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Series: Pragmatic trials and real world evidence: Paper 2. Setting, sites, and investigator selection

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Abstract

This second article in the series on pragmatic trials describes the challenges in selection of sites for pragmatic clinical trials and the impact on validity, precision, and generalizability of the results. The selection of sites is an important factor for the successful execution of a pragmatic trial and impacts the extent to which the results are applicable to future patients in clinical practice. The first step is to define usual care and understand the heterogeneity of sites, patient demographics, disease prevalence and country choice. Next, specific site characteristics are important to consider such as interest in the objectives of the trial, the level of research experience, availability of resources, and the expected number of eligible patients. It can be advisable to support the sites with implementing the trial-related activities and minimize the additional burden that the research imposes on routine clinical practice. Health care providers should be involved in an early phase of protocol development to generate engagement and ensure an appropriate selection of sites with patients who are representative of the future drug users.

Keywords: Pragmatic; Trial; Study design; Real world; Usual care; Site selection; Research naive

1. Introduction

There is growing interest, both from prescribers and users of new medications, in the generation of evidence to assess the effectiveness and safety of a drug in a real-world population. Pragmatic trial design offers the opportunity to deliver robust data from a representative population.

Schwartz and Lelouch [1] who first recommended the use of pragmatic designs acknowledge that most (trials) contain both explanatory and pragmatic elements. Although some trials such as the Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia trial, a randomized registry trial [2], can be delivered through a very pragmatic design, other trials, particularly for pre-launch drugs, will require the introduction of interventions through site selection and safety monitoring, which will result in a trial that can still mostly be pragmatic but does contain some compromise.

The key elements of trial design are used in the PRECIS-2 tool [3], which enables the scoring of a trial across a range from very explanatory to very pragmatic. The range of potential scores provided by the PRECIS-2 tool is reflective of the multifactorial nature of trial design and the challenges associated with the delivery of a fully pragmatic trial.

The GetReal consortium has carried out literature reviews and extensive interviews with stakeholders. From this work, a series of articles on pragmatic trials has been

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What is new?

Key findings

- Successful selection and inclusion of usual care sites requires prospective analysis of the many variables to be considered when answering the research question.

What this adds to what was known?

- For pragmatic trials, we have integrated knowledge on challenges, implications, and potential solutions for selection and inclusion of usual care sites.

What is the implication and what should change now?

- Health care providers should be involved throughout the development of the trial protocol. This engagement will ensure that the proposed study design meets their evidence needs and will also support the appropriate selection of sites.

generated (see Box 1). Site selection was identified as one of the key factors impacting pragmatic trial success and is explored in this second article in the series. Aspects to be considered during site selection include geographical setting, treatment pathways, site infrastructure, and participant characteristics. For a pragmatic trial, the provision of training and ongoing support, where needed, will maximize the likelihood of a successful outcome. However, a balance must be struck between many, necessary, design and operational choices and the impact of these on the applicability of results to the broad patient population receiving usual care.

Box 1 Series on pragmatic trials

Challenges on pragmatic trials: selection and inclusion of usual care sites

Pragmatic trials aim to generate real-world evidence on the relative effects of treatments, generalizable to routine practice. In this series, we will discuss the interplay between pragmatic trial design, operational consequences, and the interpretation of results.

1. Introduction: Pragmatic trials and real-world evidence
2. Selection and inclusion of usual care sites
3. Participant eligibility, recruitment, and retention
4. Challenges of informed consent
5. Questions, comparators, and treatment strategies
6. Outcome selection and measurement
7. Monitoring safety and trial conduct
8. Data collection and management

2. The challenges of designing a trial in the usual care setting

2.1. What is a usual care site?

For a trial to be pragmatic, the research question should be addressed in the patient's usual health care setting. However, agreeing the definition of usual care for an individual treatment can be challenging. Apart from the variations in health care that can be encountered in different geographical locations, patients may simultaneously receive care from a mixture of health care settings, including hospitals, specialist centers, and primary care. For example, a respiratory patient using bronchodilators may undergo lung function assessment at a specialist center while their routine care and prescriptions come from a primary health care setting and pharmacy. This raises the challenge of ensuring that all relevant data sources are captured to ensure that data collected fully represents the patient's usual care.

