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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.[1 2] 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.[1 3]

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.[4] The LHS focuses on 'capturing data at the clinical encounter and using those data to inform ongoing clinical and community practice'.[5] 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[6]; 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.[7]

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.[8] 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,[8] 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.[8] 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[1] 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.[1]

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.[9] 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,[10 11] 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.[12]

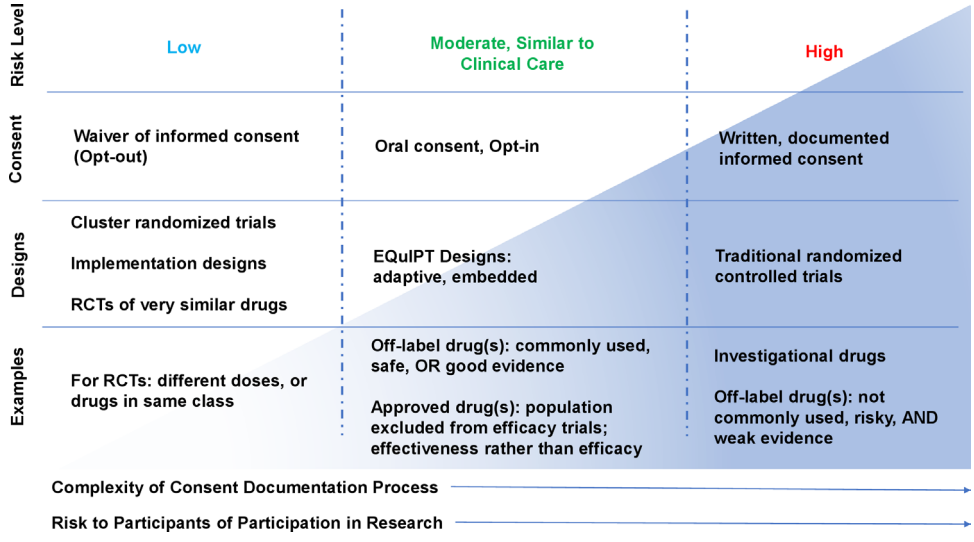

Figure 1 Spectrum of risk associated with participation in interventional clinical research, and proposed proportional gradations in the complexity of the processes of informed consent. EQuIPT, Embedded, Quantified, Integrated-into-Practice Trials (see main text); RCTs, randomised controlled trials.

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).[13] 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.[14] 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.[15]

Separately, the long-standing assertion that clinical research should be independent of clinical care is disputed by advocates of the LHS,[4] 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.'[16 17] 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).[18] 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.[19]

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).[3] 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,[15] 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.[20] 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.[21] 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

