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Reflections on the Belmont Report at 40

By Elisa A. Hurley

Last year marked an important anniversary for the research ethics oversight community: the 40th anniversary of the Belmont Report ("Belmont"), the ethical foundation for our regulatory framework for research with human subjects. I recently had occasion to reread the Belmont Report and I was struck, as I always am, by its elegance and simplicity. But I was also more aware than ever of its being a product of its time.

Before we consider how well Belmont is faring today, we should pause to remind ourselves of Belmont's time. In 1974, the National Research Act was signed into law. Among other provisions, this law created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, and charged it with "identifying the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and developing guidelines which should be followed to assure that such research is conducted in accordance with those principles."

After four years of deliberations, including an intensive four-day meeting at the Smithsonian's Belmont Conference Center, on April 18, 1979, the National Commission published what would come to be known as the Belmont Report. The report laid out three core ethical principles as relevant to human subjects research — respect for persons, beneficence and justice — and the applications of each in the respective requirements to seek informed consent, assess risk and benefit, and select subjects fairly.

The National Research Act that gave birth to the National Commission and ultimately the Belmont Report was signed into law exactly two years after revelations that the U.S. Public Health Service had, for 40 years, been conducting a study on the natural course of untreated syphilis involving hundreds of poor black sharecroppers from Macon County, Alabama. This study continued decades after penicillin had been established as an effective syphilis treatment.

The 20th century saw many examples of egregious research abuse, such as the horrific Nazi prisoner experiments, which were exposed at the "Doctors' Trial" at Nuremberg following World War II, and the intentional infection of mentally disabled children with hepatitis at the Willowbrook State School from the 1950s to 1970s, to name just two. Indeed, in 1966, Henry Knowles Beecher published his now famous article, "Ethics and Clinical Research," in the New England Journal of Medicine, detailing 22 cases of unethical human experimentation that risked the health or life of their subjects without obtaining consent.

As these research abuses came to light, the public responded with outrage and growing distrust of research and its supposed benefits. Policymakers understood that failure to address these issues would jeopardize the entire U.S. research enterprise.

These events are likely familiar history to most in the research community, but it is worth remembering that this was the climate into which Belmont was born — at a time when it was all too common for the sick, the imprisoned, and the powerless to be systematically selected as research subjects for the sake of expediency, often without their knowledge or consent.

Belmont thus emphasized respect for persons and their autonomy, that is, their ability and right to be self-determining and, in particular, to determine for themselves whether or not to participate in research — in short, respect for their right to say no.

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These principles and their application make sense as a response to research that exploited Nazi prisoners, illiterate black men, and disabled children. The Belmont Report's framework was specifically intended to prevent that sort of abusive human subjects research in the future and thereby restore public confidence in the research enterprise.

For some time, there have been calls for revising Belmont or perhaps even starting over with a new Belmont Report, given the changes in research and society since Belmont's time.

In 2016, for example, the National Academies released a sweeping report on the state of academic research in the U.S., subtitled "A New Regulatory Framework for the 21st Century." Published in the middle of the process of revising the Common Rule, the report called for a do-over, urging the federal government to start the process of revising human subjects research regulations from scratch, beginning with a new National Commission to create a more fitting foundational framework, essentially a Belmont 2.0. While the National Academies report was very influential in shaping the 21st Century Cures Act passed later that year, those recommendations were not adopted.

In addition to the National Academies report, a series of articles in both the scholarly and popular press have called for rethinking, rebooting and rebuilding Belmont, pointing out its inadequacies for research today.

The reasons people cite in calling for a Belmont 2.0 fall into three main categories: the changing nature of research, changes in social norms and public attitudes, and the distinction Belmont makes between research and practice.

The changing nature of research. The first set of reasons to revise Belmont relates to the fact that the nature of research and, therefore, the nature of research risks, have changed significantly since Belmont's day. People who make this argument point in particular to developments such as the rise of big-data research, research using the Internet and mobile devices, increased data sharing, and genomic technologies. These research methodologies have the potential to generate vast quantities of data that can be shared, combined and manipulated to generate knowledge in a variety of ways that were unimaginable when Belmont was written. Such research can often be conducted without much, if any, interaction with a person, and more and more by artificial intelligence algorithms rather than by a human investigator.

