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SERIES: PRAGMATIC TRIALS AND REAL WORLD EVIDENCE

Series: Pragmatic trials and real world evidence: Paper 1. Introduction

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Abstract

This is the introductory paper in a series of eight papers. In this series, we integrate the theoretical design options with the practice of conducting pragmatic trials. For most new market-approved treatments, the clinical evidence is insufficient to fully guide physicians and policy makers in choosing the optimal treatment for their patients. Pragmatic trials can fill this gap, by providing evidence on the relative effectiveness of a treatment strategy in routine clinical practice, already in an early phase of development, while maintaining the strength of randomized controlled trials. Selecting the setting, study population, mode of intervention, comparator, and outcome are crucial in designing pragmatic trials. In combination with monitoring and data collection that does not change routine care, this will enable appropriate generalization to the target patient group in clinical practice. To benefit from the full potential of pragmatic trials, there is a need for guidance and tools in designing these studies while ensuring operational feasibility. This paper introduces the concept of pragmatic trial design. The complex interplay between pragmatic design options, feasibility, stakeholder acceptability, validity, precision, and generalizability will be clarified. In this way, balanced design choices can be made in pragmatic trials with an optimal chance of success in practice.

Keywords: Real-world evidence; Pragmatic trial; Trial design; Generalizability; Trial conduct; Routine clinical practice

1. Introduction

Evidence on the benefits and risks of treatments in health care can be obtained through several types of research, roughly grouped into either randomized controlled trials (RCTs) or observational studies. Research aimed at synthesizing evidence combines the results of different trials (through either direct or indirect comparison) [1] or, where possible, different types of evidence [2,3]. It has been widely acknowledged that for most new treatments, the evidence at the moment of market approval is insufficient to fully guide decisions by physicians and policy makers to select the best treatment for patients in routine clinical practice [4−6]. Real-world evidence is needed.

Real-world evidence is the evidence derived from the analysis and/or synthesis of real-world data. It is an umbrella term for data regarding the effects of health interventions (e.g., safety, effectiveness, resource use, etc.) that are not collected in the context of highly controlled RCTs [7] and is assumed to provide data that are applicable to the real-life use and users of drug treatments, including data on relative effectiveness. Relative effectiveness is the extent to which an intervention does more good than harm compared to one or more alternative interventions when provided under the usual circumstances of health care practice.

Both the traditional phase III RCTs and postlaunch observational studies have limitations in providing real-world evidence on the (relative) effectiveness of treatment options [5,8−13]. The first because these trials are usually

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What is new?

Key findings

- Pragmatic trials offer the opportunity to obtain real-word data on the relative effectiveness of a treatment in an early phase of development, thus addressing the need for real-world evidence.
- Opting for pragmatic trial characteristics may lead to different and unanticipated operational challenges compared to explanatory trials

What this adds to what was known?

- In this introductory paper in a series of 8 papers on pragmatic trials we explain and discuss the main characteristics of pragmatic trial design, and the complex interplay with the operational practicality of implementation.
- Each consecutive paper in this series will focus on a domain for which specific design choices need to be made in a pragmatic trial: the setting; the study population; operationalization of the intervention and choice of comparator; the outcome measure as well as data management and monitoring.
- For each domain the papers will integrate the theoretical design options for pragmatic trials with the practice of pragmatic clinical trial conduct and raise awareness of the impact of design choices. Emphasis will be on operational implications, ethical considerations, stakeholder preferences, generalizability, validity and precision.

What is the implication and what should change now?

- To gain the benefit of the full potential of pragmatic trials, there is a need for guidance and tools in designing these trials while ensuring operational feasibility.

conducted in selected populations, in a highly controlled setting, optimized to show the effect of the drug. The second because bias, especially prognostic incomparability between patient groups in observational research, cannot be ruled out. Pragmatic trials are a valid option to provide evidence to address the issues that patients, clinicians, and policy makers face in real life [4,9–12], for instance whether a treatment improves the outcomes that are relevant to the patient in routine clinical practice [14]. In this paper, we discuss the main characteristics of pragmatic trials as well as the operational challenges of their conduct. In addition, we discuss the opportunities that pragmatic trials provide to generate real-world evidence.

2. Why randomization benefits real-world evidence generation

Well-designed observational studies are widely used for generating supportive real-world evidence [15]. They intend to explore the effectiveness of a new drug or treatment in day-to-day clinical practice without altering the normal patient and physician behavior. Yet, whereas such observational data are generalizable to routine clinical practice, they are also more likely to be confounded and therefore impact validity (see Box1).

Suppose a study aims to test whether a new drug is more effective in reducing blood pressure compared to currently existing treatment options, an observational study would typically compare the blood pressure records from a group of patients who uses the new drug to a second patient group using the current medication. The observed mean

Box 1 Key concepts

Validity: If the result of a comparison is true and not systematically (nonrandom) overestimates or underestimates the effects of the treatment, such a result is valid [16,17]. Research results that are not valid are not useable whatever the other qualities of the research are. Therefore, assurance of validity of the result of a study, through the absence of bias, in drug research is first priority. Randomization in trials provides an important means to assure that a measurement of benefit or risk between two or multiple treatment groups is not confounded by incomparability of prognosis at baseline due to differential prescribing.

Precision: The precision of an estimate of a treatment effect from a study is reflected in the confidence interval (CI) of the effect estimates, which denotes the probabilistic boundaries for the true effect of a treatment. That is, if a study was repeated again and again, the 95% CI would contain the true effect in 95% of the repetitions. The smaller the CI, the higher the precision [16]. Precision is predominantly determined by the magnitude of random error in the effect estimates and the sample size of the study.

Generalizability: The process of applying findings in a particular study to a population of patients in a particular clinical setting is called generalization and the extent to which the results of a study apply to that population is called generalizability [4]. Sometimes the term external validity is used for generalizability, but this should be discouraged because generalizability is not about the truth (validity). Validity and generalizability need separate consideration. Findings may be perfectly valid but not applicable to another group of patients and thus not generalizable. First, validity needs to be assured; next, the trial findings should be generalizable to the population of interest.