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Should desperate volunteers be included in randomised controlled trials?

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Should desperate volunteers be included in randomised controlled trials? [This is a second resubmission of paper MEDETHICS/2005/014282 in the light of reviewers' comments]

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**Should desperate volunteers be included in randomised
controlled trials?**

Abstract

Randomised controlled trials (RCTs) sometimes recruit participants who are desperate to receive the experimental treatment. Some claim this practice is unethical for at least three reasons. The first is that the notion of equipoise, which is often used as a justification for running a RCT, is subjective and value-based. Desperate volunteers are clearly not in equipoise and it is their values that should take precedence. The second is that clinicians who enter patients onto trials are disavowing their therapeutic obligation to deliver the best treatment to patients; they are following trial protocols rather than delivering individualised care. Research is not treatment; its ethical justification is different. Consent is crucial. This leads to the third reason: desperate volunteers do not give a proper consent; they are, in effect, coerced. We begin our reply by advocating a notion of equipoise based on, first, expert knowledge and, second, widely shared values. Where such collective, expert equipoise exists there is a *prima facie* case for a RCT. Next we argue that trial entry does not involve clinicians' disavowing their therapeutic obligation; individualised care based on whims and fancies is not in patients' best interest. Finally, we argue that where equipoise exists it is acceptable to limit access to experimental agents. In the cases desperate volunteers are not

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coerced because their desperation does not translate into a right to receive what they desire.

Introduction

The following quotes come from people involved in a recent neonatal randomised controlled trial (RCT) who were interviewed as part of a qualitative sub-study.¹ The first is from a mother who gave consent:

“I remember saying to him, ‘Oh great, great, like some effing placebo’ is what I said to him; so, no, I totally understood that idea, so I was kind of glad [because the baby received active treatment.]”

The second is from a clinician:

“... it’s easy for someone to put a gun to your head and say it’s your decision. And the gun being that their baby is born and is damaged and is needing a lot of resuscitation and here we are saying, look there’s a trial happening and this is the only thing available, and there’s nothing else available...”

The quotes illustrate the desperate volunteer problem: RCTs sometimes recruit patients (or their proxies) who are desperate to be placed on one particular arm of the study. They consent because the treatment they desire is available only through that study and are disappointed if randomised to the “wrong” arm. The problem arises usually where the RCT is investigating a new treatment into a serious or terminal illness where current treatment options are limited.

Some argue directly that it is unethical to recruit desperate volunteers to RCTs.^{2;3} Others imply it is unethical by arguing that it is right to recruit only participants who are indifferent between treatment arms.⁴ The issue has been discussed most in relation to patients with serious and terminal illness including Human Immunodeficiency Virus (HIV), Acquired Immune Deficiency Syndrome (AIDS)^{3;5} and variant Creutzfeldt-Jakob disease (vCJD).⁶ In the United Kingdom, parents of two young men with vCJD challenged in court the decision of doctors not to use a drug that was still in the early (animal) research stage.⁶ This opens the possibility that desperate volunteers could similarly challenge a placebo-controlled RCT.

In this article we defend the recruitment of desperate volunteers into RCTs provided the condition of equipoise is met. As this is a term used in different ways we first need to set out what we mean by it. We then set out our argument in more detail and examine it in relation to the arguments of those who believe it unethical to recruit desperate volunteers. (Throughout this discussion we shall use the term “equipoise”; others prefer “uncertainty”.^{7;8} This distinction makes no difference of substance here.)

Equipoise

It is often said that for a RCT to be ethical a condition of equipoise must prevail. Roughly this means that there should be no grounds to prefer any particular arm of the trial. Early discussion of equipoise

focused on whether the condition should pertain to each individual clinician.⁹⁻¹¹ The problem is that clinicians often have hunches, anecdotes and small trial evidence that lead them to prefer a treatment arm. Freedman argued that it is ethical to conduct such a RCT provided that a condition of collective (or what he termed “clinical”) equipoise exists, that is, where there is sufficient doubt in the clinical community as a whole.^{12;13} The notion of equipoise we intend to use in our argument is akin to Freedman’s collective equipoise (although our emphasis on the value element within equipoise is not matched in Freedman’s own account). Now let us turn to problems in applying this notion in the justification for recruiting desperate volunteers.