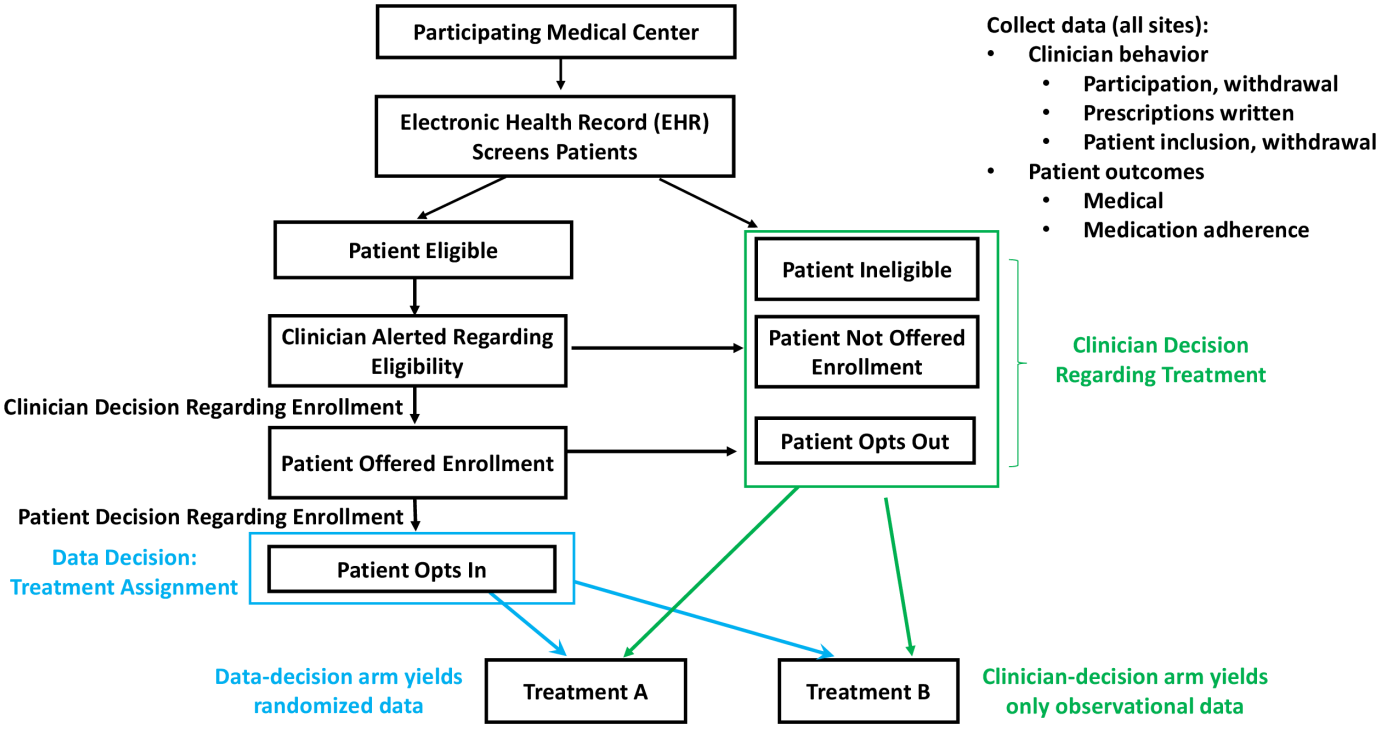

Figure 2 Design of a pilot study to measure the adoption of an EQuIPT study, in addition to answering a clinical question. EQuIPT, Embedded, Quantified, Integrated-into-Practice Trials.

the LHS framework, and EQuIPT trials would align with a proposed ethical framework for LHS.[4 7] 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.[17] 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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Patient and public involvement statement As this is a preliminary concept and thought-generating manuscript, there was no patient or public involvement. Future formative work will include these key stakeholders.

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SUPPLEMENTARY TEXT

US Regulations on Informed Consent and Privacy in Research

Two sets of regulations govern the need to obtain informed consent for research in the US: 45 CFR Part 46 (containing the Department of Health and Human Services' "Common Rule," revised 2018) and 21 CFR Parts 50 and 56 (Food and Drug Administration, FDA), for studies that involve use of FDA-regulated products, even if no Investigational New Drug application or Investigational Device Exemption is required. The need for informed consent can be waived or altered by an Institutional Review Board (IRB) if all criteria listed in section 46.116(f)(3) of the Common Rule are met:

(i) The research involves no more than minimal risk to the subjects;
(ii) The research could not practicably be carried out without the requested waiver or alteration;
(iii) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
(iv) The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
(v) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

Rules for the *documentation* of informed consent are found in section 46.117. However, if only a waiver of the requirement for documentation (i.e. a signed informed consent form) is sought, then the usual 9 specific "Basic" elements of informed consent in 46.116(b) and 8-9 specific additional elements of informed consent in 46.116(c) must be included in the consent process, which must also be conducted using the 6 General requirements in 46.116(a).

In contrast, FDA regulations for IRB review (21 CFR 56.109) provide circumstances for waiver of *documentation* of informed consent (again with the criterion of "no more than minimal risk"), but do not yet include provisions for waiver of *consent* itself, except in the setting of life-threatening emergencies (50.23 and 50.24).[1] However, in a step toward reconciliation with the revised Common Rule after passage of the 21st Century Cures Act in 2016, the FDA issued a

Guidance in 2017 entitled “IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects,” containing criteria virtually identical to those in the Common Rule.

