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A Framework for Analysis of Research Risks and Benefits to Participants in Standard of Care Pragmatic Clinical Trials

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Abstract

Background/Aims—Standard of care pragmatic clinical trials (SCPCTs) that compare treatments already in use could improve care and reduce cost but there is considerable debate about the research risks of SCPCTs and how to apply informed consent regulations to such trials. We sought to develop a framework integrating the insights from opposing sides of the debate.

Methods—We developed a formal risk-benefit analysis framework for SCPCTs and then applied it to key provisions of the U.S. federal regulations.

Results—Our formal framework for SCPCT risk-benefit analysis takes into account three key considerations: the *ex ante* estimates of risks and benefits of the treatments to be compared in a SCPCT, the allocation ratios of treatments inside and outside a SCPCT, and the significance of some participants receiving a different treatment inside a SCPCT than outside the trial. The framework provides practical guidance on how the research ethics regulations on informed consent should be applied to SCPCTs.

Conclusions—Our proposed formal model makes explicit the relationship between the concepts used by opposing sides of the debate about the research risks of SCPCTs and can be used to clarify the implications for informed consent.

Keywords

Comparative effectiveness randomized control trials; pragmatic randomized control trials; informed consent; research risk analysis; research ethics

Introduction

Pragmatic clinical trials in real-world settings that compare widely used and accepted treatments (i.e., pragmatic trials comparing ‘standard of care’ treatments; hereafter referred to as standard of care pragmatic clinical trials or ‘SCPCTs’ for brevity) have been heralded as an opportunity to improve care and reduce costs.¹ However, there are concerns that the

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usual regulatory oversight, including lengthy consent procedures, poses potential obstacles to such research.²⁻⁴ Given these SCPCTs compare ‘standard of care’ treatments, with the only research component being randomization in some cases,⁴ there seems to be little or no additional risks to research participants. Since minimal risk studies are candidates for less restrictive rules, such as a waiver or alteration of informed consent, there is great interest in examining SCPCTs’ risk status.²

Commentators have been divided over whether SCPCTs pose incremental research risks over risks of clinical care. Some have noted that “there is no additional risk or burden to patients, and the quality and experience of patient care are minimally affected [when a trial evaluates] widely used and well-tolerated interventions.”⁵ In support of this position, commentators have appealed to two considerations: 1) that the *ex ante* estimates of the relative risks and benefits of the treatments to be compared are equivalent—as reflected in, for example, the statement that “[t]here are a number of such products..., with substantial differences in price but without substantial differences in efficacy or side effects”⁶; 2) that the allocation of treatments inside and outside a trial is equivalent—“to the extent that there is widespread practice variation, the resulting allocation of treatments will look very much like the allocation that will result from randomization.”^{2, 7}

However, some commentators have been more skeptical of the claim that “there is no additional risk or burden to patients” in SCPCTs.⁸ This view emphasizes the implications of patients receiving one standard treatment outside the SCPCT but a different standard treatment inside the SCPCT. The Draft Guidance issued by the Office of Human Research Protections states that research risks can exist even when all of the patients in a trial receive widely accepted treatments because in a SCPCT, at least some subjects will receive an intervention that is “different from the standard of care that they would have received if they were not participating in the study” and “there might be different risks associated with those standards of care.”⁸

Each of the three considerations—the relative *ex ante* risk-benefit estimates of the treatments to be compared; the allocation ratios of treatments inside and outside a SCPCT; and the implications of some patients receiving one treatment in the clinical setting and a different treatment in the SCPCT—individually represent ethically important considerations but their relationships to each other have not been adequately explored. There is a pressing need to understand research risks involved in SCPCTs and their implications for informed consent. But a consensus seems unlikely unless these driving intuitions of contrasting viewpoints are evaluated and given due consideration within a single framework. We propose a formal framework in order to make explicit these implicit ethical considerations and the relationships between them. Its primary purpose is to examine the currently competing proposals for evaluating the risk-benefits of SCPCTs. As such, the framework is not put forward as a quantitative algorithm to be used by, for example, institutional review boards. Nevertheless, it will be able to provide useful conceptual guidance in evaluating SCPCTs.

A framework for analyzing incremental research risks of SCPCTs

Imagine a SCPCT involving two widely accepted treatments A and B, and assume that they are the only ones used for treating disease X. For simplicity, we consider only SCPCTs that compare two treatments. The model described in Box 1 determines the *ex ante* estimated welfare difference for research participants, as compared to the clinical setting, attributable to a given SCPCT.

