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IRBs and The Protection-Inclusion Dilemma: Finding a Balance

Dr Phoebe Friesen,
McGill University, Biomedical Ethics, Montreal, Canada

Dr Luke Gelinas,
Advarra IRB, Columbia, United States

Dr Aaron Kirby,
Harvard Medical School, Boston, 02115 United States

Dr David H Strauss,
Columbia University Medical Center, Psychiatry, New York, 10032-3784 United States

Dr Barbara E Bierer
Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard, Cambridge, United States

Brigham and Women's Hospital, Boston, 02115-6195 United States

Harvard Medical School, Boston, 02115 United States

Abstract

Institutional review boards, tasked with facilitating ethical research, are often pulled in competing directions. In what we call the protection-inclusion dilemma, we acknowledge the tensions IRBs face in aiming to both protect potential research participants from harm and include under-represented populations in research. In this manuscript, we examine the history of protectionism that has dominated research ethics oversight in the United States, as well as two responses to such protectionism: inclusion initiatives and critiques of the term vulnerability. We look at what we know about IRB decision-making in relation to protecting and including 'vulnerable' groups in research and examine the lack of regulatory guidance related to this dilemma, which encourages protection over inclusion within IRB practice. Finally, we offer recommendations related to how IRBs might strike a better balance between inclusion and protection in research ethics oversight.

Keywords

IRB (Institutional Review Board); research ethics; human subjects research; race and culture/ethnicity; gender / sexuality; BIOMEDICAL RESEARCH

Introduction

Institutional Review Boards (IRBs) play an essential gatekeeping role in the research ethics ecosystem. Introduced in response to significant harms which took place in research settings,

(Corresponding Author) phoebe.friesen@mcgill.ca.

IRBs have long played the role of protecting research participants from the reoccurrence of such harms. Since that time, however, increasing attention has been paid to the way in which some communities and populations have been excluded from research, often in the name of protection. This has led to a growing recognition of the importance of another role for IRBs, one which involves facilitating the inclusion of diverse populations in research. These two roles are in tension when IRBs are required to prioritize either the protection or inclusion of research participants, as might occur with older patients, those with reduced decision-making capacity, or with children. For example, an IRB may recognize the value of studying the effects of a biomedical intervention in an older population but also recognize that participation of older individuals may be associated with greater research-related risk. While in some cases the regulations may directly require protections or exclusionary measures (for example, with prisoners and children), in most cases the regulatory text will admit of multiple defensible interpretations and IRBs will need to make difficult decisions about how to balance competing considerations of inclusion and protection. In addition, the regulations that guide IRB processes, and the culture in which they exist, tends to focus on the importance of protecting research participants, even at the cost of excluding them. We call this the protection-inclusion dilemma. Below, we aim to explore the basis for this dilemma and the way it plays out in IRB processes today. In the first section, we unpack the history of protectionism that characterizes research ethics oversight, and two important responses that have developed in reaction to this history: inclusion initiatives and critiques of the term vulnerability. In the following section, we describe the protection-inclusion dilemma in more detail, discuss what is known about IRBs' tendencies in response to the dilemma, and examine the lack of regulatory guidance related to these two responses. Finally, in the last section, we make several recommendations regarding considerations that should be taken into account if a balance is to be struck between inclusion and protection in research ethics oversight.

I. Looking at the Past: Behind the Dilemma

A History of Protectionism—Contemporary concepts in clinical research ethics and current practices of research oversight developed in response to highly publicized cases of human rights abuses in research involving marginalized populations. Paradigmatic examples of the types of research abuse that spurred the development of research ethics and regulatory oversight frameworks include the U.S. Public Health Service (USPHS) Syphilis Study at Tuskegee, which failed to offer effective treatment for syphilis to the many Black men enrolled in the study, despite the availability of penicillin early in the course of the 40-year study, and the Willowbrook State School hepatitis studies, in which children with intellectual disabilities were intentionally infected with hepatitis (Phoebe Friesen et al. 2017, Beecher 1966). As a result, the importance of protecting vulnerable research participants and populations is central to many foundational documents in research ethics, including the Declaration of Helsinki, the Belmont Report, the International Ethical Guidelines for Health-related Research Involving Humans, and the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans in Canada (Assembly 1996, Ryan et al. 1979, Tri-Council Policy Statement 2018, Council for International Organizations of Medical Sciences 2017).

While protectionism within research ethics stems from an important recognition of the harms that can befall certain individuals or populations as a consequence of research, over-protection, especially when it takes the form of exclusion from research, can lead to significant negative consequences as well (Koski 2014, Charo 1993, Beauchamp 2008, Rhodes 2010, King 2005, Sherwin 2005, Baylis and Kaposy 2010). Attention to these unwanted consequences has led to two complementary initiatives within academic and policy-based discussions related to research ethics oversight: 1) the push towards greater inclusion of many historically underserved and underrepresented groups in research, and 2) an exploration of the concept 'vulnerability' and its application to research protections. We describe each of these below.

