HHS Public Access

Author manuscript

Clin Trials. Author manuscript; available in PMC 2024 December 01.

Published in final edited form as:

Clin Trials. 2024 December ; 21(6): 659–665. doi:10.1177/17407745241266155.

Individualized Clinical Decisions Within Standard-of-Care Pragmatic Clinical Trials: Implications for Consent

Isabel M Astrachan[1], **James Flory**[2], **Scott Y H Kim**[1]

[1]Department of Bioethics, Clinical Center, National Institutes of Health, Bethesda, MD, USA;

[2]Memorial Sloan Kettering Cancer Center, New York, NY, USA

Abstract

Pragmatic clinical trials of standard of care interventions (SOC PCTs) compare the relative merits of medical treatments already in use. Traditional research informed consent processes pose significant obstacles to these trials, raising the question of whether they may be conducted with alteration or waiver of informed consent. However, to even be eligible, such a trial in the US must have no more than minimal research risk.

We argue that SOC PCTs can be designed to ensure that they are minimal research risk if the random assignment of an intervention in a PCT can accommodate individualized, clinically-motivated decision-making for each participant. Such a design will ensure that the patient-participants are not exposed to any risks beyond the clinical risks of the interventions, and thus the trial will have minimal research risk. We explain the logic of this view by comparing three scenarios of SOC PCTs: one with informed consent, one without informed consent, and one recently proposed design called Decision Architecture Randomization Trial (DART). We then conclude by briefly showing that our proposal suggests a natural way to determine when to use an alteration versus a waiver of informed consent.

Keywords

Standard of care pragmatic clinical trials; informed consent; waiver of informed consent; alteration of informed consent; integrated consent; research risk; clinical risk; minimal risk

Introduction

Pragmatic clinical trials comparing standard of care interventions (SOC PCTs) promise much needed ‘real world’ data on the relative merits of treatments already in broad use. In contrast to trials of novel interventions, SOC PCTs may be readily integrated into ordinary

Correspondence: Scott Kim, Department of Bioethics, 10 Center Drive, 1C118, Bethesda, MD 20892-1156, Scott.kim@nih.gov.
All authors contributed to the initial conceptualization of the paper, IA wrote the first draft, all edited the entire draft for intellectual content, and all approved the final version.

Disclaimer: The ideas and opinions expressed are the authors’ own; they do not represent any position or policy of the National Institutes of Health, the Department of Health and Human Services, or the U.S. government.

The authors have no competing interests.

This paper does not require an ethics approval statement as it does not involve human subjects.

clinical practice using electronic health records with minimal disruption of clinical care, potentially informing healthcare policy and treatment decisions at significantly lower cost (and inconvenience to patients) than typical randomized trials. But research ethics oversight that is disproportionately burdensome, especially in the form of lengthy informed consent processes, could prevent implementation of such SOC PCTs, by undermining their central, 'pragmatic' aim.[1] Proportionate oversight requires a proper understanding of the actual research risks to participants, but what these risks are remains a topic of discussion.[1]

SOC PCTs are challenging to conduct with traditional research informed consent because it is difficult to integrate a time-consuming conversation into the usual workflow of busy clinics and hospital units. Primary care physicians in the US have a limited number of minutes per patient visit, so any additional time taken could noticeably impact the work of the clinic or displace elements of care that physicians already find challenging to fit into their encounters.[1–5] Although a research team could obtain informed consent outside, or prior to, a patient's clinic visit,[6] such a system may not work for all studies and requires dedicated research personnel. It is reasonable to assume that requiring traditional informed consent for SOC PCTs results in fewer such trials being done.

