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Distinctive aspects of consent in pilot and feasibility studies

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Abstract

Prior to a main randomized clinical trial, investigators often carry out a pilot or feasibility study in order to test certain trial processes or estimate key statistical parameters, so as to optimize the design of the main trial and/or determine whether it can feasibly be run. Pilot studies reflect the design of the intended main trial, whereas feasibility studies may not do so, and may not involve allocation to different treatments. Testing relative clinical effectiveness is not considered an appropriate aim of pilot or feasibility studies. However, consent is no less important than in a main trial as a means of morally legitimizing the investigator's actions. Two misperceptions are central to consent in clinical studies—therapeutic misconception (a tendency to conflate research and therapy) and therapeutic misestimation (a tendency to overestimate possible benefits and/or underestimate possible harms associated with participation). These phenomena may take a distinctive form in pilot and feasibility studies, owing to potential participants' likely prior unfamiliarity with the nature and purposes of such studies. Thus, participants may confuse the aims of a pilot or feasibility study (developing or optimizing trial design and processes) with those of a main trial (testing treatment effectiveness) and base consent on this misconstrual. Similarly, a misunderstanding of the ability of pilot and feasibility studies to provide information that will inform clinical care, or the underdeveloped nature of interventions included in such studies, may lead to inaccurate assessments of the objective possibility of benefit, and weaken the epistemic basis of consent accordingly. Equipoise may also be particularly challenging to grasp in the context of a pilot study. The consent process in pilot and feasibility studies requires a particular focus, and careful communication, if it is to carry the appropriate moral weight. There are corresponding implications for the process of ethical approval.

KEYWORDS
clinical trial, consent, ethics, feasibility study, pilot study

1 | INTRODUCTION

In systematic evaluation of clinical interventions, pilot and feasibility studies (PFSs) are increasingly carried out prior to a definitive, or main, randomized clinical trial;[1,2] usually a phase 3 trial. The term 'pilot study' is sometimes applied to phase 1 trials, or to preliminary studies receiving small seedcorn institutional grants prior to an external funding application, but these differ from the type of pilot study considered here, which is further downstream and occurs more or less immediately before a definitive phase 3 study, and after any phase 1 and 2 trials have been completed.[3]

The purpose of PFSs is to gather information that will optimize the main trial—such as by estimating the number of eligible potential

participants, the consent rate, loss to follow-up, treatment fidelity, and compliance, and by testing methods of randomization, blinding and outcome measurement.[4,5] PFSs may additionally serve to inform a sample size calculation,[6] refine or fine-tune the interventions to be tested in a main trial,[2] and assess the acceptability of such interventions and study procedures.[1] They may also be used—with questionable appropriateness[7]—to obtain preliminary estimates of treatment effects. Importantly, any such estimates should not be subjected to formal statistical testing to determine treatment effectiveness, this being the role of a main trial.[2,3] In these ways, PFSs can inform a decision as to whether a main trial is viable (Table 1).

A feasibility study and a pilot study are often distinguished from each another as follows.[3,8] Feasibility studies are any study carried out to inform the design or delivery of a subsequent main trial, and do not necessarily adopt the design of the main trial. Pilot studies are, more specifically, a version of the main trial run on a smaller scale, either in its entirety or in part, and therefore involve allocating participants to two or more treatment groups. Accordingly, whilst all pilot studies are feasibility studies, not all feasibility studies are pilot studies. For the most part, this paper will focus on PFSs jointly, but where there is a separate focus on either a pilot or a feasibility study, as distinguished above, this will be indicated. Additionally, the type of pilot studies at issue will be those carried out in advance of a main trial ('external' pilot studies), rather than those that may be carried out as a preliminary phase within the main trial ('internal' pilot studies).[9]

TABLE 1 Purposes for which main trials and pilot or feasibility studies may be used

