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The Interaction Between Equipoise and Logistics in Clinical Trials: A Case Study

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Abstract

Introduction—Equipoise is usually discussed as an ethical issue in clinical trials. However, it also has practical implications.

Background—Clinical equipoise is usually construed to mean uncertainty or disagreement amongst the expert clinician community. However, an individual physician's sense of equipoise may vary by location, based on the local standard of care or availability of specific treatment options, and these differences can affect providers' willingness to enroll participants into clinical trials. There are also logistical barriers to enrollment in international trials, due to prolonged timelines for approvals by government agencies and ethical review boards.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

Case Study—A multinational clinical trial of bridging strategies for treatment of non-adherent HIV-infected youth, experienced differing perceptions of equipoise due to disparities in availability of treatment options by country. Unfortunately, the countries with most demand for the trial were those where the approval process was most delayed, and the study was closed early due to slow accrual.

Discussion—When planning multicenter clinical trials, it is important to take into account heterogeneity among research sites and try to anticipate differences in equipoise and logistical factors between sites, in order to plan to address these issues at the design stage.

Keywords

Equipoise; international clinical trials; enrollment; logistics; HIV/AIDS

Introduction

Equipoise is an underlying foundation for ethical clinical trials. It tends to be discussed more in the abstract, as an issue for ethicists and medical philosophers, than as a pragmatic issue in the design of studies. However, varying perceptions of equipoise at different study sites can have practical implications for successful participant enrollment into clinical trials, especially when they interact with logistical issues that also vary by location. This article examines this issue and presents a case study; it then suggests strategies to increase the likelihood of successful implementation of studies that are conducted across multiple settings with heterogeneous conditions.

Background

Accruing adequate numbers of participants is one of the major challenges in randomized clinical trials.[1] Inadequate accrual can lead to premature study closure which, besides being frustrating, exhausts resources – money, investigator and support staff time and effort, and the contributions of those patients who were willing to participate but whose time and data will not provide answers to the clinical question at hand. One potential barrier to accrual is clinicians' willingness to enroll their patients into a study. A factor influencing this is whether clinicians believe that there is true uncertainty about which treatment under study is better – in other words, whether they perceive there to be a state of clinical equipoise.

In their review of current arguments about equipoise, Van der Graaf and van Delden[2] characterize the concept of equipoise as springing from the clinician's obligation to provide competent care and posit that "patient equipoise and individual physician equipoise are irrelevant" to the question of whether a study is ethical; only uncertainty in the expert medical community matters. However, as a practical matter, individual physicians' perceptions of equipoise have an effect on their willingness to enroll participants in clinical trials. Paradis[3] discusses issues that arise in practice when there is scientific uncertainty about best practices but individual physicians disagree, using the example of a study where surgeons volunteered to enroll participants in a randomized clinical trial, acknowledging uncertainty and the need for the study, yet 73% failed to actually enroll many patients.

Van der Graaf and Van Delden[2] state that a favorable risk benefit ratio is required for equipoise. With the growth of multinational clinical trials that include research sites in developing countries, varying resources and standards of care around the world lead to differences in risk-benefit balance and therefore perceived equipoise by location. For example, a trial of a drug that is potentially more effective than the standard of care but only safe with frequent blood tests to monitor for potentially severe adverse events may have perceived equipoise for clinicians in resource-rich settings but not in settings where routine blood work is not available. While there are questions about how to define standard of care for purposes of determining whether a study is ethical and whether it should be in reference to global versus local standards of care,[4] clinicians' willingness to enroll their patients in a trial is likely to be based on the de facto local standard of care and how that affects their perceptions of study equipoise.

In addition to differences in perceived equipoise between locations, logistical barriers that vary by location can also affect the conduct of international clinical trials. For example, opening a U.S.-based clinical trial in other countries requires getting approval from foreign governmental agencies – a bureaucratic process that can take a year or more after U.S. approvals have been received, depending on the country, even if the approval agency has no concerns about the study. As a result, a study may start accruing at U.S. sites a year or more before it has been approved for other locations. Other logistical concerns can involve the availability of resources such as certain lab tests or reliable electricity, or participants' difficulties in getting to research clinics.

When planning a study, it is usual to assess logistical issues that may affect successful conduct of the study. However, study teams usually proceed without considering that variations in perceived equipoise across sites may cause problems. This can be exacerbated if there is an interaction between equipoise and logistics – that is, if the studies with the fewest logistical issues are the ones where clinicians are least inclined to enroll participants because of a lack of perceived equipoise. This article examines the case of a clinical trial that was closed early due to low accrual, International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) P1094,[5] and how it was affected by the above factors. It then discusses considerations for the design phase of clinical trials to help anticipate and hopefully avoid similar problems.

