

RESEARCH REPORT

Ethical issues in pragmatic trials of “standard-of-care” interventions in learning health care systems

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Abstract

Introduction: Learning health care systems (LHS) hold the promise of improving medical care by systematically and continuously integrating the delivery of medical services with clinical research. One important type of integration would involve embedding trials that compare interventions that are already commonly in use (as “accepted” or “standard of care”) into the clinical setting—trials that could cost-effectively improve care. But the traditional requirement of informed consent for clinical trials stands in tension with the conduct of such trials.

Method: Narrative analysis.

Results: Although some have suggested that the idea of LHS makes the distinction between research and ordinary clinical care obsolete, the distinction remains ethically relevant even when it comes to randomized clinical trials (RCTs) that compare standard-of-care interventions. This paper presents an ethical framework for analyzing standard-of-care RCTs in resolving the tension between such trials and traditional requirements of research ethics.

Conclusion: It is important not to treat all standard-of-care RCTs as a monolithic category of special ethical status. Close attention to ethical issues in specific standard-of-care RCTs is crucial if the LHS movement is to avoid ethical lapses that could be counterproductive to its long term vision.

KEYWORDS

informed consent, pragmatic, randomized clinical trial, standard-of-care

1 | INTRODUCTION

Learning health care systems (LHS) hold out the promise of improving medical care by systematically integrating the delivery of medical services with clinical research. In LHS, the generation of knowledge would be “embedded into the core of the practice of medicine” leading to “continual improvement in care.”¹ The advent of a modern electronic health record system makes it feasible and relatively inexpensive to conduct studies in the context of routine clinical practice.² One type of integration would involve embedding comparative effectiveness

randomized clinical trials (RCTs) into the clinical setting, especially trials that compare interventions that are already commonly in use (as “accepted” or “standard of care”). These trials are much needed because clinicians often face situations in which there is more than one treatment that is generally accepted, known to be efficacious, or FDA approved for their patient’s condition, and it is usually not clear which is superior or how best to use the treatments. Aside from improving care, there is great potential for cost savings as well. The need for such pragmatic³ comparative effectiveness RCTs to make clinical practice truly evidence-based is integral to the vision of a LHS.¹

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2 | THE ETHICAL TENSION

The characteristics that make pragmatic RCTs of standard-of-care interventions so valuable, however, create an inevitable tension with existing ethical frameworks for overseeing clinical trials. Specifically, the vision of a low-cost, pragmatic, continuous program of RCTs mimicking ordinary health care delivery appears incompatible, or at least in tension, with the requirement to obtain written informed consent (often involving lengthy and detailed forms), leading some observers to comment that the requirement of informed consent is a “critical barrier” for comparative effectiveness RCTs.⁴ To incorporate a lengthy informed consent process would be in tension with the ordinary workflow of a busy clinic (such a practice would not mimic “real world” practice in which most interventions do not require detailed written consent) and would be so costly as to make a continuous integrated practice of RCTs not feasible.

How should this tension be resolved? A notable feature of comparative effectiveness research involving standard of care treatments is that every participant will receive a clinically accepted or at least commonly used intervention for his or her condition, as distinct from trials of novel or experimental interventions.⁵ Thus, some commentators note that “... standard-of-care research does not expose participants to risk beyond the risk they might be exposed to outside the study.”^{6,7} Indeed, some argue that within learning health systems, the traditional distinction between research and treatment is problematic and outmoded^{8,9} and that the regulations “no longer match current needs”⁸ and others argue that some types of RCTs do not need informed consent.¹⁰ One group has developed a framework of moral principles for evaluating the ethics of LHS activities.¹¹ They argue that, following others,¹² these principles yield the result that in some pragmatic comparative effectiveness trials, the randomized assignment of treatments need not be disclosed to patients, and thus, no express informed consent for research participation is ethically necessary.¹⁰

