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QUALITY OF CARE IN OSTEOPOROSIS (S SILVERMAN AND J CURTIS, SECTION EDITORS)

Pragmatic Clinical Trials in Osteoporosis

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Abstract

Purpose of Review In this review, we present the application of pragmatic clinical trials for evaluating interventions in osteoporosis, and we discuss methodological considerations for designing and conducting a pragmatic clinical trial compared with a classical randomized clinical trial.

Recent Findings Pragmatic clinical trials are a popular study design testing effectiveness of health interventions and are intended to address the limitations associated with traditional explanatory randomized clinical trials testing efficacy of interventions. To date, only few pragmatic clinical trials have been conducted in osteoporosis.

Summary Pragmatic clinical trials are conducted under routine clinical practice setting and are intended to inform policy makers and clinical decisions. Osteoporosis is a chronic disease well-suited to this particular study design given the existence of a clear and specific natural endpoint, namely fracture occurrence, and the availability of several treatments to prevent fractures.

Keywords Osteoporosis · Pragmatic clinical trials · Effectiveness · Randomized clinical trials

Introduction

Making results more generalizable and assessing effectiveness of interventions in the routine practice are important limitations of traditional explanatory randomized controlled trials (RCTs). A pragmatic clinical trial (PCT) is a study design which proposes to address these limitations of RCTs [1], by providing evidence on the relative benefits and harms of alternative health interventions in real-world settings [2]. PCTs can inform clinical and policy decisions by providing a more accurate measurement of the effectiveness of interventions with a greater generalizability (external validity) compared with RCT. However, the distinction between explanatory clinical trials and pragmatic clinical trials represents a continuum, not an either/or dichotomy, and thus, some PCTs can be more pragmatic than others [3]. To represent the differences between pragmatic and explanatory trials, the PRagmatic-Explanatory Continuum Indicator Summary (PRECIS) tool was proposed. The original PRECIS tool included 10 domains [3], while the newer version, PRECIS-2 has 9 domains, each scored on a 5-point Likert continuum (from 1 = very explanatory to 5 = very pragmatic) [4••].

Osteoporosis is a chronic condition characterized by bone fragility that predisposes the affected individuals to a higher risk of fractures [5]. Osteoporosis treatment aims to reduce the number of fractures through increasing bone density or limiting bone loss [5]. The existence of a clear and specific natural endpoint, such as presence of a fracture, and the availability of several treatments to prevent fractures, make osteoporosis a condition particularly appropriate for conducting PCTs. Thus, the goal of PCT in osteoporosis is to test interventions that effectively reduce fracture risk while at the same time being simple to use and scalable in usual clinical practice.

In this review, we present the application of PCTs for evaluating interventions in osteoporosis, and we discuss methodological considerations for designing and conducting a PCT compared with RCT (Fig. 1).

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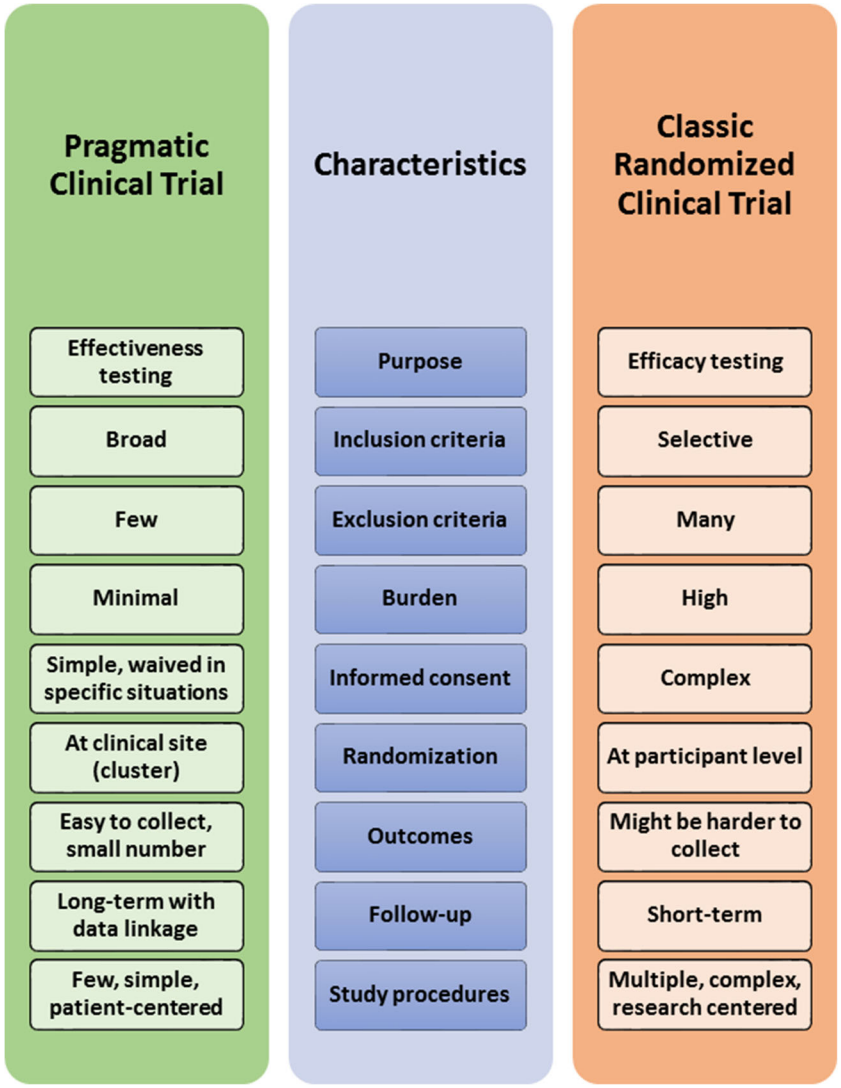