These technologies have also brought with them risks for new kinds of harms, what we call "informational" or "dignitary" harms, which have to do with revealing one's identity or other sensitive, private information about oneself, one's family, or one's community in unpredictable or unwanted ways. Indeed, some have suggested that these are quickly becoming the most common and concerning risks of contemporary research, a far cry from Belmont's claim that the mostly likely types of harm to research subjects are physical pain and psychological injury. Belmont, the argument goes, therefore provides the wrong ethical paradigm for recognizing, let alone addressing, today's risks.

Changes in social norms and public attitudes. The second set of reasons people point to as a rationale for revising Belmont relates to changes in social norms and public

attitudes. Since Belmont's time, we have seen a democratization of knowledge production, along with increasing skepticism and distrust of expertise and authority, accompanied by demands that institutions of power be more transparent about their activities so they can be better held to account. Patient and disease advocacy groups have been at the forefront of some of these trends, and today the idea of patient-centered research has fully taken hold.

Patient-centered research calls for the engagement of research participants as genuine partners in the research enterprise, involved in everything from identifying research questions, to participating in subject recruitment, to collecting and analyzing research data. The citizen science and patient-led research movements go even further: patients and members of the lay public self-organize and initiate research projects themselves.

The response to the 2010 revelations about Henrietta Lacks and the "immortal" cell line derived from her cancer cells illuminates some of these shifting attitudes. While the collection and use of Lacks's cancer cells without her knowledge or consent did not violate human subjects regulations, then or now, the public discourse around the case revealed a prevailing sense that Lacks and her family were not properly engaged as stakeholders in the collection and research uses of her cells, whether in terms of being informed, being acknowledged and thanked or, as some have argued, sharing in the financial gains that resulted.

The point here is that we have a much more participatory concept of research and the research enterprise today than we did in 1979. Questions exist about how Belmont can accommodate these values, norms and expectations, given that terms like "partnership," "engagement," "reciprocity" and "transparency" do not appear in the Belmont Report.

The distinction Belmont makes between research and practice. The third set of reasons to revise Belmont, according to some, concerns the distinction Belmont makes between research and practice, in order to delineate which activities should undergo review for the protection of human subjects, and whether that distinction still holds. The expansion of research in "usual care settings," including comparative effectiveness research, pragmatic clinical trials, and analysis of medical record databases, along with the rise of quality improvement research and the concept of a learning health care system, all further blur the traditional boundaries between clinical research and clinical practice upon which the Belmont framework rests.

According to Belmont, whether an activity is research as opposed to practice is the trigger for prospective and robust ethical review of that activity (This distinction is reflected in the regulations as well). Critics suggest two basic problems with this distinction: First, some of the activities that sit along the boundary are hard to classify as either research or practice, according to Belmont's definitions, but clearly require some kind of ethical oversight. For instance, they might pose significant risks due to an innovate treatment design. Second, the ethical framework provided by Belmont might not be appropriate for some of the activities that blur this research/practice distinction. For example, it is not clear that the sort of robust prior ethics review entailed by Belmont is necessary for an observational study that does not in any way change a patient's clinical experience or increase his or her risks.

These three reasons all raise legitimate and important concerns. There is no question that the Belmont Report, as written, is dated. If we were to write a new Belmont Report today, it would likely look very different from the Belmont we have inherited. It might include additional or different principles, and it might incorporate some of the values and concepts we have touched on above.

However, it is hard to imagine we will get a new Belmont Report anytime soon. After all, it took seven years just to get some rather modest revisions to the Common Rule.

So, where does that leave those who do the work of supporting and advancing ethical research as it is conducted today? These challenges to the adequacy and fit of Belmont might make us feel unmoored, like we are standing on an unstable foundation as we try to address today's most pressing research challenges.

The good news is that the original Belmont is more flexible than its critics have given it credit for. We need to make a distinction between the three principles laid out in Belmont — respect for persons, beneficence, and justice — and the applications of those principles that Belmont articulates — in informed consent, balancing risks and benefits, and selecting subjects fairly. The former are actually quite enduring, flexible and resilient, while the latter are very much a product of their time and should be seen as such.

We already have examples of the research ethics oversight community making this distinction, adapting the Belmont principles to new applications.