Criticism 1: Equipoise is subjective and value-based

Being in equipoise implies being uncertain which of two or more treatments is better and, therefore, which to choose. However, there are ambiguities here in the notions of uncertainty, being better and choice. Let us take these in turn.

1. Uncertainty

RCTs are powered to avoid error to a certain degree. Typically they are set up to show an effect to a level where $p \leq 0.05$. This means that the researcher can say, roughly, that she will be wrong on 5/100 occasions if she concludes that there is an effect. However, setting the p-value at this level seems arbitrary. Why not choose, say, $p = 0.07$ or

0.03 (where the researcher can say she'll be wrong on 7/100 or 3/100 occasions if she concludes there is an effect)?

Gifford tackles this question by drawing a distinction between policy decisions and present patient decisions.¹⁴ One may not have sufficient evidence for a treatment to recommend it as part of policy guidelines; nonetheless, there may be enough evidence, particularly trends from a RCT, to prefer a treatment arm for one's particular patient. Gifford suggests that clinicians may have a different threshold for initiating a treatment for a particular patient and for making a policy recommendation. Any desperate volunteer is likely to take a "particular patient" view, desiring the treatment even though it is not yet proven fully enough for a policy decision. Furthermore, in reality, the equipoise is not balanced concerning the treatment about which evidence of effectiveness is sought, since phase III RCTs only receive funding if there is some early phase trial or case study evidence which suggests that the experimental arm might be more effective in treating an illness.¹⁵⁻¹⁷

2. Being better

A treatment's being "better" is not a matter of fact, it is a judgment based on the facts.¹⁸ For example, it might be that, say, mastectomy offers a slightly higher chance of survival at five years than does lumpectomy. However, mastectomy is more disfiguring. Which is thought "better" will depend on the individual's values: some will

prefer the greater chance of survival, others the less disfiguring surgery. If values are crucial to equipoise then surely it is the values of participants that matter most; they should be in equipoise if their participation is to be ethical.^{4;19}

3. Choice

Uncertainty about a treatment's efficacy does not necessarily translate to uncertainty about whether one would choose it. Even if one had no idea whether a treatment might turn out to be efficacious one might still want it. Typically this would happen where one's current situation is dire and a treatment offers hope, distant though it may be. These ambiguities render equipoise incapable of providing justification for RCTs. Indeed, on one account, this was Fried's point when he originated the term "equipoise".²⁰

Criticism 2: Equipoise disguises the therapeutic misconception

The opponents of equipoise say that when clinicians enter patients into RCTs they disavow the therapeutic obligation to recommend and deliver the best treatment. This is because such clinicians no longer deliver individualised care. Instead they are committed to a trial regime. This has a number of effects, for example:

- Such regimes are focused on particular endpoints that are of import to the researchers but may not be of the same import to the patient. A clinician might, for example, see that some side effects are particularly important to a patient (as tremor would

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be to a concert pianist, for example) and can treat accordingly.

In a RCT, the patient's values are set to one side.

- A clinician committed to a trial regime cannot make subtle alterations in dosage.
- She cannot follow her personal belief that the balance of evidence favours one treatment rather than another.
- Participants in RCTs may be subject to (clinically) unnecessary additional procedures.
- Participants in RCTs may receive inert and pointless placebos.

Opponents of equipoise argue that its use reflects and reinforces a false identification of research with treatment (the “therapeutic misconception”).^{10;11;21-25} Being “in equipoise” is supposed to reflect a clinician's being unsure of the best action for a patient: the options include trial entry or individualised care. Equipoise, insofar as it means anything, simply reflects a general lack of knowledge of the effects of treatment on a whole class of patients; in practice, clinicians will always have some notion of which course of action they would prefer to take with a particular patient, including the need for subtle alterations of dose and so forth.

