent to treat analysis combined with an open label protocol, while providing important insights into how patient and provider characteristics influence adherence to treatment regimens, is less robust in identifying the contribution of a specific drug to health improvements. In the three highlighted trials, there was substantial switching among treatment groups. Finally, treatment in a usual care setting may be confounded even though allocation is randomized, as there may be non-random distribution of inadequate follow-through of treatment. Notably, all of the Eli Lilly-sponsored PCTs were in the area of mental illness, which may have colored their experience. Dr. Berger suggested using "clinically indicated care" as a way to avert some of the difficulties with isolating a treatment effect in PCTs. "Clinically indicated care" is care that would require investigators to adhere to protocol-prescribed care where the protocol is based on a formal treatment guideline appropriate to the clinical setting where care is typically delivered. For a summary of this presentation, please refer to the **Presentation 2** text box.

Several reasons for the current low numbers of PCTs emerged from the group discussions, both at the beginning of this meeting as well as following the two presentations described above. Among the most prominent are:

- **Incentives:** Manufacturers have much to lose by designing comparative trials in Phase III/IIIb. One major risk in a head-to-head trial would be that their drug would never make it to market.
- **Timing:** It is important to consider where to draw the line between pre- and post-regulatory space or, more generally, when it is appropriate to broaden the study population and relax the inclusion/exclusion criteria. Sufficient safety data are needed before it is ethical to relax the inclusion/exclusion criteria. And in addition, one needs to have a robust understanding of the effects of dose on efficacy and safety. However,

Presentation 2: A Review of Published PCTs

Marc Berger, MD

A literature review of articles published between the years 1996 and 2008 identified only 36 PCTs, most of which were conducted during phase IV to provide payers with information on usual care use of treatments not available from RCTs. Of these 36 trials, 23 were studies of pharmaceutical interventions and 11 of these were sponsored by pharmaceutical companies. Two early adopters of PCTs were Eli Lilly and Merck. Several lessons from Eli Lilly's experience with these trials include:

- It is difficult to detect differences across treatments when the number of treatment arms is large.
- In the "real world", there is a lot of switching, discontinuation, restarting, and "add on" therapies. In pragmatic trials that permit these care patterns, it is difficult to determine the effectiveness of a given therapy.
- Intent to treat analysis combined with an open label protocol, while providing important insights into how patient and provider characteristics influence adherence to treatment regimens, is less robust in identifying the contribution of a specific drug to improved health.
- "Usual care" in a PCT is not a stable comparator as treatment is generally modified (perhaps due to study participation) until clinical response is obtained.

A potential alternative study design that may help address some of these issues is the use of clinically-indicated care. Clinically-indicated care refers to protocol-prescribed care, which is based on a formal treatment guideline appropriate to the clinical setting where care is typically delivered.

there is a disincentive to participate in trials once a drug is widely available so there is a need to find a middle ground in terms of the timing of these trials.

- **Funding:** The costs of head-to-head trials that are adequately powered can be large, and pharmaceutical companies would be unlikely to place a high priority on funding these relatively expensive trials to bring their drugs to the market. Public funds may be needed to support these.
- **Identification of appropriate therapeutic areas:** There are certain therapeutic areas that have a greater need for pragmatic trials and some where it may be more difficult to design pragmatic trials. For instance, many trials for treatments of cardiovascular disease have been pragmatic because FDA regulators have required more pragmatic features for registration trials in this disease area. These trials often have broad study inclusion criteria, use simple (or at least streamlined) study protocols, and incorporate clinically-relevant patient outcomes. However, there are fewer good examples of PCTs in other therapeutic areas. In some clinical areas, like diabetes, it may be more difficult to conduct PCTs with a sufficient sample size and over the necessary time frame to allow the collection of the types of outcomes that are relevant for decision makers, as these may occur less frequently and many years after the intervention. Strong signals from the FDA can greatly help to improve the state of evidence.
- **Selection of patient-reported outcome measures:** There needs to be a common understanding of what patient-reported outcomes measures are appropriate in Phase III/IIIb clinical trials and whether these outcomes will be accepted by the FDA, although the FDA is developing a guidance document on this topic, some participants felt there was room for greater clarity. (U.S. Food and Drug Administration, 2006)

