

# BMJ Open Reconsidering 'minimal risk' to expand the repertoire of trials with waiver of informed consent for research

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## ABSTRACT

**Background** Progress in therapeutic research is slowed by the regulatory burden of clinical trials, which provide the best evidence for guiding treatment. There is a long delay from evidence generation to adoption, highlighting the need for designs that link evidence generation to implementation.

**Objective** To identify clinical trial designs that confer minimal risk above that inherent in clinical care, to obviate the need for cumbersome consenting processes to enrol patients in prospective clinical research studies. These designs extend the scope of the Learning Healthcare System, a framework for leveraging retrospective 'big data' to advance clinical research, to include data collected from prospective controlled trials.

**Summary** Pragmatic trials may use simplified eligibility criteria, unblinded interventions and objective outcome measures that can all be monitored through the electronic health records (EHR), to reduce costs and speed study conduct. Most pragmatic trials continue to suffer from substantial regulatory burden. Written consent to participate in research can be waived only if the research produces minimal risk above what is encountered in everyday life. However, the 'consent' processes for prescribing Federal Drug Administration-approved medications in clinical medicine are informal, even when they involve decisions of uncertain benefit and higher levels of risk. We propose that trial designs that mimic clinical decision-making in areas of uncertainty (clinical equipoise) and in which no data are generated outside of usual care (ideally by EHR embedding) confer minimal additional risk. Trial designs meeting this standard could, therefore, be conducted with minimal documentation of consent, even when interventions contain different risks. To align with risk encountered in clinical practice, allocation to treatment arms should change (adaptive randomisation) as data are collected and analysed. Embedding of informatics tools into the EHR has the additional benefit that, as adaptive randomisation progresses, evidence-generation transitions into implementation via decision-support tools—the ultimate realisation of the Learning Healthcare System.

## INTRODUCTION

The current approach to conducting randomised clinical trials (RCT) in the USA is widely regarded as overly complex, inefficient and expensive.<sup>1 2</sup> The concept of

*pragmatic trials* was developed to reduce these barriers and provide data about effectiveness in real-world settings. Features of pragmatic designs may include simplified eligibility criteria, straightforward outcome measures, avoidance of placebo controls and maximal use of electronic health records (EHR) to screen for eligible subjects and collect data on outcomes and adverse events in an automated manner.<sup>1 3</sup>

The use of pragmatic designs facilitated by the EHR is aligned with the premise of the Learning Healthcare System (LHS) framework, in which the generation and analysis of data to improve care are considered an ethical imperative.<sup>4</sup> The LHS focuses on 'capturing data at the clinical encounter and using those data to inform ongoing clinical and community practice'.<sup>5</sup> An LHS would leverage electronic data for continuous quality improvement as a mechanism to combine the generation of evidence with implementation, but as currently conceived would be limited to observational data. Bartlett *et al* found that observational 'big data' could feasibly replace only 15% of RCT findings using currently available EHR data<sup>6</sup>; thus, realisation of the LHS to truly advance care must include *prospective* in addition to retrospective data collection.

Improvement in efficiency and reduction in costs theoretically achievable through pragmatic trial designs are usually limited by a requirement to obtain written informed consent by a credentialed member of a research team, and often also by authorisation to obtain and use protected health information from each study subject. If the nature of the study requires study staff to be present onsite, then, cost is expected to increase dramatically, and participation is likely to be limited to large academic medical centres or healthcare systems with existing research infrastructure, as it is true of conventional approaches to conduct of trials.<sup>7</sup>

Institutional review boards (IRBs) or ethics committees regard risk as binary (minimal or more-than-minimal), and *risks associated with interventions* are often inappropriately conflated with the *risks of participation in research*. Although there is disagreement on the subject, it is our opinion that participation in a comparative effectiveness study of two drugs approved by regulatory agencies such as the US Food and Drug Administration (FDA), with long-track records for safety does not necessarily confer substantial additional risk, depending on whether an adaptive design is used and whether data are collected solely for study purposes. Study of FDA-approved drugs used off-label may or may not confer risk beyond that of usual care, depending on how widely the drug is used off-label in the community. Studies of new, unapproved medications with prospect for harm should continue to be conducted through the typical process of oversight by IRBs and the FDA (or analogous agencies in other countries) including documented informed consent. There is, thus, a spectrum of research questions for which a graded approach to regulatory oversight and documentation would be appropriate.<sup>8</sup> For many circumstances, in which the FDA would not require an Investigational New Drug application, a streamlined process for consent and its documentation process could be used.

