Uninformative Research

Context

Recent events, including renewed attention to justice, the politicization of science, and the response to vaccines and public health measures in the COVID-19 pandemic have exposed a deep, if uneven, distrust in the research enterprise and academia. This distrust represents a threat to the acceptance of research as a public good and to the adoption of science-based recommendations that would improve health and quality of life.

It is in this context that SACHRP takes up the question of the role of the IRB system, and more generally the role of Human Research Participant Protection Programs, in assessing whether research is designed to be "informative." Informative research has two qualities – it seeks to answer questions that are important (*i.e.,* justify the use of resources and asking individuals to participate) and it is designed to make it likely that the research activities will actually answer those important questions. Assessing the importance of a question (the "value" of the research) is contextual; even if the answer is impactful, the research would not be necessary if the question had already been answered, or if other research was underway that could be expected to provide an answer. Regarding the likelihood that that the research will be able to answer the question (its "validity), it is the nature of science that not all studies, no matter how well designed, will answer their research questions; the recommendations that follow address research that is *foreseeably* uninformative. Poor design, lack of methodologic/statistical expertise, the under-appreciated impact of resource limitations, and simple wishful thinking may lead to research projects that are foreseeably unlikely to meet their goals, waste time and resources, and devalue the contributions of research subjects.

Regulatory Framing

The Common Rule, the *de facto* standard for the protection of participants in research with human subjects, embraces the values articulated in the Belmont Report: Respect for Persons, Beneficence, and Justice. Respect for Persons is partly addressed by the requirement for informed and voluntary consent, constraints on deception, and additional protection for those with diminished autonomy contained in §'s 116, 117, and Subparts C and D. Among other requirements, informed consent must disclose that the activities described *constitute research* and provide an explanation of that research's purpose. Research in the context of the rule is explicitly defined as a "systematic investigation… *designed to contribute to generalizable knowledge.*" Research that is not so designed (*i.e.,* is foreseeably uninformative), cannot meet this definition.

Beneficence is operationalized by the explicit requirements in §111 that research is approvable only if "risks to subjects are minimized" and "risks to subjects are reasonable in relation to anticipated benefit, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result." It is the task of the IRB to determine that these criteria are satisfied. Risk is not justifiable by activities that lead neither to direct benefits nor to knowledge, and level of risk must be calibrated to both to direct benefits and to the importance of the research question.

Justice is the Belmont principle that addresses the broader context of research and is operationalized in §111 as "selection of subjects is equitable." That regulatory paragraph makes clear that the purpose of this criterion is to avoiding exploiting "populations of convenience." More recent considerations of justice

have asked if it should also address the exclusion of communities from research when that exclusion is based on societal circumstances (*e.g.,* race, income) rather than scientific concerns. Further, communities have been historically disadvantaged under the assumption that these societal circumstances *are* scientifically relevant (i.e., racism, eugenics). The reality is that lived circumstances (geography, quality of diet, air and water, etc.) *have* health impacts, and that these impacts can be associated with variables such as race in ways that reflect social structures, not biologic causality.

Issues of justice cannot be cleanly separated from issues of scientific validity, in that the results of research are not generalizable to populations beyond those studied without rigorous justification. This consideration makes equitable selection both a social concern and a scientific concern. Whether justice and equitable selection should be considered as necessary elements of informative research is unclear, because knowledge that is not fully generalizable may still be of some value. §111(a)(2) explicitly requires the IRB to consider "the importance of the knowledge that may reasonably be expected to result." In so far as diminished value (*i.e.,* not fully generalizable knowledge) equates to diminished importance, concerns of justice and scientific value overlap but are not identical.

Charge to SACHRP

1. What level of rigor, completeness, and accuracy should the IRB require or expect an investigator or sponsor to provide when assessing the "importance of the knowledge…?"

It is the role of the IRB to bring a critical eye to the sponsor or investigator's assessment of the importance of the research. The IRB should expect sponsors or investigators to provide a summary of relevant literature, typically as citations within the protocol, and a summary of ongoing research in the same area (a "landscape analysis"). In evaluating these summaries, IRB must keep in mind the perspectives of the investigator or sponsor, and feel free to question any material that raises concerns. Further, the IRB must be open to the possibility that the existing base of research reflects long-standing bias or incorrect results.