These challenges have led many authors to ask whether SOC PCTs may be eligible for alteration or waiver of informed consent. To even be considered for this, however, a trial conducted in the US must meet several regulatory criteria, most notably that "the research involves no more than minimal risk to the subjects" (45 CFR 46.116). When the sole research intervention is randomized assignment to one of two standard interventions, some writers argue that since both arms are standard, the trial should be deemed minimal risk.[7, 8] But this kind of risk analysis is problematic, as it cannot account for the fact that for some participants who enter SOC PCTs (we use a per person reference class for determining risk), there is a realistic prospect of a significantly different welfare outcome that is solely attributable to the research.[1, 9] That is, the research risk arises 'for the sake of' conducting research, and such risk may not be minimal at all.[9]

In this paper, we argue that SOC PCTs can be designed to ensure that they are minimal research risk if they incorporate individualized, clinically-motivated decision-making. To demonstrate this, we begin by defining some key terms. We then explain how informed consent can make what would otherwise be a SOC PCT with *research* risk (due to randomized assignment of interventions) into a trial with only *clinical* risk. We then show —using the example of a PCT design called a Decision Architecture Randomization Trial (DART)[10] which incorporates individualized clinical decisions without traditional informed consent—that traditional informed consent is not the only way to shift the source of a PCT's risk from research to clinical. We then extend the point to SOC PCTs in general: by incorporating individualized clinical decisions, these trials can be made no or minimal research risk. In the final section, we briefly discuss the implications of our argument for determining when it is ethically appropriate to use complete waivers versus altered consent in SOC PCTs.

Key concepts

Determinative clinical preferences

By ‘determinative clinical preference,’ we mean a preference based on clinical reasoning that is individualized to suit that particular patient. This choice is frequently (though not always, as when the choice of intervention is made solely by the doctor, as often occurs in the ICU) the outcome of some level of interaction between doctor and patient. To illustrate how one arrives at a determinative clinical preference, consider patient P’s doctor, who knows there is no rigorous RCT data that compares the relative merits of A versus B (assuming both are standard treatments). Yet she might feel, from her many years of clinical practice as well as her knowledge of P’s condition, general health status, family history, habits, personality, etc., that she prefers A for P. She discusses this with P and together they reach the opinion that A is indeed the better option for P. Again, P’s doctor acknowledges that there is insufficient evidence to support a *policy* standardizing A as the default, but feels it is right for P in this instance. (Note that it could turn out that the doctor’s individualized clinical reasoning for P is that A and B are equally good treatments for P. It is not that the doctor does not care about what the patients receives—she still wants and indeed recommends the best individualized treatment—but rather she believes that A and B are equally good options.)

We make the modest claim here that we ought to show *some* deference to the doctor’s clinical experience as a rational, legitimate clinical basis for decisions. There is a tendency to think that if a lack of strong comparative effectiveness data has led to community-level equipoise among clinicians, then any decision to favor A over B cannot have any rational clinical basis. This view is too strong: we can recognize that the preferred basis for decision-making is rigorous RCT-based comparative data without demoting all other bases as irrational or clinically irrelevant.

The decision-making unit

Usually, the unit is the doctor and patient collaborating (to some degree) to reach agreement, but there can be a range of involvement of the patient. For some decisions, the patient’s views will weigh heavily (e.g., when two interventions have similar efficacy but differing side effects); for others, the doctor’s opinion will weigh more heavily. Sometimes the decision-making unit will even be the doctor alone, as in many ICU treatment decisions (though not all; e.g., the decision to forgo aggressive treatment). We return to these different options below, as the makeup of the decision-making unit has important implications for our discussion of waiver versus alteration of informed consent in the final section.

Quantity of risk as distinct from attributed source of risk: research risk vs clinical risk

In PCT risk analysis, it is crucial to distinguish between the *quantity* (magnitude and probability) of risk and the *source* of risk. By source of risk, we mean the attribution of the *potential* (risk is *prospective uncertainty*; it cannot be decided after the fact) adverse event, burden, or differential benefit associated with treatment interventions to either research or clinical care. To answer whether the risk taken on is research or clinical risk, one needs to ask the reason for which one takes on that risk. A *research* risk is taken on for the sake of the

research (i.e., the patient's body is used to generate knowledge, with their permission), not the need to treat the patient; a *clinical* risk is the burden taken on for the sake of the patient's welfare.

