

Series: Pragmatic trials and real world evidence: Paper 4. Informed consent

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Abstract

The GetReal consortium of the Innovative Medicines Initiative aims to develop strategies to incorporate real-world evidence earlier into the drug life cycle to better inform health care decision makers on the comparative risks and benefits of new drugs. Pragmatic trials are currently explored as a means to generate such evidence in routine care settings. The traditional informed consent model for randomized clinical trials has been argued to pose substantial hurdles to the practicability of pragmatic trials: it would lead to recruitment difficulties, reduced generalizability of the results, and selection bias. The present article analyzes these challenges and discusses four proposed alternative informed consent models: integrated consent, targeted consent, broadcast consent, and a waiver of consent. These alternative consent models each aim at overcoming operational and methodological challenges, while still providing patients all the relevant information they need to make informed decisions. Each consent model, however, relies on different attitudes toward the principle of respect for persons and the related duty to inform patients as well as represents different views on whether the common good demands moral duties from patients. Such normative consequences of modifying consent requirements should be at least acknowledged and ought to be assessed in light of the validity of empirical claims. © 2017 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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1. Introduction

Pragmatic trials hold potential to deliver the high-quality scientific evidence needed to guide health care decision-making by regulatory bodies, medical practitioners, and health technology assessment (HTA) agencies [1–3]. Traditionally, explanatory randomized controlled trials (RCTs) have served as the main source of clinical evidence supporting market authorization decisions of new drugs. However, because of differences in use and users of drugs as tested in explanatory trials vs. those as prescribed in the real world, a so-called knowledge gap between drug efficacy and effectiveness has arisen [4]. Explanatory trials aim to obtain knowledge about the biological effects of new drugs in highly standardized and idealized settings, whereas pragmatic trials collect real-world comparative

effectiveness data in patients who are treated in routine clinical practice [5,6]. The term pragmatic trial is typically used to refer to randomized trials comparing different routine care interventions, although it is now acknowledged that pragmatic trials can also be conducted in earlier stages of the drug life cycle with new interventions. As such, the GetReal consortium of the Innovative Medicines Initiative (IMI) explores ways to implement pragmatic trials earlier into the process of drug development and evaluation [7].

For all pragmatic trials, whether in earlier or later stages, a significant challenge is to preserve the real-world nature of the trial. Some have raised concerns that current ethical trial regulations compromise that character, such as the requirement to obtain extensive, written, and prospective informed consent [8,9]. Discourse concentrates on the question whether all traditional requirements for informed consent for RCTs are ethically necessary to sufficiently protect the rights and interests of participants in a pragmatic trial.

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What is new?

- We analyze claims about the challenges that traditional informed consent procedures might pose to the practicability of pragmatic trials.
- We discuss four alternative consent models that were proposed to tackle these challenges: integrated consent, targeted consent, the broadcast approach, and a waiver of consent.
- Before considering alterations or waivers, it is important to provide compelling arguments why a particular pragmatic trial becomes impracticable with traditional informed consent. The relative impracticability needs to be weighed against the implications of reducing the degree of transparency and limiting patients' freedom of choice regarding treatment options.

Moreover, it has been argued that certain requirements are so restrictive that some pragmatic trials become impossible to conduct [10–12]. This article first analyzes claims about the challenges that traditional informed consent procedures might pose to the practicability of pragmatic trials (See Box). Subsequently, the article discusses four alternative informed consent procedures proposed in response to these claims. Before considering alternative consent models, we conclude that it is important to provide compelling arguments why a particular pragmatic trial becomes impracticable with traditional consent requirements. The relative impracticability needs to be weighed against the implications of reducing the degree of transparency and limiting patients' freedom of choice regarding treatment options.

Box. 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. Traditional requirements for informed consent

Informed consent is based on the principle that competent individuals have a right to choose freely whether to participate in research. Enshrined in the Declaration of Helsinki, the obligation to obtain informed consent protects the individual's freedom of choice and respects the individual's autonomy [13,14]. Moreover, the notion of informed consent is rooted in our aspiration to protect research participants and secure people's trust in clinical research overall. Many guidelines and regulations for clinical trials in Europe have incorporated the duty to seek written and prospective informed consent from research participants, such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice Guidelines and the European Clinical Trials Directive (2001/20/EC) [15,16]. To ensure valid and voluntary informed consent for clinical trials involving medicinal products, these trial regulations require that potential participants are informed about the purpose of the study, the fact that it constitutes scientific research, the potential risks and benefits, the trial's procedures, and that participants can withdraw at any time during the study without consequences. In addition, researchers must ensure that the potential participant has understood the information and decided on participation without having been subjected to coercion or undue influence [13,14]. Recently approved amendments to the European Directive state that only one type of trial may be exempt from the consent requirements: cluster RCTs in which groups of subjects rather than individual subjects are allocated to receive different approved medicinal products may make use of simplified means to obtain informed consent [17]. Necessary conditions are that there are no interventions other than the standard treatments and that the protocol justifies the reasons for obtaining consent by simplified means. The trial should also classify as a low-intervention trial indicating use of approved products in accordance with the marketing authorization and with minimal risk or burden from additional diagnostic or monitoring procedures. The 2012 Ottawa Statement presents similar conditions for a waiver or alteration of informed consent for cluster RCTs, knowingly, that the research is not feasible without modified consent, and that the research-related procedures do not pose more than minimal risk [18]. Pragmatic trials that randomize individual participants or that investigate unapproved products are still required to obtain full or traditional informed consent from participants.

