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## Improving the efficiency and effectiveness of pragmatic clinical trials in older adults in the United States

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### Abstract

Pragmatic clinical trials (PCTs) seek to improve the generalizability and increase the statistical power of traditional explanatory trials. They are a major tenet of comparative effectiveness research. While a powerful study design, PCTs have been limited by high cost, modest efficiency, and limited ability to fill relevant evidence gaps. Based on an American Reinvestment and Recovery Act (ARRA) supported meeting of national stakeholders, we propose several innovations and future research that could improve the efficiency and effectiveness of such studies focused in the U.S. Innovations discussed include optimizing the use of community based practices through partnership with Practice Based Research Networks (PBRNs), using information technology to simplify PCT subject recruitment, consent and randomization processes, and utilizing linkages to large administrative databases, such as Medicare, as a mechanism to capture outcomes and other important PCT variables with lower subject and research team burden. Testing and adaptation of such innovations to PCT are anticipated to improve the public health value of these increasingly important studies.

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## Keywords

Pragmatic clinical trials; Large simple trials; Comparative effectiveness research; Practice Based Research Network

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## 1. Introduction

Pragmatic clinical trials (PCTs) are prospective, randomized studies designed to compare the effectiveness of treatments in real world settings. As opposed to explanatory trials, which are designed to determine whether a treatment is efficacious under ideal conditions, PCTs tend to address practical questions about the effectiveness, risks, and sometimes costs of an intervention as they would occur in routine clinical practice. PCTs are characterized by the use of active comparators, broad inclusion criteria, large and diverse patient populations that are representative of those treated in practice, and easily measurable clinically relevant endpoints [1–4]. They are one type of study design that will be a critical component of comparative effectiveness research (CER) when randomization is necessary to achieve the most valid and reliable results. While the basic tenets of PCTs are seemingly simple [5], designing studies that can be efficiently implemented while enrolling a large and diverse patient population remains difficult and costly.

To date, many PCTs have been administratively cumbersome, lengthy, and expensive. Well-known examples include the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials, which cost an estimated \$130 and \$300 million, respectively [6]. Some critics have argued that despite their cost, these trials had modest impact on clinical practice [7–10]. There have been some examples of efficient PCTs that have substantially changed clinical practice. Most notably the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (The Italian Group for Studying Streptokinase in Myocardial Infarction)—also known as GISSI [11,12], enrolled patients suffering from myocardial infarction from approximately 90% of coronary care units in Italy and cost only \$50,000 to complete [13]. Before GISSI was completed almost no centers were using thrombolysis, but after the study showed dramatic reductions in mortality, nearly 70% of centers routinely used thrombolysis. With a burgeoning number of questions about the comparative effectiveness of therapies and progressively more limited national research funds, investing in a myriad of PCTs that are performed using more traditional approaches may not be feasible. Therefore, it is critical to design more efficient PCTs, like GISSI. This point was underscored recently in a proposed agenda for the advancement of clinical research by the National Clinical and Translational Science Awards (CTSA) Strategic Goal Committee on Comparative Effectiveness Research, which called for improving methods to increase the efficiency of comparative effectiveness research (CER) trials, improving methods to recruit and retain previously excluded populations, and finding better ways to incorporate stakeholder preferences and values into clinical research design [14].

To advance the science of PCTs, with a focus on the U.S. health care system, we convened a face-to-face meeting of representative stakeholders in May 2011 to examine the example of an osteoporosis PCT in older adults. To obtain broad stakeholder discussions around key study design and administrative decisions, the meeting included many experts in comparative effectiveness research methods, clinicians, federal regulators, payers, patient advocates, and pharmaceutical manufacturers. This meeting was supported by an American Recovery and Reinvestment Act (ARRA) CER supplement to the UAB Clinical and Translational Science Award (CTSA) grant, and was held in collaboration with the Center for Medical Technology Policy.

In this paper, we summarize viewpoints on novel and lower cost approaches to the design of PCTs resulting from our meeting of stakeholders and from the post-meeting discussions among the authors listed. The innovations that were discussed and which will be described include: 1) mechanisms to expand the settings and health care providers through which PCT participants can be recruited using Practice Based Research Networks (PBRNs); 2) simplifying enrollment procedures and data collection requirements through Internet technology; and 3) the use of administrative data linkage to identify selected outcomes as main endpoints of the trial (see Fig. 1 for a diagrammatic representation of these innovations) reducing the cost and measurement burden on the trial. Of added importance is the need to engage end-users (patients, clinicians, and payers) early in the design of PCTs to help ensure their relevance for decision making.