As was noted above, "informative" does not simply mean being likely to answer a question, but also means that the question is worth answering. Having established that the IRB has a central obligation to assess whether research is designed to answer important questions, the limitations of any *review mechanism* must be acknowledged. Research often comes to the IRB as a final step, after a protocol has been written and gone through other sponsor- or institution-specific reviews, and the IRB must look to the investigator or sponsor to justify why the importance of the knowledge to be gained justifies the risks. The role of the IRB should be to evaluate this justification from a broader institutional and societal perspective, one informed by a membership selected "to promote respect for its advice and counsel." This role *assumes* that the IRB can expect the investigator/sponsor to accurately depict the scientific background and the research landscape from the perspective of societal value, but such an assumption is not always realistic. Investigators may have goals and incentives that are different from those of the IRB. Research is driven by curiosity and a drive to solve social or health-related problems, as well as more immediate needs to publish, to sustain or obtain funding, to advance careers and, in some cases, to bring products to market rapidly and at the lowest possible cost.

It is not realistic to expect an IRB to have deep expertise in all possible study topics and methodologies with which it could be presented. Particularly in cases where the risk to participants is high, the IRB might choose to supplement its own expertise by seeking the opinion of others in the field (consultants). In the end, it is the responsibility of the investigator to make the research purpose and design accessible to

the IRB; the IRB should be comfortable asking for more information and a better explanation if the research rationale, risks, and benefits are presented in a way that can only be understood by a small number of narrowly trained individuals.

Other ongoing research can mean that the importance of a research question changes over time. The IRB must assess this importance both *prospectively,* at the time of initial review, and concurrently, at the time of continuing review of research. At all those times, it should expect researchers to provide update, if necessary, to the scientific and landscape context along with study statistics.

2. How should IRBs assess *study design* to decide that such knowledge "may reasonably be expected to result" from the research?

It is not up to the IRB to either design or improve research methodology, but only to identify research that it finds is unlikely to achieve its stated goals. The regulatory charge to the IRB is to assess whether "Risks to subjects are *reasonable in relation to anticipated benefits,* if any, to subjects, and the importance of the knowledge that may reasonably be expected to result." In contrast to the requirement that risks be minimized, the charge to the IRB is *not* to maximize anticipated benefits or the value of the knowledge to be gained. While the IRB may serve as a scientific resource to investigators and institutions, its authority to disapprove or require changes is limited to circumstances where risks are unreasonable, or changes are required to satisfy the balance between risks and benefits.

However, if the importance of the scientific *question* (the knowledge to be gained) justifies exposing individuals to the risks of the research, such exposure cannot be justified if the study design is unlikely to answer the question. Research methods are continually evolving, seemingly more and more rapidly as the capabilities of data science expands. IRBs must know how to assess basic statistical plans or equivalent techniques for qualitative research and must have access to specialized expertise where the proposed research goes beyond traditional methods (*e.g.,* machine learning).

In practice, IRBs routinely suggest changes that they expect will reduce risk, improve science, or optimize the use of resources. There is thus a tension between the regulatory authority of IRBs as oversight bodies and their use as an institutional resource to improve the ethics and quality of research, and this tension can lead to an adversarial relationship with investigators who expect the former but receive the latter. Some institutions and sponsors have sought ways to reduce this tension; they may extend the role of the IRB or create other institutional structures to proactively incorporate ethical considerations and/or to give ethicists, IRBs, communities, and potential participants a voice in study design. While the Common Rule describes no specific structure for such involvement, SACHRP endorses this approach, and recommends that the Secretary support it through guidance and research into its effectiveness.