W_A and W_B are *ex ante* estimates of welfare that patients are expected to derive from receiving treatments A and B respectively. We use the term “welfare” to refer to both the likelihood and magnitude of an outcome. The outcomes can be clinical states (death, stroke, symptom severity, etc), utilities, or other ways of expressing welfare, as long as consistency is maintained. W_A and W_B are *ex ante* estimates based on the best evidence available prior to the SCPCT and do not presume *ex post* knowledge of actual results of the proposed head-to-head SCPCT. In fact, *ex post* results of the SCPCT could confirm, contradict, or leave uncertain the *ex ante* estimates.

Our model does not assume that all variables will be easily quantifiable, only that it is important to consider the relevant variables and their relationships in the overall risk-benefit analysis. The accuracy and precision of W_A and W_B will depend on available evidence. For example, SCPCTs that compare two widely known, FDA-approved drugs that have had some small head to head trials comparing them have a stronger evidence base regarding W_A and W_B than SCPCTs that compare two surgical or other procedural interventions that have only observational outcomes data with no direct comparisons. It is also possible that, despite widespread use of A and B, there is so little data that one cannot reasonably give a quantitative answer to whether W_A is equal to W_B . Even in such cases some form of risk-benefit analysis is necessary (if only based on expert clinical impressions or sparse suboptimal data) and our framework is useful in guiding this analysis conceptually.

Similarly, it will often be difficult to obtain a precise estimate of the treatment allocation probabilities of the treatments outside the trial [as represented by $P(A_o)$]. The estimate should be based on a reference class of patients that is as close as possible to those who will enroll in the SCPCT. For example, if a trial comparing two widely prescribed anti-depressants is proposed at a specific hospital, it may be possible to estimate the allocation ratio by examining the hospital’s prescription database. If the study is a multi-site national study, a weighted average across institutions or a national database could be used to estimate the probability of allocation. Again, in some cases, there may only be crude approximations. Just as in the cases where W_A and W_B may be difficult to obtain, our model points out the need to make explicit the limits of the approximations that must still be made in the overall risk analysis.

In the model, the overall *ex ante* estimated welfare difference (ΔW) can be unknown, zero, negative, or positive; for instance, there is no mathematical restriction to the estimated welfare of a SCPCT *exceeding* that estimated for regular treatment. Note that ΔW is only one component in determining whether a SCPCT is, all things considered, ethically justified as a scientific protocol. Our model focuses on ΔW for participants because it is the focus of

the current debate on SCPCTs. The ethical acceptability of any given SCPCT depends on additional considerations, including its social value, which are not incorporated in our model.

As an illustration, consider the following example. Consider a SCPCT comparing two treatments when the *ex ante* estimate of welfare for one is greater than that for the other and the allocation ratio inside and outside the trial are not the same. Suppose that these treatments are for a potentially disabling or fatal illness that is fairly prevalent for which there is only one shot at treatment. Treatment A is more widely used; treatment B is newer, extremely expensive, and not yet easily available but existing data show that B may be better than A (say, has 3% higher response rate). Although W_B is greater than W_A by a small margin, the evidence for the difference is not sufficiently robust (no head-to-head trial evidence) to recommend B over A in practice. The purpose of all randomized trials is to reduce uncertainty to some desired level and the value of a given amount of reduction in uncertainty will vary depending on the context. In this case, there is significant public health value in obtaining sufficiently robust evidence. Thus, the study may still be justified even though W_A and W_B are not equal.

Conditions under which $W=0$

The above model specifies that, for a given patient eligible for a SCPCT, the SCPCT creates no overall *ex ante* incremental welfare difference (i.e. $W=0$) relative to the clinical setting when one (or both) of the following conditions is met:

Equal Estimated Welfare: The *ex ante* estimates of welfare for A and B are the same, i.e., $W_A = W_B$.

Equal Probability of Allocation: The probability of receiving treatment A and B in the clinical setting is the same as that in the SCPCT, i.e., $P(A_i) = P(A_o)$.