Thus, because equipoise is subjective and value-based it cannot provide an objective standard that justifies the running of RCTs. Furthermore, equipoise amongst clinicians about the effectiveness of a treatment cannot justify disavowing the therapeutic obligation. RCTs

can still be justified, but their justification will be based on a different set of principles to those of treatment.^{10;26;27} Where beneficence and the best interest of the patient are central to treatment, autonomy and informed consent are central to research. It is permissible to disavow the therapeutic obligation provided the risks are acceptable and, especially, provided the patient gives informed consent.

Criticism 3: equipoise is used to justify coerced trial entry

Desperate volunteers provide a vivid illustration of the inadequacy of equipoise. To desperate volunteers, the setting aside of the therapeutic obligation is clear; they strongly believe there is a better alternative than the one being presented to them by their clinician. Similarly, the failure of fully informed consent is clear; their consent is not truly voluntary; they are effectively coerced into trial entry. Their subsequent anger at this injustice is shown by their campaigns and court cases.⁵

We shall argue that at least in some cases it is not unjust to recruit desperate volunteers. We do this by tackling the three criticisms.

Reply to criticism that equipoise is subjective and value based

Our first task is to suggest a conception of equipoise that is robust enough to do some work in justifying RCTs. The criticism that it cannot do this arises from three ambiguities.

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The first ambiguity concerns uncertainty: the emergence of trends undermines equipoise for present patient decisions before we reach the level of statistical certainty necessary for policy decisions. However, Yusuf looked at the data from a number of studies into cardiac treatments.²⁸ Early trends were often deceptive. In one study, aspirin appeared little better than placebo as a treatment following a heart attack when 3000 patients had been recruited. It was only when 16,000 had been recruited that the clear trend favouring aspirin emerged. More strikingly, a study of atenolol following heart attack had a clear trend suggesting it was harmful that did not reverse until 300 deaths had occurred and several thousand patients been recruited. Yusuf's finding is repeated elsewhere.^{29;30} This suggests that Gifford is wrong to postulate a yawning gap between the evidence ethically required for decisions about individual patients and that required for policy decisions. If doctors in the atenolol example had made "particular patient" decisions then, first, the trial may have collapsed and never have uncovered the truth and, second, the particular patients themselves would have been harmed. Turning to the statistical limits set in trials, these are not arbitrary but rather are those that experience suggests lead to reliable results in well run RCTs; those that allow for early misleading trends.

Hence there is no reason necessarily to expect clinicians to form strong preferences for a treatment for their individual patients before they form an opinion about its use for patients in general. Indeed,

there is something intuitively odd about the idea that they would. From this point we are able to develop a notion of collective equipoise that is more than the headcount of personal clinicians' opinions, one that is best represented by the Data Monitoring and Ethics Committees (DMEC). They have an overview of all the data and are able to judge this data against the level of statistical proof required by the protocol. Whilst the DMEC is in equipoise, collective equipoise can be said to obtain.

What of the second ambiguity concerning the meaning of a treatment's being better? The DMEC might be in equipoise over certain endpoints but these might not be of import to the patient. However, this disjunction in values is likely to be rare. In most cases, the endpoints of value to researchers, such as disease-free survival, will also be of great value to patients. Were this not the case then the desperate volunteer problem would be echoed in many RCTs; for example, it would be commonplace for people to complain about the group into which they are randomised. There seems no evidence for this.³⁰ In those rare cases of potential significant disagreement over the value of endpoints researchers will need to ensure that participant equipoise is present (as in the mastectomy/lumpectomy and concert pianist examples; also see a case described by Lilford³¹). In the case of desperate volunteers, however, their concerns are with survival and quality of life; these are matters which researchers will hope the experimental agent tested in the relevant RCT will improve.