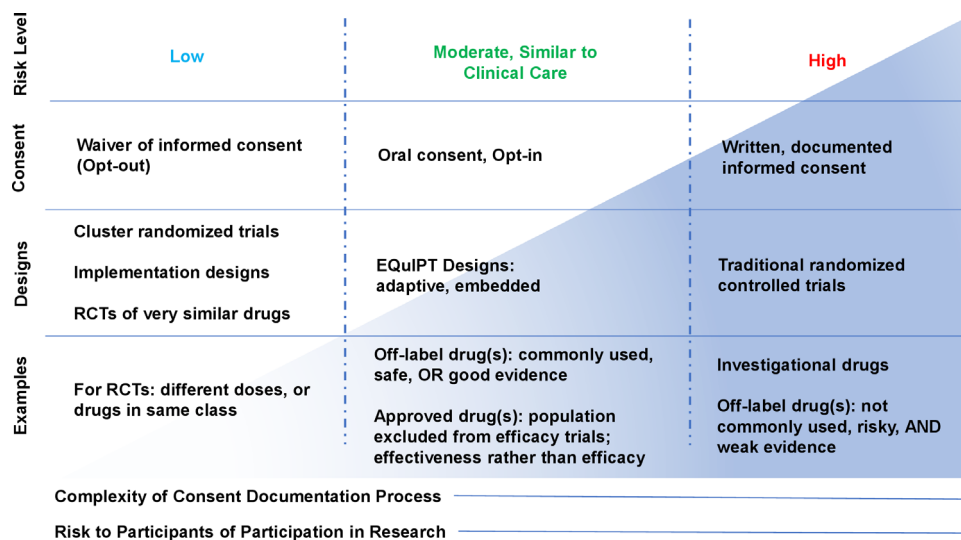
To facilitate the extension of the LHS framework to include prospective trials, we propose a set of trial features that would allow such streamlined processes. The designs themselves are not novel but represent a move from regarding risk and informed consent as binary to viewing risk of participation in research as occurring on a spectrum,<sup>8</sup> with the complexity of the consent process varying accordingly (figure 1). Our call for simplified approaches to obtain and document informed consent is not new.<sup>8</sup> We suspect that a major reason these calls have not been heeded despite use of terms such as ‘urgent’ and ‘crisis’ repeatedly since at least 2014<sup>1</sup> is that the case

has not focused on identifying the widest range of trials that can be considered ‘minimal risk’, amidst multiple other reasons that trials are cumbersome and difficult to participate in, both for the patient and the provider.<sup>1</sup>

A true LHS should not only gather and analyse data but use it to improve care. Translation of evidence into practice is a major challenge, with an average 17-year lag between the time evidence is generated until it is adopted in clinical practice.<sup>9</sup> Although pragmatic trials focus on generation of real-world clinical evidence, considerations for future implementation of advances into usual care are often lacking. Hybrid study designs,<sup>10 11</sup> which include both clinical and implementation outcomes, partially address this gap but are highly complex and typically require research teams with expertise in both clinical trials and implementation science and, thus, are expensive and challenging to conduct. Thus, there is a major need to link evidence generation to implementation using the same informatics tools, to speed improvements in bedside care. The broader the range of participating sites in trials, the broader the reach of linked implementation strategies will be.

The core of our argument is that a much broader range of clinical trials could be performed using greatly simplified procedures for informed consent, because participation would confer minimal additional risk *beyond what is inherent in usual clinical care*. Whether the acronym catches on or not, we will refer to such trials as ‘Embedded, Quantified, Integrated-into-Practice Trials’ (EQuIPT), since an abbreviation is needed within this Commentary.

