Journal of Clinical Epidemiology 88 (2017) 14–20

Journal of Clinical Epidemiology

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

Sally D. Worsley[a,*], Katrien Oude Rengerink[b], Elaine Irving[a], Stephane Lejeune[c], Koen Mol[d], Sue Collier[e], Rolf H.H. Groenwold[b], Catherine Enters-Weijnen[b,f], Matthias Egger[g], Thomas Rhodes[h], On behalf of GetReal Work Package 3

[a]*Real World Evidence, GSK R&D, Gunnels Wood Road, Stevenage, Hertfordshire SG12NY, UK*
[b]*Julius Center for Health Sciences and Primary Care, Universiteitsweg 100, 3584 CG, Utrecht, The Netherlands*
[c]*European Organisation for Research and Treatment of Cancer, 83 Avenue Mounier, Brussels 1200, Belgium*
[d]*EMEA Medical Affairs, Janssen Pharmaceutica NV, Turnhoutseweg 30, Beerse 2340, Belgium*
[e]*Respiratory Therapeutic Area, GSK R&D, Stockley Park West, 1-3 Ironbridge Road, Uxbridge, Middlesex UB11 1BT, UK*
[f]*Department of Primary Care Research, Julius Clinical, Zeist 3703 CD, The Netherlands*
[g]*Institute of Social and Preventive Medicine & Department of Clinical Research, Clinical Trials Unit, University of Bern, Finkenhubelweg 11, Bern CH-3012, Switzerland*
[h]*Center for Observational and Real-world Evidence (CORE) - Pharmacoepidemiology, MSD, 351N. Sumneytown Pike, North Wales, PA 19454, USA*

Accepted 3 May 2017; Published online 11 May 2017

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

* Corresponding author. Tel.: +1-44-7814766147.
E-mail address: sally.d.worsley@gsk.com (S.D. Worsley).

http://dx.doi.org/10.1016/j.jclinepi.2017.05.003

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