Fig. 1 Pragmatic clinical trial and randomized clinical trial

Distinction Between Pragmatic Clinical Trials Versus Traditional Randomized Clinical Trials

Study Population Eligibility

Participant recruitment criteria are one of the crucial differences between PCTs and RCTs. In general, RCTs include a very homogenous study population, which is selected based on limited inclusion criteria and extended exclusion criteria. These characteristics of the recruitment process are hallmarks of RCTs and might lead to the enrollment of individuals at lower risk of adverse events than patients who are typically treated in routine practice [6]. This undesired effect might be particularly true in RCTs testing interventions for conditions for which effective interventions currently exist. Indeed, investigators are more inclined to withhold from a research study those potential participants with greater risk of adverse events or negative outcomes [6].

Compared with explanatory RCTs, PCTs aim to recruit a more heterogeneous population, so that the study population reflects the patient population that would utilize the intervention in routine practice. Because of their minimal inclusion and exclusion criteria, the findings of PCTs are more generalizable, and the external validity is increased. Indeed, PCTs have expanded and more flexible recruitment criteria compared with RCT. For example, in the alendronate pivotal RCT [7], women with vitamin D deficiency, those with a history of hip fracture and those with prior anti-osteoporosis (OP) treatment were excluded. These exclusion criteria importantly limited the generalizability of the results since many of these women are likely osteoporosis treatment candidates. Moreover, patients with vitamin D deficiency are at a greater risk of experiencing adverse events related to bisphosphonate use (e.g., hypocalcemia) [8]. In contrast, the VERO study (VERtebral fracture treatment comparisons in Osteoporotic women) compared the efficacy of teriparatide in preventing

clinical fractures with risedronate in post-menopausal women [9]. The VERO study had more flexible enrollment criteria and included osteopenic women with at least two moderate vertebral fractures or one severe vertebral fracture based on Genant's semi-quantitative score for vertebral fractures [10].

Engagement in the Study, Flexibility in Delivery, Setting, and Organization

Another important limitation of RCTs is the degree of engagement required of both participants and study investigators, their clinical staff, and the resources needed to conduct explanatory RCTs. Usually an RCT requires significantly more effort and time from physicians and other healthcare providers involved outside the usual clinical practice. In contrast, conducting a PCT requires lower financial resources, with less effort from patients and physicians. Indeed, there are less frequent and simpler follow-up visits [11]. For these reasons, patients and investigators are more likely to participate in PCTs compared with RCTs, a preference that might reflect higher recruitment rates for PCTs. Particularly in osteoporosis, given the easier access to efficacious anti-osteoporosis medications in the past decade, patient interest in participating in RCTs evaluating/testing new osteoporosis drugs has decreased. As a result of this decline, the research community has placed greater emphasis on PCT, which as noted have decreased burden to both patients and investigators [11].

Informed Consent

Clinical trials are conducted following Good Clinical Practice guidelines, including the essential process of reviewing and obtaining informed consent. Thus, although ideally all patients eligible for a PCT study protocol with minimal inclusion/exclusion criteria should be included in the study, a lengthy, complex informed consent procedure might limit interest from community investigators without dedicated study staff [12]. Further, some patients might believe that the PCT will test a new drug with potential unknown side effects or that the trial will place additional burden on them. Moreover, some patients might fear inefficacy of a new treatment and may lack family support in participating clinical research.

