The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard Bioethics Collaborative

Tuesday, June 27, 2023 | 1:00 PM – 3:30 PM EDT
Virtual Meeting

Blurring boundaries: Revisiting the distinction between research and care
Meeting Summary

Introduction

The distinction between research and clinical care has been fundamental to bioethics since the release of the *Belmont Report* in 1978.[1] The distinction is also a cornerstone of federal regulations, with activities containing research elements triggering the need for human subjects protection oversight under the Common Rule and Food and Drug Administration (FDA) regulations.[2–4] Recent shifts in the clinical research space — including the move toward decentralized clinical trials (DCTs), the entrance of non-traditional entities (such as pharmacies and retails chains) into the research space, and the growing use of embedded pragmatic studies — have generated questions about the nature of the distinction between research and care. These include questions not only about how the distinction should be understood and applied in increasingly complex environments, but also its continued usefulness, making this an opportune time to reconsider the topic.

The research-care distinction amounts to a theoretical framework that yields answers to the question of which activities should be formally regulated as research and provides background assumptions that often figure in substantive research ethics positions and debates. Theoretical frameworks are not static or beyond reconsideration but should be judged by how helpful and fruitful they prove themselves to be in light of current and evolving realities. The essential question driving this Bioethics Collaborative meeting was whether the research-care distinction continues to be a useful lens through which to approach the regulation of clinical research and topics in research ethics more generally. Are there subtypes of research (e.g., pragmatic trials, comparative effectiveness research, point of care trials) that should be considered differently, and if so, does that, and how does that, change the roles and responsibilities of investigators? Are there considerations that suggest the need for a new framework? If so, what are they? What considerations continue to support the research-care distinction as the dominant framework? If a new framework were adopted, how might it be constructed, and what would the ethical implications be, both for the regulation of research and beyond?

Presentations and Discussion

The meeting began with a short introductory presentation, which included an historical overview of the distinction between clinical research and clinical care. There are two ways to approach the distinction between research and clinical care and two ways in which the distinction might be challenged or blurred. The first, theoretical or conceptual blurring, occurs when features thought to be distinctive to research and to distinguish it from from care are, on deeper examination, shown to be shared by at least some cases of clinical care (or vice-versa), and thus cannot be what distinguishes them. For instance, many have held that what distinguishes research from care is that research aims primarily to yield generalizable knowledge, whereas care aims to benefit particular patients via personalized decision-making. However, in some cases, such as learning health systems, clinical care may also aim to generate knowledge without sacrificing personalized care. By contrast, practical blurring occurs whenever it is difficult in practice to separate care from research elements in contexts where both are present and may intertwine. For example, practical blurring might occur in a cluster-randomized trial where the unit is a hospital; patients visiting the hospital for routine procedures may not know about the trial or fully understand what elements of their experience are driven by research protocols as opposed to personalized clinical judgment.

Some meeting participants quickly voiced the opinion that eliminating the distinction between research and care would be dangerous and is unwarranted. Activities may have elements of both research and clinical care, but these elements are fundamentally distinct and should be treated as such. All social concepts, including research and clinical care, have gray and fuzzy boundaries; this should not be taken as supporting a new framework but as a recognized fact about our attempts to categorize and understand the world. Further, this is compatible with acknowledging that the current regulatory system is prone to apply safeguards disproportionately to risk and is in need of reform. Other participants seemed less certain that research and care can always be separated in principle, wondering what element makes them fundamentally distinct. This provided the opportunity to reflect on a common answer to this question — namely, that it is the presence of personalized clinical judgment that separates research from care. Not everyone seemed certain that this feature always or necessarily separates research from care, given that certain types of research may incorporate personalized judgment of clinicians. Other meeting participants voiced the idea that activities containing elements of both research and care exist on a continuum.

The topic of quality improvement (QI) was raised early on as a type of activity that has perennially been challenging to characterize unambiguously as either research or care. Indeed, some participants expressed skepticism over whether a principled distinction between QI and

research is even possible, remarking rather skeptically that the category of QI is used in practice as an attempt to bypass institutional review board (IRB) scrutiny. Some have suggested distinguishing QI and clinical research by the intention to publish research, but not QI. However, there appeared to be widespread agreement that this is an inadequate basis for the distinction, not least because QI efforts are in fact often, and should be, published so that others can benefit from the knowledge gained.