Inclusion Initiatives—The most significant response to protectionism in research ethics has been the waves of initiatives in recent decades that have sought to promote the inclusion of groups who have historically been excluded from medical research (Oberman and Frader 2003, Lau et al. 2008, Bayer and Tadd 2000, Caplan and Friesen 2017, Joy L Johnson and Beaudet 2013, Epstein 2008). Many of these initiatives stem directly from the recognition of how harmful exclusionary practices have contributed to the lack of relevant health data for under-represented populations, as well as growing appreciation of the importance of equity and access to novel treatments, which is sometimes only possible through participation in a clinical trial (B.E. Bierer et al. 2020). As such, exclusion from research can be seen as both an epistemic shortcoming, in that it jeopardizes the essential scientific aim of generalizability, and an ethical failure, in that it unfairly deprives some groups of opportunities to participate in research and contributes to an unjust distribution of the benefits of medical research between groups in the long term.

It is important to note that exclusion from medical research is attributable to a range of factors, although concerns related to protecting the vulnerable have played an important role. Distinct histories and narratives of exclusion characterize the exclusion of women, children, and racial minorities, among others, from research, all of whom have been left with significant gaps in health information pertaining to them. Women, for example, have long been intentionally excluded from medical research both because of concerns related to how shifts in hormonal states may complicate research findings and as a result of concerns about how experimental treatments might impact a fetus (Holdcroft 2007). Similarly, the vulnerability of children, and challenges related to consent, have played a significant role in their exclusion from medical research (Diekema 2006). In contrast, racialized populations have not been so intentionally excluded, but have largely been left out of medical research because of a lack of effort to make such research accessible, affordable, and available to such populations, which are often disenfranchised and (justifiably) distrustful of medical research and institutions. It's worth noting, however, that racialized communities are often overrepresented in phase 1 trials, but underrepresented in phase 3 trials (Fisher and Kalbaugh 2011).

In the case of women, particularly those of childbearing potential, exclusion on the basis of protection has had a significant impact on health research. In 1977, the U.S. Food and Drug Administration (FDA) instituted a ban on including women of childbearing potential in medical research (Food and Drug Administration 1977). While this ban was meant to

primarily apply to phase 1 and 2 trials, not to phase 3 or any trials for life-threatening conditions, in practice “the broad and automatic exclusion of premenopausal women from new drug development [became] commonplace” (Joy L Johnson and Beaudet 2013, 64). For instance, in 1991, a woman diagnosed with AIDS was denied access to clinical trials, the only option for any treatment, because her past medical history made her a poor candidate for an IUD (Epstein 2008, 85). Further, the development of medical treatments tested primarily on men has led to the withdrawal of several medications from the market after approval, because of unexpected side effects and/or a lack of efficacy in women (Light et al. 2006, Simon 2005). As can be seen in these examples, some forms of protectionist exclusion are embedded in the regulatory requirements (also consider protections linked to categorical levels of risk and benefit for the inclusion of children in research under Subpart D), while others are derived from a culture of ethics review that has been considered overly risk averse and which fails to calibrate protections with actual risk (Baily 2008).

Responses to the documentation of harms resulting from the exclusion of populations from medical research resulted in the introduction or adaptation of research ethics regulations and guidelines calling for greater inclusion efforts.[1] The National Institutes of Health (NIH) introduced regulations requiring the inclusion of women and minorities in research in 1993, and extended these in 2001 to make inclusion a factor in funding proposals, and require analysis of data according to sex/gender and racial/ethnic differences, particularly in phase III trials; in 2017, the statute was further amended to require such analyses to be submitted to clinicaltrials.gov (Geller et al. 2011, National Institutes of Health 2008, 2017). The FDA published guidelines overturning the ban of women of childbearing potential in early trials in 1993, and released guidelines in 2020 outlining how eligibility criteria, enrolment practices and other aspects of trial design can promote inclusion in industry-led trials (Food and Drug Administration 2020, 1993). The FDA has also introduced incentives to motivate research involving historically excluded populations, such as the Pediatric Exclusivity provision of 1997 (Food and Drug Administration 2018). Guidelines related to the inclusion of diverse participants in medical research have also been released by the Agency for Health Research and Quality and the Centers for Disease Control and Prevention (Geller et al. 2011).

Despite the introduction of these regulations and other initiatives meant to promote inclusion, substantial concern related to diversity within medical research still exists (Oh et al. 2015, Knepper and McLeod 2018, Joy Johnson et al. 2014). An analysis of federally funded randomized control trials published in prominent medical journals in 2009 found that 75% (of 56 trials) failed to report outcomes by sex and more than half (64%, of 86 trials) failed to include any subgroup analysis related to race or ethnicity (Geller et al. 2011). Similarly, an analysis of cardiovascular cohort studies found that more than half limited their samples to only white participants or failed to include any reporting or analysis relating to race or ethnicity (Ranganathan and Bhopal 2006). Such continued under-representation

[1]It is worth noting that these initiatives, part of what Stephen Epstein has described as the inclusion-and-difference paradigm, are not without their shortcomings and their critics (Epstein 2008). Such inclusion efforts often rely on categories of difference that are far from clear cut, built up from historical and social processes that fail to carve nature at its joints, and so may not always be the most effective for medical research. We do not take up the question of whether these inclusion efforts rest on appropriate categories here; see (Spencer 2018) and (TallBear 2013) for some interesting discussions of the topic.

is particularly troubling in light of growing findings from genetic research, indicating particular risks and benefits specific to racial groups and subgroups (e.g., the anti-seizure drug carbamazepine leads to a severe skin reaction in 12% of people of Asian ancestry, including South Asian Indians, who share a genetic predisposition (Mehta et al. 2009, B.E. Bierer et al. 2020, Lim, Kwan, and Tan 2008).