Comparative effectiveness research of 2 or more interventions, even when they are “within the standard of care,” has generated much ethical controversy, as exemplified in the 2013 Office of Human Research Protections investigation of the SUPPORT study—a randomized controlled trial of 2 contrasting oxygen saturation settings in mechanical ventilation of premature infants within the established standard of care.^{13,14} The OHRP convened a public meeting in August 2013 on “Matters Related to Protection of Human Subjects and

Research Considering Standard of Care Interventions” and issued draft guidance on “Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care.”¹⁵ This guidance—which in essence says that merely because 2 “standard-of-care” treatments are being compared in an RCT is not a reason to confer on the RCT a special ethical status—has been sharply criticized.^{6,16}

3 | THE LIST OF OPTIONS TO RESOLVE THE ETHICAL TENSION

Given the well-recognized tension between the pragmatic standard of care RCTs in LHS and traditional procedures for informed consent, what is the solution? Before discussing how one might arrive at the solution, it will be useful to get a sense of the range of potential outcomes in the ethical analyses of standard of care RCTs. They are summarized in Table 1.

If it is deemed that some change to the traditional informed consent process would be acceptable for a given standard-of-care RCT, such modifications of the informed consent process might involve one of the following possibilities. Perhaps, simply shortening the informed consent form (eg, one page form) may ease the burden of the process enough to make some standard-of-care RCTs practicable, although given that such a procedure would still involve significant deviation from the routine work flow of a clinic—reviewing a number of items and obtaining a signature—such a solution may apply in only a very few cases. Strictly speaking, such a shortened form could actually conform to the regulatory requirements of informed consent but is included here as it would be a deviation from most IRBs' actual practices.

Another option is to retain all of the elements of informed consent but to simplify the process by not requiring a written form or signature and permitting lack of objection (opt out) as sufficient evidence of consent. Something like this seems to be the approach that is permitted by the European clinical trials regulations for a narrow range of RCTs—low risk cluster trials involving standard of care interventions.¹⁷ Of course, verbal consent could be simplified even further, to a very brief consent for research participation (eliminating unnecessary elements such as provisions about confidentiality since the conversation is already within the context of physician-patient communication) with documentation in the medical records, mimicking the clinical practice of a brief conversation a clinician may have with a patient when starting a new medication.¹⁸

TABLE 1 Possible outcomes of ethical analysis when a standard-of-care randomized clinical trial is impracticable to conduct without forgoing or modifying traditional informed consent (IC) process

Ethically acceptable to forgo or modify traditional informed consent	Ethically not acceptable to forgo or modify traditional informed consent
<ul style="list-style-type: none"> • Shortened IC form • Simplified consent (eg, verbal IC with opt out) • Verbal consent with EHR documentation by clinician • General notification and broad consent on joining LHS • No consent or notification • Other 	<ul style="list-style-type: none"> • Modify the RCT and conduct with traditional IC; less pragmatic but ‘pragmatic enough.’ • Not conduct the RCT because modifying it to accommodate traditional IC will make it not worth doing scientifically or would require resources that are not available.

Some have advocated—if cultural changes in the future lead to an overall acceptance of the mission and practice of LHS by patients in a health system—that perhaps general notification and some form of broad permission regarding future well-vetted standard-of-care RCTs without express consent might be sufficient.¹⁹ Finally, it is theoretically possible that a standard-of-care RCT may meet the ethical requirements for a complete waiver of research consent without any general notifications, although that seems rather unlikely.

Of course, it is always possible that a thorough ethical analysis of a proposed standard-of-care RCT may determine that no deviation from the traditional informed consent procedures is permissible. In such a case, there are only 2 options for the researcher in the LHS. One, the RCT could be modified to accommodate a traditional informed consent process. Such a modified RCT may still be scientifically valuable and worth doing. However, it may turn out that to incorporate a full informed consent process for a given standard-of-care RCT would be such that either the cost would be prohibitive or the required modification to the RCT would make the study scientifically not worthwhile.