There have, of course, been instances of research conducted without regard to scientific validity. For example, retrospective assessments have concluded that only a minority of interventional trials conducted during the COVID-19 pandemic were designed in a way that could meet their research goals [Glasziou 2020, Haber 2021, Bugin 2021, Hutchinson 2022]. As a result, many individuals may have been exposed to ineffective or toxic therapies without justification, and this can only be seen as a failure of the reviewing IRBs (although some degree of failure is understandable, when researchers and society – including IRBs – are desperate to find therapies in a pandemic). IRBs are also familiar with so-called "marketing trials," which are created to familiarize clinicians with new interventions under the guise of

research. In evaluating such trials, IRBs must stay true to their mission of representing participant interests in the face of commercial or institutional incentives to make their review less rigorous.

3. How should IRBs assess *feasibility* to decide that such knowledge "may reasonably be expected to result" from the research?

Feasibility is an aspect of study design, but SACHRP interprets this charge to more narrowly address whether the resources of an institution or the population context of a research site will allow it to achieve the goals of its (already deemed acceptable) statistical plan. As for other assessments, the IRB will need to rely on attestations from the sponsor and investigator. For research under the jurisdiction of the FDA or other agencies that share its approach, assessing the capabilities of the investigator and site is explicitly the responsibility of the sponsor, and there are mechanisms for ensuring that these responsibilities are met, but for research under the Common Rule, the site (institution) must make its own assessment of its ability to conduct the research. While institutions should only allow their investigators to undertake research they can expect to complete, the institution itself may be as interested in the *conduct* of the research as it is in its outcome. The Human Research Participant Protection Program (HRPPP or HRPP) and the IRB must ensure that the contributions of, and risks assumed by, research subjects are appropriately valued, and this can only happen if the research can be expected to be completed. These assessments may be particularly challenging in the context of single IRB oversight of a multi-site interventional trial, where the IRB is remote and does not have first-hand knowledge of the institution/site conducting the research, its capabilities and history, and the populations it serves.

In the future, SACHRP suggests that the Secretary consider adding explicit investigator, sponsor (*i.e.,* funder) and institutional responsibilities for research conduct to the Common Rule, as appropriate, particularly for complex interventional multi-site trials that place participants at significant risk of physical harm. Such explicit responsibilities would create a stronger incentive for responsible research and for providing appropriate resources to discharge those responsibilities.

As with assessment of study design, assessment of feasibility will be informed by data reported at continuing reviews of research and at the time of DSMB or other safety monitoring committee reports. Continuing review should confirm the ability of a site or research program to enroll enough subjects to meet the goals of its design. Safety monitoring committee reports are often framed as recommendations to research sponsors, but IRBs should receive such reports and should be authorized to act on their recommendations. Should the progress of the research reveal that enrollment goals were unrealistic, the IRB should ask for an updated plan that provides justification for continuing the study or should explore orderly termination of the research or the site in a way that protects subjects already enrolled, maximizes the value of their participation, and prevents others from being exposed to risks for no scientific purpose.

4. How should an IRB evaluate study design with respect to generalizability, subgroup analysis, equity of selection and opportunity to participate? Are such considerations part of an assessment of whether research is informative, or should they fall under a different set of IRB responsibilities (e.g., Justice)?

Considerations of social justice in research, as well as questions about generalizing research results to understudied and underserved populations, have led to institutional and agency expectations that these issues be explicitly addressed in study design. Researchers must balance justice and generalizability against constrained resources; it may not always be practical for a single study to answer its research question, to fully allow all necessary subgroup analyses to be adequately powered, and to proceed in a

way that addresses longstanding inequities in research. In the face of tension between practical concerns and scientific aspirations, researchers and sponsor may be tempted to promise enrollment goals for subpopulations that are unrealistic. As with assessment of feasibility, the IRB is likely to have limited knowledge of institutional and population context and may not know enough to challenge such promises at the time of initial review. If it suspects the stated goals are unrealistic, the IRB should encourage investigators and sponsors to set more realistic targets and explain why a single research study may not be able to satisfy all the requirements of social justice and subgroup analysis. In the end, it is the *research program that* must be held to these standards – it may well be justifiable for individual studies within that program to have more limited ambitions.

Qualitative research faces similar challenges that may be harder to quantify. While study designs may not lend themselves to subgroup analyses or power calculations, conclusions drawn from the shared experience of participants will be sensitive to what groups are studied. Again, researchers should be encouraged to enroll as broad a group as appropriate to answer the research question, and to be explicit about the scope and limits of that answer.