In the clinical setting, where P would receive A based on individualized clinical reasoning, we would just treat the potential for an adverse reaction as a *clinical* risk of intervention A; P is exposed to that risk for the sake of clinical aims. But that possibility of an adverse event can become a research risk if the potential welfare *difference* is *solely* attributable to P's participation in the SOC PCT, i.e., it is taken on *for the sake of* research. For instance, suppose the patient in question would have received B outside the trial based on a determinative clinical preference (of the kind we discussed above, not, e.g., based on some arbitrary reason like B having a shorter name than A, making it more frequently prescribed). Suppose in the trial, P is randomly assigned A and that is the sole reason why she receives A rather than B. Since she is randomized to and receives A for the sake of the trial, not for clinical reasons, she is exposed to a *research* risk. Thus, the same physical reaction to A can be either *clinical* risk or *research* risk, depending on why that risk was taken on.

Informed consent and source of risk in SOC PCTs

For SOC PCTs, informed consent can transform the trial's risk to the participant from a research risk to a clinical risk. Table 1 splits patients who will enter a SOC PCT (or are considering it) into three groups: those with a determinative clinical preference for intervention A over B, or B over A (Groups I and III), and those for whom A and B are equally acceptable (Group II). For now, we need only focus on second and third columns of the Table, as they illustrate the role of informed consent on source of risk by comparing SOC PCT with informed consent vs. one with a full waiver.

In SOC PCTs with informed consent, Group I and Group III patients would opt out of participating, since they have a determinative preference for an intervention which they may not receive in the PCT. The priority of clinical considerations is retained at the expense of their research participation. There is obviously no research risk for those groups who do not enroll in the PCT; what they face is clinical risk.

For patients in Group II, enrolling in the PCT with informed consent results in no incremental increase in *research* risk. This is the case because whether P is randomly assigned A or B, P has an opportunity to accept or decline that assignment according to their determinative clinical preference; P would receive whatever is randomly assigned, but only after P (with their doctor) decides that it is consistent with her clinical interests. Importantly, the fact that they receive one or the other inside the trial does not represent a departure from what clinically motivated decision-making would indicate in their ordinary care; indeed, their clinical interest has priority over any research procedure (such as randomized selection of intervention). As such, the risk that they take on in the trial is clinical risk, not research risk.

To illustrate, imagine a scenario where P (a Group II patient with a determinative clinical preference for either A or B) receives A in the trial, but P, and indeed most patients with P's

condition, would have received B in ordinary care, but not because they have determinative clinical preferences for B. Rather, B is easier to prescribe (e.g., has a shorter name, is the default option or the first that comes to mind, etc.) so a large majority of doctors simply do what is the clinically equivalent but easier thing to do: prescribe B over A. In this case, a trial that randomizes 50:50 to A and B would mean that many patients who ordinarily would receive B in clinical care will receive A instead. Some may worry that this introduces research risk because this situation would not have occurred if the research project did not exist (i.e., many patients, 'but-for' the research, would have received B and not A). In our view, however, whatever potential welfare difference in outcome that could result from receiving A instead of B is properly attributable to clinical risk, not research risk since there is a judgment that A is consistent with P's individualized and determinative clinical preferences, and this judgement is given priority over whatever the randomization assigns. P (with their doctor) in effect takes ownership of P receiving the assigned intervention (or could reject it if they felt it was not in P's best clinical interest). The insertion of this step prioritizes the clinical motive—P and their doctor have the authority to override the suggested assignment. Thus, it is incomplete and inaccurate to say P receives A 'solely' due to research; that way of framing the process ignores the agency of P and their doctor in their decision-making.

