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SERIES: PRAGMATIC TRIALS AND REAL WORLD EVIDENCE

Series: Pragmatic trials and real world evidence: Paper 3. Patient selection challenges and consequences

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Abstract

This paper addresses challenges of identifying, enrolling, and retaining participants in a trial conducted within a routine care setting. All patients who are potential candidates for the treatments in routine clinical practice should be considered eligible for a pragmatic trial. To ensure generalizability, the recruited sample should have a similar distribution of the treatment effect modifiers as the target population. In practice, this can be best achieved by including—within the selected sites—all patients without further selection. If relevant heterogeneity between subgroups is expected, increasing the relative proportion of the subgroup of patients in the heterogeneous trial could be considered (oversampling) or a separate trial in this subgroup can be planned. Selection will nevertheless occur. Low enrollment and loss to follow-up can introduce selection and can jeopardize validity as well as generalizability. Pragmatic trials are conducted in clinical practice rather than in a dedicated research setting, which could reduce recruitment rates. However, if a trial poses a minimal burden to the physician and the patient and routine clinical practice is maximally adhered to, the participation rate may be high and loss to follow-up will not be a specific problem for pragmatic trials.

Keywords: Pragmatic trial; Real-world evidence; Participant; Recruitment; Enrollment; Representativeness

1. Introduction

Pragmatic trials compare the effectiveness of an intervention in a randomized study under real-world conditions, identify the optimal treatment for patients, and inform health care professionals, payers, and the general public about the effects of treatment for patients in day-to-day clinical practice [1–3] (Box 1).

Explanatory trials often include highly selected, ''ideal'' patients, hoping to show maximal treatment effect with minimal adverse effects and/or minimize the required number of patients to obtain the results. These patients may, however, not be comparable to real-world patients with respect to relevant treatment effect modifiers, like comorbidity, disease severity, and risk factors [4]. As a consequence, the generalizability of the study findings to a

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What is new?

Key findings

- All patients who are potential candidates for the treatment in routine clinical practice should be considered eligible for a pragmatic trial, including vulnerable populations. Patients with known contraindications should be excluded.
- If important heterogeneity between subgroups is expected, a specific trial of sufficient size to address the subgroup of interest can be planned. Alternatively, the relative number of patients in these subgroups can be increased (oversampled) in the heterogeneous trial and taken into account in a pooled analysis.
- As in any trial, low enrollment and loss to follow-up can introduce selection and reduce generalizability. To improve participation and reduce the feeling of being observed in a trial, routine clinical practice should be maximally adhered to.

What this study adds to what was known?

- For pragmatic trials, we have integrated challenges and recommendations on eligibility, recruitment, and retention of participants.

What is the implication and what should change now?

- Pragmatic trials should align to clinical practice as much as possible, to improve both the generalizability of the trial results as well as the recruitment rates. Engaging health professionals and patient in the protocol development phase could help to achieve this.
- The aim and methods used in pragmatic trials should be clearly communicated to health professionals and potential participants.

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

setting with diverse patients, practices, and conditions may be limited or uncertain. Pragmatic trials therefore adopt more lenient eligibility criteria that reflect the diversity of patients who are treated in routine clinical practice.

Pragmatic trials aim to investigate the effectiveness of a treatment delivered under routine care conditions to all those eligible to receive treatment. Although there will be no deliberate selection in pragmatic trials, the act of enrolling in a trial will invariably lead to some selection [5]. We need to be aware that patients who consent for the trial may differ from those who do not, which may compromise generalizability of the results [4]. Low recruitment rates not only increase the duration and costs of the trial, they also may hamper a sufficiently large sample size and accurate conclusions. After patients have consented to participate, it is key to retain them in the trial until the end points have occurred, to prevent (selective) loss to follow-up. In this paper, we discuss challenges and solutions of selecting, recruiting, and retaining participants in pragmatic trials, guided by three questions: (1) who should be eligible for the trial, (2) who actually enters the trial, and (3) who stays in the trial until completion.

