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Fair Subject Selection in Clinical and Social Scientific Research

Abstract

This chapter provides a critical overview and interpretation of fair subject selection in clinical and social scientific research. It first provides an analytical framework for thinking about the problem of fair subject selection. It then argues that fair subject selection is best understood as a set of four sub-principles, each with normative force and each with distinct and often conflicting implications for the selection of participants: fair inclusion, fair burden sharing, fair opportunity, and fair distribution of third-party risks. It then defends an approach to navigating the conflicting imperatives of these sub-principles, one which privileges the need to include epistemically distinct groups in research, before concluding by considering the most pressing research questions regarding fair subject selection.

Keywords: Fair subject selection; clinical research ethics; social scientific research ethics; fair inclusion; fair opportunity; justice.

Text

With the publication of *The Belmont Report* in 1979, the principle of fair subject selection was established as a central requirement of ethical research with human subjects, alongside the more familiar requirements of informed consent and favorable-risk benefit ratio (The National Commission 1979, 9). Since then, considerations of fairness and justice in the selection of participants and the conduct of human subjects research more broadly have received increasingly

greater attention. However, scholars have also noted important shifts over time in interpretations of fair subject selection by ethicists, investigators, and regulators. With respect to clinical research in particular, fair subject selection was understood to require the protection of burdened and/or vulnerable populations in the 1970s, fair access to the benefits of research in the 1980s, and fair representation of clinically distinct groups in the 1990s and 2000s to ensure generalizability (Weijer 1996; King 2005; Meltzer and Childress 2008). This latter push for fair representation is still with us as stakeholders argue in support of greater inclusion of pregnant women in clinical research (Lyerly, Little, and Faden 2008), racial and ethnic minorities in genomic research (Popejoy et al. 2018), and people with disabilities in public health research (McDonald and Raymaker 2013).

My aim in this chapter is to provide a critical overview and interpretation of the requirement of fair subject selection in clinical and social scientific research. I first provide an analytical framework for thinking about the problem of fair subject selection that explains how it is possible for stakeholders to arrive at different interpretations of this requirement. I then argue that fair subject selection is best understood as a set of four sub-principles, each with normative force and each with distinct implications for the selection of participants: fair inclusion, fair burden sharing, fair opportunity, and fair distribution of third-party risks. I turn next to identifying the most pressing research questions regarding fair subject selection. I argue first that these four sub-principles can yield conflicting imperatives and that scholars must develop principled ways to navigate them. I defend an approach that privileges the need to include epistemically distinct groups in research, that is, groups which differ in ways that are relevant to the production of knowledge. I argue second that

important work remains to be done concerning the comprehensive specification of these sub-principles.[1]

The Problem of Fair Subject Selection

Considerations of fairness or justice arise directly in the context of cooperative social practices. In such practices people cooperate to produce some set of benefits, and questions of fairness arise regarding both the distribution of these benefits, as well as the burdens of the cooperative practice itself. If you and I decide to set up a lemonade stand, we face questions of fairness regarding both the distribution of the labor as well as any profits. Speaking more broadly of society as a system of social cooperation, John Rawls (1999: 4) motivates the need for principles of justice or fairness this way:

> Let us assume, to fix ideas, that a society is a more or less self-sufficient association of persons who in their relations to one another recognize certain rules of conduct as binding and who for the most part act in accordance with them. Suppose further that these rules specify a system of cooperation designed to advance the good of those taking part in it. …A set of principles is required for choosing among the various social arrangements which determine [the] division of advantages and for underwriting an agreement on the proper distributive shares.

Research with human subjects is of course distinct from society considered as a system of social cooperation; however, it too can be helpfully understood as a set of cooperative social practices.

[1] For ease of expression, I shall largely speak of "investigators" as bearing the principal responsibility to select participants fairly. However, the requirement of fair subject selection applies to all agents who make decisions regarding participant selection.

Sponsors, investigators, and participants, among others, work together to produce different forms of knowledge regarding human minds, bodies, behaviors, practices, institutions, and societies. Questions of fairness or justice therefore arise regarding the distribution of the various benefits produced by these practices, and the burdens involved in their production (The National Commission 1979, 5).

The question of fair subject selection in human subjects research, I suggest, concerns a small part of this broader question of fairness. The selection of participants has implications for the distribution of the benefits and burdens of research qua cooperative social practice, and so participants need to be selected in a way that ensures that these benefits and burdens are distributed fairly (Emanuel et al. 2000, 2705; MacKay and Saylor 2020, 6).