Now consider the SOC PCT conducted with a full waiver of informed consent, thus precluding clinically motivated individualized decisions for at least some patients. Group I and Group III patients would be unaware that they are to be randomized to an intervention, and unaware that (assuming 50/50 randomization) there is a 50% chance they will not receive their intervention of choice. Even if they gave consent to research in general upon intake at this healthcare system, they are likely unaware of the specific instances in which research considerations are prioritized in their clinical care, and for those who receive an intervention counter to their individualized clinical preferences, the research is prioritized at the expense of their clinical preferences. Some patients in a SOC PCT without informed consent will receive an intervention contrary to their determinative clinical preference. These patients will be exposed to research risk, not merely clinical risk, since the exposure to the potential for change in welfare is for the sake of research. This research risk could be minimal or substantial, depending on the nature of the interventions being tested.[1]

However, an important caveat is needed: the views expressed above about research risk in SOC PCTs conducted with a full waiver are dependent upon the design of the particular SOC PCT in question. These views apply exactly as we have described if the protocol requires randomization to A or B with no room to incorporate individualized clinical reasoning. However, if the decision-making unit (doctor alone or doctor-patient dyad) is given the opportunity to make a post-randomization decision based on individualized clinical considerations (e.g. should P agree to take A when randomized to do so, or should she switch to receive B instead for clinical reasons), then the source of any risk to which P is exposed would be clinical, not research, as there is no additional incremental risk that is taken on for the sake of research.

What about Group II patients in PCTs with a waiver, whose determinative preference is that either intervention is acceptable? Here, if there is a complete waiver of consent,

for the sake of illustration we assume the kind of clinical decision that usually does not involve the patient (e.g., some ICU decisions), i.e., the decision-making unit is the doctor. (See our discussion below of when a waiver versus an altered consent is appropriate.) For these patients, determinative clinical preferences are satisfied whether their randomized assignment is A or B since the physician will have the authority to exercise a determinative clinical preference regarding the randomly suggested treatment. So, based on the same reasoning for this group in the case of SOC PCTs with informed consent, the risk to Group II patients in SOC PCTs without consent cannot be distinguished from ordinary clinical risk.

In summary, for the very same SOC PCT, informed consent results in a trial with no additional research risk over clinical risk, but waiving consent will result in that trial having research risk. Thus, *informed consent affects the source of risk*, even if quantity of risk (i.e., potential change in welfare) remains the same. One obvious implication of this finding is that if the minimal risk status of an SOC PCT is dependent upon there being full informed consent, then that minimal risk status cannot be appealed to as meeting one of the waiver/alteration criteria. In evaluating a SOC PCT for a waiver of consent, therefore, it is not enough to determine that it would be minimal risk *with* consent.[11] To meet the regulatory requirement of minimal research risk for the purposes of determining eligibility for a waiver or alteration of consent, a study must be minimal risk even if a waiver or alteration of consent were permitted.

Informed consent is not the only means of shifting source of risk in SOC PCTs: decision architecture randomized trial (DART)

There are other ways of ensuring that the SOC PCT is minimal research risk (again, not simply because the quantity of burden or potential harm is minimal but because of source of risk). Here we use the example of DART (Decision Architecture Randomization Trial), a novel clinical trial design.[10] In it, participants are randomized to one of two groups, each associated with an easily ignorable nudge to their healthcare provider (e.g., a default selection of A or of B in electronic ordering system). When a clinician goes to the electronic health record system to prescribe an intervention for their patient, they can easily override the default of A and choose B instead if they have a determinative preference for it. The ability to easily override the nudge is crucial, and our argument assumes use of only nudges where this is the case. To the extent that nudges have an effect, however, one can analyze outcomes associated with the randomly assigned intervention.[10]

A full explication of DART[10] is beyond the scope of this paper and is not needed for our argument: we use DART merely to illustrate that there can be other ways, aside from obtaining informed consent (such as brief modified consent or another procedure that ensures that a determinative clinical preference is respected—see below), of designing a SOC PCT in which the source of risk is clinical, not research. For our purposes, the key ethical point is that the doctor and patient can easily override the randomized default *even if neither has any idea a research study is being conducted*; this preserves the priority of individualized clinical reasoning—any dyad with a determinative clinical preference can opt for their intervention of choice. As shown in Table 1, in DART, when patient and doctor