As the morning progressed, there seemed to be growing consensus that it would be possible to design PCTs that simultaneously relax some of the restrictions of traditional clinical trials and maintain enough

Box 2: *Currently, pragmatic clinical trials for pharmaceuticals are rare, especially within the Phase III space. However, examples of Phase IV pragmatic trials include:*

1. *Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)(Davis et al., 1996)*
2. *Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (Stroup et al., 2003)*
3. *Similar Effectiveness of Paroxetine, Fluoxetine, and Sertraline in Primary Care: A Randomized Trial (Kroenke et al., 2001)*

of the structure required for regulatory review. Further, there appeared to be common ground between the desires of regulators and those of payers, as there is a penalty for both regulators and end users given the amount of uncertainty associated with a drug at the time of product launch. Participants discussed how to balance the two-fold objective of improving external validity while maintaining internal validity. One participant noted: “What troubles me is this conversation about balancing internal and external validity as though you trade them off”, while others emphatically noted that there is indeed a tradeoff, and that designing a valid, reliable pragmatic study for regulators may limit generalizability. There seemed to be consensus that an appropriate balance could be reached along some of the dimensions of PCTs.

In order for PCTs to be maximally informative to multiple stakeholders, it is important to improve dialog among developers, clinical scientists, regulators, and post-regulatory decision makers (payers, patients, and clinicians) to better understand which types of questions can be answered earlier in the drug development cycle. Under the current model there appear to be many missed opportunities to generate evidence for these stakeholders earlier in the drug development cycle. In order to promote such dialogue, industry should ask payers which research questions are most important to them. There was a

willingness among payer representatives to participate and there have been efforts by various payer organizations to be more open and transparent. For example, at the Drug Effectiveness Review Project at the Oregon Health Sciences University all meetings are public so industry is always welcome to attend. However, there is currently no real infrastructure to support a transparent and collaborative dialogue on a large scale. In Australia, the Department of Health has started engaging with industry about evidence needed for decision making before new health technologies reach Phase III/IIIb research. However, this type of communication has not been conducted in a coordinated way across countries. Different regulatory agencies have different evidence standards for approval, and different payers have different standards for reimbursement. Payers would like to engage regulators, such as the FDA and EMEA in these discussions early in a product's development, as well.

Additionally, if payers were to require that evidence of clinical effectiveness be generated prior to broad coverage and were willing to help financially support the required research to generate such evidence, there would be a stronger incentive for industry to generate this information. One possible avenue to promote this type of research is coverage with evidence development, although this may not be viable in the Phase III/IIIb space. Payers could also think about making coverage or reimbursement more pragmatic, meaning that the level of reimbursement for a new therapy could reflect the level of certainty that the product provides a clinical benefit to patients, similar to the concept of value-based insurance design. This would also require some level of commitment from post-regulatory decision makers to use the information generated from PCTs when making clinical and health policy decisions if those PCTs are included in development and implementation of these trials.

It also would be beneficial if there were more guidance on appropriate patient-reported outcomes and quality of life measures. Although the FDA has indicated that it would accept evidence from well-validated health-related quality of life measures, pharmaceutical companies are still uncertain. If FDA guidance were more specific about which patient-reported outcome measures were acceptable, it would likely increase the use of more patient-centric outcomes earlier in the drug development process.

The idea of incorporating clinically-indicated care into study protocols, as mentioned in presentation 2, also deserves further exploration. This is one way to maintain a focus on drug efficacy, while still allowing for the incorporation of more pragmatic features in the design. Some participants agreed that studying switching patterns across treatment arms and patient compliance may be more of a health services research question reserved for post-coverage decisions. One concern about using clinically indicated care is that it may add an unevaluated component into clinical trials. For instance, if the protocol improves adherence in the intervention arm, will the drug be marketed and used in clinical practice in a similar manner once approved? The above may apply to the comparator arm, especially in cases in which the comparator is used in the "real world" in ways that are not in alignment with the approved indication.