Our target audience is above all the IRBs and ethics committees that oversee research on human subjects, but in addition, the approach we advocate will only succeed if physicians and patients choose to participate. Our hope is that physicians, patients and institutional leaders who see the value in EQuIPT trials will provide essential advocacy to turn the concept into reality.<sup>12</sup>



**Figure 1** Spectrum of risk associated with participation in interventional clinical research, and proposed proportional gradations in the complexity of the processes of informed consent. EQuIPT, Embedded, Quantified, Integrated-into-Practice Trials (see main text); RCTs, randomised controlled trials.

The argument we present will be:

1. Facilitating the conduct of controlled clinical trials is an ethical issue, in terms of increasing the pace of the advance of knowledge, expanding the range of locations where patients can enrol in trials and increasing the pace at which advances are implemented in practice.
2. Existing US regulations would permit IRBs to interpret risk more liberally than they have traditionally done, that is, there are no statutory nor regulatory barriers in the US.
3. Treatment decisions in usual clinical practice contain considerable risk but usually do not specify a process analogous to informed consent for research.
4. A clinical trial that confers minimal risk beyond what is experienced in everyday care should mimic good practice by changing quickly in response to new information as it is obtained. The most rigorous, and well-established, way to do this is adaptive randomisation.
5. ‘Embedding’ of trial-related data and simple ‘opt-in’ consent processes in an EHR is not essential from the perspective of ethics, but it is highly desirable for minimising the burden on physicians and patients, and, in the USA, for avoiding the need for separate consent related to the privacy of medical records. Embedding would also allow seamless transition from trial results to implementation.

### Personal perspective

We were motivated to explore the possibility of simplifying the processes of informed consent based primarily on our experience running a clinical trial during the emergency circumstances of the COVID-19 pandemic (NCT04359901).<sup>13</sup> The power of leveraging the Veterans Affairs EHR for screening, randomisation, medication dispensing and data collection was obvious—we saw the prospect of an LHS. The barrier we encountered was in the unnecessarily complicated informed consent process.<sup>14</sup> Ironically, our trial would not have qualified for the abbreviated consent process we advocate in this paper, because it conferred risk on participants. However, our additional experience serving on an IRB and participating in other clinical trials and in implementation science meant that we were primed to explore ways that pragmatic trials could be performed more efficiently without compromising ethics. For one of us (PAM), the (in)ability to enrol patients in studies has depended entirely on the (lack of) availability of study staff paid directly from funding for that specific study, and on the (lack of) availability of research space, and on being (un)able to place limits on the numbers of patients scheduled in clinic sessions. Finally, in our clinical practices, we need to either devise treatments for multidrug-resistant infections in patients following organ transplantation (WB-E) or use off-label immunosuppressive drugs for patients with rare inflammatory diseases (PAM), otherwise patients will die. Many of our practice decisions are based on anecdotal evidence—including personal experience—because it is

not feasible to conduct traditional RCTs to determine the best strategies for a wide range of research questions in rare diseases.

### Access to interventional trials as an ethical issue

Many clinically relevant questions can only be answered through clinical trials. Barriers to conduct of trials, including the requirement for a detailed and complex written informed consent process, reduce the number and range of trials that can be done and, therefore, slow progress in quality of care. Laborious processes for consent and data-collection also create a barrier to individual patients’ access to trials, because only large academic centres or healthcare systems with existing and expensive research infrastructures are likely to be able to participate.<sup>15</sup>

Separately, the long-standing assertion that clinical research should be independent of clinical care is disputed by advocates of the LHS,<sup>4</sup> and the assertion that clinical trials should not be designed with the hope of giving benefit to participants is equally antiquated.

Although patients should be discouraged from *expecting* benefit in a trial testing a research question with appropriate clinical equipoise, it is naïve to believe that even the best-informed patients enrol in trials with the primary goal of advancing science and helping others. There are many circumstances in clinical medicine where a patient has no option for treatment other than an unproven treatment or an experimental drug. If such treatment is only available in a clinical trial done at a limited number of sites, there is inequity that may be unavoidable. However, many important questions about clinical management do not involve new drugs with unproven safety and adverse event profiles.

Under circumstances where multiple treatment options are available, a trial may still aim to identify which treatment is better or better tolerated and, therefore, provide benefit to at least some participants: a design in which probability of assigned treatment changes based on results in the trial to date offers potential benefit to patients enrolling later in the trial if one of the treatments turns out to be superior. Expanding the number and type of sites that can participate, most conveniently through a shared EHR but possible through other methods of simplification and electronic data capture, therefore, extends the range of patients who can benefit from participation. Designing a trial to include informatics tools that can be readily adapted to promote implementation of advances confers an ethical benefit in speeding improvement in care for future patients.