Continuing reviews also offer an opportunity for the IRB to judge whether these aspects of study design were realistic. The IRB may be faced with the situation that the study *will* be able to answer its broad scientific question but will not meet the other goals described above. In such circumstances, orderly termination may not be the best option; among other things, it would devalue the contribution of subjects who have already participated in the research. It is still important for the IRB to hold sponsors and researchers to their stated goals, or to explain why such goals will not be met and provide plans and commitments to address them in future research studies. The IRB should also seek assurance that limitations in the generalizability and applicability of the study's conclusions be made explicit at the time results are disseminated, even though such a dissemination requirement does not fall within its explicit authority. SACHRP suggests that the Secretary consider adding disclosures requirements that explicitly describe such limitations to clinical trial reports on clinicaltrials.gov.

SACHRP notes that, in all domains of research, the IRB cannot discharge its responsibility to ensure that "Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result" if limits on the value of the knowledge to be gained are not honestly described. Systematic mischaracterization of research to give the *appearance* of addressing other institutional or societal concerns is not an acceptable approach to such concerns.

5. Are there special cases where the benefits to society are significant, if remote and not directly the outcome of the specific study, that warrant special consideration (*e.g.,* student research, where the primary goal may be to teach research design as an investment in future knowledge; underpowered or infeasible trials that may make value contributions to later meta-analysis)?

Yes. The two examples listed in the charge represent different challenges to the IRB. Student research often presents minimal or low risk, and IRBs have been permissive in allowing such research to proceed even when it will be uninformative. In most cases, it is not the IRB, but the mentors and institution where the student is studying that should be responsible for the quality of the research. However, either may take a permissive stance when the research presents little risk of obvious harm from the perspective of the researchers or students. In such cases, the hope is that the student will learn from their experience, but the cost is that subjects are likely to be told that they are giving their time, their data and sometimes their bodies to "research," when the activities are not well designed to contribute to generalizable knowledge.

In a very real sense, this is not "research," but rather "rehearsal of research." Although subjects may not be physically harmed, their rights and autonomy are compromised if they are recruited under a false premise. Recognizing the importance and value of student research as part of the education of researchers, SACHRP understands that it may be reasonable to hold it to a different standard of scientific rigor if the risk to subjects is minimal. Indeed, the updated Common Rule made such a different standard explicit in its expansion of exemptions: research deemed exempt is not held to the traditional standards of the Common Rule. SACHRP recommends that the regulatory community be reminded that *all* research should be held to the Belmont standards, even if the regulations do not give the IRB its typical authority. Consistent with the principle of Respect for Persons**,** SACHRP recommends that, when the *primary* purpose is of the research is educational, this should be explicitly disclosed to potential participants during the solicitation of informed and voluntary consent.

For small trials that cannot realistically answer the question they are meant to address, but which, in aggregate, may allow that question to be answered at a later point, some of the same issues apply. Subjects should not be recruited under the guise that the study will answer the question at hand, as this is misleading. On the other hand, if the study is properly designed to allow later pooling of data in a way that would contribute to such an answer, subjects *will* be contributing to science in a meaningful way**.** The IRB should ask that such studies be explicit about their limitations, both in their protocols and in their informed consent forms, and be designed to facilitate data sharing and meta-analysis (e.g., by using commonly accepted outcome measures, inclusion/exclusion criteria, and scales).

6. Should a requirement for assuring research is informative be limited to research funded by HHS or other Common Rule agencies? Should self-funded or institution-funded research be subject to different standards?

From a scientific and ethical perspective, the obvious answer is "no." There is no justification for lowering the standards of science or allowing individuals to be exploited under the guise of science simply because research is not federally funded. However, federal funding implies that research is conducted for the public good; the same cannot be said of commercial research or, possibly, of research with personal or institutional goals in addition to, or instead of, advancement of science. Further, one justification for IRB oversight of federally funded research is that such research is publicly funded*,* and in this context the IRB helps ensure that public funds are spent in ways that are ethical and accountable.