In selecting research sites for a pragmatic trial, it is important to accommodate both the patient's and physician's preference and minimize both the burden for the patient and the disruption to usual care. For example, a survey of palliative care health professionals showed that very few of them were willing to refer their patients with end-stage disease to studies involving extra tests or hospital visits [4]. In identifying the routine care setting for a pragmatic trial, it is not only important to be aware of the location where the usual care takes place, and where the trial-related procedures are performed, but also where patients are most likely to be enrolled.

2.2. Patient population characteristics

The distribution of patient characteristics that influence treatment effect will differ across sites. This, in turn, may impact research findings: when sites are highly selected, the applicability of the results to a more general patient population may be reduced [5,6]. In an explanatory trial to assess a treatment for psychotic depression, it was found that patients with a distinct demography who were added late into the trial showed a different treatment outcome from those patients at the original planned sites, rendering the results statistically insignificant. The authors noted that increasing the patient sample size, by recruitment from sites that have patients with different characteristics, does not necessarily increase power [7].

When there are less strict inclusion criteria, as in a pragmatic trial, intersite differences reflecting different patient demographics, clinical characteristics, and treatment patterns may be considerable: severely diseased patients are usually treated in secondary care, whereas patients with mild diseases tend to remain in primary care. However, including a diversity of sites will promote the generalizability of the research findings to a wide range of patients who will receive the treatment in the future. The selection

of diverse, yet representative, patient characteristics across study sites will be trial specific, and this is an important area of focus for study teams.

2.3. Country setting

The location of pragmatic trial sites may greatly impact the usefulness of results. It is also a focus of regulatory discussion. A European Medicines Agency position article on the applicability of results from trials conducted outside the European Union (EU) asks for prospective analyses to determine the relevance of the results to the EU population [8]. One reason for this is that disease prevalence and natural history may vary greatly both within a country and across different countries. For example, the effectiveness of BCG vaccination has been found to vary between 0% and 80% with strong correlation with latitude [9]. The efficacy of the vaccine was found to decrease with distance from the equator, possibly because of greater exposure nearer to the equator to environmental nontuberculous mycobacteria, which may confer protection that mirrors that conferred by BCG vaccine [10].

Another source of diversity is availability and accessibility of health care, which may lead to a change in the outcome for the patient. For example, if a required blood transfusion cannot be performed, this may lead to a fatality that would not have occurred in a more affluent setting. Both high- and low-quality health care may alter the apparent effectiveness of the treatment [5,7,11,12]. An explanatory trial in 12 European countries to assess the impact of early surgical intervention found that outcome for the patient was heavily impacted by their country health care system, which determined the speed with which they were treated [13]. Clearly, geographical variations in site resources can impact the outcome of a pragmatic trial.

Although ideally the full diversity of health care settings and countries should be reflected in a pragmatic trial, the choice is often limited by financial, practical, and regulatory issues. For example, a sponsor may design an effectiveness trial in specific regions for reimbursement purposes. Specific countries may be selected based on a greater recruitment potential and reduced administrative burden [14−16]. In addition, rigorous regulatory requirements, predominantly in place for explanatory trials, may not be feasible for a pragmatic approach. For example, European Medicines Agency guidance on interventional studies requires frequent reporting of adverse events (AEs) that may not be necessary or possible in some pragmatic trials. Clearly, researchers must be aware of the unique ethical and legal frameworks for each individual country with regard to the conduct of clinical research [15−17]. Combined with the restrictions on data transfer across country boundaries, these challenges may lead to a highly restricted selection of countries. An early engagement of regional authorities may facilitate the inclusion of a broader range of countries, which may yield a more appropriate reflection of the patient population that will be treated in future clinical practice.