Critiques and Complications of 'Vulnerability'—Another response to the protectionism that underlies research ethics involves efforts to gain a better understanding of the concept of 'vulnerability', which has often been used as a shorthand for those in need of special protections. Several accounts and taxonomies of vulnerability have been put forward, with the aim of clarifying and contextualizing the term (Coleman 2009, Hurst 2008, Rogers, Mackenzie, and Dodds 2012, Lange, Rogers, and Dodds 2013, Luna 2009, Racine and Bracken-Roche 2018, Rogers and Lange 2013, Fineman 2010, Kipnis 2001). Samia Hurst argues that vulnerability involves an "identifiably increased likelihood of incurring additional or greater wrong", but that various wrongs are possible (e.g., breach of confidentiality, being denied benefits of research) (Hurst 2008, 195). Philip Nickel has proposed that cases of vulnerability in research ethics can be divided into consent-based forms, in which autonomy is compromised, and fairness-based forms, in which participants may be more likely to take on the burdens of research without fair compensation (Nickel 2006). Margaret Meek Lange, Wendy Rogers, and Susan Dodds have put forward a variety of distinctions to parse the various meanings of vulnerability, proposing that there are inherent, situational, and pathogenic forms of vulnerability, each of which can be either occurrent or dispositional (Lange, Rogers, and Dodds 2013). Carl Coleman has proposed a taxonomy of vulnerability that places the basis in three features of research ethics: consent, risk, and justice (Coleman 2009). While each of these accounts can be evaluated according to their merits and shortcomings, what they share is an acknowledgement of the complexity of the concept of "vulnerability" and the various forms of vulnerability that can arise in research settings (Luna 2009).

Discussions and debates surrounding the notion of vulnerability have advanced the field of research ethics considerably. The value of defining vulnerability in a way that has practical import for investigators and those working within research ethics review has been emphasized by many (Hurst 2008, Lange, Rogers, and Dodds 2013). There is also widespread agreement on the importance of specifying differences in forms of vulnerability in order to develop appropriate responses to these differences, rather than merely excluding those deemed vulnerable (Racine and Bracken-Roche 2018, Coleman 2009). For example, a vulnerability related to decision-making capacity, which may have important implications for the informed consent process and proxy designations, will not require the same response as a vulnerability based on insurance status, which may impact requirements related to ancillary care. Similarly, vulnerability is well recognized as a feature that, like decisional capacity, can change over time, or can arise only in particular circumstances, such as when a research project involves problematic recruitment techniques or when an individual may be inclined to act out of desperation (Lange, Rogers, and Dodds 2013).

The notion of vulnerability in relation to pregnancy is a case in point. While those who are pregnant may incur novel risks in research, both to themselves and to the fetus, they have no

impairments with regard to decision-making capacity; they are not vulnerable insofar as they are able to assess the risks and benefits of a given study in relation to their values. Despite this, pregnant people have historically been categorized as vulnerable and systematically excluded from research, and now lack relevant health data that could be used to guide their care during pregnancy (Mazure and Jones 2015). They must choose, for example, whether to begin (for acute conditions), continue (for chronic conditions), or suspend (for existing conditions) taking medications on the basis of little or no evidence, thereby potentially exposing the fetus and/or themselves to unintended harm (Baylis and Kaposy 2010, Lyerly, Little, and Faden 2008, Macklin 2010, Blehar et al. 2013). As a result, many have argued that the categorization of pregnant people as vulnerable has led to more harm than good (Kottow 2003, C. Levine et al. 2004), leading to pregnant people no longer being described as such in several regulations and guidelines [2] (Schonfeld 2013, Baylis and Kaposy 2010).

These developments demonstrate how simple notions of vulnerability and recommendations to address vulnerability through exclusion, may, while well-intentioned, may be misplaced and even harmful.

II. Looking at the Present: IRBs in Conflict

The Protection-Inclusion Dilemma—IRBs sit at the center of this history and these developments. Tasked with reviewing every research protocol before it can begin with an eye to potential ethical issues that might arise, IRBs are obligated to protect research participants and play an essential gatekeeping function in the research ethics ecosystem. IRB chairs and members are uniquely faced with the challenge of both protecting those who are vulnerable and ensuring that perceived vulnerability does not lead to unjustified exclusion, a tension we call the *protection-inclusion dilemma*. As inclusion initiatives and pressures to collect health data pertaining to historically excluded populations grow, and as the importance of improving trust in medicine with historically excluded groups garners increasing attention, IRBs are often faced with research protocols that pull in opposing directions. For example, a given protocol may propose to exclude older people, in order to avoid novel and unpredictable risks, as a result of comorbidities and polypharmacy. However, by failing to include a diverse sample with regards to age, the data collected will be limited and may not apply to a significant portion of the population hoping to benefit from the research. This leads to the protection-inclusion dilemma, in which IRBs must reconcile their responsibilities to protect the safety and welfare of participants with those aimed at promoting their inclusion[3].