Take the principle of justice. As noted above, Belmont defines justice as the fair distribution of the burdens and benefits of research. The application of this principle in Belmont is very clearly and rather narrowly focused on protecting those who are vulnerable or already burdened from being asked to bear the additional burdens of research. In contrast, beginning in the 1980s, AIDS activists, followed by other patient advocacy groups, began to demand access to clinical trials and to their potential benefits as a matter of justice. Today, most of our community understands justice to require that we think just as carefully about how to ensure broad and equitable access to research and its potential benefits as about how to protect people from its burdens and harms. In fact, the idea that justice includes the right to the benefits of research has, in some circles, been further expanded to include the right to ancillary care or post-trial benefits.

This evolution in thinking about justice did not require or involve making changes to Belmont. Rather, it represents a shift in our collective conception of how to adequately and appropriately apply Belmont's framework, specifically, its justice principle, given changing social circumstances and norms. In fact, it could be argued that it is by appealing to an accepted and agreed-upon justice principle that the research community has been able to engage in conversations and negotiations about how the application of this principle had to evolve to address the full range of justice concerns that have emerged since Belmont's time.

Consider, as another example, respect for persons. In the Belmont Report, respect for persons is framed as respect for the individual's autonomy and protection for those with diminished autonomy, and finds application in the requirement to seek informed consent for research participation. While informed consent is still, of course, a big piece of how we think about operationalizing the principle of respect for persons, it is quite common these days to hear that respect for persons requires other practices, such as sharing research results, making post-trial arrangements for access to care, and paying research subjects. None of these practices were on anyone's radar at the time of Belmont.

Whether these practices are ethically required, and, if so, what scope of obligations is involved in each, are not settled matters within the research oversight community. Nevertheless, again, we did not need to make any adjustments to Belmont to address these new expectations. If anything, Belmont's principle of respect for persons is the guidepost that has led us to these new applications. As we have faced changing social norms and expectations around public and patient engagement, partnership and transparency, we've had to re-examine how best to respect research subjects as persons, just as Belmont instructs.

I mention these examples to suggest that perhaps we do not need to feel unmoored without a new Belmont because we have been very good at thoughtfully adapting the "old" Belmont

to changes in research and society. In that sense, Belmont remains an incredibly useful ethical touchstone for examining research as it is conducted today.

To be sure, there might very well be values and norms that we now consider central to the research enterprise that are not captured by Belmont's principles. For example, Belmont's focus on the individual poorly supports respect for communities and the protection of communities from harm, including dignitary harms.

In addition, very compelling claims have been made that Belmont's concept of justice as the fair distribution of benefits and burdens of research, even when applied in the expanded ways discussed above, might still be too narrow to address important questions, such as, given our current recognition of social and economic inequalities, who gets a seat at the table when the broad research agenda is being set?

In addition, the expansion of "learning" activities that blur the boundary between research and practice are certainly pressing the question of whether we need different or additional principles for the ethical conduct of these activities, including, for example, a principle that says individuals have an obligation to participate in low-risk activities for the common good.

It also remains an open question whether the Belmont principles, despite their flexibility, can adequately address the ethical issues associated with big-data research, which is of such great concern these days. We know the regulations are not keeping up, since such research often involves combining publicly available sets of de-identified data to create new types of data that pose novel and often unforeseen informational, privacy and dignitary risks. How, exactly, should the Belmont principles be applied when data on millions of people are collected from hundreds of sources, then reused and combined?

Do the Belmont principles provide an appropriate framework for determining what adequate protections and practices might look like for big-data research in all its variations? I am more confident than some others that the answer might very well be yes. At its most fundamental level, Belmont requires us to respect the subjects of research to minimize harm to them and ensure any potential harms are reasonable in relation to the anticipated benefits, and to make sure the balance of who benefits from research and who bears its burdens is fair and just. That deceptively simple foundation gives us a lot to work with for thinking about what the guidelines for big-data research might look like — at least once everyone acknowledges that data points correspond to persons, which is, itself, a big hurdle. To me, the question here might not be so much does Belmont provide an adequate ethical framework on which to base guidelines for big-data research as is there the will or the incentive to seriously think about how to apply Belmont's principles in this domain. But that is the subject for another day.

Forty years on, it might very well be time for a new Belmont Report, but until that new report arrives, I believe the original will continue doing its job of lighting our way through the research wilderness.

Author

Elisa A. Hurley, PhD, is Executive Director of Public Responsibility in Medicine and Research (PRIM&R). Contact her at ehurley@primr.org.