A cautiously optimistic tone emerged from the morning session as it appeared that there are opportunities for stakeholders to work together to identify evidence gaps and unanswered questions and determine whether or not it would be feasible to fill such knowledge gaps. Not all questions can be addressed in Phase III/IIIb trials, but it does seem possible that there are opportunities to improve Phase III/IIIb trials so that they are more informative to post-regulatory decision makers. There will be barriers and variation by therapeutic area but these barriers are not necessarily insurmountable. For instance, a few participants noted that payers could do substantially more to support clinical research. Policies about non-payment for experimental technologies, for example, are a major financial barrier to conducting some types of research. Medicare's inability to adjust the co-payments for care received in

clinical trials is another example of a financial barrier to research. While Medicare does pay for the usual care costs, separating out these costs from those driven by the protocol is a major headache for research facilities, adding considerably to the paperwork and administrative burden of trials. Further, if investigational sights make a mistake in billing for non-covered costs, there are potential penalties for fraud.

Key Issues in Study Design

The next portion of the meeting was devoted to two separate break-out sessions. The objective of these break-out sessions was to explore and discuss potential topics for a Guidance Document on PCTs within Phase III/IIIb as well as to begin to develop an initial outline and set of recommendations for the document. During the first session, participants discussed issues in study design including the selection of appropriate comparators, heterogeneity of the patient population and study sites, enhancing the generalizability of the patient population, and relaxing intensity of monitoring and clinical trial protocol-driven care. The second session focused on the financial, ethical, and regulatory barriers to PCTs including expanding research to the community setting, dealing with cultural acceptance of PCTs, reducing cost and improving efficiency of PCTs, and addressing regulatory barriers.

- ***Selecting Appropriate Comparators***

All participants agreed that the selection of appropriate comparators is an important topic to include in a guidance document, but there is no simple answer as to how best to do this. Several factors that researchers should consider when selecting comparators for PCTs include the point of view of decision makers and the types of questions they are asking, the setting (e.g. country) within which the trial is taking place, current and expected future changes in practice patterns, and the state of existing evidence. The last item is an important place to start. For example, when designing a cancer trial, appropriate comparators would be those chemotherapeutic regimens in current use that are known to be effective; however, trials might be ongoing that would change the appropriate comparator by the time the trial is completed.

There was a dynamic discussion of whether a trial should include a placebo. While some participants felt a placebo control is always important, there was extensive disagreement. Some participants argued that placebo control is not important if there is a strong consensus about which existing treatments are effective. The problem with this approach is that the belief about what is an effective treatment may be based on poor-quality evidence. The choice about whether or not to include a placebo arm should be informed by what outcomes are being considered. In the early thrombolysis trials, for example, the outcome was all-cause mortality, which is an unbiased endpoint; therefore, a placebo control was not necessary. On the other hand, if the outcomes require adjudication or patient input, reporting may be biased and a placebo control is required.

There was also a rich discussion of the issues raised by including usual care as a comparator. The two main issues this elevates are: 1) usual care is heterogeneous, and it is not always easy to define; and 2) usual care can be 'unusually' good. Designers of the Multiple Risk Factor Intervention (MR FIT) trial (Multiple Risk Factor Intervention Trial Research Group, 1982) which examined various interventions for smoking cessation and other poor health behaviors hypothesized that the usual care group would serve as an appropriate control group, showing higher mortality than the "special intervention" group, but that is not what happened. Instead, both groups experienced substantially lower mortality than

anticipated, which reduced the statistical power of the comparison. If the comparator is usual care, there may be confounding by indication.