Main (definitive) randomized clinical trial	Pilot or feasibility study
To determine comparative treatment effectiveness, through statistical testing	To assess feasibility of trial processes (eg, recruitment, screening, consent, blinding)
To examine subgroups effects and/or treatment mediators	To estimate clinicians' willingness to randomize patients and patients' willingness to be randomized
To conduct a health economics analysis (eg, cost-effectiveness or cost-utility analysis) of the treatments tested	To assess treatment fidelity (clinicians) and treatment adherence (participants)
To plan implementation of trial findings	To refine or optimize one or more of the intended treatments
	To test outcome measurement and select a primary outcome measure
	To determine the acceptability of intended treatments
	To estimate parameters required for a sample size calculation for a main trial (eg, standard deviation of scores, rate of missing values)
	To gain preliminary estimates of treatment effect
	To inform a decision as to whether a main trial should be undertaken

Notwithstanding these definitions and distinctions, it is only recently that a consensus has been approached on the nature and role of PFSs,[8] and the clinical research community have historically not been clear on how they should be defined. Given this, and in the light of evidence that public understanding of clinical research is limited,[10-12] it is perhaps safe to assume, in the absence hitherto of clear empirical data, that patients' understanding of the nature and purpose of PFSs will be even less robust. Plausibly, such understanding that patients have of clinical research is likely to relate more closely to conventional main trials.

The benefits that flow from PFSs differ from those of a main clinical trial. In the latter, the aim is to secure clinical benefit for future patients by assessing the merits of competing treatments. In contrast, PFSs assist the development and conduct of a subsequent main trial and/or inform the decision as to whether such a trial should be undertaken. The proximate benefit arising from PFSs relates therefore to the social value of informing researchers where they should best direct their efforts and research resources, and to the scientific value of optimizing methodological rigour. Any generalizable clinical benefit from a PFS will be therefore indirect, as it can only occur through the subsequent clinical trial, and uncertain, to the extent that it is contingent on the subsequent trial taking place. From an ethical perspective, the nature, magnitude and likelihood of the benefit anticipated from a study play a part in justifying any risk of harm that it may involve.[13] In a conventional RCT, a justification specifically in terms of clinical benefit assumes that the trial is likely to generate findings that have clinical utility, whereas in a PFS it assumes not only that a subsequent trial will generate such findings but also that such a trial will take place. Justification of a PFS should not, therefore, rely solely on contingent clinical benefit, but should rest principally on its more immediate and more assured social value in informing subsequent research.

As pilot studies, and most feasibility studies, involve human participants, they raise ethical issues similar to those of other clinical studies, but have received little specific attention in the literature. Moreover, PFSs, although subject to the same requirement as main trials for approval from an institutional review board or research ethics committee, do not feature in major guidance on research ethics.[2] Compared to main trials, PFSs are on a smaller scale and have an apparently ancillary status, which might suggest that the demands of consent are less stringent. However, they raise similarly challenging issues. This paper will focus on these issues and will suggest in particular that some aspects of consent should be reconceptualized, given the differing aims of these studies from those of main clinical trials. Some practical issues will also be explored.

2 | CONSENT IN CLINICAL STUDIES

Consent serves to protect and support autonomous decision-making on the part of the potential research participant.[14] It therefore has a legitimizing function in relation to actions that the researcher wishes to perform that would be impermissible in the absence of such consent.[15] As lack of information constrains autonomous decision-making, disclosure

on the part of the researcher and comprehension on the part of the participant are prerequisites for consent.[16] Many of the problematic aspects of consent centre, however, on these aspects,[17] and an important issue here is what Sisk and Kodish[18] call therapeutic misperception.

