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Journal of Clinical Epidemiology 90 (2017) 92–98

Journal of Clinical Epidemiology

SERIES: PRAGMATIC TRIALS AND REAL WORLD EVIDENCE

Series: Pragmatic trials and real world evidence: Paper 5. Usual care and real life comparators

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Accepted 3 July 2017; Published online 8 July 2017

Abstract

Pragmatic trials may deliver real-world evidence on the added value of new medications compared with usual care and inform decision making earlier in development. This fifth paper in a series on pragmatic trials in the Journal discusses usual care as a comparator and the allocation of treatment strategies. The allocation and implementation of treatment strategies should resemble clinical practice as closely as possible. Randomization at the level of the site, as opposed to at the individual level, may be preferred. Data analysis according to the intention-to-treat principle is recommended, and crossover between treatment arms and strong treatment preferences may be accounted for in the study design in specific situations. Although usual care is the comparator of choice, this may differ substantially between centers and countries complicating comparator choice. Using clinical guidelines to define usual care can be helpful in standardizing comparator treatments; however, this may decrease the applicability of the results to real-life settings. Conversely, using multiple usual-care treatment arms will increase the complexity of the study. The specific objectives of the trial and design choices should be discussed with all stakeholders to realize the full potential of the pragmatic trial.

Keywords: Real-world evidence; Pragmatic trial; Usual care; Comparator choice; Treatment strategy; Routine clinical practice

1. Introduction

New drugs are typically examined for their efficacy and safety in randomized clinical trials (RCTs), under strictly controlled conditions in highly selected patient groups. If the results obtained by these explanatory trials do not reflect treatment effects in patients seen in day-to-day clinical practice, they cannot adequately guide physicians' treatment decisions [1,2]. Pragmatic trials can deliver real-world evidence on the value of new treatments compared with usual care [1,3]. When executed well, pragmatic trials maintain the strength of an RCT but also generate results that are applicable to routine clinical practice.

Treatment-related study procedures in pragmatic trials should not change routine clinical practice. Decisions on drug dosage, co-interventions, and the management of adverse effects are therefore left to the physician [1]. Placebos and other methods of blinding patients and physicians for the assigned treatment group are generally not used in pragmatic trials, as knowledge of the treatment status, and expectations or behavior changes associated with that knowledge are part of the treatment effect in real life. In addition, any measures taken to promote treatment adherence should reflect routine clinical practice [4]. The focus therefore is on comparing the effectiveness of treatment strategies rather than on the efficacy of single compounds [5].

The Pragmatic Explanatory Continuum Indicator Summary (PRECIS) tool [6] has been developed and revised

Conflict of interest: M.G.P.Z., P.M.J.W., G.J.M.W.v.T., A.C., M.J.C.E., and M.E. have no conflict of interest. R.A.-C. is an employee of GSK. L.E. is an employee of Sanofi.

Funding: The work leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no. 115546, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007/2013) and EFPIA companies in kind contribution.

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http://dx.doi.org/10.1016/j.jclinepi.2017.07.001

What is new?

Key findings

- Pragmatic trials can deliver real-world evidence on the added value of new medications to support clinical decision making earlier in drug development.
- The research question determines whether new treatments are started or an existing treatment is continued, whether treatment switches between arms are allowed, and whether a superiority or noninferiority design is more appropriate.
- Usual care is the comparator of choice for pragmatic trials, but implementation may be difficult if usual care differs between centers or countries.

What this adds to what was known?

- In this paper, we discuss the operational and methodological challenges in pragmatic trials related to defining and comparing treatment strategies and the choice of suitable comparator(s).

What is the implication and what should change now?

- In pragmatic trials, all elements of trial conduct should interfere with or change routine clinical practice as little as possible.
- Treatment strategies under study should resemble routine care as closely as possible, including dosing, comedication, and the supply and reimbursement of drugs.