Subtopics for a guidance document include:

1. Usual care: In addition to the issues raised above, discuss the role for more formally defining the usual care arm, such as the use of clinically-indicated care
2. The circumstances under which a placebo control arm might be omitted
3. Selecting comparators for international trials, where appropriate comparators may vary across countries
4. The role of indirect versus head to head comparisons (Notably, many participants argued that the current state of science did not support the use of indirect comparisons, while payers and industry participants noted that payers are increasingly calling for them.)
5. Recommendations on who should pay for the comparator in head-to-head trials, and how to address issues where payment decision-makers may differ for selected comparators (e.g., Medicare Part D versus Medicare Part B)
6. The role of genotype or other biologically-defined subgroups in selecting appropriate comparators
7. Ethical considerations

- ***Dealing with Heterogeneity Overall***

A guidance document should consider multiple sources of heterogeneity including heterogeneity of the patient population, intervention dose, comparators, and of the clinicians or providers. The ideal way to address heterogeneity is through pre-specified stratification (or randomization) by subgroup during the design of a trial. One participant further qualified this recommendation by suggesting a classification scheme for the inclusion or analysis of subgroups: ‘good’ was reserved for stratified randomization; ‘be careful’ for pre-specified, but not stratified subgroups; and ‘be very careful’ for all other subgroup analyses. Addressing heterogeneity is not just about increasing the precision of your estimates. Both the NIH and FDA require certain subgroup analyses in their policies on inclusion of women and minorities. In general, findings about differences in subgroup benefits and harms are more robust when derived from a heterogeneous population within a given study than from comparisons across two different trials examining different populations. Regarding the question to the group about whether there were ways to circumvent the need for large sample sizes to address heterogeneity, the answer was a resounding, “No.”

Participants noted that there has been a trend toward specifying a large number of subgroups in advance with the hope that one might show significant benefit. This is balanced by the potential risks of delaying or threatening drug approval if harms or poor response is observed within a pre-specified subgroup. There was a great deal of discussion about retrospectively-defined subgroups and their relevance for decision-makers. Some payers stated they do not use them. Others, such as NICE which uses incremental cost-effectiveness ratios, are under intense public pressure to approve new drugs, they actively search for subgroups where they can find a benefit. There is a preference that subgroups be pre-specified. The FDA has observed a movement toward displaying information on a large number of subgroups in forest plots. In some instances, such as the case of the trial of losartan versus atenolol, which showed a reduction in stroke risk for whites, but the reverse for blacks, the retrospective subgroup analysis could not be ignored and was included in the label.(Dahlf et al., 2002)

Subtopics for a guidance document include:

1. How to select appropriate stratification variables. For example, in a PCT, it may be important to stratify on those characteristics that are observable in usual care, and possibly modifiable. Genetics, where testing is not commonly used in practice, would not be an appropriate stratifying variable.
2. Criteria for selecting the number and types of subgroups to include. The recommendation was

Presentation 3: PCT Design and Use: Insights from Pre-Meeting Participant Interviews

Penny Mohr, MA

CMTF conducted a series of pre-meeting interviews with a number of participants to understand current thinking about PCTs. A central theme that emerged from these interviews is that one must design a trial fit for its purpose. If the goals are to be maximally informative to decision makers, while still meeting regulatory requirements, one needs to better understand what decision makers want to know that is not currently being addressed in Phase III trials. With this information it will be possible to determine which of those questions can be addressed in Phase III research. Design features that decision makers who were interviewed view as central to understanding the effectiveness of an intervention are inclusion of a range of patients, providers, and healthcare settings that more closely reflect the patients, providers and settings where the drug will be used, the use of active comparators, and including clinically-meaningful outcomes, with more of an emphasis on functional status, quality of life, and longer-term impacts.