First, the selection of participants has implications for the distribution of the principal benefit of human subjects research, namely knowledge. In cases where people, practices, and institutions differ in epistemically relevant ways, investigators must study particular types of people, practices, or institutions to gain knowledge about them. The choice of participants thus has implications for which types of people, practices, or institutions investigators produce knowledge about. In the context of clinical research, people often differ in clinically relevant ways, whether due to sex, race, health status, or environment. For example, people with comorbidities may react differently to an experimental intervention than people without these comorbidities. To produce knowledge that is generalizable to a particular clinically distinct sub-population then, a sufficient number of members of that sub-population must be enrolled in clinical studies. Similarly, in the context of public policy research, to determine if a particular educational intervention is as effective for low-income students as it is for high-income students, investigators must enroll sufficient numbers of both types of students. In other forms of human subjects research, the point is almost too obvious to make. To understand how rural white Americans without a college education form

political opinions political scientists must study rural white Americans without a college education. To understand the cultural practices of a particular indigenous group in northern Canada, anthropologists must study members of that group. The selection of participants therefore has implications for the distribution of the principal benefit of research: generalizable knowledge.

Human subjects research may also directly benefit participants, leaving them better off than they would be outside of the study. For example, participants in clinical research may receive a treatment that is expected to be superior to the care they would otherwise receive. Similarly, participants in policy research may access an intervention that is expected to be more effective at realizing health or educational outcomes than the status quo interventions. Participants in anthropological or sociological research may come to know things about themselves that they would otherwise not know. Participants may also be better off if they have a preference to participate in research, for example, because they see it as a meaningful activity, or if they are given financial compensation for their participation.

Participation may also be burdensome, however, leaving people worse off than they would otherwise be. Participation may be time intensive, taking people away from activities in which they would prefer to engage. Data collection may expose participants to risks to their privacy. In the context of clinical or policy research, participants may be worse off qua participants if the experimental intervention proves to be inferior to the intervention (or non-intervention) to which they would otherwise be subject. Qualitative research that requires participants to relive or discuss sensitive matters could be emotionally harmful or even traumatic.

Finally, human subjects research may also be harmful to third parties, and the selection of participants may influence whether and which third parties are harmed. For example, Donald Warwick (1982, 113-116) argues that social research on minority groups could lead to a number of different types of harms to members of these groups, including victim-blaming in cases where social

researchers conclude or imply that members of disadvantaged group are responsible for their plight. Similarly, clinical research involving minorities may also contribute to discrimination against, and stigmatization of, members of these groups who do not directly participate in a study. For example, a survey of prospective participants for genetics research found that a majority were concerned that the research could contribute to racial discrimination (Goldenberg et al. 2011). Certain forms of clinical and public health research could also expose third parties to health risks, and the selection of participants may influence both the size of these risks and who is exposed to them. For example, controlled human infection studies in which participants are deliberately infected with an infectious agent, could expose family members of participants to the risk of infection. Prospective participants may also vary in the likelihood of transmitting the infectious agent, and certain types of third parties may be more susceptible to these risks than others.

The selection of participants therefore influences the distribution of a number of benefits and burdens of human subjects research. Participants must be selected in a way that ensures that these benefits and burdens are distributed fairly. In the next parts of the paper, I discuss what this entails.

Four Faces of Fair Subject Selection

The ethical requirement of fair subject selection, I suggest, is best understood as involving the selection of participants to ensure the fair distribution of the above-mentioned benefits and burdens: epistemic benefits to groups, direct benefits to participants, direct burdens to participants, and risks to third parties (MacKay and Saylor 2020, 6). Accordingly, the principle of fair subject selection can be helpfully understood as a bundle of four distinct sub-principles, with each governing the distribution of one of these benefits or burdens. I discuss each in turn.

Epistemic Benefits to Groups: Fair Inclusion

Consider first the principal benefit of human subjects research: knowledge. Where sponsors of research or investigators have obligations to produce certain forms of knowledge about particular groups of people, investigators must select participants in a way that realizes this goal. For example, governments have obligations to improve the health and wellbeing of all citizens, regardless of sex, gender identity, race, ethnicity, or socio-economic status. When it comes to the funding and design of human subjects research that may improve people's health and wellbeing, governments have an obligation to ensure that this research is sufficiently inclusive to ensure that citizens benefit fairly from it. For example, the goal of clinical research is to produce clinically relevant knowledge and so to improve health outcomes for populations. If clinical research is not sufficiently inclusive, such knowledge will be produced for some clinically distinct populations and not others. Indeed, the failure to include pregnant women in clinical research means there is a dearth of evidence regarding the safety and effectiveness of many interventions for members of this group (Lyerly, Little, and Faden 2008). Similarly, in the context of public policy research, failure to include members of different groups may mean that policymakers know how to improve certain types of outcomes for some types of people but not others (Glennerster and Powers 2016, 373-374).