(PRECIS-2) [4] to support investigators in making trial design choices that are in line with the purpose of their study. Topics include for instance eligibility criteria, patient recruitment, and organizational considerations. Our series of eight articles in this journal (see Box 1) aims to extend this work by describing potential challenges and solutions in conducting trials that address the relative effectiveness of drugs in real-world clinical practice, specifically before or shortly after a drug is licensed and launched on the market.

In this paper, we discuss the choice of the usual-care comparator, which is a central issue in pragmatic relative effectiveness research but is largely missing from PRECIS-2 [7]. We describe the operational and methodological challenges in pragmatic trials pertaining to defining and comparing treatment strategies and the choice of suitable usual-care comparator(s) for drug evaluation [8]. These factors affect the applicability of the results and their acceptance by different stakeholders [9].

Box 1 Series on pragmatic trials

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

1. Introduction
2. Setting, sites, and investigator selection
3. Patient selection challenges and consequences
4. Informed consent
5. **Usual care and real life comparators**
6. Outcome measures in the real world
7. Safety, quality and monitoring
8. Data collection and management

2. Research questions and comparisons

A treatment in routine clinical practice can be compared with usual care in several ways in a pragmatic trial, depending on the question that is addressed. For example, patients with well-controlled type-2 diabetes using oral antidiabetic medication can be randomly assigned to either switching to a new treatment or to continuing their current treatment. This would address a first question of whether the new treatment has advantages over usual care with regard to adverse effects, costs, convenience, or the control of body weight while maintaining glycemic control. If the new treatment is expected to have certain advantages but equal effectiveness, a noninferiority design may be appropriate [10]. Alternatively, for patients whose blood sugar is not well controlled, a second question arises, namely whether blood sugar control could be improved with a new treatment. In this case, either the new treatment could be compared to continuation of the current treatment, or different new treatments can be compared. Third, newly diagnosed patients may be randomized to a treatment recommended by current guidelines or a new treatment strategy. Depending on the research question and characteristics of treatments, noninferiority or superiority designs may be appropriate in the latter two situations.

It is essential to define the question a pragmatic trial is supposed to answer. The question will inform the design choices and determine how investigators deal with switches (crossovers) to the treatment in the other trial arm (see Section 4.5 and Table 1). The first question mentioned previously may be the easiest to address from an operational perspective because eligible patients can readily be identified among a pool of patients with type-2 diabetes; but trial results will not be applicable to patients newly diagnosed

Table 1. Questions, comparisons, and treatment switches that should be allowed in pragmatic trials

Question	Comparisons	Switches
Should the new treatment be approved and made available?	A health system with access to the new treatment and UC (arm 1) is compared to a health system with access to UC only (arm 2).	Switches from new treatment to UC are allowed in arm 1. No switches are allowed in arm 2.
Which of two approved treatment should be the first-line treatment of choice?	A health system with access to two treatments. In arm 1, therapy is initiated with the first treatment, in arm 2 with the second treatment.	Switches in both directions are allowed.
Should a new treatment replace an old treatment on the list of approved treatments?	A health system using only the new treatment is compared to a system where only the old treatment is available.	No switches should be allowed.
Should the new treatment be used as first-line or second-line treatment, or not at all?	A health system using the new treatment as first-line and UC as second-line treatment (arm 1); a health system with UC and the new treatment as second-line treatment (arm 2); a health system with access to usual care only (arm 3).	Switches are part of the intervention in arm 1 and arm 2, but not allowed in arm 3.

Abbreviation: UC, usual care.
Adapted from Torrance et al. [11].

with diabetes. A challenge of questions demanding a non-inferiority design is that generally more patients are needed for such a design [10].

3. Choice of usual-care comparators

The choice of appropriate comparators is a central issue in pragmatic trials. The European Network for Health Technology Assessment (EUnetHTA) defines a comparator in a relative effectiveness assessment as "[…] a health care intervention or other technology with which a pharmaceutical is compared in order to establish if it has an added therapeutic benefit. Such comparator could be another pharmaceutical, but also a medical device, a procedure or psychological approach, radiotherapy, physiotherapy, surgery or, if appropriate, providing advice, for example advice on diet or smoking, a combination of health care interventions carried out simultaneously or in sequence, or 'watchful waiting' (no intervention)" [12].