2.1 | Therapeutic misperception

Two main types of therapeutic misperception have been identified. *Therapeutic misconception*, first articulated by Appelbaum et al,[19,20] concerns participants' potential misunderstanding of the nature and purpose of a clinical trial, and a tendency to confuse research with therapy.[21] Therapeutic misconception centres firmly on the purposes of a trial, not its consequences, and exists

> when individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial.[22,p. 1736]

Therapeutic misconception has two main elements: first, 'an incorrect belief that the patient/participant's individualized needs will determine assignment to treatment conditions or lead to modifications of the treatment regime' and, second, 'an unreasonable appraisal of the nature or likelihood of medical benefit from participation in the study, due to misperception of the nature of the research enterprise'.[20,p. 636] These misunderstandings are likely to be accompanied by a poor comprehension of the methods used to achieve the goals of the research. Hence, trial participants may not appreciate that randomization is a purely stochastic process and has nothing to do with—indeed, is largely incompatible with—the provision of personalized care, despite receiving a prior explanation to this effect.[23,24] Of course, the simple fact of taking part in a clinical trial may in itself be beneficial[25]—a phenomenon referred to as 'inclusion benefit'.[26] However, the trial is not designed to provide *individualized* benefit to participants. Although the way in which a treatment is defined in a protocol for a pragmatic trial may be sufficiently flexible to allow the clinician to *deliver* that treatment with some regard to the participant's particular clinical presentation, this does not equate to personalized care, as the *allocation* of the participant to the treatment in that arm of the trial is predetermined at the point of randomization. Therapeutic misconception may also relate to an understanding of the nature of the interventions within a trial, such as the use of a placebo, as suggested by Appelbaum's report of a participant in a trial of pharmacological interventions for a psychiatric disorder who believed that the placebo 'would be given only to those subjects who "might not need medication"'.[20,p. 22]

Therapeutic misestimation is a similar but distinct phenomenon. It has to do with the way in which participants may overestimate the benefits and/or underestimate the harms associated with taking part in a trial;[27] this may reflect a broader tendency, beyond the research context, for patients to inflate possible benefits and downplay possible harms.[28] Therapeutic misestimation may stem from an erroneous processing of specific factual information that the investigator has provided as part of the consent process, or it may represent prior assumptions on the part of the participant that are wide of the mark.

Common to both of these forms of misperception is likely to be an underlying hope of therapeutic benefit from research participation.[18,29,30] With regard to consent, these misperceptions become morally significant to the extent that they influence the individual's motivation to enter a trial and, thereby, his or her decision either to grant or to withhold consent.[31,32] I will argue, however, that the way in which we conceptualize such misperception should differ somewhat in relation to PFSs.

3 | THERAPEUTIC MISPERCEPTION IN PILOT AND FEASIBILITY STUDIES

At the root of participants' misperception of clinical research may be their attempt to understand aspects of the research situation in terms of one that is more familiar to them. Thus, in conventional clinical trials the individual may reinterpret the researcher-participant relationship in terms of the more familiar doctor-patient relationship.[33,34] In PFSs, however, this reinterpretation may take an additional form. If, in addition to drawing upon their experience of the clinical encounter, potential participants seek to make sense of such a study in relation to any understanding they may have of clinical research, as argued earlier this is more likely to be in the context of a main trial than the less familiar context of a PFS. Hence, in addition to their assimilation in participants' minds to clinical practice (with potential misunderstanding as to the issue of individualized care), PFSs may be assimilated to main trials (with potential misunderstanding as to the production of generalizable clinical insights).

3.1 | Therapeutic misconception

So, participants in PFSs may be subject to an additional form of therapeutic misconception that differs somewhat from its conventional definition in the context of a main trial (Table 2). As well as assuming that taking part in a study will allow them to receive personalized care—the traditional interpretation of therapeutic misconception—they may also assume that their participation will contribute to evidence that can be applied directly to broader clinical practice. Thus, not only may they misconceive the likelihood of their own individualized medical benefit *within* the study, but they may further misconceive the likely medical benefit for patients more widely *beyond* the study. This is problematic for consent in two ways. First, potential participants bring with them their own personality and other individual characteristics and may have a variety of reasons for taking part in a PFS; but if, through a sense of altruism, they base their consent on this mistaken belief in generalizable clinical benefits, it will be founded on a misunderstanding and its legitimizing moral force will be

TABLE 2 How therapeutic misperception may occur in main trials and in pilot and feasibility studies