It is important to note that exclusion of populations from medical research has not always been the result of their perceived vulnerability, although there is substantial overlap between the groups that have historically been excluded from research as a result of perceived vulnerability and those that there is now an impetus to include (Welch et al. 2015, Gennet, Andorno, and Elger 2015). Children, the elderly, individuals with intellectual and cognitive

[2]Of course, concerns related to the exclusion of pregnant people from clinical trials persist; for a recent example, see (Shimabukuro et al. 2021).

[3]It is important to acknowledge that we do not have any empirical data on whether and how often the IRB community acknowledges or seeks to address this dilemma.

disabilities, those living within institutions, and those at risk of suicide are often excluded to avoid potential risks and complications. In other cases, exclusion has not been based on the perceived vulnerability of those excluded, but because research initiatives sought to include a fairly homogenous sample in order to prevent noise in the data, or because of mere convenience. For example, some research protocols only include English speaking participants in order to avoid perceived costs and time delays associated with translating participant-facing materials, but this can lead to substantial exclusions of racial and ethnic minorities in settings in which a significant portion of the population does not speak English fluently. In still other cases, protection is essential, but inclusion is less of a worry. This is the case with prison populations, historically subject to a great deal of coercive and exploitative research, who are now involved in research only under very limited conditions[4]. While it is important to include prisoners in research if they are likely to benefit from such research, either directly as individuals or because the research is specific to prison populations, this applies to a very narrow subset of research. For example, it is important to include prisoners in research aimed at identifying factors related to tuberculosis (TB) transmission in prisons, but not in research assessing TB transmission rates in schools, hospitals, or other non-prison contexts.

IRBs in Practice: Protecting, not Including—Given the history of research ethics discussed above, it is unsurprising that in practice, most IRBs tend to be protectionist in nature (Geisser, Alschuler, and Hutchinson 2011, Klitzman 2015). Franklin Miller and Alan Wertheimer have defined IRBs as essentially grounded in paternalism, in that their decisions restrict the freedom and opportunities of potential research participants (Miller and Wertheimer 2007). This tendency towards protectionism can be seen in the processes taken up within IRBs on a daily basis. It is not unusual to have investigators complete a checklist asking them whether vulnerable populations are likely to be enrolled in their research. A checklist inquiring about unjustified exclusions, however, is much less common. In line with this, Elizabeth Peter and Judith Friedland have commented on how IRB members often struggle to understand vulnerability because of their distance from research with populations deemed vulnerable and therefore tend to "generate an excess of possibilities regarding risk" (Peter and Friedland 2017). Roxanne Lai and colleagues called for an investigation into the attitudes of IRB members towards those with intellectually disability, suggesting that these attitudes may impact the general failure of research to include this population (Lai, Elliott, and Ouellette-Kuntz 2006). Relatedly, Lea Tufford et al. described cases in which the protective stance of IRBs interfered with the goals of inclusion, which may have stemmed from biases and stereotypes members held related to lesbian, gay, and bisexual populations (Tufford et al. 2012).

On the other hand, ethical imperatives related to including understudied participants and populations do not appear to have had a significant impact on IRB functioning. Research

[4]It's worth noting that restrictions on prison research imposed by the Common Rule were heavily criticized at the time, in part because they only applied to federally funded research and allowed other biomedical research in prisons to continue without regulation (McDermott 2013). In response, the Institute of Medicine (now the National Academy of Medicine) formed a committee to evaluate the Subpart C of the common rule which pertained to research in prison, which led to the publication of a report in 2006 entitled "Ethical Considerations for Research Involving Prisoners", which outlined five recommendations related to the conduct and oversight of research involving prisoners (Pope, Vanchieri, and Gostin 2007).

surveying IRB members has raised worries about the ability of IRBs to promote the inclusion guidelines of the NIH, revealing that only one quarter of those surveyed believe that greater inclusion has resulted from the guidelines (Taylor 2009). Another study found that investigators were optimistic about the impact of the NIH policy with regard to the inclusion of women, but saw little change in relation to the inclusion of racial minorities in research (Corbie-Smith, Durant, and George 2006). With regard to the inclusion of pregnant women specifically, Levine has argued that IRBs are unlikely to play a significant role in promoting such inclusion because of the differing interpretations of guidelines, the conservative nature of many IRBs, and the frequency of contraception requirements for women during research (Robert J Levine 2010).