### US regulations on informed consent and privacy in research

We provide a detailed discussion of the relevant US regulations in the online supplemental file 1. The only challenging case to make is that a controlled trial of therapeutics can impose only ‘minimal risk.’<sup>16 17</sup> Per US regulations (45 CFR 46.102(j), 21 CFR 50.3(k)), ‘*Minimal risk*’ means that the probability and magnitude of harm

or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests'. We propose that in modern medicine, prescription drugs constitute 'daily life' and have often been proved to do more good than harm—a standard that many physical examination manoeuvres and tests would not meet assuming the physician takes action on perceived abnormal findings.

### The risks of usual clinical care

Many prescription medications, and certainly all medical procedures, carry 'significant risk' as would be defined by clinical *research* standards. Currently, only invasive procedures and some intravenous treatments require written consent in usual care. If the standards of informed consent for research were to be applied to everyday clinical practice, every prescription would require a lengthy discussion and a signature on a form.

Effective physicians attempt to inform patients adequately about known risks, unknown risks and uncertain benefits of the treatments they are recommending. There is insufficient time during a 20 min appointment to review the entire FDA-approved package insert, but there is often enough time to cover medication risks at the same level of detail as they appear in a typical informed consent form, plus patients can be given or directed to printed or online sources of reliable information. Furthermore, the best approaches to education differ among patients and would not be optimised by a rigid structure, particularly for patients who do not have functional health literacy (36% of the US population).<sup>18</sup> For research studies embedded into the EHR, using medications with documented safety records, the rationale for substantially different consent processes for clinical use and research investigation of approved drugs, on the basis of risk, is weak.

### How doctors make treatment decisions and implications for trials

Whenever possible, physicians should base their clinical decisions on high-quality evidence, adjusted to the circumstances of the patient. However, where there are inadequate data, or a patient would have been excluded from gold-standard clinical trials, the physician has no choice but to base clinical decision-making on experience, either personal or combined informally with the experience of colleagues, rather than high-quality evidence. Thus, clinical care in many settings, particularly new or rare diseases, is necessarily guided more by opinion than evidence. This situation creates risk and uncertainty. Inherent to experiential 'evidence,' these decisions are likely to be biased by errors of human cognition, such as anchoring on previous bad outcomes, for example, one patient's severe allergic reaction to a medication making the physician averse to prescribing it to future patients.

Because the process of decision-making in clinical practice is inherently flawed, identifying methods to

quantify the physician's or the community's experience and basing decisions on cumulative evidence should improve outcomes over time. As experience changes, practise should change accordingly. Thus, a trial that simulates good practise should be *adaptive*, with likelihood of assignment to a treatment group changing, in one of several possible ways, based on previous results in the trial.<sup>19</sup>

### Adaptive designs for minimal risk trials

In order for risk to mirror that of clinical care, and to achieve a smooth transition from evidence-gathering to implementation, a core element of EQUiPT designs is that intervention assignment changes based on previously collected results. This approach, whether or not it involves randomisation, mimics decision-making made in usual clinical care, which is often anchored on experience and expert opinion, both of which evolve. EQUiPT aims to quantify the results of this experience and use it to guide evolution of practice rationally.

Different approaches for assignment to adapt are described in the online supplemental file 1. The most rigorous of these is adaptive randomisation, in which the probabilities of randomisation to different arms change based on the positive or negative outcomes seen previously in the trial in a Bayesian manner. At the onset of the study, the probability need not be an arbitrarily chosen 0.5. Probabilities to use at the start of a period of adaptive randomisation could be determined by polling of physicians or content experts, collection of data on medication use in practice, making an estimate based on the literature or other methods.

We regard use of some type of adaptive design as essential to regarding a trial as conferring minimal risk beyond what is inherent in clinical practice, because practice should change as new data are obtained. In contrast, there is not a sound reason that the design must mimic the typical decision-making processes of physicians, as long as such a design does not confer additional risk.