We believe this gives us enough to posit a robust conception of clinical equipoise. It is represented by experts conceiving and funding bodies peer-reviewing trials before they start and the DMEC and TSC during a trial. It is based on uncertainty about the effectiveness of one or more trial treatments around endpoints that are likely to be widely shared by clinicians and patients. Where it exists, there is a *prima facie* case for a RCT.

Clearly this “expert view” account of collective equipoise does not equate to having no idea about the efficacy of treatments being tested in a RCT. RCTs begin with a hope that a new treatment will be effective. This hope is based on evidence from other sources (such as phase I and II trials) and from positing a plausible mechanism. However, such evidence is limited both statistically and in terms of evidence of treatment effectiveness in the clinical situation. RCTs aim to look at a wider range of endpoints including compliance, unexpected side effects and the chance that early indications of effectiveness were rogue results. It is this whole picture that will determine whether or not a new treatment is deemed an improvement or not. And the judgment of this will be a function of values. For example, a treatment may extend life but at the cost of an awful side effect, such as uncontrollable nausea. Thus, when setting up a RCT clinicians may have strong grounds to believe a treatment is more effective in terms of a particular endpoint; what they don’t know is its value overall.

Hence, the role of values in collective equipoise means that equipoise does not equate to epistemological uncertainty. This is seen in another way: sometimes clinicians can be epistemologically unsure of the effectiveness of a treatment but not be in equipoise about its use. An example of this is the argument that a RCT is unacceptable in relation to the use of Quinacrine in vCJD because the prognosis on the best alternative treatment is so dire.³² In situations such as these the clinicians are in agreement with the desperate volunteers; they are not in equipoise. Hence it does not follow that wherever there is an experimental treatment whose effectiveness is unknown there is collective equipoise. *Ex hypothesi* lack of knowledge only justifies a RCT where it exists alongside collective, expert equipoise.

However, perhaps this only reinforces the problem of the third ambiguity. It remains the case that epistemological uncertainty is not necessarily matched by uncertainty of desire and choice. Whilst the values of clinicians may leave them in equipoise, the values of desperate volunteers do not; they will clutch at straws. Does collective equipoise justify limiting their options such that the straw they are forced to clutch is RCT entry? Proponents of the idea that research is a fundamentally different activity to treatment would say it is not. The only possible justification for RCT entry is informed consent, something absent where consent is coerced. Hence we must look at the notions of therapeutic obligation and misconception.

Reply to criticism that equipoise disguises therapeutic misconception

Our response to this criticism is that there is no necessary clash between, first, delivering the best available treatment for a patient and, second, resolving uncertainty about treatment. An aim of well-designed trials is for RCTs to resolve uncertainty by delivering the best treatment.³³ In making this claim it is crucial to separate it from a different dispute about the use of placebos. Much discussion of therapeutic misconception originates in the United States where, whilst the regulatory Food and Drug Administration (FDA) stipulates new drugs may be tested against a known effective alternative³⁴ there is a tendency to prefer placebo trials in such situations.³⁵ Like many, we believe this to be unethical and to contravene the Helsinki accord.³⁶⁻³⁸ Entering patients onto a trial using placebos in this way would certainly violate the therapeutic obligation. However, when correctly used, placebos represent the best alternative treatment.¹⁷ Provided this is so, clinicians unsure of which treatment is best are acting both in the best interest of the patient and in the interest of ending uncertainty when they enter patients into RCTs.