In addition to documenting informed consent, persons who enroll in research studies in the US also typically provide written authorization for collection and use of their Protected Health Information (PHI), in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), which includes a Privacy Rule described in 45 CFR Part 164. An IRB or Privacy Board may approve a waiver of authorization [164.512(i)(1)(i)] if specific criteria are met [164.512(i)(2)(ii)]: no more than a minimal risk to the privacy of individuals, including adequate plans to protect identifiers from improper use, reuse, retention, or disclosure; inability to practicably conduct the research without a waiver; and inability to practicably conduct the research without use of PHI.

It is easy to demonstrate that inexpensive pragmatic trials cannot be conducted without the waiver of written consent (criteria ii and iii). As long as participation is voluntary and research questions have clinical equipoise, the studies will not adversely affect the rights and welfare of subjects (criterion iv), and linkage of trial results to implementation ensures that patients may be informed of results (criterion v). The only challenging case to make is that a controlled trial of therapeutics imposes “minimal risk.”[2 3] 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 maneuvers and tests would not meet assuming the physician takes action on perceived abnormal findings.

Adaptive Designs of EQuIPT Trials

In order for risk to 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 randomization, 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.

We regard use of an 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.

Probability-based: adaptive randomization

In adaptive randomization, the probabilities of randomization 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 randomization 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 the novel approaches we will describe in the next sections.

Although no practicing physician would make a decision by using a random number and a probability between 0 and 1, it could be appropriate for a trial algorithm to make such an assignment as mimicking the behavior of the medical community. For example, if 70% of physicians would choose treatment A based on what is known so far, then giving that treatment assignment a probability of 0.7 is similar to a patient randomly selecting a provider and receiving the typical care provided by that practitioner.[4] Determining how that probability should change as results are obtained includes several options, such as randomized play-the-winner, contextualized multi-armed bandit, and others.[5]

Most recently successful strategy

"Recency bias" is a tendency to make decisions on the basis of one's most recent experience. However, in the setting of having little indication to prefer one approach over another, basing the next decision on the most recent result, or a string of results, is reasonable and is defensible to incorporate into a trial design, especially in a very small trial or early in a trial that will use a different mechanism when more data are available. This is the original "play the winner" design, but we refer to it as "most recent" to distinguish it from the "randomized play the winner" and "winning strategy" approaches. Depending on the clinical event being assessed, a "most recent" design could either give the treatment that succeeded most recently, or the opposite of the treatment that failed most recently.

Use the winning strategy

This approach is easiest to defend as not requiring consent for research because it is based on data and does not involve randomization: the treatment that is working better so far in the study is assigned. The decision-making is no different than if a physician were using well-established evidence or were basing the decision on experience in the absence of evidence, or were polling a group of colleagues and following the majority opinion. The "winning strategy" approach is most likely to be appropriate once criteria for a likely winner have been met, but more data are needed to strengthen the evidence – or to call the previous results into question. Further, because the transition toward the "better" treatment occurs naturally over time, and because the assignment is embedded within the EHR, evidence generation and implementation are coupled, potentially increasing the translation of new data into clinical practice.

Clinical Trials with Waivers of Consent: Current Approaches

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 randomization occurs at the level of the physician or practice, rather than at the level of the individual patient (cluster randomized trials).

Examples of minimal-risk interventions are vitamin supplementation, behavioral interventions,[6] and efforts to improve communication or monitoring. Many such studies include study-specific data collection and therefore require informed consent or HIPAA authorization, but if conducted as a simple study embedded in the EHR with objective outcomes, and particularly without limitations on other behaviors for study participants, they could reasonably be conducted without consent.