2. Who should be eligible for trial?

2.1. Why is the population studied relevant?

Specific characteristics of a selected patient group can modify the nature and magnitude of an intervention effect, this is called effect modification or heterogeneity of treatment effects. In the pragmatic STAR*D study, only 22% of the patients met the inclusion criteria commonly applied in phase III explanatory clinical trials in depression. The patients who met these stringent inclusion criteria had a shorter illness duration, tolerated the tested drug better, and had a higher response to the treatment compared to the patients not fulfilling these criteria [6]. In another study, the efficacy of the newer generation antidepressant escitalopram was shown to be higher in patients with severe depression compared to patients with milder depression [7]. There are other examples of factors that are known to influence drug efficacy and adverse events. In patients with a suspected diagnosis, the magnitude of the response may be smaller than in patients with a confirmed diagnosis. In elderly patients, age-dependent changes in metabolism and comorbidities may affect drug efficacy or adverse events [8].

Participants' behavior could also modify the effect of a drug, for example, when influencing drug adherence.

Ideally, we would like to have patients enrolled in the trial who are, as a group, representative of the target population in terms of all factors—known and unknown—that may modify the effect of the treatment. Some degree of effect modification can be expected in almost all studies. While randomization in trials takes care of (un)known confounding, random sampling takes care of unknown effect modification, since it is expected to result in a group of patients enrolled in a trial who are representative in terms of (un)known effect modifiers [9].

Although we aim for random sampling, in practice, random sampling is hardly ever done, but we try to approximate this random sampling by including (in the selected sites) all patients without further selection. Despite efforts made by the researchers, in practice, those enrolled in the trial may not comprise a random sample of the target population. Notably, in premarket trials, it may be difficult to fully characterize a patient group that will receive the treatment in the future. Broad eligibility criteria may lead to a trial population that is likely more representative of future heterogeneous patient populations than trials with stringent eligibility criteria.

2.2. Defining eligibility

A pragmatic trial should include a set of all patients who are indicated for the treatment in routine clinical care, without further interference or selection, to maximize the generalizability to the target population [10]. The number of exclusion criteria should be kept to a minimum. Patients should be selected based on their true indication of interest, defining the target population. As in all trials, patients with absolute contraindications should be excluded. Patients should not be selected on their expected drug adherence, practical difficulties, or compliance. The International Conference on Harmonisation (ICH) guidelines generally advise against the enrollment of patients in multiple clinical trials, though the reasons why already enrolled patients should not be eligible are not addressed [11]. In the literature, concerns about coenrollment typically relate to patient safety, scientific validity, and burden for the patient [12]. These concerns are more evident in earlier phase, explanatory trials than in pragmatic trials with approved interventions. The ICH guidelines do leave some room for justified exceptions; coenrollment in some postmarket pragmatic trials might be acceptable, which is also common practice in certain countries or disease area's [13]. Allowing coenrollment holds potential to overcome the problem of underrepresentation of particular patient groups, who tend to be eligible for multiple trials, because they have multiple comorbidities. Enrollment in multiple trials also enables patients to access different (innovative) therapeutic interventions at the same time, and it could enhance trial enrollment. However, multiple inclusions could potentially impact on the power of the trial; if the intervention tested in both trials influences the primary outcome, the event rate of the primary outcome could be affected [14]. Wider inclusion criteria as used in pragmatic trials probably lead to more variability in the response to treatment and, in case of continuous outcomes, may consequently require a larger sample size.