A key point to remember is that PCTs are not necessary in all situations and it would be useful to develop a set of criteria for determining when PCTs are necessary, especially because PCTs can be expensive and incur huge opportunity costs. Value of information analysis may provide important insight into those areas that would benefit from PCTs. In addition, indirect comparisons and modeling can also be useful methods for providing information for clinical and coverage decisions.

surrounding multiple imputations to account for missing data from dropouts and how to adjust or model results with multiple comparisons within a randomized trial.

- ***Enhancing Generalizability of the Patient Population***

Groups that are underrepresented in RCTs include the elderly (over 75), people with co-morbidities, individuals without health insurance, people who take concomitant medications, and those with low literacy. Major barriers to broadening study populations to increase generalizability include concerns of creating noise and reducing the power to answer questions about relative risks and efficacy of new drugs. Concerns were expressed that more noise would lead to false safety signals, delaying or

to limit the number of subgroups. Researchers also have to consider whether there is reliable, external biological or clinical evidence that would lead them to believe there may be differential response. Surrogates for true biological markers that are exploratory in nature should not be used. In addition to examining heterogeneity in risks and benefits, researchers should consider the heterogeneity in the risk/ benefit ratio for different subgroups.

3. The role of prospective versus retrospective subgroup analyses.
4. The role of Bayesian or adaptive trial designs as a way to use prior information external or internal to a trial in other subgroups. Bayesian trials can be helpful if attention is focused on subgroups where a precise estimate of effect is most needed, but sometimes there is a loss of efficiency in terms of overall effect estimation. Further defining adaptive approaches, such as how to move seamlessly from Phase III to Phase IIIb, using early information to guide the choice of subgroups, would be very useful.

5. Analytical issues, such as those

preventing approval. Of course with a broader population, one has less precise estimates, thus requiring a larger sample size, with increased cost and longer duration. The lack of consistency across regulatory authorities in their advice about the importance of studying a drug in a broader population is also a barrier.

Strategies to broaden patient populations that might be included in a guidance document are:

1. Start with the inclusions of patients who are likely to receive the drug in clinical practice and require careful justifications for any additional exclusions
2. Have payers state that they will not pay for products not tested in the target populations

Strategies to generate evidence needed by payers include:

1. Including payers at the end of Phase II meetings with regulatory authorities. Although payers are not specifically excluded at this point, they are not typically invited to attend so infrastructure and process to support greater collaboration are needed.
2. Having payers commit to paying for clinical care in trials that address their data needs. It needs to be recognized that there may be conflicting financial incentives for all parties, which implies the need for working together to achieve solutions that address patient care needs and that do not jeopardize needed incentives to participate in trials

- ***Relaxing Intensity of Monitoring and Protocol-Driven Care***

There was a general consensus that this topic should be included in a guidance document but several group members felt that it should only be included insofar as it is permitted for regulatory purposes. One of the major points raised was that by relaxing monitoring, one is going beyond “Can it work?” to “Will it work in routine practice?” These are very different questions, and it is often not desirable to relax protocol-driven care within clinical trials (e.g., clinically-indicated care may be a good interim step). Illustrations for how protocol-driven care may differ from actual practice include use of labeled dosing regimens for the comparator, which may not be followed by clinicians in actual practice. By driving everything to optimal use, you do not get a ‘real-world’ understanding of the comparative risks and benefits of different treatment options. Trials also may be designed to use diagnostic or pharmacogenomic tests to select groups who would likely be the best responders to a drug, but these tests may not be used in practice. Participants noted a key question to address is when in the life cycle of a drug would it be desirable to relax monitoring (e.g., separate aims for Phase III/IIIb and IV)?

Subtopics under this heading to discuss in a guidance document include:

1. Cost of monitoring. Can we be smarter, less intrusive, and more efficient in the way we do monitoring? Examine the potential for adaptive or knowledge-based monitoring, rather than universal monitoring.
2. Study design issues. What are the best study designs to fit with this aim (e.g., adaptive design versus parallel follow-up studies)?
3. Ethical and liability issues. Namely, how pragmatic can we be before we understand the risk/benefit profile?
4. Regulatory heterogeneity. Most trials are international in scope. The FDA has different standards than EMEA for allowing flexibility from protocol-defined care. For investigators, they need to clearly understand the appropriate balance between ‘allowing flexibility’ and ‘protocol violation’.
5. Subpopulations. When relaxing protocol-driven care, it may be even more important to examine subpopulations, as factors influencing compliance with therapy will vary by subgroup.