have a determinative clinical preference for either A or B (Group I or III), the patient will receive their intervention of choice. This is because the doctor (and patient) can go with the nudge if it aligns with the clinical preference (e.g., the dyad has preference for A and electronic healthcare record nudges to A) or can choose to override the nudge if not. In this way DART preserves individualized, clinically motivated decision-making even if there is randomization. There is therefore no research risk involved for persons in Groups I and III. Group II patients in DART have clinically determinative preferences such that A and B are equally acceptable. Thus, as in our analyses of SOC PCTs with and without informed consent, there is no added research risk even if the nudge is 'effective' in that P opts to receive A instead of B when nudged to A, since even if they would have received B were it not for the PCT, that choice between the two would not have been for any clinical reason and, further, the decision to accept B in the PCT will be based on a determinative clinical preference.

In a DART trial, no decision for P needs be made on grounds other than P's clinical best interest. As such, patients in DART trials take on clinical risk of the intervention only, not research risk. Provided there is no other source of research risk, DART meets the minimal risk criterion. (We do not here address the ethics of nudging per se, a topic that has been given ample consideration by many authors.[12–16] We assume that nudges that do not constrain choice and are very easy to override are ethically acceptable. However, one may disagree with this, or with the acceptability of DART in general, without negating our argument, as DART is just an example of our principle at work.)

Individualized clinical decisions as the key ingredient

We have seen that traditional informed consent can change the research risk of a SOC PCT not because it reduces the quantity of risk but because it shifts the source of risk, from research to clinical. By use of the DART example, we also saw that the active ingredient is the incorporation of individualized clinical decision for every patient and that incorporating that ingredient in a SOC PCT does not require traditional informed consent. Finally, we saw that individualized clinical decision-making is in fact compatible with randomization, meaning that it is possible to design and conduct a PCT whose sole research intervention is randomized assignment to A or B without introducing any additional research risk beyond what clinical consideration for that particular patient demands.

Waiver versus alteration of informed consent

Our analysis also suggests a way to address the perennial question of whether minimal risk SOC PCTs should be done with a waiver or an alteration of informed consent. This is a complex topic that cannot be fully addressed here,[17, 18] but there is one implication of our analysis that suggests a natural way to determine when one or the other should be used.

We answer this question by looking at how exactly the individualized, clinically motivated decision will be made in the proposed SOC PCT. If the assignment of the intervention (A or B) would ordinarily, i.e., in the clinical setting, involve some expectation of patient involvement or agreement—i.e., at least some minimal level of patient-doctor interaction

and dyadic decision-making—prior to the patient receiving the intervention, then a complete waiver of consent needs to address three concerns.

First, it would involve a deliberate refraining from transparency; this is so because in ordinary clinical setting, transparency about how a treatment is chosen is expected. The only way to withhold that information is to engage in complicity of opacity, i.e., to actively hide how the decision is really made.[19] This seems disrespectful.

Second, the resulting lack of transparency is obviously incompatible with individualized clinical decision-making. Thus, the active ingredient that shifts the source of risk to clinical is lacking, so we cannot assume that the minimal risk assumption holds. When the possibility of shifting the source of risk from research to clinical is tied to transparency, a complete waiver puts into question whether the study has minimal research risk.

Third, a full waiver is not necessary to maintain the pragmatism of the PCT. These are situations where there are expectations of patient-doctor communication about the treatment decision. Since the ultimate decision is about which of the two interventions (both in clinical use, both reasonable indications) is to be chosen, as long as altered consent is sufficient to allow an individualized clinically oriented decision, the study poses minimal research risk. For instance, we have proposed elsewhere[19] that an integrated consent be used for SOC PCTs, where a brief verbal consent with clinical documentation would be ethically sufficient; such a procedure would ensure that the study has no research risk from the randomized selection of the intervention and it also ensures that in a situation where transparency is expected, respect is maintained.[19] This kind of proposal is gaining traction internationally and has been incorporated into the Health Research Authority's guidance on proportionate consent in the UK.[20]

On the other hand, where there is no expectation of patient involvement, as in the ICU where many clinical interventions are made unilaterally by doctors, it is possible to ensure individualized clinical decisions in PCTs if each randomized assignment by the research protocol is accepted or rejected by the patient's clinician based on individualized, clinical decision-making.[21]

This short discussion of alteration versus waiver of consent has three caveats. First, our goal here is not a comprehensive analysis and there are other considerations that need to be brought in to fully answer when a waiver versus alteration is appropriate, depending on the specific type of research. For instance, a cluster-cluster design where there is no way to individualize the randomized intervention (e.g., either because the intervention affects the entire setting, or because the intervention is clinically delivered in a protocolized manner) will surely need additional analysis.