These options fairly exhaust the list of potential outcomes for ethically resolving the tension between a standard-of-care RCT and traditional consent process (with one caveat—see section on impracticability below). We now move on to the key issues that must be addressed in determining which of the above options is most ethically appropriate for a given standard-of-care RCT.

4 | DETERMINING THE OPTIMAL ETHICAL OPTION

At least in the United States, there are regulatory provisions for reviewing when a deviation from traditional research informed consent is permissible. (For some options in Table 1, the issue will be a waiver of documentation of consent as per 45CFR46.117 rather than any question of waiving or altering the informed consent process itself). These provisions actually do raise the key ethical issues relevant for bypassing informed consent, and practically speaking, they are the conditions that must be met, so we focus on how they might apply to standard-of-care RCTs.²⁰ To waive or alter informed consent, the research procedures must meet the following criteria listed in Table 2. These criteria are more thoroughly discussed elsewhere.²⁰⁻²³ For the present purpose, I simply present the type of issues that need to be addressed in applying the criteria. The fourth criterion of debriefing

TABLE 2 Regulatory requirements for waiver or alteration of informed consent (45CFR46.116d)

An IRB may approve a consent procedure, which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:
(1) The research involves no more than minimal risk to the subjects;
(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
(3) The research could not practicably be carried out without the waiver or alteration; and
(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

is not discussed here as it is an after the fact issue, and the focus here is on prospective deviations from usual practice of informed consent.

The most important point about the application of these criteria is the following: The mere fact that the is similar inside and outside the involves comparison of 2 accepted, standard of care interventions does not determine the application of any of the waiver criteria. This is extremely important to emphasize because the literature is replete with the idea that somehow standard-of-care RCTs by their very nature are ethically exceptional.²⁴ It is true that in standard-of-care RCTs, everyone receives treatment that is standard of care, just as people outside the RCT receive standard of care treatment. And if the only research component is randomization,²⁵ there seems to be little or no additional risks to research participants. The problem is that various positions regarding the ethics of standard-of-care RCT tend to rely on selected specific examples of standard-of-care RCTs.^{6,15,16} It may very well be that some standard-of-care RCT are minimal risk and also may be ethically conducted with modifications of informed consent. But that cannot be true for all standard-of-care RCTs by virtue of being standard-of-care RCTs. It is critically important to recognize that there are many types of RCTs that could fall under the category of a standard-of-care RCT.²⁶

4.1 | Are not all standard of care RCTs minimal risk?

Although it may seem that if everyone in the standard-of-care RCT receives standard of care treatment, the incremental risk or burden attributable to the research is very low. But this will depend on a few issues. It can be shown formally that if one or both of the following conditions are met, then the *average* incremental risk attributable to research participation will be minimal: (1) if the ex ante risk estimate of the 2 standard-of-care interventions is similar; (2) if the allocation ratio of the 2 interventions is similar inside and outside the RCT.²¹

A full explication of the above 2 conditions can be found elsewhere²¹ but for present purposes, we note that not all standard-of-care RCTs have 2 interventions with similar ex ante risk and benefit profiles. It may be that there have been a series of small RCTs favoring one intervention over another, but the data are not definitive enough.^{21,27} For instance, the United Kingdom Dermatology Clinical Trials Network compared the effectiveness of antibiotic prophylaxis (vs no prophylaxis) for recurrent cellulitis.²⁸ Prior to the trial, 4 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).²⁹⁻³² Professional guidelines at the time recommended prophylactic antibiotic therapy.^{33,34}

Further, for a *particular* individual, it is possible that entering an RCT will change the treatment that they receive.¹⁵ Suppose that the standard practice in Mr A's clinic is to use antibiotic prophylaxis for his recurrent cellulitis. But in the standard-of-care RCT, he would have a 50% chance of receiving no prophylaxis instead. It is of course true that it could turn out that no prophylaxis is better, same, or worse than prophylaxis. But it is also true that ex ante risk analysis suggests that for Mr A, the incremental research risk is not negligible.