What, though, of the claim that clinicians entering patients into RCTs cannot give individualised care, for example, by subtly altering treatment regimes? Our response is to ask the basis of this care. Presumably the RCT regimen the clinician wishes subtly to alter is

based upon the best evidence available at the time; what else does she know? The claim that clinical judgment is impaired by RCT regimens seems to parallel the claim that such judgment is impaired by evidence based medicine (EBM) in general.³⁹ Hence the response to both claims can be the same: ‘Psychological research on problem solving and decision making has contributed to these developments [that is, evidence-based medicine and decision analysis] by showing that expert clinical judgment was not as expert as we had believed it to be’⁴⁰ (p. S135). There is plenty of evidence showing the flaws in non-evidence based clinical judgment;^{41;42} participants in RCTs are unlikely to be harmed by being deprived of it. There may be rare occasions when particular patients have features that make them exceptional, as in the concert pianist example. However, most of us hover around the average and can often be treated on shared features: try telling an actuary that we are all individuals.⁴³ The bizarre outcome of the “individualised care” argument is that, to paraphrase Smithell’s famous dictum, it appears unethical to give an unproven treatment to half my patients, but ethical to give it to all of them.⁴⁴

To summarise: we have suggested that equipoise can be robust enough to provide a *prima facie* case for a RCT. We have denied that RCTs necessarily involve a disavowal of the therapeutic obligation. Nonetheless, a central element of the case against the involvement of desperate volunteers in RCTs remains. This is that they are effectively coerced into taking part. Relatedly, given that equipoise is a function

of values, shouldn't the values of participants prevail through the mechanism of (voluntary) consent?⁴ It is to this we now turn.

Reply to criticism that equipoise is used to justify coerced trial entry

In the first place, we should note that our argument constitutes a rebuttal of the "difference position": we have argued that therapeutic research is not fundamentally different from other therapy. As such, it is governed by the same principles, including attention to the best interest of patients. It follows that one way of viewing the difference in equipoise between clinicians and desperate volunteers in RCTs is as one to do with what constitutes best interest. Why might clinicians be in equipoise in situations where desperate volunteers clearly are not?

The Quinacrine example is a case where the prospect for the patient is dire and the potential for harm from the experimental treatment almost non-existent. Such cases are not typical even in terminal or life-threatening cases. New treatments or procedures that aim to delay death, reduce the occurrence of disability and so forth can have unexpected and unwanted effects. A treatment might delay death but create unbearable nausea, for example. There is almost never a choice between, say, immediate death and a possible miracle cure. Thus one reason for the difference between clinicians and desperate volunteers is that the latter's hope for a cure obscures the reality. As one parent we spoke to put it,

“We fully understood what he wanted to do in terms of treatment ... we fully understood the side effects if there was going to be any, or the risks involved, but obviously whatever anyone tells you all you listen to is that your child is damaged ...”

Typically, from the standpoint of collective equipoise it will be important to discover whether treatments are effective, to allocate resources effectively, to avoid long-term side effects and so forth. From the standpoint of the desperate volunteer these considerations will be of little import: they will clutch at straws to avoid the harm they face now. RCTs limit their options; the straw they are forced to clutch is trial entry. Is this constrained consent justifiable?

Consent to research is generally thought to have two main functions. The first is the protection of the patient against either exposure to a harmful treatment or denial of a therapeutic one. Historically this is the most important function. The Nuremberg Code and Helsinki declarations developed from the exposure of horrific clinical trials that would never have taken place had voluntary consent been respected.^{45;46} The second function is protection of and respect for the participant's autonomy. This function has taken on increasing

importance as our culture has moved away from endorsing medical paternalism.

Our argument thus far concerning desperate volunteers enables us now to set aside the first function of consent; we do not defend RCTs that harm patients through exposure to or denial of experimental treatments. Thus the main objection to the recruitment of desperate volunteers is related to autonomy: researchers are manipulating options in such a way as to ensure that desperate volunteers consent to take part in RCTs. Such manipulation is generally taken to undermine the voluntariness of consent.⁴⁷ It may even constitute coercion. This alone is enough to make it wrong.