For medications or other interventions that confer risk, the only studies approved with a waiver of consent thus far have compared extremely similar interventions that are both considered standard of care: two ways of delivering insulin,[7] or two thiazide diuretics (NCT02185417). Even an innovative pragmatic study of two doses of aspirin (NCT02697916) involved a typical informed consent form (facilitated by an online option) and on-site study staff, and therefore was projected to cost $17 million.[8] There is disagreement about whether a trial may be considered "minimal risk" if it compares two different standards-of-care that are thought to have similar quantitative risks or risk/benefit ratios.[2 3] Some have regarded qualitative differences in risk (e.g., one medication causes fatigue and another causes nausea) as sufficient reason to require consent,[3 9] whereas others focus on the presence of protocolized limitations on other aspects of care or behavior as a key criterion to require consent, which is the stance that we share.[2]

Cluster randomization has been used, especially for minimal risk interventions in which the outcome is best expressed or evaluated at the group level, e.g., public health interventions, strategies for implementation, and evaluation of institutional policies. For interventions involving risk or a high probability of benefit to individual patients,[10] there should be a compelling reason that the intervention must be made on a group level, rather than just as a mechanism for avoiding informed consent requirements when the research question is one that should normally require individual consent. The more risk or benefit to individual patients that is involved, the

more ethically problematic it is to conduct a cluster-randomized trial,[10] especially if patients are not told they are participants in a clinical trial[11 12] or if physicians are required to participate.

Example of an adaptive, embedded trial with abbreviated consent: colchicine for primary prevention of cardiovascular events

Research Question

The anti-inflammatory drug colchicine has recently been shown, in two pivotal randomized trials, to reduce the incidence of major cardiovascular events in patients with a previous event (secondary prevention).[13 14] Since this is a relatively safe drug that has been used for other reasons for decades, there should be interest in whether it can also reduce incidence of cardiovascular events in patients without known cardiovascular disease but with risk factors. As precedents, statins are well-established for primary prevention, and also aspirin but only for a subset of patients at high risk. A trial for primary prevention would presumably need to be several times larger than the trials for secondary prevention because of a lower event rate. Considering that retrospective studies about colchicine and cardiovascular risk came to varying conclusions, it is reasonable to assume that only a controlled trial could provide trustworthy data for primary prevention, as was true for secondary prevention. Finally, although the colchicine RCTs enrolled patients in a highly relevant clinical context (the vast majority were already taking the other medications recommended for secondary prevention), a pragmatic trial to assess real-world effectiveness of colchicine would add value to the literature even if focused on secondary prevention, and the informatics tools developed for an embedded trial could be used to encourage use of colchicine for whichever patient populations are found to benefit.

Setting

The Veterans Health Administration includes 152 medical centers and approximately 1,400 additional community-based outpatient clinics throughout the US. Although the details of the EHRs differ somewhat among centers, they are similar enough that the clinical data can be collected and harmonized in a nationwide database (Corporate Data Warehouse, CDW), which is frequently updated and can be queried from any VA site with appropriate security controls and technical expertise. VA pharmacies all use the same formulary of prescription drugs. The CDW collects both structured and unstructured data, so that algorithms can be used that require use of clinic notes or operative reports (e.g., via natural language processing) in order to have high positive predictive value for identifying disease phenotypes. One downside of the VA database is that patients often get additional care outside the VA system, and the data from

other sources that can be linked are limited to administrative data (e.g., diagnostic codes, medications, dates) from the Centers for Medicare and Medicaid Services, which does not include private insurers.

Eligibility Criteria

Multiple risk estimators have been developed for use in patients without known cardiovascular disease, and they use similar data that are usually available as structured data in EHRs, such as age, sex, race, blood pressure, one or more cholesterol variables, history of diabetes, smoking status, and use of medications such as aspirin or statins. The VA-ASCVD is one such calculator, and a cut-off would be chosen as the inclusion criterion. Exclusion criteria for use of colchicine should include severe chronic kidney disease, advanced liver cirrhosis, and a small number of medications that greatly reduce its metabolism or elimination, all of which should be identifiable through the EHR using diagnostic codes, lab test results, and pharmacy data.

Embedded Tools to Communicate with Provider and Patient

The best method to notify the provider about a patient's likely eligibility and to solicit interest would probably require several iterations of discussion between providers and IT professionals. At some point before the patient's visit to primary care, a notification should be sent through the EHR. The provider then might simply be asked whether s/he would consider approaching the patient about the trial, and check yes, no, or defer until a later visit. If yes, then during the visit, the provider would be given suggested information about colchicine and cardiovascular disease to discuss with the patient (similar to what would be said during a clinical visit outside of a trial) in the EHR, with a link to print a brief information sheet about colchicine and about the study. The bottom of the information box in the EHR would then indicate whether the patient wished to participate. If yes, then a link would appear for a randomization program outside the EHR, which would then inform the provider whether or not to order colchicine through the usual pharmacy procedures.

