Randomized *n*-of-1 Trials: Quality Improvement, Research, or Both?

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The regulatory demarcations between clinical research and quality improvement (QI) are ambiguous and controversial. Some projects that were undertaken as a form of QI were deemed by regulatory agencies to be research and thus to require institutional review board approval. In the era of personalized medicine, some physicians may ask some patients to participate in *n*-of-1 trials in an effort to personalize and optimize each patient's medical treatment. Should such activities be considered research, QI, or just excellent personalized medicine? Experts in research, research regulation, and bioethics analyze these issues.

The regulatory demarcations between clinical research and quality improvement (QI) are ambiguous and controversial.[1] Some projects that were undertaken as a form of QI were deemed by regulatory agencies to be research and thus to require institutional review board (IRB) approval.[2] Different IRBs set different criteria for approving such studies.[3] In the era of personalized medicine, some physicians may ask some patients to participate in *n*-of-1 trials in an effort to personalize and optimize each patient's medical treatment.[4] Should such activities be considered research, QI, or just excellent personalized medicine? Experts in research, research regulation, and bioethics analyze these issues.

THE CASE

The following protocol is submitted to the IRB.

Study Question

Among older children with essential hypertension, are there individual differences in the response to different antihypertensive drug classes?

Background

Hypertension is increasingly diagnosed in children, many of whom need pharmacologic treatment. In essential hypertension several classes of antihypertensive agents could be considered for first-line therapy, and there is a lack of clinical trial evidence comparing these options in children. As a result, the best first-line therapy has not been defined for national guidelines, and significant practice variation exists. Children are therefore prescribed a drug, and potentially committed to this drug for many years, without ever knowing or testing whether this is the best drug choice for the patient among the various acceptable treatment options.

This study aims to determine whether individuals will have different responses to treatment via a series of randomized *n*-of-1 crossover trials to identify the preferred therapy for each patient from among lisinopril, amlodipine, and hydrochlorothiazide. Each of these therapies is used commonly in clinical practice, and all have been shown to be efficacious in blinded, placebo-controlled, randomized clinical trials.

abstract

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Eligibility Criteria

Children aged ≥9 years with essential hypertension necessitating pharmacologic therapy and without a compelling indication to choose 1 particular medication over another.

Study Design

Each *n*-of-1 trial will consist of a series of 2-week treatment periods to test the 3 drugs in random order, repeating drugs and adjusting dosages in a systematic fashion until the preferred therapy is identified. The preferred therapy is defined a priori as the medication that yields normal blood pressure, with the greatest reduction in systolic blood pressure compared with baseline, and without the presence of unacceptable side effects. The results will be applied in the clinical setting and with direct and immediate benefits to each participant.

Outcomes

The effectiveness of each therapy will be measured at the end of each 2-week treatment period with 24-hour ambulatory blood pressure monitoring, and tolerability will be assessed via a side effect questionnaire. In assessing whether one of the medications is most effective for the majority of subjects, the primary outcome will be the percentage of participants for whom each drug is selected as the preferred therapy. Secondary analyses will explore whether patient characteristics predict which medication will be selected as the preferred drug.

Informed Consent

The *n*-of-1 trial is offered to all eligible patients as an optional program. Patients are informed that participation is voluntary, and they can withdraw at any time. Verbal informed consent is obtained from each participant and parent or guardian.

AS AN IRB MEMBER, WOULD YOU CONSIDER THIS PROTOCOL TO BE QI, RESEARCH, OR A PART OF CLINICAL CARE?

Alyssa Burgart, MD and David Magnus, PhD Comments

Existing regulations require that there be a distinction made between "quality improvement" and "research," although if they are done well it becomes difficult to distinguish them. Moreover, *n*-of-1 trials may constitute a unique branch of both QI and research. If the primary objective is indeed improved individualized patient care, not the production of generalizable knowledge, then this may be classified as QI, not necessarily research. However, the use of randomization and blinding makes this project sound very much like a traditional research study, and many institutions may want the oversight that IRBs provide. In a systematic review of *n*-of-1 trials, Gabler et al[5] found that 69% of trials had obtained IRB approval. More than 90% of the trials compared different drugs. This tendency toward obtaining IRB approval may result from the unique nature of *n*-of-1 trials and the ambiguity in terms of whether such trials constitute human subjects research or are a systematic approach to delivery of usual care.

As past and present IRB professionals, we believe that any project that might be construed as research should be evaluated by the IRB for assistance in determining whether approval is necessary. This step helps address the risk that clinicians will institute protocols that meet criteria for review without appropriate oversight to ensure that participants' rights are protected. Given the rich history in research ethics of patients' rights and dignity being superseded by ulterior motives, we are hesitant to deem a study like this one exempt from review. However, there can be wide variability across IRBs, and recommendations may not be uniform. Additionally, in institutions that do not have dedicated scientific oversight committees, the IRB may be the only independent group providing feedback on the scientific value of the proposed protocol design.