### Embedding

Just as use of adaptive group assignment is essential to design a trial to resemble clinical practice, maximal embedding in the EHR is advisable. Addition of study-related procedures that are not part of usual practice, even if they are minimal risk, invites concern that patients are being asked to take additional time strictly for study purposes, or that privacy issues exceed those of observational EHR-based studies that are eligible for expedited IRB review. Thus, as an extension of the LHS framework, full embedding is the ideal way to integrate an interventional trial into clinical practice (box 1).<sup>3</sup> Another benefit of the embedding is that, when coupled to adaptive randomisation or a 'winning strategy' design, it can be viewed as an implementation strategy to speed the adoption of evidence into practice. Once a study has generated sufficient evidence to support a superior treatment, 100% of patients will be assigned to the preferred



### Box 1 Essential features of Embedded, Quantified, Integrated-into-Practice Trials

- ▶ Embedded in an electronic health record (EHR), without collection of data outside of the EHRs.
- ▶ Adaptive group assignment—adaptive randomisation is preferred. Initial randomisation probability should be based on the best available evidence (eg, inconclusive trials, observational studies, expert opinion or survey of physicians about their practice patterns).
- ▶ Eligibility criteria screens are conducted remotely using only EHR data and then are confirmed or refuted by the physician at the point of care.
- ▶ Outcomes are measured remotely without involving direct contact between the research team and the patient.
- ▶ Patient is verbally informed about the risks and uncertain benefits of interventions as would occur during usual care.
- ▶ Patient is informed about the nature of the research project: it addresses a question about which the medical community and the patient's physician are uncertain.
- ▶ Opt in by the patient and oral consent process, documented by a templated note in the EHR, that is, the patient may decline participation and decide on treatment in discussion with the physician.
- ▶ No financial incentive to the physician or patient.
- ▶ Minimal research training required: no additional research background for the physician beyond the simple technical requirements of trial participation and patient enrolment.
- ▶ Institutional review boards/ethics board review, project and data management and scientific and regulatory oversight are conducted at one experienced coordinating centre with other features decentralised.

treatment arm, and the informatics tools developed to identify patients for the trial can then be used to identify patients for whom the treatment would be appropriate in clinical care—a decision-support tool.

#### Clinical trials with waivers of consent: examples of expanding the range

To date, IRBs have agreed to waive the requirement for informed consent for RCTs under three circumstances: trials with minimal-risk interventions that do not require additional study-specific procedures, trials that compare very similar interventions and trials in which randomisation occurs at the level of the physician or practice, rather than at the level of the individual patient (cluster randomised trials). More details are provided in the online supplemental file 1. Here, we provide examples where clinical effectiveness of drugs could have been or could still be assessed in the form of prospective clinical trials conferring minimal incremental risk, rather than generating flawed, uncontrolled data.

#### Hydroxychloroquine for COVID-19

A recent example is the early use of hydroxychloroquine for the treatment of COVID-19; although academic medical centres tended to recommend its use only in a clinical trial setting,<sup>15</sup> given the clinical risk/benefit estimated by many clinicians, the medication was widely prescribed despite limited evidence. Thus, the impact

of regulatory barriers for research was to encourage use outside of a trial, ultimately slowing evidence generation. If, alternatively, adaptive designs with simple, objective criteria and outcomes had been used, more sites and patients could have participated, and high-quality evidence could have been generated more quickly, ultimately saving time, resources and speeding the review of other, more effective agents.

#### Antibiotic prophylaxis in immunosuppressed patients

Prophylaxis to prevent *Pneumocystis jirovecii* pneumonia (PJP) is widely recommended in patients who will be 'highly immunosuppressed' for 'many months,' although those terms are not specifically defined, and the medications used for prophylaxis bring risk of significant toxicity. At lower levels of immunosuppression with a wide range of drugs, it is unclear and controversial when PJP prophylaxis should be initiated or discontinued, resulting in variable practice patterns. An EQuIPT trial of PJP prophylaxis in moderately immunosuppressed patients could be performed to answer this long-standing question. The trial would likely take many years, due to the low event rates associated with prophylaxis (including mild or severe hypersensitivity reactions, kidney injury, *Clostridioides difficile* infection) and with lack of prophylaxis (PJP), but EQuIPT trials are amenable to long durations and collection of multiple important endpoints once informatics tools are working smoothly.