Second, if research risk can in fact be eliminated, leaving only clinical risk as we suggest, then it is possible that trials with endpoints of serious morbidity or even mortality may qualify as minimal risk. This may seem counterintuitive and even shocking, but it follows from our analysis. *It is crucial, however, to note that our analysis is primarily focused on laying out a conceptual framework and does not address every factor that may affect research risk*. For instance, the analysis depends on the assumption that the quality of

clinical reasoning in reaching a determinative clinical preference is reasonable. If it is threatened, there could be research risk. One obvious example is if the clinician in charge of making the individualized decision has a strong competing interest, e.g., if the clinician is also the principal investigator. Such conflicts of interest could affect clinical reasoning so that the source of risk could be shifted back from clinical to research. Another threat to individualized clinical reasoning which could shift the source of risk back to research is if the nudge in a DART trial is far too strong, such that clinicians may fail to override it even when their clinical judgment would otherwise dictate that they should. Additional review considerations, therefore, will surely be needed.

Finally, there is a broader question about whether a healthcare system that routinely conducts SOC PCTs, sometimes with complete waivers of consent, owes its patients transparency regarding the fact that such studies are taking place, with or without giving patients an opt-out option. Our own example of DART studies, for instance, can occur in the background without knowledge of patients or doctors; it may be that patients are owed some notification regarding the practice. We are inclined to think such transparency is required, but this is a general issue regarding routinized waivers of consent in a learning health care system, not a specific issue for the risk analysis we discuss here.

Conclusions

Research and care are distinct concepts, with distinct aims and standards to guide them. But they need not be mutually exclusive, as though part of a zero-sum game. The main reason we need research ethics for clinical trials is to ensure that the aims and practice of research do not expose patients to unnecessary risks or risks that patients have not agreed to. Although research and care can conflict and we need rules to govern our practice when that happens, some types of clinical trials comparing ‘within standard of care’ interventions allow an integration of research and care: individualized clinical decisions can take place even within a randomized clinical trial. Recognizing this is key to avoiding over-regulation of and disproportionate regulatory burdens on such trials.

Acknowledgements:

We would like to thank David Wendler and Holly Taylor in the Department of Bioethics at the National Institutes of Health for their helpful feedback on an earlier version of this paper.

Funded in part by the Intramural Research Program of the NIH (CL010538), and the Patient Centered Outcomes Research Institutes (ME-2022C1-26378).

References

1. Kim SYH. Comparative Effectiveness Research, Learning Health Systems, and Pragmatic Randomized Controlled Trials. In: Iltis AS and MacKay D (eds) The Oxford Handbook of Research Ethics. Oxford University Press, 2020.
2. Dal-Ré R, Janiaud P and Ioannidis JPA. Real-world evidence: How pragmatic are randomized controlled trials labeled as pragmatic? BMC Medicine 2018; 16.
3. Sugarman J and Califf RM. Ethics and Regulatory Complexities for Pragmatic Clinical Trials. JAMA 2014; 311: 2381. [PubMed: 24810723]