It is also worth noting that there are significant structural factors contributing to the protectionist tendencies of IRBs. While IRBs may be well aware that they ought to address the protection-inclusion dilemma by excluding vulnerable groups only when necessary, the levers available to IRBs to apply protections that would permit inclusion are limited, can be controversial, and require political will and energy to impose. Crucially, the incentives animating IRB decisions serve to reinforce the importance of protection, since any failure to protect participants could lead to significant negative repercussions, while few incentives exist related to the importance of inclusion. Emphasizing inclusion may also require IRBs to tolerate slightly more risk - to balance protection and inclusion and permit trade-offs between them - but this cuts against the tendency among IRBs (and often the institutions that support them) to take the route that is safest or most conservative with respect to participant risk. All of this can be seen as contributing to a default position among IRBs to permit vulnerable populations to be excluded rather than requiring their inclusion under additional protections not originally envisioned in the research plan or protocol.

A great deal of research has documented the variability and inconsistency of IRBs, suggesting that responses to the protection-inclusion dilemma are likely to vary as well (Taljaard et al. 2014, de Champlain and Patenaude 2006). For example, Shah et al. examined IRB review of research involving children and found significant variability with regard to defining minimal risk (Shah et al. 2004). In another study, Glickman and colleagues examined publicly posted policies related to the consent of persons with limited English proficiency in research and found wide variability across IRBs. While some sites noted the injustice of excluding those who do not speak English from research, others emphasized the difficulty of ensuring adequate informed consent, urging investigators to “carefully consider the ethical/legal implications of enrolling subjects who do not understand English”[5] (Glickman et al. 2011, 390).

Interestingly, while IRBs may not have the tools to adequately ensure inclusion, the majority of them would like to. A recent survey of 1,150 IRB chairs, administrators, or members found that approximately two thirds either agreed or strongly agreed that “IRBs should play a key role in ensuring diversity” (Berry et al. 2019)[6]. This suggests that IRBs are

[5]For a recent review of exclusions related to English language see (Muthukumar, Morrell, and Bierer 2021).
[6]This is a significant shift from the 1980s and 1990s, in which, according to Richard Klein, the HIV/AIDS program director in the FDA’s Office of Special Health Issues, there was “an awful lot of resistance” from IRB members to early initiatives related to

increasingly aware and invested in the importance of inclusion, especially as it relates to ensuring good, generalizable, and clinically applicable, and therefore ethical, science. However, the lack of attention paid to inclusion initiatives within the US regulatory framework creates a significant roadblock standing in their way of this goal. This may be exacerbated by common perceptions of the role of IRBs, which sometimes emphasize a distinction between science and ethics, often encouraging a 'stay in your lane' mentality for IRB members (Freedman 1987, Angell et al. 2008). The importance of IRBs in ensuring demographic diversity in research may not be recognized by all stakeholders as well. Indeed, in the survey mentioned above that found significant interest in inclusion amongst IRB personnel, only 35% of 349 primary investigators (PIs) surveyed agreed or strongly agreed that IRBs should play a role in ensuring diversity in research (Berry et al. 2019).

This suggests that, in response to the protection-inclusion dilemma, IRBs have largely leaned towards their roots in protectionism (Strauss, White, and Bierer 2021). Faced with competing demands to both protect and include those that are often deemed vulnerable in research, IRBs, understandably, look to the Common Rule, which places a significant emphasis on protection and says little about inclusion[7]. Unfortunately, in practice, prioritizing protection over inclusion may often mean exclusion or under-representation of those deemed vulnerable. While we have come a long way since the early days of research ethics defined by protectionism, and we have learned a lot from nuanced discussions of vulnerability and inclusion, these developments have not been incorporated in regulation or guidance. Significant theoretical strides have not yet been translated into practice. Finally, while IRBs may play a unique role and have unique authority with regard to oversight of subject selection, the goals of inclusion in research also rely a great deal on sponsor, funder, and researcher motivation, capacity, and behavior, as well as regulatory requirements.

A Lack of Regulatory Action—Despite increasing recognition of the complexity of vulnerability and the importance of including marginalized communities in research, the 2018 revision to the Common Rule, the central regulatory framework governing IRB decision-making in the United States, has largely failed to take up these developments, leaving IRBs to face the protection-inclusion dilemma on their own.

With regard to vulnerability, Section §46.111 of the 2018 Common Rule states that research should only be approved if:

> Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons. (§46.111(a)(3), our emphasis)

inclusion (quoted in (Epstein 2008, 65)). As Epstein writes, this may have been because IRBs had recently come into being and their development was justified by their role in protecting vulnerable subjects.

[7]While we primarily focus on the Common Rule here, we acknowledge that FDA regulations are also an important part of the regulatory infrastructure in the U.S. Much of our critique can be extended to those regulations as well.

And further requires that:

> When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects[8]. (§46.111(a), our emphasis)

While the Common Rule should be commended for moving away from vulnerability as a blanket feature that always applies to some individuals or populations, the current discussion of vulnerability still leaves a great deal unsaid. Vulnerability is only recognized in relation to coercion and undue influence, and while economically or educationally disadvantaged persons have been recognized as vulnerable, what these forms of vulnerability mean for practice in research ethics is not explained. Nothing is said about how vulnerability may be context-specific, dimensional, and transient, but instead an impression of "children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons" as essentially vulnerable is offered. Similarly, no detail is offered about how vulnerability should be responded to, aside from the term 'additional safeguards'. On one reading, one might hope that these additional safeguards might help to bridge the ethical imperatives to both protect and include. Such additional safeguards may allow for the inclusion of vulnerable populations in research, but ensure that sufficient safeguards are in place to protect them. Unfortunately, no description or examples of what such additional safeguards might look like is given; without further elucidation, many IRBs are likely to turn to exclusion, the oldest and surest response to vulnerability[9].