There was some hesitation expressed about expanding the patient population in Phase III/IIIb because of safety concerns. However, once the risk/benefit profile is established in early Phase III/IIIb, it seems possible to expand the patient population late in Phase III/IIIb. If researchers were to incorporate Bayesian methods into Phase III, it would be possible for trials to adapt as safety information becomes available, creating a seamless transition from Phase III to Phase IIIb research. The FDA is currently in creating guidance on using adaptive study designs.

Identification of Financial, Ethical, and Regulatory Barriers to Implementation

Break-Out Session 2: Implementation Barriers and Potential Solutions

- ***Expanding Research to the Community Setting***

The barriers to expanding research to the community setting include the lack of trained researchers, which leads to increased training costs, difficulties of site recruitment, problems with data quality, and an unwillingness of patients not being treated at academic centers to participate in trials. These factors all lead to added costs and duration of trials conducted in community settings, which is problematic given the need for expediency in Phase III/IIIb research.

Some affordable options to reduce these barriers that should be discussed in a guidance document include cluster randomized designs (recognizing potential statistical hurdles) and use of electronic medical records. Participants noted, however, that EMRs were not yet mature enough to improve the efficiency of research designs. To expand research to a managed care population, researchers will need to focus on research questions that can be answered relatively quickly, as turnover tends to occur fairly rapidly. Practice-based research networks may be one approach to provide an infrastructure to support the rapid design and implementation of studies, but there was not a lot of familiarity with the use of such networks in clinical trials.

- ***Dealing with Cultural Acceptance of Pragmatic Trials***

There is a natural inertia among product developers and regulators that work against the adoption of pragmatic features in Phase III/IIIb research as many of the methods and statistical analyses necessary for such studies are unfamiliar. Although not every new drug entering the market will require a PCT, there are misaligned incentives in the current health care market. In such areas there is a need for stakeholders to communicate with each other about where the current evidence is lacking. Therefore, in order to increase the use of pragmatic designs, it is essential to demonstrate the business case for undertaking this research. As was stated above, there is a need to develop a framework to ensure that studies are designed and conducted in a more efficient manner. In order to do this, it would be wise to look at those areas where researchers are currently implementing more pragmatic study design features, such as in cardiology research. Another important point is that sole source drugs should be viewed differently than new drugs entering a crowded market place.

- ***Reducing the Cost and Improving the Efficiency of Pragmatic Trials***

There are both financial (data collection, adverse event reporting, and protocol-driven) and opportunity (time to market delays) costs associated with trials. Many cost reduction techniques that are

appropriate for PCTs are the same techniques that are used with other trials. The health care community needs to articulate those research methods that are appropriate for PCTs and should use value of information analysis to determine where PCTs would be the best approach to providing evidence needed for post-regulatory decision making. Specific strategies to reduce cost include: ePrescribing, a uniform patient identifier so that EMRs can be used for data collection, integrating research into clinical practice, which could also include the use of EMRs for data collection (for example, it may be possible to have approval based on smaller trials if there are few safety signals and an agreement to do more post-approval studies), and identifying when it is possible to have fewer assays or fewer patient follow-up visits, and reducing the number of data elements collected in clinical trials.

However, significant increases in efficiency may require legislative or regulatory change. For example, changing the liability of the trial sponsor or providing support for the Centers for Medicare and Medicaid Services to implement coverage with evidence development or change its clinical trials policy. It is important that initially, efforts to improve the efficiency of trials focus on just a few areas with the greatest potential, as is being done by the Clinical Trials Transformation Initiative (CTTI).