2.3. Vulnerable or special populations

The purposive inclusion of participants in whom the intervention may act differently leads to a broad range of patients to be enrolled in a pragmatic trial. This raises the issue of eligibility of vulnerable or special populations, such as children, pregnant women and their unborn fetuses, and persons with physical handicaps or mental disabilities. Vulnerable groups have traditionally been excluded from clinical trials as they are less capable to protect their own interests. However, systematic exclusion from pragmatic trials prohibits our understanding of the real-world benefits and harms of drugs used by these groups. For example, in the United States, about two out three pregnant women use prescription medication, many of which the effectiveness and safety has not been investigated during pregnancy, as pregnant women are generally excluded from clinical trials [15].

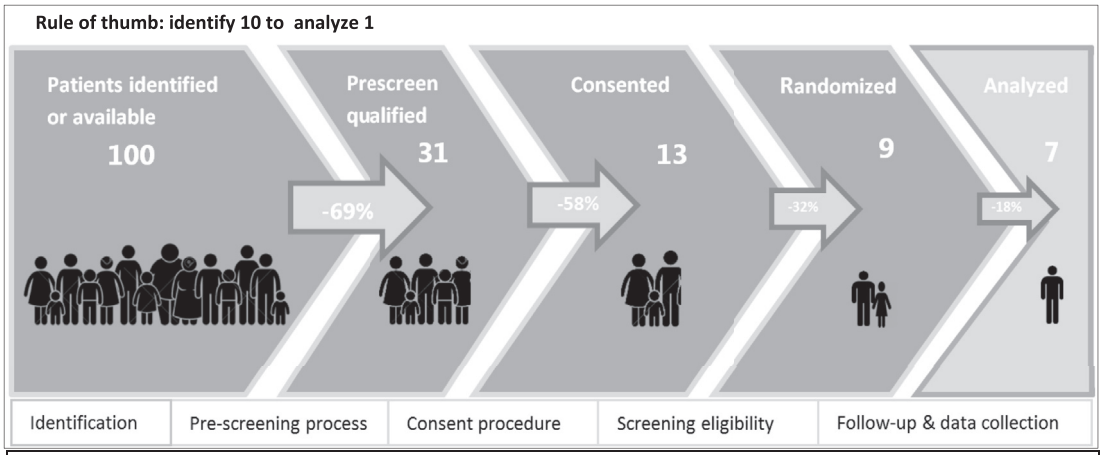
Belonging to a vulnerable population should in itself not be a criterion for exclusion from a pragmatic trial, to allow for equitable access to knowledge obtained through research. Enabling these groups to participate in pragmatic trials with novel interventions offers the additional benefit of access to a potentially advantageous treatment. Responsible inclusion of vulnerable persons in a pragmatic trial is nowadays encouraged, if additional protections are secured where deemed necessary based on expected risks, effects, and population characteristics [16,17]. A more stringent justification of the inclusion of vulnerable persons is needed in a premarket setting, where less evidence is available on the safety of new treatments.

If there are vulnerable patients for whom the effects of treatments are hypothesized to diverge from the overall trial result, a trial of sufficient size in this specific group could be planned at a stage when more data are available on safety in the population, to balance the value of including vulnerable persons against its risks and additional efforts. However, this is resource intensive, and due to limited resources, it might take years before such a trial is planned, if at all. Alternatively, one could increase the relative proportion of vulnerable patients in the heterogeneous trial (oversampling), to obtain (more) meaningful results that allow to test for interaction or its absence, and perform a pooled analysis of multiple trials to clarify differential effects in specific patient groups [18,19]. This would be particularly suitable if large differences are expected.

2.4. Subgroups

The more liberal inclusion criteria as generally applied in pragmatic trials lead to a heterogeneous patient population, which is the goal of pragmatic trials. The trial overall will show results that pertain to the heterogeneous population, including subgroups representative of the target population. If a treatment is shown to work for a diverse group of subjects in a pragmatic trial, it may be more likely to work in typical patients seen in everyday practice.