Discussions of inclusion in the federal regulations center around prisoners, children, and pregnant women[10]. The section focused on research involving prisoners sets out specific additional safeguards required for such research, including having a prisoner or prisoner representative on the IRB, ensuring risks are commensurate with those that would be accepted by non-prisoner volunteers, and several which focus on reducing the potential for coercive research practices (e.g., research must have no impact on parole decisions) (Subpart C). With regard to children, the regulations emphasize the importance of balancing the risks of research with the potential benefits to the child or those faced with similar conditions in the future, as well as the requirement of informed consent by parents and ideally, assent by the child (Subpart D). In terms of pregnant women, research can include them as long as there is a possibility of direct benefit (to the mother or fetus) or the research is minimal risk, consent is adequate, risks have been minimized as much as possible, and the research team

[8]For comparison, the earlier version of the Common Rule read "When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects" (US Department of Health and Human Services 2014).

[9]A recent charge to SACHRP (the Secretary's Advisory Committee on Human Research Protections) asked them to investigate this particular regulatory gap, asking "What measures constitute adequate safeguards in these circumstances, and how should their adequacy be assessed? Should the requirement for such safeguards be limited to those "vulnerable to coercion or undue influence" (*i.e.,* populations with diminished autonomy), or are there concerns of social justice that should lead to a more expansive interpretation of vulnerability to exploitation?" (Office for Human Research Protections 2021).

[10]We follow the language of the Common Rule here, which specifies pregnant women, as opposed to the more inclusive pregnant people.

will play no part in any termination of pregnancy or determination of viability of a neonate (45§46.204).

While these discussions related to the appropriate inclusion of vulnerable populations in research are a welcome component of the regulations, their scope is unfortunately narrow. By considering only research with prisoners, children, and pregnant women, they only apply to a limited number of those who are often excluded from research. No mention of the importance of including women, racialized groups, or underserved populations, is made within the Common Rule. Also absent are exclusions related to older people, those with a mental health diagnosis, trans or gender diverse persons, and those with intellectual disabilities.

III. Looking to the Future: Finding a Balance

Finding a Balance between Protection and Inclusion—IRBs are in need of regulatory incentive and institutional support if they are to navigate the tensions between protection and inclusion. Crucially, IRBs must maintain their role of safeguarding and protecting the rights and welfare of research participants; this is, of course, the reason they came into being (Miller and Wertheimer 2007). But such protection should be appropriate to the circumstances. In order to achieve this, IRBs would benefit from guidance with regard to how they can thoughtfully execute their obligations to protect participants while also promoting inclusion of those understudied and underrepresented in research.

IRBs are not alone in finding a balance between protecting and including. Funders, sponsors, researchers, editors, reviewers, community members, and other stakeholders in the research ecosystem also have a role to play. As a way of initiating, but certainly not concluding, a conversation about finding this balance, below we highlight four features that we see as essential to this task. While we write these with IRBs in mind, they apply to other stakeholders (e.g., to inform future revisions of the Common Rule, as researchers design protocols, as journal editors evaluate submissions, etc.) faced with similar challenges.

1. The Complexity of Vulnerability: First, it is essential to acknowledge the complexity of vulnerability. While the Common Rule currently recognizes two forms of vulnerability, that which puts one at risk of coercion or that which puts one at risk of undue influence, these distinctions fail to capture the diversity of forms in which vulnerability might appear in research contexts and the dynamic nature of the phenomenon. Vulnerability may be better understood in terms of the various risks that might arise in a given research protocol, how they are often unevenly distributed, and how they depend upon the study question and study design. At the start of a trial, some potential participants may be at greater risk of undue influence, due to their socioeconomic circumstances, while during a trial, an existing condition or genetic abnormality may put other participants at risk; after participation, other subjects may be at an increased risk of harm due to a potential data breach, given the sensitivity of the data collected about them. Sometimes it makes sense to consider communities vulnerable (e.g., because research results could be stigmatizing, harming the community as a whole), but in other cases, individuals are uniquely vulnerable (e.g., as

a result of an existing relationship with a clinician-investigator, which could contribute to therapeutic misconception).

It is essential to recognize that ‘vulnerability’ is not a categorical feature, that one has or doesn’t have, but a contextual one, which can come in and out of being depending on the research setting and changing characteristics of a participant. Take older people, a group often designated as vulnerable. In such a population, vulnerability can take a great number of shapes and require equally as many responses. Sometimes, older people are considered vulnerable because they have reduced rates of drug clearance (e.g., renal elimination), or are more likely than others to have co-morbidities or be taking multiple medications; such vulnerability is likely to introduce risks in clinical trials but not in a survey study or focus group. In other cases, older people may lack capacity, as a result of the presence of a condition like dementia; this form of vulnerability will introduce risks in any consent process, but may vary from day to day or year to year. These precise forms of vulnerability also underlie obligations to include older people in medical research, so that we have a better understanding of how a study drug might interact with other conditions or medications, or how patients with limited consent capacity experience a novel intervention.