## **2. Using community practices and leveraging Practice Based Research Networks (PBRNs) to improve efficiency and effectiveness and generalizability of patient and provider site recruitment for PCTs**

Practice Based Research Networks (PBRNs) have allowed physicians in practice to collaborate in community-based clinical research and they have been used extensively as ‘research laboratories’ to study the diagnosis and treatment of patients across a number of different disease areas [15–18]. Through standardized electronic medical data collection by clinicians in practice, centralized administrative oversight of shared research activities, and national networking, facilitated by groups such as the Agency for Health Care Research and Quality (AHRQ), PBRNs have expanded dramatically in many areas of the U.S. Since 1994, the number of PBRNs has grown substantially from 28, mostly regional, networks to over 130 primary care networks all across the United States [16,19]. PBRNs represent a rich and largely untapped resource to conduct PCTs and can draw upon the example of such research in other countries [20–23]. In theory, the implementation strategies generated using PBRNs may allow for more rapid incorporation of results into standard clinical care, thus shortening the traditional lengthy translational process whereby trial results disseminate into community practice [18,24–28]. Although many PBRNs are studying patterns of treatments across various disease areas using observational designs [26,29–33], only a few randomized large scale controlled trials have been implemented within these U.S. networks and their associated practices to compare the effectiveness of different treatments for chronic diseases [34,35]. PBRNs offer significant advantages in identifying potentially interested clinical practices through which to collect data used for research, and to define areas of clinical practice in which uncertainty remains regarding the comparative effectiveness of alternative treatment strategies. Utilizing existing PBRNs in the U.S., investigators can more easily establish the sample sizes and generalizability needed for optimal PCTs.

However, there are challenges that need to be considered in the design, implementation, and oversight of PCTs in utilizing community practices affiliated with PBRNs. For example, identifying the appropriate clinical practices within a PBRN for a given PCT can be assisted by identifying *a priori* the specific features of practices that would align with a given study, such as study-specific patient demographics or disease characteristics. While the goal is to be as inclusive as possible to maximize generalizability, there needs to be a practical balance to ensure sites can still recruit a reasonable number of patients and can carry out the necessary study procedures. In balancing real world considerations with particular study needs, it is often necessary to consider the practice’s previous experience with clinical research, access to specialized testing or drug delivery, and geographic location. Such data may be available through collaborative resources such as the Distributed Ambulatory Research in Therapeutics Network (DARTNet) [36], a system of linked electronic health

records with standardized data that facilitate identification of appropriate practices and patient populations.

There are several benefits to care providers participating in PCTs. Participation provides an opportunity to achieve a level of comfort and familiarity with innovative interventions and early evidence-based information of new research results, fostering ready adoption at the conclusion of the study. Physicians are able to provide access to patients to new therapies or new applications of existing drugs in a way that other practices may not be providing. The physicians are able to advance knowledge in questions directly relevant to their daily practice, as well as the possibility to propose research topics arising from practice problems. Many providers also find clinical research activities to be an important source of intellectual enrichment and stimulation. There can also be an enrichment benefit to clinical nurses learning new skills as study nurses. It is also hoped that the mutual benefits to care providers and researchers achieved will facilitate a culture of enhanced communication in such networks.

### **3. Use of Internet technology for more efficient and effective recruitment, informed consent, and randomization of participants**

Efficient methods for screening, enrolling, and randomizing study subjects for PCT inclusion can pose similar challenges for practices that can impact study validity, generalizability, and relevance. Community physicians and their staff typically have heavy clinical commitments and possibly little research experience, even within practices that participate in PBRNs. These medical practices may find the process of obtaining Institutional Review Board (IRB) approval, determining patient eligibility, performing the traditional detailed informed consent process, reporting and following up on serious adverse events, and randomizing their patients to study drugs unfamiliar, time consuming, and/or distracting from routine clinical activities. Burdensome consent procedures, in particular, can negatively impact practices' willingness to participate in office-based PCTs. New methods are needed for providing more efficient, effective, yet ethically acceptable informed consent to improve the feasibility of community-based PCTs. Important issues for improving community site participation include facilitating Institutional Review Board (IRB) training, use of central IRBs, identifying local IRBs, procuring IRB approvals, optimizing patient comprehension and satisfaction with informed consent materials (especially for vulnerable populations), and reducing time commitments for patients and the clinical staff [37–40].