Another potential solution to increase the efficiency of research is to spend more time in Phase II trying to better understand new drugs. This knowledge could be helpful for designing more pragmatic Phase III/IIIb trials.

In addition to discussing ways to improve the efficiency of PCTs, workgroup members also discussed more generic barriers to designing PCTs. These include:

1. There may be a limited number of clinicians and health plans that are willing to participate
2. There is a lack of infrastructure to support data collection and electronic medical records will not completely solve the problem
3. There is a fear that PCTs will jeopardize FDA review

Potential solutions include providing public funding or incentives to support PCTs, defining a business case for PCTs, developing an infrastructure to support discussions among stakeholder groups, and identifying those areas that would benefit the most from PCTs.

- ***Addressing Regulatory Barriers***

In this last summary of workgroup deliberations of the day, delivered by a representative from the FDA, the main message was that regulators are open to considering trial designs that would better meet the needs of post-regulatory audiences. The FDA is open to various endpoints. They are not opposed to Bayesian design, and are interested in reducing data collection burdens, such as reducing the intensity of monitoring. For example, the International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use – Consolidated Guideline for Good Clinical Practice (ICH-E6) clearly states that the frequency of monitoring should be guided by the nature of the trial, but the FDA is still receiving protocols with more intensive monitoring than is necessary. (International Conference on Harmonization, 1996) It is sometimes hard to get trialists to change their approach, even when they are given permission to do so. There are some regulatory barriers to PCTs, including current requirements for reporting serious adverse events (SAEs). These requirements are burdensome and the FDA is rewriting their guidance for reporting SAEs. Mandated safety data collection such as this can undermine the goal of non-intrusive measurement and require more intensive monitoring. Institutional Review Boards also pose a challenge to the design of more pragmatic trials. As a rule, the FDA does not require comparative data. Therefore, if payers are interested in comparative studies for a whole class of drugs, they need to understand that drug companies will rarely fund these studies. These studies will need to

be supported by public research money. Industry and payers need to more clearly communicate to regulators what pragmatic features they want included in clinical trials. It is true that the FDA has 16 reviewing divisions, and there is not always consistency among them, but it is possible to obtain a second opinion from an outside division, such as the Office of Policy, when there is resistance to new ideas. There will also need to be clear communication from senior FDA officials to the reviewing divisions. This presenter underscored a common theme for the day, which was a need for better communication among all parties involved to produce studies that are more informative for decision makers.

Concluding Points

PCTs are RCTs that are designed to be more informative to post-regulatory decision makers. Incorporating this concept into Phase III/IIIb trials will involve a process of identifying trial designs and methodologies that are sufficiently informative to both regulators and post-regulatory decision makers. There is willingness among stakeholder groups to engage payers in the study design and implementation process and among regulatory agencies to accept alternative study designs, such as Bayesian adaptive designs. For PCTs to be sustainable there need to be strong incentives for assuming the risk and costs of conducting PCTs. In order to encourage further discussions of PCTs, it is important to think about PCTs in the context of what is already being done, to keep stakeholders engaged in the discussion, and to identify those therapeutic areas that could benefit most from Phase III/IIIb PCTs. Incorporating pragmatic features into Phase III/IIIb pharmaceutical trials will not require a complete new trial structure and it is likely not possible to address all question of importance to post-regulatory decision makers in the Phase III/IIIb space.

Clear guidance on how to approach designing PCTs is probably something that can only really be addressed in the context of specific therapeutic class or more specifically on a drug by drug basis or the combination of drug and indication. However, there are some general principles that are applicable across different therapeutic areas that became apparent during the course of this meeting. Therefore, CMTP, in collaboration with meeting participants, will develop a Guidance Document outlining these general principles in the form of study design recommendations.