If *n*-of-1 trials will be more consistently used in the future, institutions and their IRBs should seek to generate appropriate policies and guidelines to assist in determining when additional oversight is warranted. The authors of the case allude to 1 such institutional policy from UTHealth.[6] In this case in particular, where patients are vulnerable minors, IRBs may have a lower threshold for opting to maintain oversight. If there is a plan to analyze aggregated data of the series of *n*-of-1 patients in an attempt to determine possible generalizable results, then IRB approval should be obtained. If more questions are determined after the data has been collected, approval for retrospective chart review seems appropriate.

The anticipated risks to participants appear minimal and not significantly different from the risks of a patient receiving the same therapies in a less standardized fashion. However, given the controversy surrounding the SUPPORT trial, we must take care to closely question any claims that research on medical practice is no more risky than usual treatment. Ex ante, there is no reason to believe that these patients are exposed to any greater risk than patients receiving usual care. Ex post, we may discover that the first treatment they received was the best, so that they would have received less than optimal care for the later weeks. Or the treatment they would have received in ordinary clinical care was the best option, and they were therefore exposed to side effects that would not otherwise have occurred. However, these are not really differences in risk (which are a product of the probability and

the magnitude of ex ante anticipated harm).

Minor risks related primarily to protocol design may include anxiety and frustration with the complicated nature of randomization and blinding, as well as the risk of nonadherence to the trial and forgoing the information about whether 1 treatment is superior or inferior for the patient. For the individual patient, the time and effort involved in determining the best therapy may be arduous. Other less obvious risks also relate to the ability to garner valid scientific results from the proposed design. If the project design is not scientifically rigorous or data are not properly analyzed, the patient may complete the trial and gain no information on the best therapy. Worse yet, major errors in analysis could potentially lead to a less effective therapy being chosen incorrectly. If the study is not well designed and analyzed, then each patient's participation will be wasted, and even minimal risk of participation is unacceptable.

A standard "consent to treat" form, as most patients sign to receive clinical care, is usually understood to indicate that the patient will receive "usual care." By design, *n*-of-1 trials deviate from usual care. Whether and how to obtain informed consent depends critically on whether this is really a research protocol rather than QI. Regardless, respect for the patient necessitates a more detailed and organized approach to communicating the nature of the activity and to ensure understanding by the patients or their parents. Current regulations may allow waivers of documentation of consent (or even waivers or alteration of consent itself under narrow circumstances). However, there is a strong prima facie case to be made to ensure a robust informed consent. Given the complexity of the proposed protocol, written explanation of the trial may be helpful. Adequate communication with the physicians will be essential. Parental consent and patient assent will ensure an opportunity to discuss expected risks and benefits, to decline participation, to leave the trial at any time, and alternatives (eg, return to "usual care"). If there is a plan to aggregate data for additional analysis, perhaps to discover more generalizable information, then patients and parents should be notified that their data may be used for such purposes before enrollment. The team's plan for data security should also be addressed.

Drs. Samuel, Wootton, and Tyson Comments

The question, here, is whether any and all *n*-of-1 trials should be designated as research, simply because they involve randomization and systematic data collection and analysis.

Research is defined under 45 CFR 46.102 as "a systematic investigation…designed to develop or contribute to generalizable knowledge." However, *n*-of-1 trials are designed to benefit individual patients rather than to produce knowledge generalizable to other patients. Randomization and systematic data collection and analysis are merely methods that may be used in either human subjects research or QI projects[7] to promote unbiased and precise assessments. *N*-of-1 studies are not without difficulty, may not be definitive, and are appropriate only for comparing therapies that are used for chronic conditions and that have measurable treatment effects. However, when they can be conducted, *n*-of-1 trials have been referred to as the ultimate strategy for individualizing medical treatment.[8,9]

The proposed *n*-of-1 trials project avoids multiple sources of error and uncertainty in the way clinicians usually assess the response to antihypertensive agents: "white coat hypertension" during clinic visits, a limited number of blood pressure assessments in a clinic setting with no ambulatory blood pressure monitoring, and the evaluation of only a single medication in the absence of obvious treatment failure. With *n*-of-1 trials, unnecessary treatment may be avoided. When treatment is needed, the benefit of identifying the preferred therapy for the individual patient may be augmented by greater adherence to this treatment as a result of being actively involved in demonstrating its value.[7,10]

SHOULD THIS *N*-OF-1 PROJECT BE CONSIDERED RESEARCH BECAUSE IT MAY PRODUCE GENERALIZABLE KNOWLEDGE?

Whereas the primary aim is to benefit the patients, secondary aims include assessing the percentage of patients for whom each therapy is preferred and the factors that might help predict which therapy would be best for future patients. The involved physicians may also learn much about the acceptance and value of *n*-of-1 trials to identify the preferred treatment of their patients. Does the acquisition of this knowledge, knowledge that would probably generalize to future patients in their center, if not in other centers, require that this project be considered research as well as QI?