A pragmatic trial creates the opportunity to explore the consistency of the effect in different subgroups. However, subgroup analyses in general remain a topic of debate. When looking at the—often relatively small and underpowered subgroups—relevant group differences may remain undetected. At the same time, due to chance finding, differences may be detected which do not exist in the total population. Current opinions vary from always using the overall effect, whatever subgroup effect is of interest or whatever effect expected, to encouraging the performance



EXPECTED CHANGES IN THIS TYPICAL FUNNEL FOR PRAGMATIC TRIALS			
Identification and pre-screening	**Consent procedure**	**Screening eligibility**	**Follow up and data-collection**
Wider eligibility criteria: more diverse range of patients to enter the trial – Disease or health status related criteria limited to those defining the target population, and excluding patients with an absolute contraindication – No selection based on likely adherence – No selection based on practical difficulties – Belonging to a vulnerable population not necessarily exclusion – Exclusion because of safety concerns – Concurrent inclusion in multiple trials not allowed prelaunch, could be justified post launch	**Setting further away from dedicated research setting could reduce recruitment rate. However, the more the protocol is in line with usual practice and little extra effort needed, the higher the consent rate is expected to be.** Factors influencing informed consent: – Health care professionals less time for and experience with recruitment – Health care professionals might refrain from inviting vulnerable patients to the study – Health care professionals and patients might be unfamiliar with necessity for performing trials and have a negative feeling towards trials – The design better mimicking clinical practice could improve participation (open design, two active strategies, less complex and stringent protocol, already information about side effects) – Pragmatic trials could reduce practical barriers for trial participation, being in line with usual practice	**Limited number of eligibility criteria probably reduce the effort and dropout during screening**	**If the trial is in line with routine practice, without any additional visits or the use of placebo, attrition might be less of an issue. Especially if electronic health records can be used for data capture.** **However, quality and completeness of data might be lower if existing data sources are used.** **Additional collection of data on safety might increase the burden for participation.**

*The typical funnel is based on about 15 years recruitment funnel data across all therapeutic areas and indications

Fig. 1. The typical ''ratio of patients identified and analyzed and expected changes in the funnel for pragmatic trials (adapted from Forte Research systems [23]).

of subgroup analyses based on well-defined hypotheses, among others for equity [18,20]. As a potential bridge between these extremes, approaches that shrink the subgroup treatment estimates toward the average treatment effect across all participants could be considered [21,22]. Subgroup analyses may also help to explain differences between the results observed in a pragmatic and explanatory trial comparing identical interventions. If the results from explanatory and pragmatic trials yield discordant results, it may be—among other reasons—because the therapy works in some patients and not in others, and the patient mix in these trials is different.

Analytic strategies to optimize the value of pragmatic trials for the diversity of patients, like individual patient data meta-analysis, deserve further attention.

3. Who actually enters the trial?

Even though the goal is to recruit all patients concerned by the treatments being evaluated by the trial, selection will nevertheless occur. Only a proportion of eligible subjects will actually enter the trial.

Selection occurs at the level of the health care professional and the patient, as depicted in Fig. 1. Health professionals might not join the trial. If they joined the trial, not all their eligible patients may be invited for the trial. If invited, patients may decide not to participate. This may ultimately lead to a patient set that responds differently to the intervention than the targeted population. The response by the patients may also be altered due to unintended consequences of the prerandomization process, assessing eligibility, providing study information, and signing informed consent [24,25]. This may affect generalizability, as extrapolation of the findings from the trial to future users of the drug may be limited and may give a biased effect estimate. How much selection takes place may vary between countries, health professionals, patient populations, and disease areas.

Many trials face challenges with recruitment of a sufficient number of participants [5]. For pragmatic trials, this may be particularly the case as the trial is conducted in a routine care setting, where health professionals may be less experienced in and have fewer resources dedicated to recruiting subjects to trials, as opposed to a more experienced and dedicated research setting [26,27]. On the other hand, trials that are embedded in routine care and require limited additional activities, pose fewer barriers for health care professionals and patients to participate.