To ensure that epistemically distinct groups within society are fairly benefitted by human subjects research therefore, such research must be sufficiently inclusive. I call this dimension of fair subject selection *fair inclusion* (MacKay and Saylor 2020, 7).

> *Fair Inclusion: The selection of research participants must be sufficiently inclusive to ensure that the research in question fairly benefits members of society.*

The precise content of this principle will depend on the obligations that the relevant sponsors or investigators have regarding the production of knowledge (MacKay and Saylor 2020, 7). For example, as I note above, government sponsors of clinical, public health, and policy research clearly

have obligations to produce knowledge that fairly benefits citizens. As such, they have a duty to conduct research that is inclusive of epistemically distinct groups. However, it might be that non-governmental sponsors or investigators conducting different types of research may have obligations that are less robust, if they have them at all. For example, it may be that political scientists or sociologists at private universities and conducting research with private funds have wide discretion regarding the research questions they pursue. It may therefore be permissible for them to conduct research that generates epistemic benefits for only a small slice of the broader population.[2]

Fair inclusion is widely recognized in the research ethics literature as a requirement of fair subject selection (Levine, 1982, 139-141; Kimmel 1988, 78; Weijer 1996, 340–4; Emanuel, Wendler, and Grady 2000, 2704; Corbie-Smith, Moody-Ayers, and Thrasher 2004, 1362; Ginsberg and Mertens 2009, 598; Meltzer and Childress 2011, 379–80; Friedman Ross and Nelson 2018, 84–86; Kass and Lyerly 2018, 91–92; MacKay and Saylor 2020, 7).[3] For example, in the context of public policy research, Glennerster and Powers (2016, 373-374) stress that randomized controlled trials should either be run on large representative samples or in multiple, distinct contexts in order to ensure that the results of such research are appropriately generalizable. In the context of public health research, Katherine E. McDonald and Dora M. Raymaker (2013) argue that investigators must include people with developmental disabilities in research in order to address health disparities experienced by people with such disabilities. Similarly, Patricia A. King (2018, 128) argues that clinical researchers must take steps to include African Americans in order to develop clinically

[2] To my knowledge, there is no systematic discussion of research priority setting in the social sciences. However, Leah and Pierson and Joseph Millum (2018) have recently made significant progress on this question in the context of health research.

[3] Though Kirstin Borgerson (2020) makes a good case for relocating this dimension of fair subject selection to the social value requirement of ethical clinical research.

relevant knowledge regarding factors that are specific to the health of African Americans. The requirement of fair inclusion is also prominently featured in the National Institutes of Health Revitalization Act of 1993. This Act requires that women and members of minority groups be included and sufficiently represented in clinical research, and that each trial is "designed and carried out in a manner sufficient to provide for a valid analysis of whether the variables being studied in the trial affect women or members of minority groups, as the case may be, differently than other subjects in the trial (US Congress 1993)."[4]

Direct Benefits to Participants: Fair Opportunity

Human subjects research not only benefits groups, but also sometimes benefits participants. In cases where participation is ex ante net beneficial (compared to a baseline of non-participation), investigators have a duty to ensure that prospective participants have a *fair opportunity* to access the benefits of participation (MacKay and Saylor 2020, 9).[5] This second sub-principle of fair subject selection thus governs the distribution of direct benefits to participants.

> *Fair Opportunity: Prospective participants must be granted a fair opportunity to participate in research that is expected to be net beneficial.*

[4] Ana Iltis (2020) offers an excellent analysis of the further questions that need to answered and requirements specified if fair inclusion is to be realized in the context of clinical research.

[5] I recognize that there are difficult questions regarding the factors that should be considered when determining if a study is ex ante net beneficial or not. For example, in the context of clinical research, it is uncontroversial that potential health benefits from the experimental intervention should be considered. But what about health benefits from any ancillary care that is offered to participants? Payment for participation? Or, simply the satisfaction of a preference to participate? Unfortunately, resolving this question is beyond the scope of this chapter.

The justification for this sub-principle is that people are moral equals, and so their interests deserving of equal consideration. When deciding whom to enroll in an ex ante net beneficial study, investigators should recognize that all prospective participants who meet the scientific requirements of the study have a prima facie equal claim to participate (Emanuel, Wendler, and Grady 2000, 2704-2705; MacKay 2016, 274). This sub-principle applies equally to private and public sponsors of research since all investigators have a duty to treat prospective participants as moral equals. For example, private for-profit companies, just like public employers, may not discriminate against people seeking employment or wanting to purchase their goods or services – i.e. treat them worse on the basis of their membership in a socially salient group.