We think not. Such a requirement would extend the purview of busy IRBs to many activities that IRBs do not currently attempt to regulate and that are considered desirable features of clinical practice, such as routine data collection within or outside practice networks to monitor and augment patient care and outcomes. Moreover, almost any QI project aims to produce knowledge generalizable to future patients in at least the same center. (Otherwise the project would not be conducted.) Whether the findings generalize to

other centers is irrelevant to the above definition of research or to basic ethical principles, there being no important ethical distinction between patients in different centers.

For these and other reasons, prominent ethicists and others have criticized the above definition and similar definitions of research as ambiguous, outmoded, and counterproductive.[11,12] Kass et al[11] note that "the labels 'research' and 'practice' are poor proxies for what should be our central moral concerns" and call for a system of health care "in which learning and clinical practice are deliberately and appropriately integrated." Likewise, the Institute of Medicine advocates a learning heath care system in which the development of generalizable knowledge is built seamlessly into the provision of health care to most rapidly augment patient outcomes.[13] In such a system, *n*-of-1 studies may be viewed as a quintessential example of how learning can be a byproduct of efforts to optimize the care of individual patients.

SHOULD THIS PROJECT REQUIRE REVIEW AND OVERSIGHT FROM A QI COMMITTEE, IF NOT AN IRB, AND WRITTEN INFORMED CONSENT FROM PATIENTS OR SURROGATES?

With the ongoing changes in health care, the appropriate role of IRBs in a learning health care system has become increasingly controversial.[14–16] In decisions whether this or other QI projects are judged to be under the purview of the IRB, a QI committee, or simply the involved physicians, we doubt that research, QI, and patient care can be separated into mutually exclusive categories and believe that the central issue should be whether patient risk is increased.

QI projects generally implement interventions that are assumed to be beneficial. However, as in clinical practice, many widely recommended treatment methods have unproven value,[17] and some will ultimately be shown to be not only ineffective but harmful.[18] Thus, it should not be assumed that any proposed QI project will be beneficial. The best available evidence should be used in assessing whether it will increase the risk that patients experience were it not conducted.

There is no evidence that the care in this project would be inferior to usual care or that there would be reasonably foreseeable incremental risks. It exclusively uses low-risk interventions that are widely used in usual care. The use of ambulatory blood pressure monitoring minimizes the risk for inaccurate or misleading measurements that could lead to prolonged overtreatment or undertreatment. The potential benefits are likely to outweigh the extra effort and inconvenience and any additional costs.

If the responsible IRB or QI committee agrees, we believe this project should be viewed as a QI project that involves minimal if not reduced risk and does not require written informed consent. In obtaining the agreement of the child and family to participate, the discussion should convey the rationale for the *n*-of-1 trials, the expected benefits, the additional effort required of the family, and the fact they may opt out or may withdraw at any time during the trial. This effort may be most effective if a written description is provided as well.

John D. Lantos, MD Comments

All clinical treatment is, in a sense, a series of *n*-of-1 trials. As physicians, we try a treatment, evaluate whether it works, and decide whether to continue the treatment or change to an available alternative. The main difference between that time-honored and ubiquitous approach to clinical care and a formally designed *n*-of-1 trial such as that outlined here is that the formally designed one is likely to find the best and safest treatment of each patient sooner than an informal and haphazard approach.

There are many good reasons to require IRB oversight of clinical research. Researchers have different goals than clinicians and may sometimes be tempted to compromise patient interests for the sake of a more rigorous study. Patients who participate in research need to know that. Research that is designed to evaluate a new or inadequately studied innovation may have unknown or unforeseen risks. Patients who are asked to participate in research designed to evaluate such innovations should do so voluntarily and with information about the risks. IRBs ensure that consent for such projects is obtained. In this *n*-of-1 study, neither of these concerns is present. The goal of the clinicians who conduct such an *n*-of-1 study is only to improve the treatment of their individual patients. The interventions in the study are all approved, freely available, and widely used. Clinicians would, presumably, seek informed consent for treatment with each of them before initiating treatment. This protocol is designed to reduce risk, increase benefit, and improve outcomes for each patient. It is better for each patient to be treated by such an *n*-of-1 protocol than for that same patient to be treated based on the imperfect clinical judgments or the ingrained habits of their clinician.

In this case, the protocol has a format that we associate with research. It involves randomization and treatment by protocol. That format should not, in itself, trigger the need for IRB oversight. The focus of IRB oversight should be on protecting patients from any risks that are associated with research involving human subjects. If there is no plausible reason to think that a particular *n*-of-1 protocol is associated with increased risks, and

especially if there are good reasons to think that it decreases risks and improves the efficacy of clinical care, then there is no justification for requiring IRB approval or oversight. The question, then, is whether investigators, knowing the rules, can make that judgment themselves, or whether only an IRB can determine that a protocol is exempt from IRB oversight. If the latter, then the rule contains its own contradiction, and nothing is truly exempt from IRB oversight.

ABBREVIATIONS

IRB: institutional review board
QI: quality improvement

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