While the goal of generalizable knowledge is explicit in the Common Rule's requirements for informed consent and its definition of research, this may not be the goal of privately funded research. Where private entities are involved, "research" can describe a spectrum of activities, from activities indistinguishable from those properly under the jurisdiction of the Common Rule, to collection of personal data or personal services under commercial contract. Where an entity not under the regulatory jurisdiction of the Common Rule seeks IRB review, possibly out of concern about subject welfare, liability, or a future intention to publish, their activities should be held to the same standard as federally-funded research, with some flexibility not to apply elements of the rule that are ill-suited to their activities (*e.g.,* description of alternatives to participation for a study that is not offering a potentially therapeutic biomedical intervention). Most such other "research" activities are probably socially acceptable if they meet the Belmont Principles, even if they do not meet all the requirements of the Common Rule. In these cases, Respect for Persons dictates that individuals be told about the purpose of the research and its possible risks of harms; Beneficence dictates that individuals should not be exposed to risk for reasons not directly

related to explicit and acceptable goals; and Justice dictates that opportunity be open to as broad and inclusive a population as possible.

General Perspective

The U.S. system of IRB oversight was established in response to instances of research that was once deemed acceptable, but that was inconsistent with a society increasingly committed to recognizing the humanity of all its members. A principle-based formulation ensured that practical subject protections could continue to evolve in step with evolving science and societal progress.

SACHRP endorses a similar approach to a rapidly evolving research environment. While SACHRP has suggested some specific approaches (*e.g.,* landscape analysis), the Committee encourages the regulated community *not* to make these approaches blanket requirements across the domains of regulated research. They should constitute elements of a toolkit, not items on a checklist. Any specific technique should only be used if it contributes substantively to the goal of reducing uninformative research, and when the real possibility of uninformative research justifies placing the additional burden described here on researchers and the research enterprise. The reality is that many different scientific domains conduct research with human beings as the subject, and practical contexts vary widely within these domains. At one extreme is high-risk biomedical research, which presents risks of immediate physical harm to participants, but also commands the most resources. At the other extreme is student-driven social and behavioral research, which is often exempt from most regulatory requirements, may present few risks of physical harm, and, in the case of student research, explicitly has an educational as well as a scientific purpose. Given this spectrum, there cannot be a single set of benchmarks for the IRB. Further, any such narrowly defined tools or techniques risk becoming regarded as ends-in-themselves, obscuring their goal of protecting the rights and welfare of research participants.

The purpose of the IRB is to represent the interests of those participants. In the context of informativeness, the critical question that the IRB must answer is whether the proposed research presents a reasonable opportunity to offer to potential participants – individuals who may not have the knowledge, resources, or objectivity that the IRB can bring to answering that question. A well-constituted IRB can also help balance the interests of investigators, institutions, sponsors and participants. Except in the case of willful research misconduct, *each* of these interests is legitimate and justified, but there is almost always a tension that requires compromise. In this regard, the IRB's role is unique, and it must act with understanding of all roles in the complex research environment.

SACHRP also notes that the charge implicitly assumes the that the IRB will be serving its traditional role of research *oversight.* As noted in the response to the second question in the charge, the complexity of the current research environment invites other approaches to ensuring that research is ethical. Seeking the perspective of potential participants and/or the IRB earlier in research could lead to increased scientific value; decreased overall burden on the research enterprise; and increased trust in the people, processes and institutions of research.

Lastly, SACHRP notes that responsibility for all the determinations described above sits with the IRB/HRPPP *not* because the IRB is necessarily resourced or constituted to best address the concerns, but because the IRB is the only entity explicitly identified by regulation with these responsibilities. Institutions, funding agencies and companies may create and better support other oversight or review bodies to explicitly address issues like scientific importance or feasibility, and in such cases the IRB

should be expected to accept the determinations of these other entities unless it has reason to question their competence or their objectivity.

Appendices

Notes on implementation

SACHRP is aware that recommending additional activities for the IRB/HRPPP raises practical challenges. In this regard, two issues arose repeatedly in the subcommittee's deliberations: the role of the investigator and the issue of the limited resources available to the IRB/HRPPP.