The analysis of incremental research risks of standard-of-care RCTs turns out to be quite complex. The point here is that a thorough

and systematic, case by case analysis is required and that the mere fact of 2 standard-of-care treatments being compared does not imply that the RCT is minimal risk.

4.2 | Waiver or alteration does not adversely affect rights and welfare of participants

This condition states that the waiver or alteration does not disadvantage participants by depriving them of goods that they otherwise would be entitled to expect. For example, there may be regulations or laws aside from the research regulations that confer on the participants certain rights to information. Or they would have benefited from some arrangement that they would fully expect to receive but which would be threatened if the waiver or alteration were granted.

The most obvious way in which this condition would apply is in regard to their expectation that certain types of medical decisions are “preference sensitive”—that is, in some quantitative sense, the overall utility of the 2 treatments might be similar, but the nature of the treatments is such that personal preferences are important to consider. For example, in a study testing 2 surgical procedures for breast cancer, one procedure might be more invasive and disfiguring with greater adverse effects but may be thought by many surgeons to be more effective.³⁵ 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.³⁶ It is not difficult to see that these are precisely the kinds of situations in which the patients' preferences are especially important—thus, some standard-of-care RCTs will require more, not less, attention to informed consent, to ensure that the patients have an opportunity to choose according to their own values and preferences. The above considerations are recognized in some form by various commentators, as factors that would “engage preferences or values that are meaningful to patients.”¹⁰

4.3 | Impracticability condition

As Table 1 shows, the tension between a pragmatically designed RCT and the requirements of informed consent can be resolved by either modifying the informed consent process (if doing so is ethically acceptable) or by modifying or abandoning the RCT. One aspect of the Table 1 that needs further elaboration is the fact that there could be ethically acceptable solutions that involve *both* a modification of an RCT and some alteration of traditional informed consent. For example, theoretically, there could be an ethically acceptable alternative in which some verbal consent mechanism is used but which requires, on average, that a clinic schedule slightly fewer patients than usual during the period of protocol recruitment and to rewrite some additional software for the electronic health records so that the documentation of consent can be reliably verified. The cost of implementing these modification to the pragmatic trial may be acceptable, and from the ethical point of view, the verbal consent may be sufficient (upon analysis of a particular study).

Another issue that the impracticability criterion raises is that the condition essentially assumes a default: A waiver or alteration cannot be considered as an option unless the RCT is impracticable without

waiver or alteration of the informed consent procedures. However, from an ethical point of view, it is possible that for some RCTs, this default could be challenged. Perhaps, in fact, an RCT would be practicable with full informed consent, but in fact, not all the elements of informed consent are ethically necessary. Or, more likely, to perform the RCT with traditional informed consent would require resources that could be mobilized but which the LHS would rather spend elsewhere (for example, in patient education programs). There will be competing intuitions in such cases. Some may argue that informed consent is so fundamental that it should always be the default so that some modest or even moderate use of resources should always be accepted. Others may argue that if it can be established that a full informed consent is not necessary ethically, then it makes no sense to require it and expend unnecessary resources. The solution may depend on whether the vision of the LHS as creating a new culture of health care delivery and research is successful to such an extent that patient expectations are changed in the long run—which may in turn create a new default position.

5 | CONCLUSION

An LHS does not erase the distinction between research and ordinary clinical care when it comes to RCTs that compare standard-of-care interventions. But it does make the identification of the relevant ethical issues more difficult. On the one hand, this is because the close integration of research and ordinary delivery of care does indeed *sometimes* involve research scenarios of lower risk—especially when compared with RCTs that test novel procedures or interventions. However, it is important not to make the mistake of treating *all* standard-of-care RCTs as a monolithic category of special ethical status. In fact standard-of-care RCTs come in various categories, and serious ethical breaches will occur if this essential fact is forgotten. Indeed, such lapses may in the long run be counterproductive to the vision of an LHS in which patients are active collaborators in the integration of learning and delivery of evidence-based care.

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