2.4. Heterogeneity of selected sites

A heterogeneous selection of sites is often preferable for a pragmatic trial to ensure that the design includes a range of settings, clinical patient characteristics, and patient demography relevant to the research question. The decision to select homogenous sites (or a single site) may, however, still be appropriate for some trials, particularly if strict inclusion and exclusion criteria cannot be avoided or there is a requirement for a specific diagnostic test or the trial has complex and non-routine end points. Often single and/or homogenous centers are sought out to fulfill a need for specialist expertise or commitment to a trial design that cannot be replicated in other settings. One example is the PRIME Malaria trial that was designed to include a relatively homogenous group of public health centers to accommodate complex fever case management [18].

However, it is important to be aware that by restricting the site selection to single and/or homogenous sites, there is an increased risk that the results from such a trial will not be applicable to the full diversity of sites and their patient population [19−21]. A large trial that mostly comprised surgical patients who were admitted to the intensive care unit (ICU), reported beneficial effects on mortality after intensive insulin treatment in ICU [22], but this outcome has not been replicated in two subsequent multicenter studies that included a broader patient population admitted to ICU with sepsis [23,24]. In fact, a recent meta-analysis found no benefit but a significant increase in the risk of hypoglycemia [25]. Often, even when the positive outcome can be replicated, the introduction of a more heterogenous site selection with a broader patient population can influence the size and precision of the effect because of the variations in health care delivery across sites.

Careful consideration should be given to fully understand the factors that impact the mixture of sites selected. Even the size and complexity of the hospital can influence results: in many therapeutic areas, patients often have better clinical outcomes treated in higher volume hospitals [19].

The research question dictates the most appropriate mixture of sites for a pragmatic trial; but this will always be balanced with the associated operational considerations.

3. Selecting sites for a pragmatic trial

Selecting the centers for explanatory trials can be very straightforward. Decisions can be driven by practical issues, such as previous experience, success in recruiting patients, the willingness to participate, and a history of