3. Challenges to the practicability of pragmatic trials

The traditional requirements for informed consent have raised issues with respect to the practicability of the research [19,20]. Considerable loss of real-world features diminishes the value of a pragmatic trial as generalizability of results to usual practice is a key aim and begs the question whether the trial is worth doing at all. If the research

question cannot be satisfactorily answered because of consent requirements, the trial becomes impracticable [21,22]. Traditional informed consent procedures are believed to make pragmatic trials impracticable if they lead to low enrollment and a study sample that is not representative of the real-world patient population [2,10–12].

With respect to enrollment challenges, reluctance of physicians toward spending time on consent procedures has been described as an important factor for trials failing to reach patient recruitment targets [8,23,24]. General practitioners report that obtaining informed consent for a pragmatic trial during a regular consultation would probably not be feasible even if they believed the study was worth doing [8]. It has been argued that the requirements for informed consent and regulatory oversight for clinical trials in general are time consuming and expensive and may be disproportionate for pragmatic trials that compare routine care interventions that have already been shown to be safe and are in widespread and routine use [25].

Regarding the challenge of obtaining reliable and generalizable data, lengthy consent forms have been argued to deter specific groups of patients from participating in a clinical trial. Nonparticipation for this reason could be because of time constraints, overestimation of the study risks, or any other kind of misunderstanding of the provided information [23,26]. As a result, standard consent might lead to selection and the underrepresentation of particular groups of patients. If, for example, patients of lower socioeconomic status or sicker patients are less likely to consent, the trial results will be less applicable to the more heterogeneous real-world population. This selection might lead to an effect estimate that is not generalizable to the broader population as defined by the initial inclusion criteria [2,10,11,22]. It has also been suggested that once patients are enrolled in a trial, their behavior might be affected by awareness of being observed. Such phenomena (described as the Hawthorne effect [27]) are still poorly understood but have led some to believe that the more elaborate an informed consent procedure is—or in other words, the more it deviates from how treatments are prescribed in real life—the less generalizable the trial findings will become to the real world [20].

4. Examining the impracticability argument

The first issue that needs to be addressed is whether an informed consent procedure actually leads to impracticability, and next if proposed alternatives are ethically justifiable and effective. Impracticability in terms of pragmatic trials tends to refer to a compromise on real-world features that makes it (almost) impossible to answer the research question. This can be because of limited generalizability, low recruitment rates, and/or selection bias.

It seems that the issue of reduced generalizability can emerge because of the mere act of asking consent or through the mode of recruitment (e.g., lengthy forms or

time-consuming procedures). If eligible patients decline study participation because of reasons that are intrinsic to the purpose of informed consent (e.g., because patients do not wish to change their current therapy), alterations to traditional consent procedures are never defensible. Only if refusing participation is because of practical reasons that are extrinsic to the purpose of informed consent (e.g., physicians do not have time for consent procedures), altering traditional consent could be an ethically defensible solution. Such reasons may allow for leaving out some of the traditionally required information to approach real-world conditions and to enhance comprehensibility of the forms.

Still, true impracticability may be dependent on the availability of options to enhance recruitment. To what extent deviations from real-world practice are acceptable is a matter of degree. Therefore, some compromise on real-world conditions might be acceptable if it means increasing the number of enrolled patients. If physicians are the limiting factor because of time constraints, economic resources provided by the sponsor could be used to reimburse physicians for time spent on consent procedures during clinic hours or to contract study nurses to take on part of the workload. The premarket pragmatic Salford Lung Study used these strategies, and a preliminary publication on the design and current conduct of the trial does not suggest that consent procedures made the study impossible [28].