Case study

Clinical background

The standard of care for HIV infection is treatment with combination antiretroviral therapy using medications from multiple classes. Non-adherence can quickly lead to antiretroviral drug resistance, not only to the individual medications but also others in the same drug class.[6,7] Given the chronic nature of HIV disease, medication fatigue and decreased adherence to antiretroviral regimens are pervasive problems. In older HIV-infected children and adolescents, parents may begin to relinquish the responsibility of medication administration and their children may start to rebel against taking medication, resulting in incomplete adherence.[8]

In the setting of incomplete adherence, an optimal treatment strategy would be one that safely bridges the period between the recognition that a regimen is failing due to adherence barriers and the initiation of a new regimen, providing time for interventions to improve adherence to be effective while avoiding disease progression but also minimizing accumulation of additional drug resistance mutations. The problem of drug resistance mutations is especially acute in resource-limited settings, where there may only be first-line and second-line treatment options available for a disease that requires lifelong treatment.

P1094[9] was a study comparing two approaches to treatment for non-adherent youth on combination antiretroviral regimens with detectable HIV viral load, due to poor adherence and with pre-existing M184V NRTI resistance mutation, which confers resistance to emtricitabine and lamivudine while also reducing viral replication. It compared the immunologic outcome of continuing failing combination antiretroviral treatment versus temporarily treating with only either lamivudine or emtricitabine monotherapy as a "bridging strategy" to subsequent suppressive combination antiretroviral therapy. The strategy of using monotherapy bridging had been examined previously in two small studies.[10,11] P1094 was an international study with planned sites in the U.S., Thailand, South America, and Africa. All sites were required to receive approval for the study through their local institutional review boards. Participants or their parents/guardians signed an informed consent prior to participation; assent was obtained as required by local institutional review boards.

Development of the study

Because of the nature of the trial, the protocol development process included a survey of IMPAACT network medical providers about management and acceptable strategies for non-adherent patients. In addition, an ethicist was included in the study team. Among the 57 providers who responded, out of 75 in total, 96% indicated they would be willing to enroll patients in a clinical trial of the bridging strategy.

In adherent patients, it would be unethical to compare a known effective treatment (combination antiretroviral therapy) with one known to be inadequate for virological suppression (monotherapy) and an expedient change to a fully suppressive regimen using two or more active drugs would be indicated. By contrast, in the survey, HIV medical providers caring for patients failing antiretroviral therapy due to poor adherence reported hesitancy to change to a new regimen prior to resolution of adherence barriers, mainly due to concerns for emergence of new resistance mutations and further reduction in future treatment options. However, at the time the study was designed, there was only limited data available for the comparison of being non-adherent to combination antiretroviral therapy versus being non-adherent to monotherapy, and it had been previously shown that completely stopping treatment is detrimental.[12] This raised questions: Would being on a simpler regimen lead to greater adherence? Would there be a large difference in viral control or in the development of resistance? These questions were the basis for assessing equipoise. During the planning phase, the study team discussed equipoise at length, included an ethics section in the protocol (see online Supplementary Appendix), and an ethical review was conducted prior to study initiation.

Varying perceptions of equipoise

A major part of the rationale and ethical justification for use of monotherapy as a bridging therapy was to avoid the development of resistance mutations to classes of antiretrovirals that might be needed for future treatment. The study team had hypothesized that monotherapy bridging offered a favorable risk-benefit tradeoff for participants at all study sites, including in the U.S. Investigators believed it was desirable in all settings to avoid the emergence of resistance to second line regimens, while maintaining the M184V resistance mutation with its effect on HIV replication capacity. Therefore, the strategy was not designed specifically for resource-limited settings, and its control arm was the continuation of the participants' current combination antiretroviral treatment. However, what differed most among sites was not the standard of care for treating non-adherent patients but, rather, the available choices for future HIV treatment options post-study – that is, the anticipated future local standard of care. The team had no reliable way to predict the changes that occurred in future treatment availability at some sites but not others.

In the United States, the number of available classes of antiretrovirals increased during the period P1094 was being developed and implemented, meaning that if a patient's virus developed antiretroviral drug resistance, there were likely to be other treatment options still available. This proved to be a more important factor in clinicians' decision-making than the research team had anticipated because it reduced perceived equipoise among the U.S.-based physicians; there was less concern about preventing resistance to preserve treatment options, so the risk-benefit ratio of measures to avoid resistance changed. By contrast, in many parts of the developing world there are only first-line and second-line treatments available, with no third-line options after that.[13] This difference in antiretroviral drug availability meant that avoiding development of resistance to treatment might be considered by individual practitioners to have less risk to successful long-term treatment in the U.S. than in most low- and middle-income countries, where the vast majority of HIV-infected individuals live.