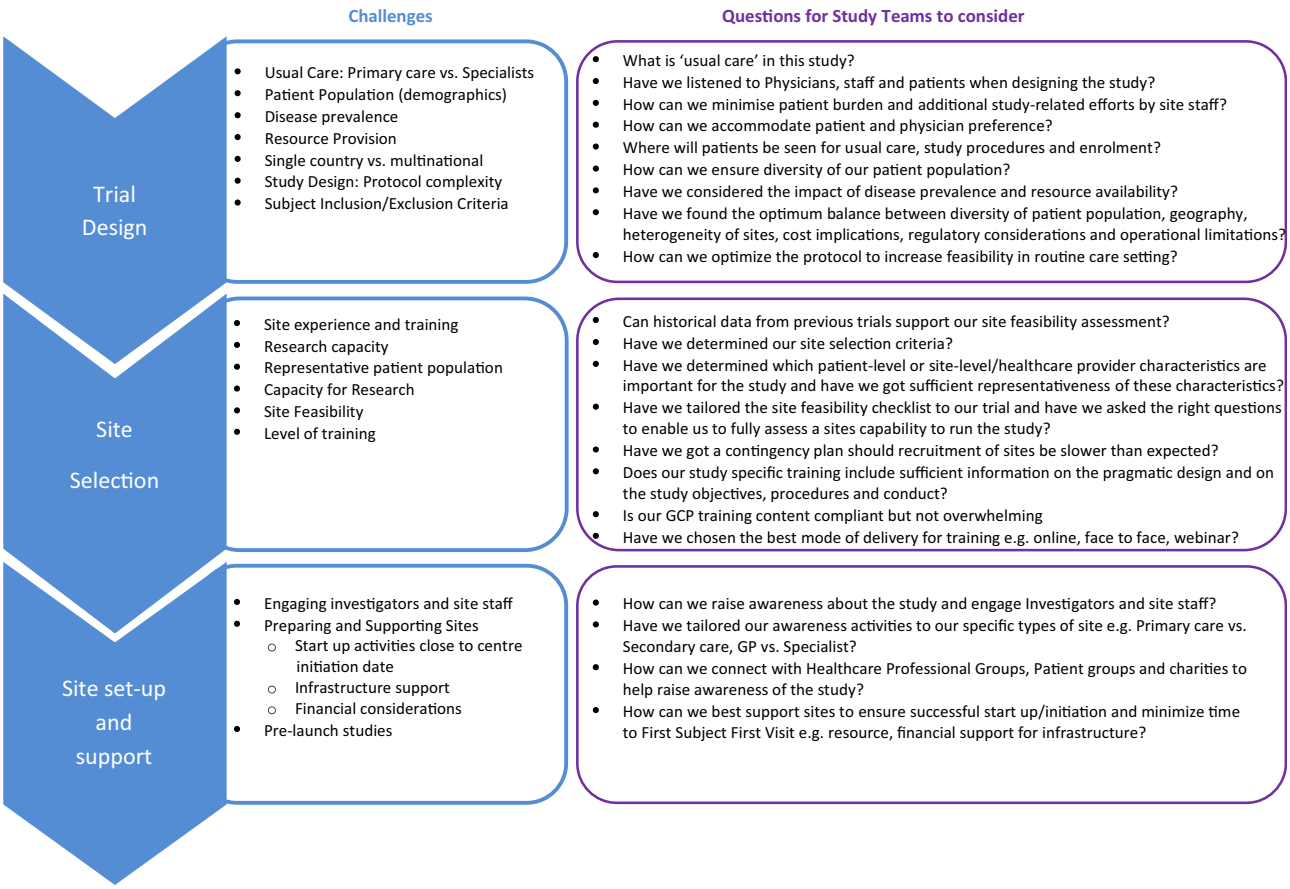

Fig. 1. The challenges of selection and inclusion of usual care sites for pragmatic trials. A schematic to illustrate the key site features for consideration during each stage of pragmatic trial execution.

good communication with the trial co-ordinating center [26]. Pragmatic trial site selection, however, raises many additional elements that need to be considered in much greater detail when planning the trial. These are illustrated in Fig. 1.

3.1. Assessment of feasibility and capacity for research

Sites that are most likely to encounter difficulties in executing a clinical trial are generally the smaller sites with limited resources that struggle to deliver trial-related procedures in addition to usual care [19,27]. A site feasibility checklist is recommended to guide the process of site readiness, address the feasibility of data collection and the presence of supporting staff such as a research nurse, and clarify the expected number of potential participants. Other important factors that generally facilitate trial execution are alignment of the protocol with routine clinical practice, ensuring that the research does not interfere with optimal care, and minimizing the additional trial-related efforts for the patient and the hospital staff. The feasibility of the trial and the alignment with routine care can be optimized by involving physicians and staff early in the protocol development phase [28].

3.2. Training the site in trial-related procedures

To ensure the quality and validity of data, physicians and nurses who are new to clinical research may require training in aspects of trial conduct. They will also need to complete the International Council for Harmonisation E6 Good Clinical Practice (GCP) qualification. However, the introduction of GCP training to a research-naive physician may lessen the degree to which a trial is pragmatic, introducing requirements for specific monitoring, and may impact the delivery of usual care.

A further difficulty is that the time-consuming [29] nature of training may deter physicians from participating in pragmatic trials [30]. However, the burden of training can be reduced when using online modules, tailored to the needs of the trial, as more flexibility can be provided in the timing and contents of the training. For example, the TransCelerate Site Qualification and Training Initiative has developed basic online GCP modules for site personnel. This has been accepted for GCP qualification by all major pharmaceutical companies. In addition to completion of GCP training, site staff will need to be trained on the objectives and procedures of the trial to ensure compliance with the protocol [31,32].

3.3. Site initiation and support

Key to the success of trial conduct is the selection of sites that are supportive of the objectives and willing to invest the required time and resources. Most usual health care takes place at primary care sites, and therefore, these are often the sites of preference for a pragmatic trial. A number of studies have investigated the attitudes of primary care physicians to clinical research to better understand both the potential challenges to participation and the drivers for active participation [28,30,31,33−38]. In general, primary care physicians are reported to be supportive of conducting clinical research. However, from a practical perspective, many primary care physicians often find it challenging to dedicate time to participate in research [39].