Ascertainment of Cardiovascular Events

The cardiovascular events collected in almost all trials include myocardial infarction, coronary revascularization (angioplasty/stenting or surgical bypass), stroke, peripheral revascularization,

and hospitalization for heart failure, all of which have had algorithms developed in multiple EHRs. An entirely EHR-based study should probably focus on these objective outcomes and steer clear of angina and transient ischemic attacks, although use of diagnostic codes for these less-severe events could be collected as secondary outcomes. As a quality-control measure, detection of a major cardiovascular event (within the VA EHR or externally) could prompt a message to the primary care provider in the EHR to confirm or refute the occurrence of such an event, and to estimate a date if the event is only detected through use of diagnostic codes on an outpatient basis at some point after the event occurred.

Ascertainment of Adverse Events

The groups receiving or not receiving colchicine could be compared for the occurrence of a huge range of future medical problems, although some would be pre-specified. For this study, the rate of side effects severe enough to be equivalent to a major cardiovascular study would be extremely low. However, for some research questions, both the outcomes being prevented and medication toxicities could have similar magnitudes and both be used to alter the randomization ratio. An example would be thromboembolic events versus major bleeding events. Weighting of events could be used as well, but for this study pooling “major cardiovascular events” into one primary endpoint has a long history of use.

Quality Control

As above, the primary care provider plays a key role in deciding whether a patient is truly eligible and appropriate to consider for enrollment, in adjudicating cardiovascular events, and also in determining whether colchicine should be stopped due to toxicity. Pharmacy records provide data on how often a prescription is being filled and therefore a good estimate of medication use. This is a particular strength of the VA CDW database, since patients who receive care outside the VA almost uniformly fill their outpatient prescriptions at the VA.

Adaptive Randomization

A statistician skilled in Bayesian trial design would be relied upon to specify how often the randomization ratio should be re-calculated and what the changes should be based on the data observed. Criteria to stop the study due to excess harm or very low likelihood of benefit should

be developed in advance. The initial randomization ratio could be 1:1 or determined by informal polling of the institution's cardiologists. In contrast, if the study were a pragmatic trial for secondary prevention, the initial ratio should favor colchicine, on the basis of results from the RCTs.

Implementation

The EHR-based dialogue used to communicate trial eligibility and enrollment procedures to the provider could, with little modification, be modified into a decision-support tool to identify patients in regular practice for whom colchicine might be appropriate, and then facilitate delivery of high-quality information to patient. If the local community were to be enthusiastic about use of colchicine for secondary prevention based on the literature, such tools could be developed for routine clinical use and trial use simultaneously.

Caveats

This example is based on a healthcare system with which we are very familiar, and which has established mechanisms for gathering and analyzing data from a frequently-updated nationwide database, communicating through an EHR that is used both at large medical centers and small community-based clinics, automatically converting such dialogues into permanent notes in the EHR, ordering medications and tracking prescriptions, and even linkage to outside data sources. The methods for doing so are known to only a small number of trained professionals, so an efficient system for running EQuIPT studies would benefit from – and probably would require – a network of stable coordinating centers (such as the VA has) rather than assembling a group as needed for each study. It is easy to envision economies of scale with expansion of such a program.

We have also chosen a research question in which eligibility and outcomes should be relatively easy to assess, and in which it is appropriate to use a well-established pooled primary cardiovascular outcome as the only indication to change the randomization ratio, and in which there is support for the hypothesis from RCTs for a closely related topic. However, "low-hanging fruit" is a good place to start for developing and refining novel methods, and advances in use of EHR data for disease phenotyping will broaden the range of research questions. Progress made using the LHS framework for retrospective data will provide hypotheses to test

in controlled prospective LHS trials, which almost by definition will have adequate methods for ascertaining eligibility and outcomes.

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