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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