Usual care is the comparator of choice in pragmatic trials [4,6]. Although conceptually straightforward, choosing an adequate comparator in pragmatic trials can be challenging [13,14], for example, when several usual-care options exist or when guidelines differ from usual care. The definition of usual care in multicenter trials may be complicated by variations in usual care across centers, regions, or countries [15]. In these situations, the applicability to a center or region has to be weighed against wider generalizability of results to a country or countries. In trials with a long duration, usual care may change during the conduct of a trial, for example, due to changes in reimbursement or a new medication that becomes available on the market. In this situation, changes in usual care in newly recruited patients, or switches to a new usual care regimen in enrolled patients, may be appropriate to continuously reflect routine clinical practice.

3.1. Fixed or flexible choice of usual care

In determining usual care, there may not always be a single, optimal comparator. Rather, several appropriate choices may exist [16]. Different usual-care options may be included as separate arms, but this will increase complexity and costs, and physicians may object to (some of) the options [15,17]. Alternatively, different usual-care options may be combined into one comparator arm with the choice of treatment left to the physician. Although this approach may follow routine clinical practice most closely, the results might be applicable to a smaller number of settings with a similar mix of usual-care options. In addition, the estimates of relative effectiveness compared to a mix of usual-care options may be more relevant to policymakers than to clinicians whose primary interest is to find the best treatment for individual patients. In general, in pragmatic trials clinical investigators will less likely be faced with a conflict of duties (strict adherence to study protocol vs. provision of optimal patient care) [18] than in other trials, for example, placebo-controlled trials, because pragmatic trials mimic routine clinical care.

3.2. Clinical guidelines and usual care

According to the Declaration of Helsinki, new treatments must be tested against the best proven intervention or interventions [19]. Using less-than-optimal comparator treatments in trials of new drugs may disturb equipoise and raise ethical concerns [17,20]. EUnetHTA has published recommendations for the choice of comparators for relative effectiveness research that are relevant for pragmatic trials (see Table 2) [12]. These recommendations can help identify comparators that comply with the aim of comparing a new treatment strategy against usual care while respecting the ethical principles of providing patients with the best available care. The recommendations state that the choice should

Table 2. EUnetHTA recommendations for the choice of comparators in relative effectiveness studies

- The comparator should be the reference treatment according to up-to-date high-quality clinical practice guidelines at European or international level. If no such guidelines exist, evidence is required that the chosen comparator intervention is routinely used in clinical practice.
- Evidence that the intervention is used in routine clinical care could come, in order of preference, from
  - National reimbursement lists if available
  - Prescription statistics (if appropriate)
  - Market surveys
  - Discussion with clinical specialists and patient organizations
  - Registries
  - Validated clinical protocols
  - Internet searches, in particular patient and professional web sites
- The choice of comparator should be supported by evidence on its efficacy and safety profile described in published medical literature, and based on randomized controlled trials, pragmatic trials, or good-quality observational studies.
- Pharmaceuticals have to be optimally dosed or scheduled in line with marketing authorization or high-quality clinical practice guidelines.
- Where patient subpopulations are considered, for example, according to disease severity, lines of treatment, stages of disease, or genetic characteristics, additional comparators may need to be included.
- The most appropriate comparators should be identified before the assessment begins or in the early phase of an assessment.

Abbreviation: EUnetHTA, European Network for Health Technology Assessment.
Adapted from EUnetHTA methodological guideline for relative effectiveness assessment (REA) of pharmaceuticals [12].

be based on up-to-date high-quality treatment guidelines or, if no such guidelines exist, evidence that the treatment strategies are routinely used in clinical practice. Using treatment guidelines to define usual care can be helpful in standardizing comparator treatments; however, this will decrease the level of pragmatism and may reduce the applicability of the results to routine clinical practice. The routinely used treatments can, on the other hand, vary considerably between countries and settings, depending on the health care system and availability of resources [21,22]. Some centers will follow (inter)national treatment guidelines, whereas others may have developed their own recommendations. The results of a trial may, therefore, be applicable to a specific setting (e.g., where guidelines are followed) but may not be generalizable to others.