Fair opportunity is also recognized as a central requirement of fair subject selection in the research ethics literature and regulations (Lyerly, Little, and Faden 2008, 6–7; Meltzer and Childress 2011, 378-379; Weijer 1996, 338-340; MacKay and Saylor 2020, 9). For example, *The Belmont Report* states that "Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer prospectively beneficial research only to some patients who are in their favor (National Commission 1979, 9)." In the context of clinical research, I argue elsewhere that investigators must comply with the principle of formal equality of opportunity, according to which investigators should treat prospective participants the same unless differential treatment is required by the scientific goals of the study or necessary to protect participants' medically related interests (MacKay 2016, 675). Similarly, in the context of social scientific research, Allan J. Kimmel (1988, 78) argues that investigators must take care to ensure that their recruitment strategies for ex

ante net beneficial studies reach all eligible prospective participants, regardless of socio-economic status, race, or ethnicity.[6]

Direct Burdens to Participation: Fair Burden Sharing

In cases where participation in research is ex ante net burdensome (compared to a baseline of non-participation), the burdens of participation must also be shared fairly. As with other cooperative projects in which people take on a burden in order to produce benefits for all, these burdens should be shared fairly among the population, not borne by particular disadvantaged groups. Fair burden sharing is thus a third dimension of fair subject selection (MacKay and Saylor 2020, 8).

Fair Burden Sharing: The burdens of participation in research must be shared fairly.

This sub-principle is also widely recognized as a requirement of fair subject selection in the research ethics literature (Diener and Crandall 1978, 28-29; Loo 1982, 112-113; Weijer 1996, 336–38; Emanuel, Wendler, and Grady 2000, 2704; Iltis 2009, 71-74; Meltzer and Childress 2011, 377–78; MacKay and Saylor 2020, 8). For example, The Belmont Report states that investigators should not "select only 'undesirable' persons for risky research (National Commission 1979, 9)." It goes on to make clear that participation in burdensome research should be allocated according to a principle of ability to bear the burden in question: "social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further

[6] While many scholars understand fair opportunity to require equality of access to ex ante net beneficial studies, it could instead require preferential access to such studies for people who are worse off. Thanks to Joseph Millum for this suggestion. Iyer, Hendriks, and Rid (2020, 37) raise further possibilities, for example that fairness may require prioritizing past participants on grounds of reciprocity.

burdens on already burdened persons (The National Commission 1979, 9)." In the context of public policy research, Dawn Langan Teele (2014, 133) raises the concern that the burdens of participation in research may too often fall on people who are economically and/or politically vulnerable. Similarly, with respect to research on violence against women, Lisa Aronson Fontes (2004, 160) criticizes recruiting practices that target shelter and mental health clinics or that rely on policy reports or emergency room referrals. Such practices, Fontes argues, are likely to disproportionately include participants less able to bear the burdens of research, namely, women from lower socio-economic groups. [7]

Some scholars argue further that it is unfair to include people in research for whom the risks of participation are unacceptably high. For example, Alex John London (2007, 110) argues that each person's interests must be treated fairly and with equal concern, and so there is a limit to the level of risk it is permissible to ask people to bear in order to benefit others. It is thus unfair, according to London, to ask some individuals to sacrifice their basic interests in order to benefit others. Risks to participants are therefore reasonable only if they "are consistent with an equal regard for the basic interests of study participants and the members of the larger community whose interests that research is intended to serve (London 2007, 110)."[8] Annette Rid and David Wendler (2011, 165) argue similarly that there are limits to the level of risk it is acceptable to ask prospective participants to bear and that such levels must be determined by a "fair consideration" of participants' interests and the interests of those who may benefit from the research. Fair burden sharing has thus been

[7] In these examples, the people best able to bear the burdens of research are those who are better off at baseline – e.g. are healthier and not subject to socio-economic disadvantage. It is also plausible to think that one person is better able to bear the burdens of research than another if the expected burden is smaller for the former than the latter. Thanks to Joseph Millum for this raising this point.

[8] For a critique of this line of argument, see Robert Steel (2020)'s paper, "Risk Limits in Fair Subject Selection."

understood to require that those prospective participants best able to bear the burdens of research be selected, and also that prospective participants likely to face unacceptably high risks be excluded from research.