2. The Diversity of Responses to Vulnerability: Currently, the Common Rule offers the term ‘additional safeguards’ to characterize the ways in which IRBs and investigators can ensure that appropriate responses to different forms of vulnerability may be built into research protocols. Unfortunately, the vagueness of this term, and lack of explicit examples, leaves many without tools for the practical application of these additional safeguards. A clearer picture of how vulnerability might manifest and how it can be accommodated, ideally without resorting to mere exclusion from research, is needed. While examples of inclusive responses to vulnerability exist, the detailed project of connecting forms of vulnerability to appropriate safeguards, especially those that promote diversity and inclusion in medical research, is yet to be completed.

As an example, in the case of low-risk research involving patients with dementia who lack, or have impaired, decision-making capacity, there are a variety of additional safeguards that can be introduced to support inclusion rather than exclusion. These might include consent enhancement (e.g., teach-back techniques), the involvement of a legally authorized representative (LAR), ongoing capacity assessments, supported decision making, the ongoing participation of caregivers, and flexible scheduling (Stroup and Appelbaum 2006, Barbara E Bierer et al. 2021). In contrast, when an older person may be at a greater risk in a clinical trial due to comorbidities, other responses to this vulnerability may be appropriate. These might include increased and closer monitoring throughout the trial, very clear withdrawal criteria if harms or risks are identified, an enhanced consent process that covers what the novel risks may be, as well as the involvement of a loved one in monitoring efforts. In other cases, safeguards might apply at the level of community. For example, a community of drug users may be essential to include in a trial for a novel harm reduction intervention, but may be vulnerable to exploitative research or research that contributes to stigmatizing narratives; in such cases, community consent or community ethics review can be sought (Neufeld et al. 2019, Martin del Campo et al. 2013). See Box 1 for an example

of additional safeguards relevant to a trial that involves the discontinuation of anti-psychotic medications.

3. Differing Obligations Regarding Protecting and Including: Third, the ways in which obligations related to protection and inclusion differ in different groups ought to be made clear. While the regulations currently acknowledge the unique cases of children, prisoners, and pregnant women, many other populations are also impacted by the protection-inclusion dilemma. Still other populations should not be impacted by this dilemma, but are caught up in responses related to it, and unjustifiably excluded. As discussed above, some populations, in some research settings, are in need of both inclusion initiatives and special protections, such as individuals with intellectual disabilities. In contrast, women and racialized groups, who have historically been understudied, require inclusion in research but are not generally in need of additional safeguards by virtue of their being women or racialized. In other cases, special protections but not inclusion will be required, such as in the case of trials involving high risks and no direct benefits to the population (e.g., children)[11]. Without this clarity, these imperatives related to protection and inclusion, and where they come apart, can become fuzzy in IRB decision-making, leading to assumptions around vulnerability about groups that are not in need of protection (e.g., women of child-bearing potential).

4. The Impact of Potential Risks and Benefits on Obligations to Include: Finally, requirements related to protection and inclusion shift with regard to the risks and benefits present in a given research protocol. In many cases of low-risk research, exclusion of those deemed vulnerable in other contexts is unwarranted, because risks are minimal; while pregnant people can justifiably be excluded from some early phase interventional trials, excluding them from participation in a survey or focus group is rarely justified. In high-risk research, the prospect of direct or population benefit or risk significantly impacts obligations to include. As a result, in cases where early data suggests one racial group may have a unique response to a study drug, or when the exclusion of some portion of the population has led to significant harms in the past (e.g., women and cardiovascular research), their inclusion in early trials is essential.

Achieving appropriate diversity in clinical research, therefore, requires a context-specific analysis (B.E. Bierer et al. 2020). This was recognized in the Belmont Report, which acknowledged that: “When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits” (Ryan et al. 1979). Unfortunately, the mechanisms of research ethics that developed after the report was published largely responded to the emphasis on risks in this statement, and paid less attention to the importance of benefits.

IRB Practices—There are also several ways in which IRBs can build attention and thoughtful responses to the protection-inclusion dilemma into their day-to-day processes.

[11]An important exception to this generalization is with regard to research that can be stigmatizing to a particular community, such as what occurred in the Havasupai case (Reardon and TallBear 2012).

We recommend that IRBs build reflective questions into their review processes or guides, drawing attention to the places in which conflicts can arise between obligations to protect and obligations to include. Box 2 offers several examples of questions that could guide such reflection.