#### Colchicine for primary prevention of cardiovascular events

In the online supplemental file 1, we outline practical details of how such a study could be done within the US Veterans Affairs healthcare system.

#### Limitations

Above all, our argument will face an uphill battle with the essential gate keepers: IRBs and ethics committees. However, for the EQuIPT approach to succeed, physicians will also need to develop the mindset that by relinquishing their autonomy under appropriate circumstances, they may deliver better care for their patients. Patients will need to be convinced that a doctor who acknowledges uncertainty is not inferior to a doctor who speaks with great confidence, and that enrolment in a trial could improve care for that patient, although the physician should downplan that possibility. The processes of abbreviated opt-in consent will only be used by physicians in the USA if they add very little time to a clinic visit. Some institutions may reasonably require an electronic signature rather than accepting the provider's checkmark for consent to enrol, but the process for obtaining the signature and documenting its having been obtained must be simple.

In order to ensure that patients are not enrolled inappropriately, prospects for abuse must be sought and removed, such as monetary incentives for physicians to enrol patients. Making enrolment in a study mandatory could only be entertained if at least one of the treatments

being studied truly could not be prescribed outside of the trial. The scope of research questions will be limited to eligibility criteria and outcomes for which algorithms with high positive predictive value can be developed, and by the essential feature that participation will not constrain other aspect of patients' medical care and behaviour any more than it would in usual care.

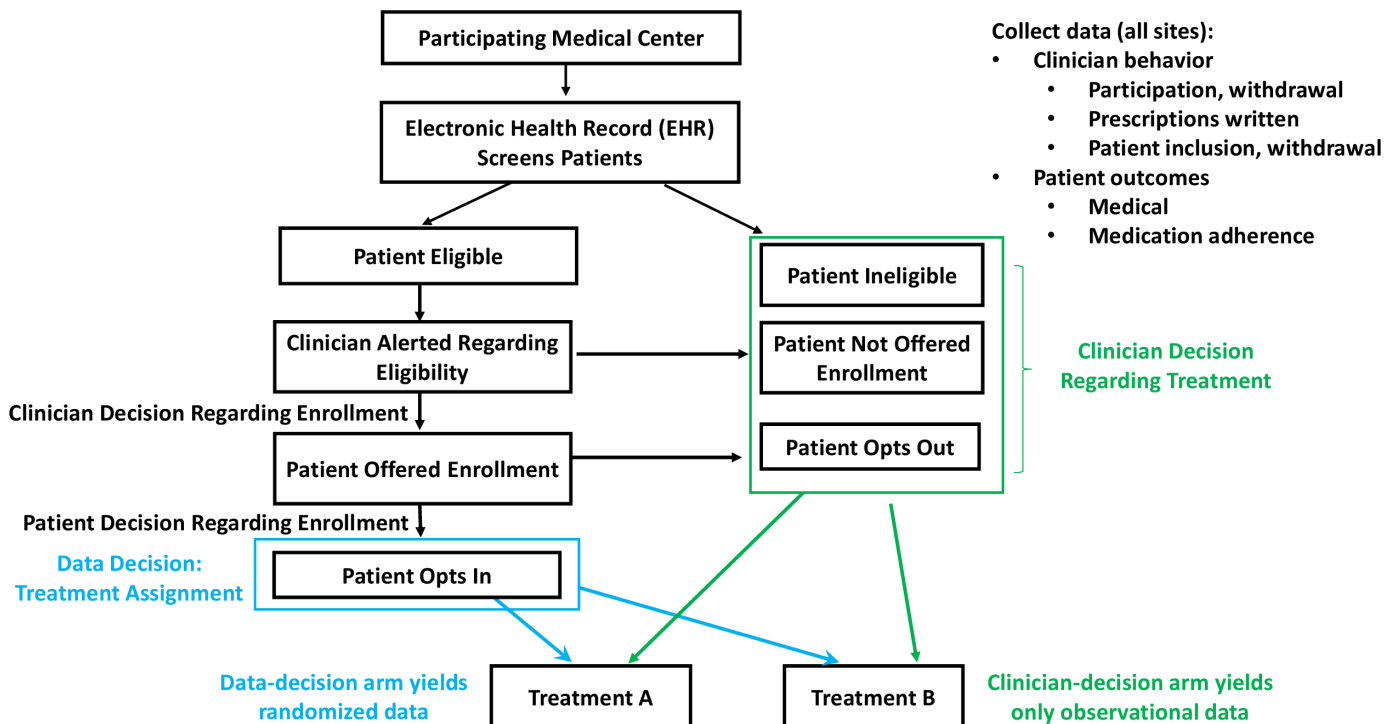
It may be argued that a signature from a patient is a critical guarantee that the patient wished to participate. We argue strongly that the presence of a signature, with or without an approved consent form, provides no guarantee that the patient understands the study, nor even that the informed consent process was conducted properly. The fact that study participants often have little understanding of the studies in which they have enrolled probably represents an amalgam of insufficient health knowledge and inadequate consent discussions.<sup>20</sup> Finally, our proposal is obviously focused on the USA, and even within the USA, it is most appealing in healthcare systems with shared EHRs. Other countries may have regulations that define 'minimal risk' more stringently or have privacy laws that would disallow removal of data from records without consent even if individual patients cannot be identified. In low-income and middle-income countries, strategies already being used for pragmatic trials—simple eligibility criteria, objective outcomes, low burden for data collection and innovative use of app-based systems—may be the cornerstone of successful trial conduct if EHRs are not available either for remote data collection or for checking accuracy.<sup>21</sup> While the access issue would not be entirely resolved, it would be improved, and expanding use of EHRs should lead to additional improvements