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Appendix 1: Participant List**Pharmaceutical Pragmatic Phase III/IIIb Clinical Trials Meeting****Academia**

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Appendix 2: Meeting Agenda

Agenda Topics	Led by	Items for Discussion
Breakfast 8:00am-8:30am		
Introductions and Meeting Goals 8:30am-9:00am	Cliff Goodman intro Sean Sean Tunis, CMTTP	<ul style="list-style-type: none"> ▪ Introductions ▪ Purpose of Meeting: To develop a conceptual, methodological and policy framework to make phase III pharmaceutical trials more “pragmatic” and more informative to post-regulatory decision makers. . ▪ Desired Outcomes: <ol style="list-style-type: none"> 1. White paper and issue brief summarizing the discussion, areas of agreement, areas of disagreement. 2. Guidance Document targeted to clinical researchers and product developers outlining a framework for design of pragmatic phase III clinical trials 3. Specific follow up activities that would build on ideas generated at this meeting
Developing a Common Framework 9:00am-9:30am	Jodi Segal, Johns Hopkins University	<p>Brief presentation of the white paper developed for this meeting that provides a historical background for pragmatic clinical trials, identifies barriers to implementing these trials, and provides suggestions regarding the possible place of PCTs in the drug approval process with 15 minute discussion period.</p>

Literature review of Pharmaceutical PCTs 9:30am-10:00am	Marc Berger Eli Lilly and Company	Presentation of the findings of a recently completed synthesis of the literature on pragmatic trials and lessons learned from selected case studies conducted by Lilly with 15 minute discussion.
Group Discussions 10:00am-10:45am	Cliff Goodman, Lewin Group	Participants have the opportunity to discuss their expectations for this meeting, the topics that will be important to address in an Guidance Document, and what the structure of the guide should be.
Break 10:45am-11:00am		
Key Issues in Study Design (Break Out Session 1) 11:00am-11:30am	Pre-assigned breakout groups led by: Mark Gibson, Marc Berger, Seren Phillips, Peter Juhn	Topics for discussion: <ul style="list-style-type: none"> ▪ Selecting appropriate comparators ▪ Relaxing intensity of monitoring and protocol-driven care ▪ Enhancing generalizability of patient populations ▪ Dealing with heterogeneity overall
Each group should address their assigned topic, providing each participant with the opportunity to contribute to the discussion.		
Group Presentations and Discussion 11:30am-12:00pm	Cliff Goodman, Lewin Group	Each breakout group will be asked to present the topics and issues discussed within the group and offer preliminary recommendations for consideration in the guidance document.
Lunch 12:00pm-12:30pm		
Identification of Financial, Ethical, and Regulatory Barriers to Implementation 12:30pm-1:00pm	Penny Mohr, CMTP and Cliff Goodman, Lewin Group	Brief presentation of barriers that were mentioned by participants during pre-meeting interviews and discussion of additional issues encountered by meeting participants.
Implementation Barriers and Potential Solutions (Break Out Session 2) 1:00pm-1:30pm	Pre-assigned breakout groups led by: Mark Gibson, Marc Berger, Seren Phillips, Peter Juhn	Structure to be determined by pre-meeting interviews Topics for discussion: <ul style="list-style-type: none"> ▪ Reducing the cost and improving the efficiency of pragmatic trials

	Each group should address their assigned topic, providing each participant with the opportunity to contribute to the discussion.	<ul style="list-style-type: none"> ▪ Expanding research to the community setting ▪ Addressing regulatory barriers ▪ Dealing with cultural acceptance of pragmatic trials
Group Presentation and Discussion 1:30pm- 2:00pm	Cliff Goodman, Lewin Group	Each breakout group will be given the opportunity to present the topics and issues discussed within the group and offer preliminary recommendations for consideration in the guidance document. Following each presentation, meeting participants will discuss the points raised by the breakout groups.
Debriefing and Next Steps 2:00pm-3:00pm	Sean Tunis, CMTP	Review common themes and conclusions from the day, outline topics that will be covered in the Guidance Document, decide on an appropriate structure, and discuss follow-up activities that will help promote the design and implementation of Pragmatic Clinical Trials.