Misperception	Main randomized clinical trial	Pilot or feasibility study
Therapeutic misconception	A mistaken belief that the goal of the trial is personalized care, rather than research	As for a main trial, but additionally a mistaken assumption that the findings of the study will directly inform broader clinical practice, rather than informing a subsequent trial with that aim
Therapeutic misestimation	A tendency to overestimate the magnitude of potential benefit, and underestimate the magnitude of potential harm, involved in taking part in the trial	As for a main trial, but additionally an overestimation of the *possibility* of gaining clinical benefit during or after the study, given that the design of a pilot or feasibility study and/or the stage of refinement of the intervention may not conduce to such benefit

undermined accordingly. Second, and relatedly, a decision to consent is likely also to have been based, at least in part, on a relative assessment of the potential benefit and harm associated with participation.[35] For this assessment to be epistemically sound, the particular nature of the benefit at stake should not be misconceived, as assessing the magnitude of a benefit cannot be separated from an understanding of the form it will take.

It follows that, in order for their consent to carry the necessary moral weight, participants should not mistakenly assume that their participation will contribute directly to generalizable clinical benefit for future patients—such benefit will derive from a subsequent main trial and is, moreover, contingent on this later trial taking place. However, it is important that potential participants should have the necessary information to exercise their autonomy in relation to both the giving and the withholding of consent. Accordingly, in addition to understanding what the immediate benefit of a PFS is *not*, they should understand what it *is*—the higher-order value of directing research efforts and resources appropriately and of maximizing the scientific value of clinical research. In this way, a decision either to accept or to decline participation will have a sound epistemic basis.

Therapeutic misconception may arise in somewhat different ways in pilot studies vs non-randomized feasibility studies. As pilot studies are designed to resemble the main trial in a number of respects, misunderstanding as to their capacity to produce evidence of generalizable treatment effectiveness may be pronounced. In a non-randomized feasibility study, however, this problem might be mitigated, insofar as there is less resemblance to a main trial. Notwithstanding this, another countervailing feature of feasibility studies may potentially widen the gap between assumed and actual evidence of clinical effectiveness. Many of the elements that might inform subsequent clinical management may simply be missing from a non-randomized feasibility study. For example, if only one intervention is delivered, in order to determine treatment fidelity or assess its acceptability to participants, the absence of a comparator intervention will prevent useful information being obtained on an appropriate choice between different treatments.

3.2 | Therapeutic misestimation

Therapeutic misestimation may also take a distinct form in PFSs. One way in which it may manifest itself relates to the intervention included within a pilot or feasibility study. In a main trial (eg, a phase 3 or phase 4 trial), the interventions tested will normally have been fully refined in terms of their individual efficacy. In a PFS, this may not be the case, as one of its objectives may be to optimize the nature, dose, frequency or method of delivery of an intervention. However, participants in these studies may wrongly assume that the study treatments, one of which they will receive, have previously been optimized in the same way as prior to a main trial. They may appreciate that the *relative* effectiveness of the study treatments is as yet undetermined, but they will quite probably assume that the *absolute* effectiveness of each of them has largely been established. In this way, the overestimation of benefit that is part of therapeutic misestimation may be compounded in a PFS if its objectives include the development of the study interventions.

Another respect in which therapeutic misestimation is troublesome relates to perceptions of possible benefit through modification of treatment. In some situations, participants may understand that a trial is not concerned with individualized treatment selection, but may nonetheless anticipate that they will benefit from what is learned from the trial data, through alterations to their treatment regimen. Whilst this may not be the case in clinical trials centred on illnesses with a rapidly evolving trajectory or those evaluating 'one-off' surgical procedures—where participants have little or no opportunity to benefit clinically from the knowledge gained at the end of the study—in the case of chronic diseases participants' own clinical care may subsequently be informed by the trial's findings. However, as gauging treatment effectiveness is not an appropriate goal of PFSs,[2,3] there is little likelihood of the participant's own future clinical care being directly influenced by the results of these studies. This must await the results of any subsequent main trial. Accordingly, if a participant anticipates this type of clinical benefit from enrolling in a pilot or feasibility study, the fact that treatment effectiveness will not be informed by such a study may bring about a misestimation of benefit. This differs somewhat from the traditional construal of therapeutic misestimation in a conventional trial; there, the misperception centres principally on how *much* clinical benefit can be expected through taking part, whereas in PFSs it relates more to the *possibility* of clinical benefit (Table 2).