over time. For trials that fall into the middle range in the spectrum of risk, that is, EQuIPT, the mindset that a discussion between provider and patient about participation in this type of study differs little from a discussion about different treatment options should facilitate communication.

## CONCLUSION

EQuIPT trial designs so closely resemble usual practice that they bring minimal incremental risk beyond what is encountered in everyday care. The spectrum of trials for which an abbreviated 'opt-in' consent process during clinical care is considered appropriate by IRB needs to move beyond comparison of extremely similar interventions toward more ambitious questions. Use of sophisticated statistical analysis to analyse data and adapt treatment assignment adds rigour but not risk when compared with everyday practice. Even for interventions for which evidence is strong, every treatment decision is an 'experimental therapy' for each patient, and the likelihoods of treatment success and adverse events can only be expressed as probabilities. Practising physicians should want the growth of clinical knowledge to be based on solid evidence, with appropriate statistical analysis employed to tell us whether our experience is likely to reflect truth or random chance and to guide our future practice.

A trial with adaptive assignment to groups based on previous results aims to benefit many of the patients enrolled in the study, not just patients treated after publication. This mindset rejects the assertion that research and clinical care are fundamentally at odds, a theme of



**Figure 2** Design of a pilot study to measure the adoption of an EQuIPT study, in addition to answering a clinical question. EQuIPT, Embedded, Quantified, Integrated-into-Practice Trials.

the LHS framework, and EQuIPT trials would align with a proposed ethical framework for LHS.<sup>4,7</sup> Use of an ‘opt-in’ embedded in the EHR should not be a burden on providers and should improve the likelihood that they will properly inform patients about the risks and uncertain benefits of proposed treatments inside or outside of a trial. Would physicians enrol patients in studies of clinical research questions for which EQuIPT trial designs are appropriate or would they and their patients prefer to retain all decision-making? It is easy to envision pilot studies that would simultaneously address clinically important questions and assess the feasibility and acceptability of EQuIPT trials (figure 2).

With embedding of all data used for eligibility and outcomes, EQuIPT studies could be conducted in a much wider range of clinic settings than traditional RCTs, which, if desire to improve care through trial participation is appropriately acknowledged, corrects an inequity. Finally, we note that ‘doing nothing’ is an active decision with ‘risk’ and therefore ethical implications.<sup>17</sup> Risk exists on a spectrum, and unnecessary barriers to evidence generation should be removed to reflect this reality. As electronic medical data continue to become more amenable to analysis, the more problematic it is if barriers remain in place to prevent them from being used in the most rigorous and efficient ways possible to answer important questions and advance the health of the population in ways that would not be achieved otherwise.

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