Below we will discuss the factors influencing enrollment of participants in pragmatic trials. In the previous paper in this series, the selection and inclusion of usual care sites have been discussed [28]. We proceed from the point where health professionals select their patients. It should be noted that strategies aiming at improving recruitment could also introduce selection, if targeted at or invoking a response from a specific subpopulation.

3.1. Factors influencing enrollment: the strategy used to identify and approach eligible patients

The way eligible patients are approached for participation influences the selection of patients enrolled in the trial. For a clinical condition, the most pragmatic approach would be to recruit patients with an indication for the treatment as they present themselves in routine care, without further interference or selection [10]. This is also known as ‘‘point-of-care’’ randomization. Using point-of-care randomization, the health care professional must be vigilant to invite their patients for participation during a routine patient visit and must have sufficient time for and knowledge about the study to adequately inform the patients [29]. Pop-up menus embedded in the electronic health record can help to alert a health care professional that a patient is eligible [26]. If patients are approached by their trusted health care provider, this can promote enrollment rates, and usual care conditions are best maintained [26]. Dedicated study staff may be employed to overcome operational challenges for recruitment during a routine visit [28].

Practitioner databases or electronic health records can also be used to select eligible patients with a chronic condition. These patients could be invited into the health center via a mail-out or informed about the study while they are in the waiting room for a regular visit. Direct contact in the waiting room has been shown to promote the participation rate but was considered less efficient than a mail-out [30]. Accessing electronic patient information or contacting patients has been shown to be a challenge for recruitment through databases [31]. Another alternative is directly calling on participants through newspaper advertisement or social media, although this method may also reach a selected (patient) group.

3.2. Factors influencing enrollment: the patient or disease under study

The more lenient inclusion criteria as applied in pragmatic trials may increase the number of eligible patients and reduce the total efforts needed for screening potential eligible patients. Health care professionals may nevertheless have their reasons for not inviting a patient for a trial, based on certain patient or disease characteristics, for instance, because of expected practical or language difficulties or concerns for the elderly participant [32,33]. The risk of reduced generalizability in this way could be limited by ensuring that the study protocol has a maximal resemblance with day-to-day clinical practice [26] and by encouraging health care professionals to invite all eligible participants.

3.3. Factors influencing enrollment: unfamiliarity with research and research procedures

Many of the barriers for participation in research relate to the fact that patients are generally unaware that clinical research is required to improve patient care. This lack of awareness can lead to doubts about the study's intent and cause a reluctance to participate [34]. Patients report a distrust toward the researchers and a discomfort with the trial setting, a computer ''deciding their fate'' (i.e., treatment allocated), or the research process in general [33,35]. Patients often feel unable to decide whether to participate, generally resulting in nonparticipation [36]. A strict and elaborate informed consent procedure could increase these feelings of distrust, and these feelings may also be stronger when the trial is conducted before the drug is licensed, as often less is known about potential (long term or rare) side effects. The rationale, the methods, and the potential benefits of the specific study should therefore be explained clearly [26]. Involving patient representatives at an early stage may help to improve the content of the information and modes of communication [37].

Health care professionals, patients, and the general public could be reminded that clinical research aims to improve the quality of treatments, for example, using media campaigns. If the opportunity to participate arises, the principles of research will already be more familiar and patients may be more likely to engage [38]. The treatment guidelines of health professionals could incorporate that when a pragmatic trial is ongoing, the current best treatment option is to offer the patient participation in the trial. Patients should be made aware that the decision to participate or not will not affect their relationship with their health care professional [39]. Emphasizing that treatment by their trusted health care professional will be continued in either study group may improve the perception of the research process.

3.4. Factors influencing enrollment: study design and treatment groups

In general, participants will know which treatment they are receiving in a pragmatic trial. Such open label research designs have been shown to increase recruitment rates [40]. A randomized design, where patients do not have the option to choose for a preferred intervention, is often viewed as a barrier for trial participation [33,35].