Role of the investigator

Scientific value and validity, and the protection of the rights and welfare of human subjects, are properly responsibilities of the investigator. Investigators are responsible for the actual conduct of the study – no level of external oversight, such as is provided by the IRB, can prospectively ensure that this responsibility is discharged. Further, it is the role of the investigator to formulate the question, design the study, and justify its use of resources. In another sense, however, while these *responsibilities* sit with the investigator, the role of the IRB and HRPPP is to provide *accountability.* The Common Rule was enacted because history showed that responsibility alone was not enough to adequately protect human research subjects, in that investigators might fail to fully consider broader social values or the perspectives of others. This was most obviously demonstrated in the historical use of populations of convenience but is increasingly relevant as the research environment becomes more complex and new ethical issues arise, issues that should not be left to the values and discretion of a single individual.

Resources for the IRB/HRPPP

The role of SACHRP is described in the committee's charter as:

> *The Committee shall advise, consult with, and make recommendations on matters pertaining to the continuance and improvement of functions within the authority of HHS directed toward protections for human subjects in research.*

These duties are discharged by providing "expert advice and recommendations to the Secretary, through the Assistant Secretary for Health."

Historically, SACHRP's advice has informed agency guidance, but has also been used directly by the regulated community as that community wrestles with novel procedural and ethical questions. These two roles are aligned, but not always the same, and reflect two different purposes for regulation. Per the preamble to the First Biennial Report on the Adequacy and Uniformity of Federal Rules and Policies, and their Implementation, for the Protection of Subjects in Biomedical and Behavioral Research, published in the Federal Register in 1982, which framed the later research regulations,

> *Just as society must rely on the experts' wisdom, so too must it rely on their consciences - for which reasonable and well-formulated regulations may still provide both instruction and incentive.*

Regulation, and by extension, SACHRP's deliberations, provides both **instruction**, and **incentive**. Absent regulation, institutions may choose to minimize resources to be used for oversight and ethics to use those same resources to pursue primary research goals or other institutional agendas. If resources are too limited to adequately protect research participants, it is the responsibility of institutions to adequately resource their HRPPPs.

The two threads of investigator responsibility and institutional resources come together in the Common Rule's general approach. Where the FDA regulations at 21 CFR 312 and 812 place explicit responsibilities on the investigator, 45 CFR 46 uses the Federal-wide Assurance to hold the *institution* (generally through its HRPPP) accountable for the responsible conduct of its investigators. An institution should only accept this responsibility if it resources its HRPPP and IRB to discharge it.

Conflict of Interest

Conflicts of interest, or competing interests, are described in several places in the document, and are at the center of the IRB's role. Conflict of interest (COI) has become a value-laden term, as such interests typically enter the public eye when they lead to inappropriate constraints on other goals. In the context of uninformative research, an example would be the continuation of a study to sustain funding, even when it cannot achieve its stated purpose. Because COI is often discovered in such circumstances, it has taken on a negative connotation in *all* circumstances, but this ignores the social values and structures that drive such conflicts. It would be naïve to suggest that a pharmaceutical company does not seek to maximize its profits and minimize its costs. Market incentives are a proven and widely embraced tool for innovation and advancement. Similarly, academic researchers are rewarded for the number and quality of the publications they produce. Such publications help individual studies contribute to a growing base of knowledge, and allow research quality to be assessed. From the perspective of the IRB, these competing interests (and "competing," in this context, implies conflicting, even if it has more benign connotations) are only a problem if they compromise the appropriate protection of research participants or lead them to be enrolled under false pretenses. As noted in the Declaration of Helsinki (World Medical Association, 2013),

> *While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.*

Examples

Why examples? The recommendations above cannot be prescriptive, because the scope and variation of "research" is sufficiently broad that no concrete requirements are likely to apply to all studies. This generality is reflected in the language of the regulations, in terms like "generalizable knowledge" and the requirement that risks be "reasonable" in relationship to benefit. It is also reflected in the purpose of the IRB, which leaves interpretation to a group of individuals qualified by their experience and knowledge, and selected to "promote respect for (their) advice and counsel in safeguarding the rights and welfare of human subjects." In this context, SACHRP's recommendations seek to articulate widely accepted interpretations to serve as a starting point for study-specific debate.