In most pragmatic trials, traditional informed consent will not make the trial inherently impossible. Rather, consent requirements can reduce the real-world character and thereby the applicability of the results. In addition, these requirements may reduce the participation rate and increase the duration of the trial because of the time needed for obtaining traditional informed consent. The degree to which these challenges lead to actual impracticability will depend on the particulars of a specific pragmatic trial. For example, a good match between trial consent and consent in the real world may not always be strictly necessary to ensure high generalizability; only if consent is a relevant modifier of the treatment response, will such a match be required [29]. However, in a number of cases, it will remain unclear to what extent informed consent procedures actually affect treatment outcomes. The notion that a more detailed consent process will make a participant behave differently throughout the trial seems to overrate the power of the potential of the consent process to affect patient behavior and outcome. In addition, for some pragmatic trials, obtaining traditional informed consent during a clinical encounter might not be as burdensome as initially believed. Physicians enrolled in the pragmatic eLung study reported that the consent process usually took 5 minutes and was feasible on most occasions [8]. As such, the only way of evaluating whether there are legitimate reasons for a pragmatic trial's impracticability is by carefully examining the arguments why this exactly would be the case.

5. Proposed alternatives to traditional informed consent

Scrutinizing claims about impracticability is important because if they turn out to be invalid, no alternative means of obtaining informed consent are required—let alone ethically justified. To put it differently, alternative consent models for pragmatic trials require justification. The impracticability of the research is not a sufficient justification, but at least a necessary condition. Another necessary condition almost always related to the permissibility of consent modifications, but which we will not discuss here, is that the research does not pose more than minimal risk [30–32]. A number of alternatives for traditional informed consent have been recently proposed for pragmatic trials that compare therapies that have already been incorporated in clinical practice [10]. All these alternatives have the objective of providing patients the information they consider relevant to their decision-making while better integrating the consent procedure within routine clinical care to overcome the challenges as discussed.

5.1. Integrated consent

The integrated consent model is targeted at pragmatic trials comparing commonly used treatments in routine practice, which have been independently validated through well-controlled clinical trials and which in practice only require verbal consent [33]. The model proposes an approach that integrates clinical and research consent within the same clinical encounter. The patient's treating physician will discuss the treatment's rationale, alternatives, use of randomization, and potential harms and benefits of the compared treatments. The patient can then opt-in through oral or written consent. The physician documents the conversation and its result in the patient's electronic health record and proceeds with the care that he or she would normally deliver in the context of clinical practice.

5.2. Targeted consent

The targeted consent model is proposed to avoid selection bias and minimize interference with clinical care when standard-of-care treatments are compared [11]. The model requires providing potential participants only the following information additional to the information that would be conveyed if the intervention was provided outside the trial: the fact that enrollment involves patients helping investigators to evaluate the treatments under study as well as all the added research-related risks. By providing this additional information, the patient can decide for herself whether to enroll. The targeted consent model consists of a verbal disclosure accompanied by a written consent form repeating the verbally disclosed information and describing the following: (1) procedures and duration, (2) instructions on taking the medication, (3) availability of the investigational treatments to patients outside the research setting,

(4) confidentiality measures, (5) contact information, and (6) a statement that the patient is free to decline research participation and to stop participation at any time without consequences. A substantial difference with the integrated consent model is that during targeted consent the patient is not informed about the randomization process.

5.3. Broadcast approach

The broadcast approach makes use of general notifications placed in prominent locations, informing patients that they could (continuously) be part of comparative effectiveness research with standard-of-care interventions (potentially pragmatic trials) [32,34]. This approach allows patients to ask questions about their participation, and if there is no option for nonparticipation at their care facility, they can decide to seek care elsewhere [10]. It is believed that as long as the trial is implemented in a health care context where patients are regularly informed that randomized research involving minimal risk is occasionally permitted to take place, no express informed consent is ethically obligatory [32].

5.4. Waivers of consent

A waiver of consent means that participants are not informed about the research and that they do not actively decide on whether to participate [10]. In Europe and the United States, consent waivers for RCTs are currently only permitted under highly restricted circumstances, which are likely to exclude pragmatic trials from consent exemptions [15,16,35,36]. Nevertheless, Truog et al. [37] have argued in favor of consent waivers for pragmatic trials in which all treatments offered in the trial may be offered outside the trial without specific informed consent, treatments do not involve more than minimal additional risk in comparison with any of the alternatives, genuine clinical equipoise exists among the treatments, and no reasonable person should have a preference for one treatment over another.

6. Implications of consent alterations

If a claim about a pragmatic trial's impracticability with traditional informed consent can be substantiated, alternative models might be considered. However, such alternatives will still need to be accounted for in ethical terms.