3.3 | The issue of equipoise

Certain feasibility objectives—such as estimating the consent rate or the degree of loss to follow-up, or gauging clinicians' willingness to

randomize their patients, or assessing the effectiveness of blinding—will normally require a randomized pilot study using the two or more interventions that would be tested in the main trial. This in turn will require a consideration of equipoise—the extent to which, at the outset of a study, the individual investigator (in the case of individual, or theoretical, equipoise) or the clinical community (in the case of clinical equipoise) is genuinely unsure of the relative merits of the interventions concerned.[36] Clinical equipoise does not require an even split of opinion in the clinical community, merely that each of the alternative interventions is favoured by some portion of this community for the disease in question.[37]

Patients' uncertainty as to the investigator's treatment preferences often underlies their decisions regarding participation in clinical trials.[38-41] This suggests that an understanding of equipoise is relevant to such decisions regarding consent, and the investigator will therefore often seek to provide such an explanation. Herein lies a particular challenge in the specific case of randomized pilot studies. As participants are being asked to agree to being allocated to one of two or more treatments, investigators face the task of explaining a belief in the equivalent effectiveness of these interventions—a challenging task at the best of times.[42,43] However, they must at the same time make it clear that the goal of a pilot study is *not* about determining the relative effectiveness of the treatments involved. Both of these considerations—the presence of equipoise and the specific purpose of the study—are likely to be relevant to a participant's decision on whether to consent,[35,38] and should therefore be communicated. However, while these considerations are conceptually distinct, they may be hard to reconcile in the participant's mind—'is this study to do with treatment effectiveness or is it not?'—and may thereby compound the difficulties associated with therapeutic misconception.

4 | PRACTICAL CONSIDERATIONS

The foregoing discussion, and the fact that PFSs are likely to be unfamiliar to many potential participants, have some practical implications for the gaining of consent. A specific requirement is to ensure, as far as possible, that participants understand not only that PFSs have goals related to research rather than clinical care, but also that these research goals are only indirectly related to improving clinical practice. Equally, irrespective of their appreciation of the scientific—rather than clinical—orientation of the study, an attempt should be made to provide participants with an appropriately calibrated understanding of the nature and magnitude of any benefit or harm that they might incur through participation. With specific respect to pilot studies, their resemblance to a conventional trial—and any explanation given of the idea of therapeutic indifference that underlies equipoise—should not lead participants to think that the aim of these studies is knowledge that can be applied directly to clinical care and to base their consent on this assumption. Similarly, with non-randomized feasibility studies, it needs to be highlighted to participants that the design and purpose of such studies allows for little in the way of direct clinically relevant insights for either themselves or other patients.

For both pilot and feasibility studies, the fact that a subsequent main trial may not take place needs particular emphasis.[2] It may also be important for participants to realize that, in some instances, consenting to take part in a pilot or feasibility will preclude them from participating in a subsequent main trial for which they might otherwise be eligible if, for clinical or methodological reasons, this later trial requires 'first-time' participants—the foreclosure of this future opportunity would likely be material to their present decision. Equally, patients should be clear as to the alternatives to participating in a PFS, in terms of treatment they would thereby receive, in the same way as in a main trial. This explanation requires their understanding of the extent to which clinical benefit could be expected from participating in the study—which, as we have seen, might be overestimated.

These are, however, challenging tasks, given trial participants' generally poor comprehension of the benefits and harms outlined in the consent process[44] and the empirical difficulties of securing understanding and recall.[16,42,45,46] This suggests that important aspects of PFSs that may not readily be grasped by potential participants should be actively explored with them, rather than simply being stated in consent documentation.[47] Asking participants to state their own understanding or expectations of the study at the outset may help.[48] In this way, the potential misperceptions discussed earlier may be uncovered and clarified.