If a study undergoes a separate scientific review, but the IRB believes the study will not be successful, (or is "uninformative"), what should be done?

There are no standard requirements for the makeup of a scientific review committee, but, in general, if such a review is conducted the IRB should expect to defer to the results of a prior scientific review. Such a situation should focus the IRB on its responsibilities to research participants; a formal scientific review should address whether the research is "informative," i.e. has value and validity.

There are no standards for scientific review, which can range from formal peer review to *ad hoc* departmental approval. If the IRB has reason to question the thoroughness of such review, or other

reasons to question the scientific value or validity of proposed research, it has the obligation and authority to have its concerns explicitly addressed, disapprove the study, or require changes, and should do so. In all cases the responsibility of the IRB is to research participants, not the institution or sponsor.

How much should IRBs defer to sponsor preferences to initiate or continue a study when accrual is low, or future feasibility is in doubt? Is this the IRB's responsibility beyond asking for an assurance that accruals can be achieved at continuing review?

"Sponsor preferences" are generally based on extensive experience with the conduct of trials or with the study product or intervention, and such experience should inform the decisions of the IRB. To "defer" generally means to follow the decision of another out of respect for their knowledge and experience; in this case, the IRB's responsibility is to research participants. It should not "defer" to sponsors (or institutions) but should consider the rationale and experience they bring.

How much should IRBs defer to DSMBs on feasibility or whether to continue a study when future feasibility is in doubt?

In general, DSMBs and DSMCs are advisory to sponsors, and it is up to study sponsor whether or not to follow safety committee recommendations to alter or discontinue a trial. Unless it is explicitly granted in the committee charter, safety committees do not have the authority to unilaterally discontinue a trial. If a safety committee recommends changes or discontinuation and the sponsor demurs, the IRB should use its authority to follow the recommendations of the safety committee, which is likely to have more current and specific information about the progress of the study than is typically available to the IRB. There can be no single recommendation for the situation where the safety committee recommends continuing a study that the IRB believes no longer believes justifies the risks and burdens to participants. In such cases, the IRB should request a discussion with the sponsor, investigator, and safety committee so that the groups can better understand their reasoning and the IRB can make a fully informed decision about how to exercise its authority.

Resources

Gelinas, L., Hutchinson, N., Zarin, D. A., Bierer, B. E., How to limit uninformative trials: Results from a Delphi working group. *Med* **4**, 226-232 (2023).

Parse, R. R., Scientific Merit: Integrity in Research. *Nursing Science Quarterly* Nurs Sci Q ***29****, 5 (2015).*

Rajadhyaksha, V., Conducting feasibilities in clinical trials: an investment to ensure a good study. *Perspect Clin Res* **1**, 106-109 (2010).

Zarin, D. A., Goodman, S. N., Kimmelman, J., Harms From Uninformative Clinical Trials. *JAMA* (2019).

Emanuel EJ, Wendler D, Grady C, What Makes Clinical Research Ethical? JAMA 2000;283(20):2701-2711

References

1. Bugin, K. & Woodcock, J. Trends in COVID-19 therapeutic clinical trials. *Nat Rev Drug Discov* **20**, 254–255 (2021).

2. Glasziou, P. P., Sanders, S. & Hoffmann, T. Waste in covid-19 research. *BMJ* **369**, m1847 (2020).

3. Haber, N. A., Wieten, S. E., Smith, E. R. & Nunan, D. Much ado about something: a response to "COVID-19: underpowered randomised trials, or no randomised trials?". *Trials* **22**, 780 (2021).

4. Hutchinson, N., Klas, K., Carlisle, B. G., Kimmelman, J. & Waligora, M. How informative were early SARS-CoV-2 treatment and prevention trials? a longitudinal cohort analysis of trials registered on ClinicalTrials.gov. *PLoS One* **17**, e0262114 (2022).