The Equal Estimated Welfare condition may be what some have in mind when they describe SCPCTs in which “[t]here are a number of such products ...with substantial differences in price but without substantial differences in efficacy or side effects”⁶ and “equally well-supported treatment option that falls within the standard range of care.”⁹ Similarly, the Equal Probability of Allocation condition is what some commentators mentioned above may have in mind when they state: “to the extent that there is widespread practice variation, the resulting allocation of treatments will look very much like the allocation that will result from randomization.”^{2, 7}

Equal Estimated Welfare Condition and SCPCTs

Some SCPCTs will meet this condition but some will not. For instance, the United Kingdom Dermatology Clinical Trials Network compared the effectiveness of antibiotic prophylaxis (vs. no prophylaxis) for recurrent cellulitis.¹⁰ Prior to the trial, four randomized controlled trials had suggested possible benefits of antibiotic prophylaxis, although none of the studies were seen to provide definitive results, either because the sample size was small (2 studies) or because the benefits observed were statistically marginal (2 studies).^{11–14} Professional guidelines at the time recommended prophylactic antibiotic therapy.^{15, 16} The *ex ante*

estimates of welfare for prophylaxis was greater than that for no prophylaxis for a patient entering this study (i.e., $W_{\text{prophylaxis}} > W_{\text{no prophylaxis}}$).

Similarly, the Time to Reduce Mortality in End-Stage Renal Disease (TiME) trial compares the effectiveness of ‘normal’ and extended dialysis sessions. There are five observational studies showing survival advantage for extended sessions^{17–21} and one study that did not show survival advantage.²²

In addition, both SCPCTs described above pose an *overall* estimated welfare difference relative to the clinical setting (i.e. $W = 0$) because the Equal Probability of Allocation condition is also likely not met. In the cellulitis trial, the overall *ex ante* estimated welfare difference ($W_i - W_o$) may be negative because the consensus guidelines recommend antibiotic prophylaxis which therefore may be assumed to be more common in the clinical setting than in the SCPCT [i.e., $P(\text{antibiotic}_o) > P(\text{antibiotic}_i)$ and $W_{\text{antibiotic}} > W_{\text{no antibiotic}}$]. In the TiME trial, on the other hand, the overall *ex ante* estimated welfare difference is *positive* because the reverse is true [i.e., $P(\text{extended session}_i) > P(\text{extended session}_o)$ and $W_{\text{extended}} > W_{\text{usual}}$].

Equal Probability of Allocation: Any random patient’s perspective or a specific patient’s perspective?

Whether the Equal Probability of Allocation condition applies in a given situation can be answered in two ways. First, consider the perspective of a random patient. When the *de facto* allocation ratio in the treatment setting is the same as that in the SCPCT, the condition is met. This is not true for all SCPCTs, however, as seen above. In fact, some trials are conducted precisely because a larger proportion of patients use one of the treatments without convincing evidence that it is better than the other treatments.^{23, 24} For example, in the case of treatment for hypertension, hydrochlorothiazide is much more widely used than chlorthalidone, despite a larger evidence-base for the use of chlorthalidone, raising the question of whether a large SCPCT should be conducted.²⁵ If such a SCPCT allocates the two drugs in a 1:1 ratio, it would not meet the Equal Probability of Allocation condition, from the perspective of a random patient.

However, the question, “In a given SCPCT, does the $P(A_i) = P(A_o)$?” can also be answered from the perspective of patients who *would have* received A or B outside the SCPCT (for brevity, we will call this a *specific patient’s perspective*). The analysis from this perspective will produce different results than that for a random patient. Consider a SCPCT that poses no *ex ante* incremental overall welfare difference (i.e., $W = 0$) because the Equal Probability of Allocation condition is met [i.e., $P(A_i) = P(A_o)$] for any random patient, but the Equal Estimated Welfare condition is not met (i.e., $W_A \neq W_B$). For such a SCPCT, any random patient faces no *ex ante* estimated welfare difference inside or outside the trial. But suppose a specific patient Mr. A would have received treatment A in his doctor’s office; thus for Mr. A, the probability of receiving A outside the trial is 100%, i.e., $P(A_o) = 1$. If Mr. A enters the SCPCT, his probability of receiving A is instead $P(A_i)$, e.g., 50% (in SCPCTs with 1:1 allocation). In addition, since we are considering a SCPCT in which $W_A \neq W_B$, his individualized W is not 0. Depending on the relationship between W_A and W_B , Mr. A’s *ex*

ante estimated welfare could be lower or higher than receiving his usual treatment outside the trial. Regardless, Mr. A's *ex ante* estimated incremental welfare attributable to participation in the SCPCT is not that of any random patient. Indeed, from a specific individual's perspective, $P(A_i)$ will *never* equal $P(A_o)$ [or $P(B_o)$ for a Mr. B who would receive B outside the trial] will always be 1. Thus, from a specific patient's perspective, whenever $W_A = W_B$, there will always be an incremental *ex ante* estimated welfare difference between being inside and outside a SCPCT.