The informed consent procedure in an explanatory RCT generally occurs during a screening visit when the trial is explained in great detail, and where appropriate, in lay language to the prospective participant. Similarly, PCTs generally require detailed disclosure of alternative interventions, their potential benefits and harms relative to the trial intervention, and the trial procedures. Since PCTs are conducted in routine practice, the time- and resource-intense procedure reviewing and obtaining informed consent, often by clinical staff without significant research background, represents a barrier limiting efficient recruitment. To mitigate this barrier, informed consent process supported by electronic tools, termed eConsent, has been implemented in some PCTs study protocols in chronic conditions including osteoporosis [13•]. For example, in one study, the electronic consent consisted of a computer-based questionnaire preceded by a short patient-directed video, tailored to underrepresented minority populations that presented an accurate and concise description of the study objectives and methodology [13•]. Electronic consent (eConsent) can be conducted by clinical care personnel who are not exclusively committed to research, thus streamlining and increasing the generalizability of patient recruitment within a multi-site trial. It is also possible to have parts of the consenting conducted by a central source, which removes time and burden from the local study team. An important advantage of electronic consenting rests on its ability to possibly reduce the variability in communicating study procedures, risks, and benefits to potential participants, variability that flaws the classical informed consent process, which may introduce consent bias, also known authorization bias or volunteer bias (i.e., participants differ because of the way they were selected) [14]. Because study details are explained in a standardized way using an eConsent, the consent bias may be reduced [13•].

An important aspect of the informed consent process is to ascertain that the patient has correctly understood the study procedures, benefits, and risks associated with participation in the proposed clinical trial. An advantage of the eConsent process is that after an introductory video explaining the study purpose and procedures, the prospective participant's comprehension of crucial study components can be evaluated with content-based questions. An eConsent process has been recently tested for feasibility and performance, compared with traditional paper-based consent, in the setting of osteoporosis [13•]. In this clinical trial, comprehension, satisfaction with the modality, and perceived duration of the informed consent were assessed with validated questionnaires (i.e., Health-Information Technology Usability Evaluation Scale [Health-ITUES] [15] and Quality of Informed Consent [QuIC] [16]). The authors found a non-significant trend toward better perceived comprehension of the study, satisfaction, and perceived time for completion with eConsent versus traditional paper-based consent [13•].

To reduce burden of the informed consent process and enhance the protection of human subjects, the Common Rule was recently revised [17••], which should make it easier to conduct pragmatic clinical trials. Indeed, according to the new Common Rule, the informed consent should be "concise and focused" with a few initial short paragraphs highlighting "key pieces of information" to explain the nature of the study and possible adverse events related to inclusion in the study. Moreover, the Common Rule does not rigorously specify the information that should or should not be included in the informed consent. Informed consent can be waived in some cases [18], such as in PCTs that compare interventions that are part of the usual care where there is clinical equipoise.

Randomization

The randomization procedure is another crucial step in conducting clinical trials, including PCTs, as it is the critical factor in interventional studies that seeks to create balance in baseline risk factors and reduce selection bias. Randomization ensures that the participants assigned to the interventional or comparator arms do not differ significantly in characteristics that might affect the interpretation of study results. Randomization is typically managed by a computer software that randomly allocates study subjects across the intervention and comparator arms [19]. In certain instances, the randomization process can be implemented within the electronic consent procedure increasing trial efficiency [13•]. Because PCTs are conducting in real-world setting, randomizing participants within the same practice or clinical site to both arms is challenging; some clinicians are more familiar with a certain clinical procedure than others [20]. As a result, cluster-randomization in which randomization occurs at the clinical site or practice level ("cluster") has emerged as an alternate randomization method for PCTs [21]. Groups of patients ("clusters") are randomized across study arms and receive intervention based on the healthcare facility they access or based on the physician they see. Although cluster-randomization may be easier to execute in some studies, in particular PCTs, it can induce a "physician spill-over" effect (i.e., a problem if physicians are caring for patients across clusters) [22]. Indeed, physicians might believe that the treatment in the intervention arm is more effective and tries, inadvertently or deliberately, to balance the two treatment arms, dedicating more attention to patients in the usual care arm. They could also receive training or change their practice in a way that influences the usual treatment arm in a manner similar to the intervention arms. This "contamination" between study arms in studies using cluster-randomization should be avoided or it can result in biased findings.

An example of cluster-randomization procedure comes from the patient activation after dual-energy X-ray absorptiometry (DXA) result notification (PAADRN) PCT [23, 24], where individuals presenting for bone density measurement via dual-energy X-ray absorptiometry (DXA) were randomized at the healthcare provider level to receive an educational brochure on osteoporosis or usual care (i.e., typical clinical practice). Providers in the PAADRN PCT were randomized in three treatment groups: A (all patients received the intervention), B (all patients received usual care), and C (in which patients were further randomized 1:1 to the intervention or usual care, mixed group) with good control for the spill-over effect described above.