Such discussion should, however, be handled carefully. Based on an ethnographic study of the consent process, Instone et al[49] suggest that terms such as 'treatment trial'—used by investigators to participants and to one another—may reinforce the therapeutic misconception among all parties, and in particular the misperception that PFSs are concerned with testing clinical effectiveness. In an earlier study, Bamberg et al[50] argue that in the process of recruiting patients to clinical research, investigators may speak in two different 'voices' at the same time—that of health care and that of research—such that the participants 'may misconceive the treatment of illness and the research project as being the same thing'.[50,p. 177] Investigators should therefore be mindful of the complex linguistic phenomena underlying what potential participants say and what they interpret from what they hear. These complexities may revolve around a problem of multiple speakers (participants may receive, from different individuals, conflicting messages around issues such as probability and therapeutic benefit), a problem of semantic ambiguity (what participants and investigators understand by what they say or hear may differ, such that they may be asking or answering different questions), or around a problem of pragmatics (the illocutionary purposes that underlie communication, such that what a participant is trying to *achieve* by a statement is a separate issue from its ostensible *meaning*).[51]

It follows that helping participants towards an appreciation of what a pilot or feasibility study involves, and which aspects are important for a decision to either give or refuse consent, does not rest simply on providing fuller or more detailed information. This has the danger of becoming a 'deficit' approach that locates the problems of misperception solely within the participant. As Mathews et al[52] indicate, 'there are two individuals, perspectives, and understandings in

each interaction, rather than one individual (the patient) with imperfect understanding'.

5 | ISSUES RELATING TO ETHICAL APPROVAL

Given the differences in purpose between main RCTs and PFSs, research ethics committees should ensure that their expectations, and what they require of investigators, are differentiated accordingly. First, the committee should ensure that participant information sheets for PFSs are clear that the study objectives are those of feasibility rather than of treatment evaluation, and do not foster or reinforce the misperceptions outlined above. Second, and relatedly, information sheets should indicate clearly what type of clinical or broader scientific benefit the study intends to provide. Third, committees should consider any provision made for sharing of research results with participants, and for communicating such plans to participants in the consent process. This may involve either the aggregate findings of a study, or individual-level results to particular participants. Notions of respect for persons and beneficence suggest that this is a prima facie ethical obligation (with some caveats in respect of individual-level results).[53-55] If so, it should be no less an expectation in PFSs than in main trials. On this basis, the committee should be satisfied that participants in a PFS will be told (or at least given the option to be told) of any subsequent decision made on progression to a main trial, as their initial decision to participate may have been premised on assisting this outcome.

Fourth, a broader consideration is that, as the results of a PFS may have relevance beyond the specific trial that the investigators propose subsequently to conduct, the committee may expect to see clear plans for dissemination of the results of the study. Finally, given that the benefit derived from PFSs is defined in terms of a subsequent main trial, the committee should be satisfied not only that the criteria on which progression to the main trial would occur are appropriate, but also that the main trial is scientifically robust on its own terms. These are, at least partly, independent considerations, given that not all aspects of the viability of a main trial can necessarily be addressed within a PFS. It follows that the committee should receive sufficient information on both the PFS and the subsequent study that is intended.

6 | CONCLUSION

If consent 'has moral power whenever the consent is voluntary, informed and decisionally competent',[56,p. 92] adequate disclosure by the investigator and adequate comprehension by the participant are crucial.[16] However, differences in the aims of PFSs from those of main trials, and the fact that these aims may be poorly understood by potential participants, create specific challenges. In particular, misperceptions such as therapeutic misconception and therapeutic misestimation require some degree of re-interpretation. A careful approach to the consent process, and specific attention to both the manifest and the latent meaning of what is communicated in both directions, may help to mitigate the challenges that are posed and give participants' consent an appropriate moral weight in legitimizing the investigator's actions.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during this study.

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