The two perspectives and preferences regarding W_A and W_B

Even when $W_A = W_B$ and a specific patient faces no estimated *quantitative* overall welfare difference, he may have *valuations* of welfare that diverge from a random patient's. For example, suppose in an oncology trial (in an extreme case for illustrative purposes) the best *ex ante* estimate of welfare shows that A potentially offers 20% chance of 10 months of progression free survival and B offers 50% chance of 4 months. In both cases, any random patient has *ex ante* estimated 2 months of progression free survival. For any random patient, there is no incremental welfare difference between being in the SCPCT and outside it. However, a specific patient may have preferred and chosen A (or B) in the clinical setting. In such cases, there is no *quantitative* welfare estimate difference between being inside versus outside the SCPCT but a meaningful preference or valuation—of welfare considerations—for A or B exists for specific individuals.

A similar issue arises in, for example, a study testing two surgical procedures for breast cancer where one is more invasive and disfiguring with greater adverse effects but thought by many surgeons to be more effective.²⁶ A specific patient may nonetheless prefer or value one treatment over another given the kinds of benefits and harms involved. In fact, patients do vary widely in their preferences in this domain.²⁷ The above considerations are recognized in some form by various commentators, as factors that would “engage preferences or values that are meaningful to patients.”²⁸

Implications of the framework

The United States federal regulations address the issue of welfare consequences of research (research risks and benefits) for at least two purposes. First, even before the issue of informed consent can be raised, a research study must be deemed to have risks that are “reasonable” in relation to its potential positive consequences.[45CFR46.111(2)] Second, research risks must be identified to meet the requirements for informed consent, both for assessing whether it could be a candidate for a waiver or alteration [45 CFR 46.116c] but also for assessing what research risks should be included among the “reasonably foreseeable” risks that must be disclosed.[45 CFR 46.116a(2)]^{2, 28, 29} According to the regulations, research risks (and benefits) are “only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research).”[45 CFR 46.111(2)] The interpretive task, therefore, is to understand the phrase “therapies subjects would receive even if not participating in research” both in determining that a SCPCT has reasonable risks and in identifying reasonably foreseeable risks relevant to informed consent (and waiver or

alteration) requirements. Should it be a random patient perspective or a specific patient perspective?

We propose that for the first purpose, that of determining that a SCPCT has reasonable risks in light of its potential benefits, a random patient perspective is the appropriate perspective. This generates the same perspective as asking ‘what is the estimated aggregate welfare difference created by this SCPCT compared to the treatment setting?’ for which the unit of analysis is the SCPCT. This is the perspective necessary to make a judgment about whether a SCPCT’s overall risks and benefits (to subjects and to society) are reasonably balanced. According to our framework, there will sometimes be situations in which, in the aggregate, there is no overall *ex ante* estimate of incremental risk that is attributable to a SCPCT, thus accommodating the intuition that some SCPCTs have no incremental research risks (when Equal Probability of Allocation or Equal Estimated Welfare conditions regarding the two treatments are met). In other words, our framework formally confirms the view that some SCPCTs evaluating two widely used, standard treatments pose little or no additional risk compared to the status quo situation in the clinic. However, as demonstrated above, the framework also clearly shows that in other SCPCTs, there can be *ex ante* incremental risk.

Risk-benefit analysis for the purpose of meeting informed consent (or waiver/alteration thereof) requirements, however, must take into account, when possible, the specific individual’s perspective (i.e., the perspective of what an individual would have received outside the trial). First, in some SCPCTs some patients will face different *quantitative* welfare prospects inside and outside the SCPCT whenever $W_A \neq W_B$. This difference in *ex ante* estimate of welfare is, for that specific patient, attributable to the SCPCT and should be disclosed. However, this difference in estimate of welfare for a specific patient does not change the overall *ex ante* aggregate incremental welfare difference attributable to the SCPCT. In fact, as we saw above, it is possible for there to be no incremental welfare difference attributable to a SCPCT in the aggregate (i.e., when the Equal Probability of Allocation condition is met while $W_A \neq W_B$), even if there is an incremental welfare difference for specific individuals. Second, even if a specific individual faces the same quantity of risk (or welfare) inside and outside the SCPCT, the patient may have *preferences* regarding the different types of risks involved. For such SCPCTs, it does not seem to be the case that the SCPCT *adds* research risks in a way that would alter the justification of the SCPCT itself. But it does seem crucially important to *disclose* the different types of risks that individual may face by virtue of being in the SCPCT.