4. Allocation and implementation of treatment

4.1. Random allocation

The random allocation of patients to treatments aims to reduce confounding due to differences in prognostic variables that may be present between treatment arms. A computer algorithm generates the allocation sequence, and this sequence is concealed from those enrolling patients because knowledge of the allocation might influence enrollment and lead to groups that differ in prognostic factors [23,24]. The randomization process can be challenging for routine care sites that are unfamiliar with clinical research [25]. Web-based randomization procedures that assign patients to groups after assessing eligibility and recording informed consent are most suitable for pragmatic trials in routine care settings [25,26].

4.2. Level of randomization

In RCTs, patients are typically individually assigned to treatment groups. However, in some situations, the randomization of groups or units such as general or specialist practices or hospitals may be preferable. Such situations arise, for example, if there is a danger that components and effects of the experimental treatment strategy spill over to the comparator care strategy, thus introducing bias, or if randomization of patients in a medical setting changes the routine care process. These situations are more common in open, pragmatic trials than in explanatory trials, and the appropriate level of randomization should therefore be explicitly considered when designing a pragmatic trial [14]. Disadvantages of cluster trials compared with individually randomized trials include the need for a larger sample size, the increased risk of imbalances in prognostic factors between groups (especially if the number of centers included is low), and the possibility of postrandomization selection bias [27,28]. In addition, specific strategies for informed consent may be needed, and these can be challenging from a regulatory and ethical perspective [29].

4.3. Dealing with treatment preferences

Patients may have a strong preference for a specific treatment based on their expectations of the benefits and their concerns about potential risks, side effects, and their attitude toward exposure to experimental drugs. The views of patients may differ from those of other important stakeholders, such as physicians [30]. Strong patient preferences may influence participation, affecting generalizability, but could also affect the validity of a pragmatic, open-label trial if patients randomized to the nonpreferred treatment experience ‘‘resentful demoralization’’ [31] and consequently show low adherence to the assigned treatment. Conversely, better adherence to a preferred treatment may produce results that exaggerate the effectiveness of the intervention [32]. A study design in which patients can choose their treatment should be considered when preferences are expected to affect recruitment or adherence [33,34]. In so-called comprehensive cohort designs, patients with strong preferences may choose their

treatment, whereas other patients are randomly allocated. As patients with and without strong preferences are included, generalizability of the randomized part of the study can be evaluated. However, comparisons between nonrandomized groups are likely confounded and inclusion of preference arms can increase the costs as well as the complexity of trial execution, which should be carefully weighed against the benefits. In the absence of a preference arm, it may still be useful to record treatment preferences to be able to assess their influence on outcomes [34].

4.4. Supply of medication

In contrast to day-to-day clinical practice, in clinical trials, the drugs are commonly directly provided to patients by the investigator. Direct supply of study medication to patients by the investigator can shorten the time to start of treatment, and it may increase the proportion of patients starting treatment and adherence and thus influence generalizability of results to the setting of interest [35]. As pragmatic trials aim to mimic real-life clinical practice, this should also be reflected in the way medication is offered to the patient. The supply of the study medication should therefore ideally be left to the health care provider rather than specified in the trial protocol [1,3,36]. Of note, if community pharmacies provide experimental medicines that are not approved, training of pharmacists in good clinical practice will be required [35].

Differences in copayment for patients between trial and daily practice also need to be considered [37]. Such differences may affect participation and reduce generalizability of results. In addition, if the experimental medicines are free or fully reimbursed (which is often mandatory) but the comparator is not, then switching of treatments may increase above what could be expected in daily practice and distort results. In this situation, full reimbursement should be considered for both arms because only providing full reimbursement for the experimental arm could give this treatment an advantage over usual care within the trial environment that will most likely not pertain in real life.