The use of information technologies such as Internet-linked real-time video, including touch screen computer tablets, smartphones and telephone support, can provide an efficient way to determine subject eligibility and improve patient understanding in the informed consent process. This can promote more successful patient enrollment in PCTs, increase research subjects' knowledge about the risks and benefits of study participation, and lead to a more efficient enrollment and randomization process. Such technological solutions could also reduce the burden on office staff for recruitment and avoid interruption in clinic flow. For example, touch pad computer technology available in an office waiting room, has been preliminarily tested for patient screening and enrollment in a hypothetical osteoporosis study, including patient self-assessment of eligibility criteria, while minimizing disruptions to a private practice office [41]. Once identified as possible study subjects, patients can then undergo simple final screening by the physician office staff to verify their qualifications as appropriate candidates for the study. Although, previous studies have shown beneficial effects of Internet technology used in a physician office or clinic for enhancing patient comprehension and consent for surgical procedures [42] and post-operative surgical rehabilitation [43], such approaches need widespread implementation in PCTs. The

University of Alabama at Birmingham (UAB) and its partners have recently received federal funding through the Agency for Healthcare Research and Quality Centers for Education and Research on Therapeutics (CERTs) programs to develop and test a centralized web based informed consent system. This study will assess the comparative effectiveness of such technology for assisting patients in completing the informed consent process at their own convenience with limited assistance from the physician office staff. As an example, these modules will provide video help screens to assist low literacy patients. Following informed consent, dynamic Internet-based patient randomization using a centralized data management site could further simplify randomization allocation to study drugs during a routine patient office visit. Such systems have been designed and used in direct-to-patient studies and previously have been approved by regional IRBs and accepted by the FDA [44].

While this technology would be beneficial in a busy clinician practice in many ways, there is still a slight potential for a loss of generalizability since such technology and devices could exclude certain vulnerable populations. People without access to a family physician or those reluctant or unable to use such technologies would not be reached in this type of study. Immobility, multiple comorbidities, and cognitive decline are common among an elderly population with chronic diseases and these persons may be unwilling or unable to complete required study questions using such a direct-to-patient format. The use of local study coordinators or caregivers to assist the patient may be required in some practice sites to help mitigate these concerns.

#### **4. Using administrative data for more efficient and effective PCT outcome assessment**

Pending more widespread availability of nationally linked electronic medical record data, access to linked administrative data, including claims for medical services and prescription drugs, can provide a major innovation in the conduct of PCTs by greatly simplifying collection of selected study outcomes, important co-variables, medication usage, and drug adherence. The availability and use of administrative claims, such as Medicare data from the U.S., are a good source of information on treatment patterns for diseases prevalent among elderly populations. These data have been used extensively by us and others in epidemiologic studies [45–48]. Although some PCTs, particularly those studying systems or organizational change, have used a Medicare data linkage [49–54], few PCTs comparing clinical interventions have used administrative data to examine long-term outcomes, and/or assess drug adherence.

The availability and scope of Medicare data have improved in the past decade, enabling easier assessment of health outcomes and expenditures among beneficiaries in the U.S. Most recently, the expansion of coverage under Medicare Part D provides a rich data set on outpatient drug use. A PCT enrollment procedure could be designed to obtain comprehensive patient informed consent to use the personal identifiers needed for Medicare data linkage. This design would facilitate outcome ascertainment in a physician office-based PCT without disrupting the day to day clinic workflow with study follow-up visits, and also reduces the amount of follow up data collected from patients at home. Another significant advantage of linking with administrative data is that once the cohort is constructed, patients can continue to be followed (with appropriate consent) for many years to assess less common or delayed outcomes, and potentially at a much lower cost than if patients were followed through clinic-based study visits. Despite these efficiencies, this design feature raises several issues.

While a major aim of PCTs is to ensure that the results generalize broadly, there are notable limitations to administrative claims data that affect this goal for administrative data



facilitated trials. One limitation is that encounter data are not available for Medicare beneficiaries enrolled in Medicare Advantage plans, and enrollees tend to be younger and have lower rates of many complex chronic conditions than their traditional fee-for-service counterparts [55]. These plans currently comprise about a quarter of the insured U.S. elderly population. In addition to baseline differences in the populations, there are losses to follow up when beneficiaries later choose to enroll in managed care plans. Concerns about excluding managed care enrollees can be partially addressed by expanding the linkage to include data from health plans (e.g. United Healthcare, Wellpoint, Aetna, etc.) that offer Medicare Advantage plans. Notably, to support CER, the federal government has invested in a large Multi-payer Claims Data base that will link Medicare, Medicaid and private claims data [56], potentially making available a powerful resource for PCTs in the future. A further limitation of claims data is the possibility of a lag time between when an event occurs and when such information is available in data files for use by clinical investigators, not uncommonly as long as 18 months. This “claims lag” has improved somewhat, at least for Medicare data. Lastly, for PCTs that require data on use of outpatient prescription drugs, another gap in Medicare data that needs to be considered is that only 60% of beneficiaries receive their drug coverage through Medicare Part D [57]. Part D enrollees tend to be poorer and less healthy than their counterparts with alternate drug coverage [58].