The integrated consent model maximizes transparency between physicians and patients, who are informed about all relevant aspects of the study. The model acknowledges that even if no a priori quantitative differences exist in the risks and benefits of the compared treatments, it is important to respect preferences and values that are meaningful to individual patients. Kim and Miller [33] judged that bypassing a person's agency—unless the person is incapable or not reasonably accessible—even for that person's own good is unacceptable. These authors stress the

importance of maximizing the degree to which the principle of respect for persons is respected: “[a]ny permissible alternative to regulatory consent should use procedures that preserve the greatest degree of respect for persons that is compatible with the practicability of the research” [21].

Targeted consent is designed to avoid the tension that waivers on one hand, and traditional informed consent on the other, create. An important difference with the integrated consent model is the nondisclosure of randomization. Wendler [11] does not explain why nondisclosure is necessary or desirable but he does provide an answer to possible objections to it: “[S]tudies indicate that when the existing data do not suggest that one intervention is better, randomization does not increase risks, suggesting that for the purpose of protecting subjects from harm, pragmatic trials do not need to disclose randomization.” This response suggests the underlying assumption that disclosure of randomization may hamper recruitment or affect the outcome of a trial in some way. It remains unclear, however, what physicians are supposed to answer when patients ask about the allocation method.

With regard to the matter of respect for patients, Wendler does concede that when the risks of the available treatments differ in ways that most individuals consider important, these differences should be disclosed (in line with the integrated consent model), after which the individual should be provided the opportunity to discuss any questions or concerns that they may have. At the heart of the discussion between the integrated consent model and targeted consent is the moral significance of the preferences of some potential participants (who regard some differences between the treatments as important while the possible differences in risks are not material or backed up by sufficient scientific evidence) in relation to those of the majority or the random patient [38].

Broadcast consent appeals to the sense of duty on the side of patients to engage in health-related research. In this model, anticipated societal benefits of research seem to be able to justify deviations from the traditional research ethics paradigm. Ruth Faden and Nancy Kass [39] frame this model in terms of justice: present-day patients benefit from clinical research performed among patients in the past, which justifies—at least to some extent—a more general moral duty to contribute to research. Broadcast consent has the advantage of prior notification so patients can seek treatment elsewhere if they do not wish to partake in ongoing research activities. Still, there is limited opportunity to object to participation as changing treatment practices can be burdensome. The model of broadcast consent may thus disproportionately burden vulnerable groups, such as impoverished or elderly patients. Furthermore, selection can occur if changing care facilities are less of an option for some patient groups compared with others. This means that in broadcast consent, the goal of advancing the common good is contrasted by the argument of unfair sharing of the burdens of research. Complete waivers of consent, at the end of the consent spectrum, remove individual choice completely and imply not only a strong moral duty on

patients to participate in research but also suggest superiority of the purpose of the research as serving the common good.

Transparency to the public is vital for trials as to secure patients’ trust in not only the whole enterprise of biomedical research but also clinical care itself. A recent qualitative study provided some preliminary evidence that relevant stakeholders find alternatives to traditional informed consent acceptable for low-risk pragmatic trials investigating widely used therapies, as long as a sufficient amount of choice is preserved [40]. Results from a recent survey among the US public ($n = 2,130$) about their views on alternatives to written consent for low-risk pragmatic trials investigating different standards of care showed that most respondents recommended written informed consent for trial participation, despite the fact that they acknowledged the value of the presented trial scenario and believed the trial did not pose additional risks [41].

7. Discussion and conclusion

Alternative consent models for pragmatic trials have ethical implications that warrant assessment of the validity of the claims about a pragmatic trial’s impracticability with traditional consent requirements in place. Traditional consent procedures have been said to diminish recruitment numbers and lead to unrepresentative samples, limiting generalizability to the population outside the trial, and introducing selection bias. Proposed alternatives for consent procedures aim at overcoming these challenges while at the same time providing patients all the relevant information they need to make informed decisions. Each consent model, however, relies on different attitudes toward the principle of respect for persons and the related duty to inform patients and represents different views on whether the common good entails particular patient duties to engage in clinical research. Especially, consent waivers and broadcast notifications imply strong duties on the side of patients and a high social value of the research.

These four models were selected from the literature as they provided the most procedural detail. We acknowledge that this list is not exhaustive and that other viable alternatives, such as a simple opt-out, are not discussed. However, our objective in this article was not to argue which model should be preferred for pragmatic trials but to show that deviations from traditional consent have ethical implications that need to be balanced. The relative impracticability needs to be weighed against these ethical implications. To adequately perform such an evaluation, it is essential to expose the reasons why traditional consent would affect a particular pragmatic trial’s practicability and examine to what degree proposed alternatives affect patients’ rights and could be actual solutions. Further work is needed to establish how a pragmatic trial’s impracticability ought be balanced against the research risks, along with other, more normative aspects such as patients’ rights, their responsibilities, and duties.

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