The research community is increasingly attentive to matters of diversity and inclusion and plausible recommendations have recently been advanced that can positively impact practice (Strauss, White, and Bierer 2021). These include requiring that investigators offer justifications for exclusion criteria, particularly those that involve historically understudied and underrepresented populations, a review of whether the demographics of the potential participants reflect those likely to be impacted by the results, as well as a review of who has actually been enrolled at continuing review, and whether changes should be made mid-study to ensure diversity (B.E. Bierer et al. 2020, 258–9). The report also suggests that reviewers can examine recruitment plans and study procedures with an eye to flexibility and potential barriers for inclusion this might create, as well as patient-facing materials, including translations, which might impact recruitment and retention (B.E. Bierer et al. 2020, 258–9).

These recommendations are helpful, while still leaving room for discretionary decision-making, which is at the heart of IRB practices (P. Friesen, Yusof, and Sheehan 2019). Indeed, universal guidelines for when IRB should require greater inclusion and when they should merely recommend greater inclusion may not be practical or desirable, as the particularities of the protocol being reviewed will always matter. In some cases, if exclusions are significant enough (e.g., an experiment on cardiovascular disease that includes only men as participants), conditioning approval on inclusion (or exacting scientific justification may be wise. In other cases (e.g., a doctoral project involving a survey that is only conducted in English), recommending greater inclusion may be sufficient.

Other Stakeholders—Responding to the protection-inclusion dilemma adequately will require support and buy-in from a number of key stakeholders within the research environment. Centrally, researchers can play an important role in adapting their protocols to prioritize inclusion alongside protection, although they will need the support of the IRB to do so. Potential research participants from populations that have been excluded from research can advocate for their inclusion, working alongside researchers to help develop appropriate approaches to promote inclusion. Funders and sponsors can elect to impose requirements related to inclusion, ensuring that researchers will work to enroll an inclusive sample while still maintaining adequate standards of protection. The Common Rule could be updated to account for the obligation to include, alongside the obligation to protect. The FDA can impose requirements related to trial data, necessitating that a certain bar of inclusivity is reached before approval for understudied populations can be granted. Journal editors and peer reviewers can also play an important gatekeeping role as well, seeking justifications for exclusive sampling and granting considerations of inclusion and sample representativeness more weight in publication standards and assessments of manuscript quality. While we have emphasized the important role of IRBs here, they are certainly not alone in responding to this important dilemma.

Concluding Thoughts

IRBs were developed in the wake of a long history of exploitation in the name of research. In this context, protecting research participants from harm was the primary purpose of research ethics review. Since this time, however, we have developed a more nuanced understanding of vulnerability and come to recognize the unwanted impact of the under-representation of certain populations in research, which has led to a growing emphasis on the importance of inclusion and diversity in medical research. This presents a dilemma for the IRB which must balance the conflicting aims of protection and inclusion. Unfortunately, the nuances of vulnerability are not currently captured by the federal research regulations or in associated regulatory guidance, which focus primarily on how IRBs can protect research participants but offer little advice on how to ensure appropriate inclusion. While there is no easy solution to the protection-inclusion dilemma, we have outlined several recommendations for how IRBs can seek a balance between these two important goals. It is necessary to understand vulnerability as complex and context dependent, taking many forms and requiring specific responses. Additionally, it is essential for IRBs to understand the unique obligations related to protecting and including that apply to different populations, and how these obligations shift both in time and in response to the potential risks and benefits of a given research protocol. Active attention to the inclusion-protection dilemma during the process of research funding, protocol development, and research ethics review can serve to balance to the inclusion of commonly under-represented and understudied groups in research with necessary protections, ultimately promoting a more fair and generalizable evidence base for healthcare.

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Box 1.

Case Study: Discontinuing Anti-Psychotic Medications

When reviewing a clinical trial involving the discontinuation of anti-psychotic medications and enrolling participants with a history of psychosis, significant risks (e.g., relapse, suicide) and forms of vulnerability (e.g., capacity, street involvement) ought to be taken into account. The identification of these risks can often lead to blanket exclusion criteria (e.g., those with a history of suicidal behavior), which can lead to less representative data being collected within the trial. Expanding on a discussion of this case developed in (Strauss 2021), here we offer a number of 'additional safeguards' that could ensure risks are minimized and benefits are maximized for research participants enrolled in such a trial, as well as that the benefits to populations impacted by the research are maximized:

- Special accommodations in consent procedure, disclosure of risks
- Formal assessment of capacity at start of trial
- Assignment of study partner appointed by the participant
- Inclusion criteria of only those that already have interest in discontinuation
- Operationalized criteria to exclude those for whom symptom worsening poses unacceptable risk (and a plan to respond to these symptoms appropriately and safely)
- Periodic expert safety and capacity assessments
- 24-hour on call clinician
- Precedent regarding unacceptable risk
- Peer specialist/ advocate within trial team
- Plan for post-protocol transition of care

Box 2.

Reflective Questions for IRBs Negotiating the Protection-Inclusion Dilemma

- Does this research exploit certain forms of vulnerability or exacerbate risk?
- What protections/safeguards would be most appropriate to mitigate the risks present in this research?
- Is there a way to ensure necessary protections/reduce risks without excluding certain groups or individuals?
- Are excluded groups unnecessarily denied benefits associated with the research?
- Which populations are excluded from this research and are those exclusions justified?
- Which populations are included in this research and are those inclusions justified?