In two recent pragmatic trials, 59% of sites initially expressed their interest in trial participation, but less than 4% of the physicians actually recruited participants [30]. As a condition to actively participate, physicians report that the research must be of scientific interest [30,40], and that additional time and administrative burden should be minimized, especially during the informed consent phase [36]. Furthermore, the perceived time conflict between providing care to patients and engaging in a trial can impede participation [28,41]. Clarifying the added value of the trial for physicians, patients, and the health care system at an early stage is important to generate engagement and participation. general practitioner networks, patient organizations, and charities can have an important role in this. Asthma UK and the European Lung Foundation, for instance, raised awareness for the U-BIOPRED study [42] by providing the trial objectives on an open access Web site, and this contributed to the successful recruitment of sites.

3.4. Preparing and supporting sites

When sites are engaged with the research question, it then follows that trial participation is likely to be high. Haidich et al. evaluated the enrollment rates in 14 randomized trials conducted by the Adult AIDS Clinical Trials Group and found that sites that had started enrolling patients soon after site initiation enrolled more than 90% of the patients [43,44]. This active site engagement may be developed through close collaboration with sites to facilitate timely start-up and recruitment. Financial support for the implementation of software systems for data capture or solutions to store files may be considered as an incentive for small sites with limited resources.

4. Particular considerations for a prelaunch pragmatic trial

To generate data on the risk−benefit profile of a new medicine in a population with health care systems more diverse than in an explanatory trial, pharmaceutical companies may plan for a pragmatic trial as part of the drug development pathway. The design of a prelaunch pragmatic trial, initiated before the availability of a drug on prescription, will face additional challenges.

In addition to the factors that will influence all pragmatic trials, it will also be necessary to consider the requirements posed by regulatory authorities, including stringent safety monitoring and investigational drug supply. One way in which it is possible to achieve AE reporting is the linkage of electronic medical records. Linking data from the general practitioner, hospitals and pharmacies allow for AE reporting with minimal impact to usual care. However, it is unlikely that an electronic health record (EHR) system will be set up to routinely capture all data required to support the objectives of a clinical trial [45]. EHRs do not have AE fields, so data elements must be identified that are representative of AEs. This can often require data collection from several fields or indeed across a number of EHR systems. Some key data may exist in text notes that are difficult to use for research [45]. This topic is discussed further in a later article in this series focused on the challenges of data collection in pragmatic trials.

For the Salford Lung Study, site selection was confined to a single region of the United Kingdom [46−48]. This made it feasible to collect dispensed prescription data from all the local community pharmacies and to deliver training in GCP to more than 1,000 nurses, pharmacists, and general practitioners. However, the convenience and feasibility provided by a single geographical setting may impact the applicability of the data to other regions and countries. Storage for the investigational drug and dispense equipment in line with GCP may also pose serious challenges resulting from the need to train and monitor local pharmacies.

The more rigorous requirements of drug provision for a prelaunch trial may greatly increase the impact of the trial on usual care and, therefore, the extent to which the trial can be considered pragmatic. To ease the burden on sites, the placement of dedicated staff has been shown to be beneficial in trial execution and recruitment [28,45,46]. But while this increases the potential to deliver robust trial results through improved operational efficiencies, it may also impact the degree to which the trial is considered pragmatic.

The many additional operational challenges associated with prelaunch pragmatic trials may deter some sponsors from venturing into this space. But with each new trial, learnings can be applied to the next, facilitating the execution of future prelaunch pragmatic trials.

5. Conclusions

The pragmatic trial that aims for generalizability to the target population by broad inclusion criteria, limited impact on usual care, and selection of a range of sites that reflect the diversity of sites across countries can also make trial execution challenging. Successful selection and inclusion of usual

care sites requires prospective analysis of the many variables to be considered to answer the research question. Full trial feasibility should involve engagement with patients, sites, and, in the case of prelaunch studies, pharmacies. All these factors will impact the resources and time required to deliver what, on the face of it, looks like a very simple trial design.

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