When an Institutional Review Board deems the risks of research reasonable in relation to the SCPCT’s potential value, it simply means, overall, the risks are such that the study can be offered to individuals to decide for themselves. IRBs should not take into account the possibility that people will prefer some types of risks differently as an *added* research risk of the study, however. It is the job of informed consent to accommodate that ethical concern.

Our framework also provides guidance for interpreting the criteria for waiver or alteration of informed consent when a SCPCT appears to have incrementally minimal research risk. A SCPCT could be deemed to have minimal risk in the aggregate but there are research risks that patients must be told, thus such studies should not be eligible for a waiver of consent.

This can be seen as an application of the regulatory criterion that “the waiver or alteration will not adversely affect the rights and welfare of the subjects.”(45CFR46.116d) In ordinary clinical care, when deciding between treatment options whose relative advantage is not known, patients have a right to information that allows their own preferences regarding different types of risk to inform their choice. Thus, even if a SCPCT has no incremental research risks, a waiver of consent would be impermissible if it would deprive persons of the right of self-determination that depends on exercising their own preferences regarding different types of risk.³⁰

Conclusion

In summary, our formal model for SCPCT risk analysis integrates important ethical intuitions of those on differing sides of the current debate on SCPCT research risk analysis, namely the relative allocation and *ex ante* estimated welfare of the treatments to be compared and the fact that some patients could receive a different treatment in the SCPCT than in clinical care. It provides a conceptual framework for applying the regulatory requirements of risk analysis and informed consent to SCPCTs, and explains why, for example, a SCPCT with little or no incremental research risk in the aggregate may have important informed consent requirements nevertheless. Thus, as a model that incorporates the ethical insights of various viewpoints into one coherent scheme, it should prove useful in assessing the variety of risk-benefit scenarios involved in SCPCTs.³¹

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Box 1**Model for Analyzing Risks and Benefits Attributable to Standard of Care Pragmatic Clinical Trials**

Let W_A and W_B be the *ex ante* estimates of welfare that patients are expected to derive from receiving treatments A and B respectively (excluding other welfare considerations that may be part of being in a research study, such as implications of protocol fidelity⁷). We use the term “welfare” to refer to a both the likelihood and magnitude of an outcome. The outcomes can be clinical states (death, stroke, symptom severity, etc), utilities, or other ways of expressing welfare, as long as consistency is maintained. Or, depending on the purpose of the analysis, W_A and W_B could focus on only the risks, the benefits, or on the benefits minus the risks (e.g., a given analysis of a SCPCT could focus only on risks, if the goal for that analysis is only to evaluate the risks).

$P(A_i)$ and $P(B_i)$ are the probabilities that a patient receives A or B, respectively, inside the trial such that $P(B_i) + P(A_i) = 1$.

$P(A_o)$ and $P(B_o)$ are the probabilities that a patient receives A or B, respectively, outside the trial such that $P(B_o) + P(A_o) = 1$.

W_i and W_o are *ex ante* estimates of welfare that patients experience inside and outside the trial respectively, such that $W_i = W_A \cdot P(A_i) + W_B \cdot P(B_i)$ and $W_o = W_A \cdot P(A_o) + W_B \cdot P(B_o)$.

Then the *ex ante* estimated welfare difference inside the trial versus outside the trial (ΔW) can be expressed as:

$$\begin{aligned}\Delta W &= W_i - W_o \\ &= [W_A \cdot P(A_i) + W_B \cdot P(B_i)] - [W_A \cdot P(A_o) + W_B \cdot P(B_o)] \\ &= W_A \cdot [P(A_i) - P(A_o)] + W_B \cdot [P(B_i) - P(B_o)] \\ &= W_A \cdot [P(A_i) - P(A_o)] + W_B \cdot [(1 - P(A_i)) - (1 - P(A_o))] \\ &= W_A \cdot [P(A_i) - P(A_o)] + W_B \cdot [P(A_o) - P(A_i)] \\ &= W_A \cdot [P(A_i) - P(A_o)] - W_B \cdot [P(A_i) - P(A_o)] \\ &= [W_A - W_B] \cdot [P(A_i) - P(A_o)]\end{aligned}$$