Modifications to the randomization process have therefore been proposed. The timing of the intervention is randomized in a stepped wedge design. In a Zelen's design, patients are invited to participate conditionally upon treatment, as randomization is performed beforehand. Another method is cluster randomization, where a particular treatment is allocated to an entire research site.

Other barriers for participation in clinical trials are the presence of a no treatment group, fear for potential side effects, and the strongly protocolled manner in which interventions are delivered [33]. Pragmatic trials reflect usual clinical practice and have a less complex and stringent study protocol, and more is known about potential side effects, which may improve patient participation [26]. Also, availability and access to a treatment that is unavailable to patients outside the study could positively influence the participation rate [34]. Where in postlaunch pragmatic trials, both interventions are often already available for all patients, this may be an incentive for participation in a prelaunch or perilaunch pragmatic trial.

3.5. Factors influencing enrollment: practical aspects of trial participation

Conducting clinical trials requires additional time and efforts for both the patient and the physician. Minimizing the administrative burden will positively affect the number of patients invited for a trial. To identify and overcome barriers of health professionals a priori, qualitative methods can be useful, for example, interviews [41]. Practical barriers for participation of specific patient groups should be identified and addressed before starting a trial, such as time and costs required to travel, hearing impairments in the elderly, arrangement of day care for children of young adults, or time schedules that do not interfere with school hours for children [37,42]. If routine clinical practice is respected without additional follow-up visits, these practical aspects should be of minor influence.

Another frequently mentioned barrier, both by physicians and patients, is an extensive and time-consuming informed consent procedure. Modifications to shorten the informed consent procedure have been proposed to better reflect real-world conditions and to enhance recruitment [43]. The specific challenges related to informed consent will be discussed in the next paper of this series [44]. Again, patient involvement in the design of the informed consent and patient information form may lead to greater public support for such modifications.

Based on recent examples, the Clinical Trial Transformation Initiative working group recommends the engagement of all stakeholders early in the trial development process to improve recruitment, although the magnitude of the improvement is still unclear [45−47].

4. Who stays in the trial?

After the patients have successfully been selected and enrolled, the final challenge is to maintain them in the trial until the outcome of interest occurs. If loss to follow-up is random, it will reduce the statistical power to detect group differences, but it will not bias the results. If loss to follow-up is differential such that it leads to incomparability of randomized groups, this could introduce bias. Bias could be introduced when inserting explanatory trial elements in one arm of the pragmatic trial only, for example when

follow-up visits are inserted in one trial arm only or drugs are provided free of charge only in the group randomized to the new intervention [48].

Since pragmatic trials are embedded in routine clinical practice, typically without any additional visits or the use of placebo, the attrition of subjects is expected to be low, especially if the outcome measures are extracted from electronic medical records. However, safety is often not recorded in sufficient detail in the electronic health record; therefore, necessary collection of data on safety may increase the burden of participation during the study compared to usual practice. This may especially be the case in prelaunch trials where little is known about the safety profile. Furthermore, the behavior of patients in a trial can be influenced by their awareness of being observed, an example of the Hawthorne effect, although the magnitude of this effect is unknown and unpredictable [49]. To maximize generalizability of the findings to the target population outside of a pragmatic trial, the feeling of being observed in the trial should be minimized, among others through minimal disruption of patient-physician encounters in routine practice, aligning informed consent with usual care, and by minimizing baseline data collection and measurements [24].

5. Conclusion

Pragmatic trials should align with clinical practice as much as possible, with additional trial-related activities minimized. All patients who will potentially receive the drug in clinical practice should be considered eligible, and the additional trial-related activities should be minimized. This will improve both the generalizability of the trial results as well as the recruitment rates and with that the feasibility of the trial. Engagement with patient representatives and health professionals is considered to provide valuable input during study development to ensure alignment with routine care and identify potential barriers to participation early in the design process.

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