However, we do not live in a libertarian society in which autonomy is considered an overarching good. Throughout Western countries people are denied access to therapeutic treatments they desire in a number of ways, such as when the treatments are available on prescription only, are illegal or unaffordable. If one believes this to be sometimes or always acceptable then, by extension, one must believe in the principle that desire for a therapy does not translate into a right to have it. In the case of desperate volunteers, these are patients who strongly believe in the efficacy of a treatment but who lack the evidence for that belief. Their strength of belief and desire does not translate into a right to receive that treatment. The terms “coercion”

and “manipulation of options” do not apply here because patients are not wronged when denied access to unproven treatments.

A critic might respond that such patients are wronged because they are harmed psychologically; desperate volunteers are often upset to be presented with limited options and *ex fortiori* disappointed when allocated to the control group. The wrong occurs if the RCT is unnecessary; the relevant information could be uncovered through other means such as alternative trial designs using patient preference models of consent^{48;49}, historical controlled, and epidemiological studies. Alternatively, RCTs could be run provided that patients had the option of receiving the experimental treatment outside of the trial.

We accept that alternatives to RCTs should always be considered in order to avoid recruiting desperate volunteers. However, the option of providing experimental treatments outside of the trial would be acceptable only where most potential participants are not desperate volunteers. Desperate volunteers will always opt for the experimental treatment. In some situations almost all potential participants will be desperate volunteers, as was the case in the trial from which we have taken quotes for this paper. A similar argument would undermine patient preference designs: desperate volunteers will always prefer the experimental arm of the trial. Historical controls deliver poor quality data: a treatment effect would have to be very large with no obvious compounding factors for one tentatively to conclude that it is effective.

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Hence if one were to have a treatment that had a useful but not spectacular effect in a desperate situation, one would have no way of discovering this fact. The weaknesses of epidemiology are also well documented, a recent example being where RCTs revealed the falsity of the epidemiological studies suggesting the protective effect of hormone replacement therapy.⁵⁰

There is here a consequentialist counter-argument;⁵ desperate volunteers will find ways around the restrictions imposed by RCTs by, for example, mixing their drugs together to ensure they get at least some of the active treatment. RCTs will then be less scientifically valid than other approaches. This is perhaps more a practical than a moral consideration. In most hospital based trials it could not occur. However, it should focus the minds of the researchers to the moral issue. Our belief is that, in the desperate volunteer situation, if the question can be answered by an alternative to the RCT then it should be. If an RCT is impractical because of desperate volunteer resistance then, in effect, the question cannot be answered to an extent that would undermine collective clinical equipoise.

Hence there are two types of argument in favour of recruiting desperate volunteers to RCTs despite the fact that they would desire an alternative were it made available. The first is, loosely, deontological: that people do not have a right to unproven therapy. (By “unproven” we mean that clinical equipoise exists in relation to

that therapy and the existing best alternative[s].) The second is more consequentialist: disallowing RCTs where there are desperate volunteers would make it difficult to generate and test new treatments in areas such as neonatology and end of life care where desperation is commonplace.

Closing remarks

Collective, expert equipoise is a *sine qua non* for setting up a RCT. In other words, there must be doubt in the clinical community about whether a new treatment is better overall than standard treatment. Personal equipoise on behalf of clinicians and participants is desirable and will be present in many cases. However, personal equipoise should be seen as a *prima facie* criterion only.

As a *prima facie* criterion, personal equipoise is defeasible. Collective equipoise trumps personal equipoise and, where it exists, there is a case for a RCT. Nonetheless, the *prima facie* criterion sets an important limit. If possible, trials should avoid recruiting desperate volunteers.³¹ However, as we have argued, there will be situations in which scientific investigation will require randomisation and the recruitment of desperate volunteers. In those situations where desperate volunteers are recruited we should seek to minimise the negative effects, for example by using unequal randomisation in favour of the experimental arm in the trial design.^{51;52}

Conclusion

It can be ethical to run RCTs that recruit desperate volunteers provided there is collective, expert equipoise, throughout the course of the trial (as assessed by the DMEC and TSC).

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Desperate volunteers