4.5. Dealing with switches

How to deal with patients wishing to switch to the other treatment arm (crossovers) depends on the research question asked [11,38] (see Box 1). Crossing over to the usual-care arm should be possible if the primary question is whether the new drug should be added to the list of approved treatments. Crossing over to the new treatment should, however, not be allowed because such switches would not be in line with current routine clinical practice (where the new drug is not available) [11]. If all treatments are already available in clinical practice, switches in both directions may be appropriate, as described in Table 1. Switches should be recorded if this is possible without interfering with routine care.

4.6. Dose and comedication

Dose of medication and comedication should be in line with routine clinical practice and left to the discretion of the treating physician who will optimize treatment in individual patients in a pragmatic trial. However, physicians may find this challenging with new medications where there is no or limited experience regarding dose adjustments and comedications, for example, prelaunch. Especially with a real-life population, it is more likely that subgroups (e.g., based on age or severity of the disease) require different doses of a drug [39]. In this situation, clinicians will need guidance based on the best available evidence, which may come from smaller (phase II) trials.

4.7. Data analysis

In any pragmatic trial, the data should be analyzed according to the intention-to-treat principle which stipulates that comparisons are according to the originally randomized groups. Other analyses, including per-protocol analyses or analyses censoring follow-up at the time of switching, will tend to be biased [40]. Patients who switch and those who use comedication will often differ from those who do not with respect to prognostic factors [38]. The focus of the analysis should be the effectiveness of the treatment strategies achieved in a real-life situation and thus include patients who switch, use comedication, or have suboptimal adherence.

5. Discussion

A well-specified research question should guide the operational and methodological design choices of pragmatic trials that aim to assess the added value of a new treatment strategy relative to a treatment strategy used in real-world clinical practice. The treatment-related study procedures, including the allocation and definition of the treatment strategy, must resemble routine clinical practice as closely as possible. Cluster randomization at the level of the site, as opposed to at the individual level, may be preferred. Data analysis according to the intention-to-treat principle is recommended to ensure valid comparisons, and crossover between treatment arms and strong treatment preferences may be accounted for in the design of the study in specific situations. Although usual care is the comparator of choice in pragmatic trials, operationalization of this design feature may be difficult, among others because usual care may differ between centers and countries.

Groups such as the Consolidated Standards of Reporting Trials (CONSORT) and Pragmatic Trials in Healthcare state that the acceptation and reporting of pragmatic randomized trials should be improved. Their statement emphasizes the necessity of a detailed description of the question that is addressed by a trial and the

relevance for health care, the specific patient selection criteria, and deviations from usual-care procedures in the research sites for the trial [41]. To make correct inferences of generalizability of trial findings to different settings, trial reporting should preferably also encompass detailed information on the treatment strategies compared (including real-life dosing, comedication, switching patterns and reasons, patient follow-up, supply of medication). However, collection of this information on administration of treatment and management of patients should not change routine clinical practice.

Pragmatic trials have the potential to provide real-world evidence on relative effectiveness early in the evaluation process to support clinicians in their treatment choices. Although the term ''pragmatic trial'' was coined in 1967 [1], pragmatic trials are a relatively recent addition to the family of methods used in clinical research, with the number of published pragmatic trials increasing steeply in recent years. Therefore, their potential contribution to the drug evaluation process and market authorization should be further emphasized and discussed, for instance regarding reducing the delay in reimbursement. In the meantime, trialists should engage in a discussion with all stakeholders on the goals of the trial, the specific question to be answered, and preferences and requirements for design choices to realize the full potential of pragmatic trials [42].

Acknowledgments

The research leading to these results was conducted as part of the GetReal consortium and included literature review and interviews with stakeholders from academia, research institutions, contract research organizations, pharmaceutical industry, regulatory authorities, health care insurers, health technology assessment (HTA) agencies, general practitioners, and patient organizations. For further information, please refer to http://www.imi-getreal.eu/.

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