Participants considered a theoretical health system* that, in addition to being a learning health system – in the sense of leveraging patient data to gain knowledge and make continual improvements – embeds clinical trials into everyday practice. Among other things, by being a patient in this health system one agrees, without specific research informed consent for each study question, to becoming a participant in trials comparing accepted practices head-to-head. This hypothetical model provided the opportunity for participants to reflect on the role of informed consent in different types of research and the conditions under which it can be ethical to waive or modify standard requirements on it. Although informed consent for embedded pragmatic studies is sometimes waived, participants acknowledged questions over whether these trials should be considered minimal risk. Further, even if these studies meet the regulatory criteria for a waiver of consent, patients may wish to know that they are being randomized, and consent may play a role in fostering transparency and public trust.

Informed consent continued to occupy a significant place in the discussion. Even when there is agreement that a waiver of consent is ethically acceptable, the discussion highlighted that there can be disagreement over *why* it is ethical. Issues of consent were also raised with regard to cluster-randomized trials, including the example of a cluster-randomized trial where different intensive care units (ICUs) cleaned their patients' wounds with different types of soap: half used regular soap and the other half used antibacterial soap, with the ICUs being randomly assigned to one treatment or the other. There seemed to be a difference of opinion among participants over whether consent would be necessary or advisable in this study. Some participants clearly stated that consent should be sought for any decision that is material to them or their interests, with some participants appearing to think that the choice between the two different soaps did not require consent. Participants also considered whether measures short of consent, such as notification via posters placed throughout a hospital, would suffice. In general, it is no secret that individual clinicians, clinics, and hospitals use treatment methods and practices that may differ from those of their peers; these differences appear to be accepted by society. If the variation was organized and recorded – as it would be in a cluster-randomized trial – important knowledge could be gained, as in the antibacterial soap trial.

* This health system (the Research-Integrated Health System) is described in Largent, Joffe, and Miller (2011).[6]

There has historically been concern about "therapeutic misconception," or the tendency of trial participants to conflate research and clinical care, though evidence supporting its occurrence is mixed. Meeting attendees posed several questions related to this. First, what responsibility is there to ensure that trial participants understand research studies and their integration with clinical care? If there is a responsibility to ensure that research participants understand, how can and should that be done? Several meeting participants agreed that signposts of some fashion may be helpful for distinguishing research from care for trial participants. Meeting participants also expressed concern about DCTs and the entry of non-research-focused entities into the research space. How will the emergence of large retailers, such as Target and Walmart, and large pharmacies, such as Walgreens, as clinical trial sites shape perceptions of medical research and its relation to clinical care?

The purpose of clinical research is to help patients and improve health outcomes. Many medical decisions are made without any solid evidence behind them. The public tends to overestimate the current state of medical knowledge and therefore does not understand the need for medical research. One can imagine a situation where a large (or non-representative) portion of the population resists the move toward trial designs that embed elements of research into clinical care and decline to participate, or are further disenfranchised if they learn after-the-fact that they have unknowingly participated. Public trust in medicine is low, particularly in the development of new therapeutics and practices. Organizations involved with clinical research should be careful to avoid actions that may further undermine public trust.

Finally, the topic of over-regulation surfaced several times. Certain research activities seem to be regulated more tightly than necessary, out of proportion to their actual risks, while others that should be more regulated are not. It may be possible to relieve some of the pressure and motivation to sharply distinguish research from care elements by implementing a regulatory system which more sensitively titrates the level of oversight to the level of risk. Relatedly, the idea of healthcare exceptionalism was raised, with participants pointing out that entities in other sectors (e.g., commerce) frequently engage in activities that would be deemed unacceptable in healthcare and are not penalized for doing so. For example, large amounts of data are collected about us via the internet that we are not aware of, some of which could cause personal damage.

References

1. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: Ethical Principles and Guidelines for the Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Published online 1978. Accessed October 20, 2022. https://repository.library.georgetown.edu/handle/10822/779133

2. *45 CFR 164.512 -- Uses and Disclosures for Which an Authorization or Opportunity to Agree or Object Is Not Required.* Vol 45 CFR Part 164. Accessed January 3, 2023. https://www.ecfr.gov/current/title-45/subtitle-A/subchapter-C/part-164?toc=1

3. *21 CFR Part 50*. Accessed May 4, 2023. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-50

4. *21 CFR Part 56*. Accessed May 4, 2023. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-56

5. Semler MW, Self WH, Wanderer JP, et al. Balanced Crystalloids versus Saline in Critically Ill Adults. *New England Journal of Medicine*. 2018;378(9):829-839. doi:10.1056/NEJMoa1711584

6. Largent EA, Joffe S, Miller FG. Can Research and Care Be Ethically Integrated? *Hastings Center Report*. 2011;41(4):37-46. doi:10.1002/j.1552-146X.2011.tb00123.x