4. Tai-Seale M, McGuire TG and Zhang W. Time Allocation in Primary Care Office Visits. Health Services Research 2007; 42: 1871–1894. [PubMed: 17850524]
5. Yarnall KSH, Pollak KI, Østbye T, et al. Primary Care: Is There Enough Time for Prevention? American Journal of Public Health 2003; 93: 635–641. [PubMed: 12660210]
6. Ishani A, Cushman WC, Leatherman SM, et al. Chlorthalidone vs. Hydrochlorothiazide for Hypertension–Cardiovascular Events. New England Journal of Medicine 2022; 387: 2401–2410. [PubMed: 36516076]
7. Lantos JD, Wendler D, Septimus E, et al. Considerations in the evaluation and determination of minimal risk in pragmatic clinical trials. Clin Trials 2015; 12: 485–493. [PubMed: 26374686]
8. Anderson CS, Arima H, Lavados P, et al. Cluster-Randomized, Crossover Trial of Head Positioning in Acute Stroke. New England Journal of Medicine 2017; 376: 2437–2447. [PubMed: 28636854]
9. Kim SY and Kimmelman J. Practical steps to identifying the research risk of pragmatic trials. Clin Trials 2022; 19: 211–216. [PubMed: 35348360]
10. Flory J, Ancker JS, Kim SYH, et al. Decision architecture randomisation: extremely efficient clinical trials that preserve clinician and patient choice? BMJ Evid Based Med 2023.
11. Dickert NW, Eyal N, Goldkind SF, et al. Reframing Consent for Clinical Research: A Function-Based Approach. The American Journal of Bioethics 2017; 17: 3–11.
12. Fridman I, Hart JL, Yadav KN and Higgins ET. Perspectives on using decision-making nudges in physician-patient communications. PLoS One 2018; 13: e0202874. [PubMed: 30231040]
13. Gorin M, Joffe S, Dickert N and Halpern S. Justifying Clinical Nudges. Hastings Cent Rep 2017; 47: 32–38.
14. Halpern SD. Judging Nudges. Am J Bioeth 2016; 16: 16–18.
15. Raskoff SZ. Nudges and hard choices. Bioethics 2022; 36: 948–956. [PubMed: 36152342]
16. Wolf A, Sant'Anna A and Vilhelmsson A. Using nudges to promote clinical decision making of healthcare professionals: A scoping review. Prev Med 2022; 164: 107320. [PubMed: 36283484]
17. Kim SYH and Miller F. Waivers and alterations to consent in pragmatic clinical trials: Respecting the principle of respect for persons. The Hastings Center Report 2016; 38: 1–5.
18. Kim SYH. Clinical Trials Without Consent? Perspectives in Biology and Medicine 2016; 59(1): 132–146. [PubMed: 27499490]
19. Kim SYH, Miller F. Informed Consent for Pragmatic Trials — The Integrated Consent Model. The New England Journal of Medicine 2014; 370; 8: 769–772.
20. Applying a proportionate approach to the process of seeking consent. In: Authority NHSHR, (ed.). UK2019.
21. Semler MW, Self WH, Wanderer JP, et al. Balanced Crystalloids versus Saline in Critically Ill Adults. New England Journal of Medicine 2018; 378: 829–839. [PubMed: 29485925]

Table 1.

The relationship between determinative clinical preferences and intervention assignment in three SOC PCT designs*

	SOC PCT w/ IC	SOC PCT w/o IC	DART
Group I: Determinative Clinical Preference for A	Unlikely to participate. 100% receive A but outside the PCT.	50% will be randomized to A and will receive A. *50% will be randomized to B and will receive B.*	50% will be randomized to A nudge and will receive A. 50% will be randomized to B nudge and override to receive A. 100% receive A.
Group II: Determinative Clinical Preference for A or B (Both Acceptable)	50% will be randomized to A and will receive A. 50% will be randomized to B and will receive B.	50% will be randomized to A and will receive A. 50% will be randomized to B and will receive B.	50% will be randomized to A nudge. 50% will be randomized to B nudge. Some receive A, some receive B.
Group III: Determinative Clinical Preference for B	Unlikely to participate. 100% receive B but outside the PCT.	*50% will be randomized to A and will receive A.* 50% will be randomized to B and will receive B.	50% will be randomized to A nudge and override to receive B. 50% will be randomized to B nudge and will receive B. 100% receive B.

*SOC PCT = standard of care pragmatic clinical trial; DART = decision architecture randomization trial; IC = informed consent.