Blinding to Administered Intervention and Adherence to Therapy

PCTs are used to test the effectiveness of a simple intervention (e.g., medication), for which efficacy usually has already been shown in a standard RCT. Moreover, given the pragmatic nature of PCTs, in most cases, the use of placebo for the control arm is not reasonable or ethical and, in addition, patients cannot be practically blinded to the intervention (i.e., a PCT testing a surgical procedure vs a medication). In PCTs, the intervention should be delivered as it would be used in routine clinical practice to measure the true effectiveness of the intervention and the research team should have less control of patient's adherence to treatment. In contrast, in RCTs, an intervention is most commonly blinded to the participant and/or the investigator and, usually, medication adherence is estimated with "pill count" and/or the use of medications diaries. In explanatory RCTs, non-adherent patients are excluded from the study during a run-in period [25] while, ideally, in the most pragmatic PCT, adherence to intervention is not even considered [1].

Outcome Assessment and Primary Analysis

Outcomes evaluated in PCTs need to be easy to collect and measure, naturalistic, and relevant to the patient health (e.g., disability, mortality, and quality of life). To limit the burden on the participant and the clinician, fewer outcomes are collected in PCTs. Most often, PCTs have a single primary outcome and only a few secondary outcomes, in contrast with some explanatory RCTs, which may also collect a significant number of secondary and exploratory outcomes [1]. For example, an outcome of interest in osteoporosis PCTs might be the rate of fracture occurrence after a specific intervention, as was used in a previously published PCT on effectiveness of vitamin D and calcium supplementation [26•]. Fracture outcomes can be assessed reasonably and accurately by self-report using mailed questionnaires or by data linkage to administrative claims data; both methods are easier to collect and do not require an in-person visit, as would be required for complex surrogate imaging outcomes (e.g., bone mineral density [BMD] measurement).

Participant Follow-up Procedures

Long-term follow-up of participants is another key issue of PCTs conducted in chronic diseases, such as osteoporosis. While long-term follow-up can be accomplished using an in-person visit, this is challenging in PCT, and a strategy to avoid multiple time-intensive in-person visits is using "data-linkages." For example, if a participant consents to disclosure of a unique personal identifier (e.g., Social Security Number, Medicare Beneficiary ID), the occurrence of fracture can be determined using validated fracture algorithms through data linkage to administrative claims data [27].

Study procedures in PCTs are usually restricted to essential procedures required for usual care, while, in explanatory RCTs, study procedures comprise multiple evaluations, usually not essential for the patient`s clinical care. For example, in the denosumab pivotal clinical trial comparing denosumab to placebo [4••], serum samples were collected on day 1 and at 1 and 6 months after the denosumab infusion, necessitating multiple study visits. In contrast, a PCT might follow the usual clinical practice, which for patients on denosumab therapy likely involves approximately one visit a year [28]. In summary, the design of the intervention and study procedures in PCTs allow reduced costs and increase generalizability of the study population.

Example of a Pragmatic Clinical Trial for Glucocorticoid-Induced Osteoporosis

Glucocorticoid-induced osteoporosis (GIOP) is the most common form of secondary osteoporosis [29]. RCTs provided evidence for efficacy of anti-osteoporotic therapies [7, 30–32] but many RCTs were designed to prove superiority over placebo in terms of BMD change in GIOP patients [7, 32]. However, given the morbidity associated with GIOP, in a pragmatic clinical trial of GIOP, it may likely be unethical to assign patients to placebo [33••]. Thus, a novel trial design with an active comparator might be required to determine efficacy of interventions for patients with GIOP. Therefore, the goal of a PCT in GIOP should be to demonstrate that an experimental medication is not substantially worse (non-inferior) than a control treatment with established efficacy and include natural endpoints (clinical fracture). Non-inferiority trials have been executed more frequently in the last decade, particularly in GIOP [31]; however, it should be acknowledged that they require more patients to be randomized than typical superiority trials. While non-inferiority trials have greater pragmatism than traditional superiority trials, when non-inferiority is not demonstrated, there is insufficient sample size to confirm or refute whether either treatment is efficacious. The need for larger sample size and for assessing clinically relevant outcomes (e.g., clinical fractures) makes GIOP an emblematic disease in which to conduct a PCT.

Conclusions

PCTs represent a well-established study design that has experienced growing popularity with investigators in recent decades. PCTs are designed to estimate effectiveness of an intervention in the real-world setting and, commonly, are conducted after traditional explanatory RCTs. Osteoporosis is a chronic disease well-suited to PCTs because of clear and specific endpoints and the availability of medications with proven efficacy. The degree of pragmatism in conducting PCTs is variable. For example, patients' lack of adherence to study procedures can be mitigated with compliance-improving strategies during the trial (lowest pragmatism), can be monitored, or can even be ignored (highest pragmatism). To ensure greater external validity and real-world effectiveness, PCTs can be integrated into routine medical care and, through implementation of minimal inclusion and exclusion criteria, may allow enrollment of highly representative participants for the study population.

Compliance with Ethical Standards

Conflict of Interest Giovanni Adami, Kenneth G. Saag, and Maria I. Danila declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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