The disparity in treatment choice availability between countries leads to differing risk-benefit analyses when evaluating the consequences of less effective treatment for a period of time versus the consequences of developing resistance. In resource-limited settings, developing resistance to any particular antiretroviral drug has a much higher opportunity cost than it does in settings where multiple alternative drugs without cross-resistance are available. In other words, this disparity leads to differences in perceived equipoise for physicians in different countries.

Logistics of international studies

In international studies, once a protocol has been approved by the original funding source, it has to go through a multi-layer approval process in the other countries where there are research sites – approval by government agencies, regulatory bodies and research ethics committees. This bureaucratic process can take over a year, even in cases where there are no concerns about the study.

The P1094 team expected that the majority of study enrollment would occur at non-U.S. sites. The protocol section on study monitoring used standard language specifying that the

team would assess accrual after half of eligible IMPAACT sites had been registered. Because so many of IMPAACT's U.S. sites registered, this threshold was reached before governmental approvals had been received in the two countries whose sites had been expected to enroll the most participants. These delays in approval were purely bureaucratic (long processing times, lost paperwork, requiring forms to be resubmitted multiple times) and did not reflect any medical or ethical concerns.

Study closure

The target study size for P1094 was 344 participants. Accrual from U.S. sites was very slow (18 participants from 11 sites over 1.5 years), even after the protocol was revised to address feedback from sites about barriers to enrollment. There was a sense that many U.S. doctors were reluctant to enroll their patients onto this study, because they no longer perceived equipoise with the beginning of the introduction of new, more potent and tolerable antiviral agents in the U.S. and knowing that if patients developed drug resistance there would be other treatment options available. By contrast, site investigators in more resource-limited countries stated that due to limited antiretroviral availability and the lack of access to third line agents, they needed the information that P1094 would provide – that is, they perceived equipoise in the study arms.

Unfortunately, the countries with perceived equipoise that were most eager to enroll patients were also the ones that had the greatest logistical difficulties and delays in securing the needed approvals. Large international sites still had not finished their approval processes over a year after P1094 opened for enrollment. The first U.S. site registered in April 2011, the first Brazilian site registered in October 2012, and the first South African site had not registered by the time the study was closed in January 2013 due to lack of accrual.

Discussion

In international multicenter clinical trials, there can be significant heterogeneity both in perceived study equipoise and logistical issues between research sites; these need to be taken into account during the planning stages. This can also be true when trials are not multinational – there can be large differences in perceived equipoise or logistics between urban versus rural areas, different regions in the U.S., or inner city versus affluent areas, that may affect the acceptability of interventions to clinicians as well as patients. For example, a study where patients are randomly assigned to have in-person versus online contact with providers may be received more favorably in areas of the U.S. where patients have to travel long distances to get care than in metropolitan areas, but those are likely to be the same areas that have fewer potential study participants.

How can a study team anticipate and plan around differences between sites? In the protocol development stage, the team should think about factors that may vary regionally. These can include differences in regulatory challenges, resource availability (treatments, diagnostic or monitoring tests, potable water in patients' homes, specialized clinician expertise), local standards of care, common comorbidities, and cultural values. Once factors have been identified, it is important to ask how these regional differences could affect local clinicians' perceptions of equipoise, and therefore enrollment and trial success. If, for example, some

sites are in areas where malaria or other diseases are endemic, will this increase clinicians' concerns about problematic drug interactions with the treatment under study? If some sites are in areas with a lack of dependable electricity, will clinicians worry that their patients won't be able to safely follow regimens that require keeping medications refrigerated? And if some sites are in places where there are many effective treatment alternatives, will physicians have ethical issues about putting their patients on an experimental regimen? If most participants are expected to come from countries known to have long approval processes, how can accrual monitoring be planned in a way that does not lead to the study being stopped for futility before sites in these countries have received approval to register?

Once differences have been identified, there may be ways to work around them, whether by adjusting site selection criteria or by making other adjustments to the protocol. One possible solution for P1094 might have been to specify that accrual monitoring for feasibility would begin after at least a certain number of sites from each country had registered. Other factors might be addressed by limiting site eligibility (in the examples above, perhaps only to sites in areas with reliable electricity or availability of specific lab tests). If no ways can be identified to work within these limitations, the feasibility of a study needs to be re-evaluated and resources possibly focused on other studies, rather than having the study not reach its enrollment targets and possibly fail after a large investment of resources.

Thinking about and planning for differences in equipoise and logistical issues during protocol design may make the difference between a study that succeeds and one that closes early, thereby doing justice to the commitment by the participants and avoiding the waste of resources involved in prematurely discontinued clinical trials.

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