While administrative data may facilitate data collection for certain outcomes [54,59], some outcomes cannot be reliably determined from claims data alone and would need validation. Hip fractures, for example, are accurately identified by administrative data [59–61]; however, some other types of fractures (e.g., clinical vertebral fractures) are more subject to misclassification. While for some diseases or conditions, the sensitivity and specificity of case definition are problematic with administrative data [62], for others administrative data can be successfully used with select outcome adjudication using medical records [63]. The decision about whether to adjudicate only a subset (e.g. random sample of PCT participants) of all outcomes of a particular type or to adjudicate all potential cases remains a challenge. If the latter strategy is deemed necessary, this can substantially limit the efficiency of using administrative data for a PCT. Other outcomes (e.g. patient reported outcomes such as quality of life, disability, impact on work and home productivity, which might be needed in studies of conditions such as arthritis) could be ascertained by supplementing claims data with periodic patient surveys, collected using computer assisted telephone (CATI) interviews or Internet-based surveys solicited via email broadcast. These surveys would allow collection of information not available in administrative data and place no further burden on the busy community practices by minimizing study visits in offices for PCT participants. These periodic surveys, while possibly subject to bias from missing data and non-response, also afford improved, near real-time assessment of important safety events avoiding the lag times of the national databases and can be targeted to informative subgroups using a priori designed nested case control studies. Finally, Medicare, in contrast to many commercial claims databases, is very good for ascertaining mortality, even for Medicare Advantage participants. The National Death Index with a similar 12 to 18 month lag period can be linked to PCTs as well, allowing investigators to obtain the causes of death.

## 5. Conclusion

Pragmatic clinical trials (PCTs) offer a national opportunity to expand the generalizability, relevance, and impact of clinical trials by enrolling a large, heterogeneous patient population recruited from diverse and typical clinical practices, thereby addressing a major aim of CER. Achieving this objective at a lower cost and in ways that most effectively intersect with busy clinical practices and ensure the needs of end users of clinical evidence including patients, consumers, clinicians, payers and policy makers is challenging. We offer select approaches

that can improve the efficiency of conducting PCTs in the U.S. Practice Based Research Networks (PBRNs) are an underutilized resource that can serve as a means of more efficiently conducting PCTs among community based practices and could lead to more rapid acceptance and implementation of clinical research findings. Advances in these networks that include standardization and pooling of clinical data will further facilitate these efforts. In order to work within the constraints of these busy clinical practices, technological innovations in patient recruitment, consent, and randomization, will help ensure broader participation of these practices and improve the efficiency and effectiveness of PCTs. Similarly, data linkage, such as broader use of Medicare and other linked administrative data, will further reduce the burden on community practices and can be reliable and relatively low-cost sources for assessing long-term sequelae and outcomes for diseases and interventions affecting the elderly. While there are recognized problems with using such data, the improvement in generalizability and the lower follow-up burden and cost from PCTs using these innovative features will likely constitute major potential enhancements relative to past PCTs.

With increased commitment to fund CER with the creation of the U.S. Patient-Centered Outcomes Research Institute (PCORI), the time is ripe for improving methods to increase the efficiency of PCTs that target key comparative effectiveness research (CER) questions and improve methods to recruit and retain previously excluded populations. We offer these approaches and research ideas and encourage the research and practice community to embrace this challenge and to continue to advance PCT methodology. Further research is needed to test the effectiveness of these new approaches to PCT implementation.

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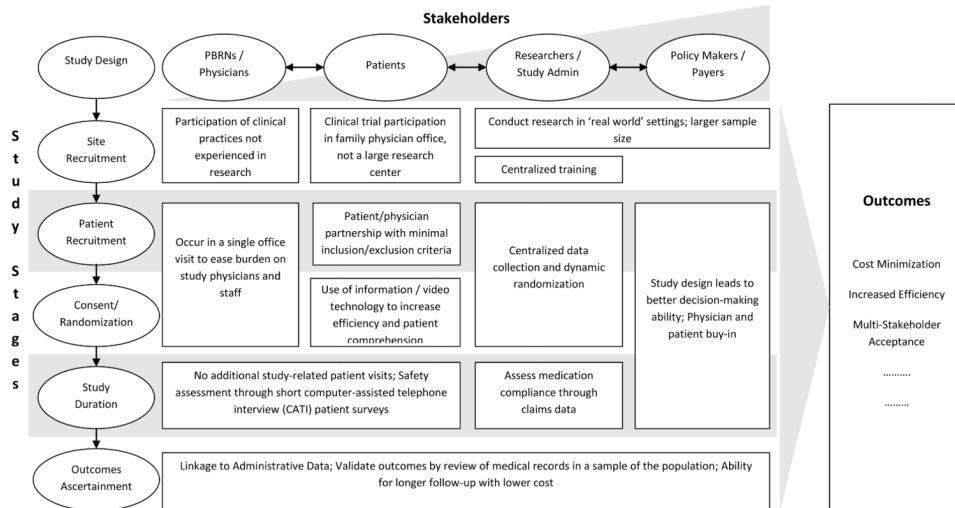
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**Fig. 1.** Overview of innovations for pragmatic clinical trials (PCTs).