Risks to Third Parties: Fair Distribution of Third-Party Risks

Finally, participants must be selected so as to ensure that third-party risks are distributed fairly. Fair distribution of third-party risks is thus a fourth dimension of fair subject selection (MacKay and Saylor 2020, 10).

> *Fair Distribution of Third-Party Risks: Participants must be selected to ensure a fair distribution of risks to third parties.*

This sub-principle is not as prominent in the research ethics literature as the other three. However, scholars are increasingly recognizing the risks that research poses to third parties and arguing that such risks need to be addressed in the ethical review of studies (Hausman 2007; Shah et al. 2018). The selection of participants can affect the distribution of risks to third parties, and so participants must be selected in a way that leads to a fair distribution of these risks. With Katherine Witte Saylor, I argue elsewhere that this implies, first of all, that participants be selected in a way that does not allocate risks to third parties who are least able to bear them, for example, people who are ill or socio-economically disadvantaged (MacKay and Saylor 2020, 10). We argue, second, that this principle should be understood to prohibit the inclusion of prospective participants whose inclusion is likely to impose a level of risk on third parties that it would be unfair to ask them to bear (MacKay and Saylor 2020, 10). This latter consideration may restrict social scientific research on members of certain minority groups since, as Warwick (1982, 113-116) notes, such research may impose

significant risks on members of these groups who are not research participants, for example, risks of death or serious injury, stigmatization, and discrimination.[9]

Fair subject selection is thus best understood as a multidimensional requirement of ethical research, featuring four sub-principles: fair inclusion, fair opportunity, fair burden sharing, and fair distribution of third-party risks. Table 1 sums up our discussion thus far:

Table 1: Sub-Principles

Principles	Definition	Implications
Fair Inclusion	The selection of research participants must be sufficiently inclusive to ensure that the research in question fairly benefits members of society.	Include and recruit members of epistemically distinct groups.
Fair Opportunity	Prospective participants must be granted a fair opportunity to participate in research that is expected to be net beneficial.	Do not exclude people unfairly from studies and make reasonable efforts to enhance people's ability to participate.
Fair Burden Sharing	Burdens of participation in research must be fairly shared.	Select participants best able to bear the burdens of research and exclude prospective participants facing unacceptably high risks.
Fair Distribution of Third-Party Risks	Participants must be selected to ensure a fair distribution of risks to third parties.	Select participants to ensure that risks to third parties are borne by those best able to bear them and exclude prospective participants whose inclusion may impose unacceptably high risks on third parties.

[9] Though one difficult challenge here is to identify such risks ex ante, particularly in the context of social research. Thanks to Danielle Bromwich for raising this issue.

Questions for Future Research

My discussion thus far has provided an analytical framework for understanding the requirement of fair subject selection and that explains why scholars often interpret this requirement in different ways. In this part of the paper, I identify two issues demanding further scholarly attention.

Navigating Conflicting Imperatives

As a multidimensional requirement, fair subject selection includes multiple sub-principles. As a *normative* multidimensional requirement, each of these sub-principles yields a set of imperatives for the selection of participants. Unfortunately, these imperatives can conflict, creating serious problems for investigators concerned to select participants fairly.

First, fair inclusion is likely to conflict with fair opportunity. Fair inclusion requires investigators to include a sufficient number of epistemically distinct group members so that any knowledge generated by the study is generalizable to members of these groups. To fulfill this principle, investigators may need to engage in a kind of affirmative action for research participants, reserving spots for, and aggressively recruiting, members of these epistemically distinct groups (MacKay and Saylor 2020, 11). Fair opportunity, by contrast, requires that all prospective participants have a fair chance to participate in ex ante net beneficial research. For example, to ensure that a study evaluating a promising treatment for prostate cancer is generalizable to people with certain co-morbidities, investigators may need to aggressively recruit prospective participants with these co-morbidities and even turn away some number of prospective participants without them, thus granting members of the former group a better chance to be included in the study than members of the latter group. Such recruitment practices may deny members of the latter group a fair opportunity to participate in the study, particularly if they stand to benefit from it to the same extent

as members of the former group. In the context of educational research, investigators may need to be very intentional about the types of schools they include to ensure generalizability, thus denying some schools the opportunity to benefit from a promising intervention.

Fair inclusion may also conflict with fair burden sharing since fair inclusion may require the inclusion of prospective participants who are already burdened, or who would face greater burdens qua study participants than others (MacKay and Saylor 2020, 11). Chalsa M. Loo (1982) describes this conflict in the context of psychological research on the effects of crowding – i.e. high rates of spatial and social density. To produce knowledge that is scientifically valid and socially beneficial, investigators must include as study participants those individuals who are likely to be exposed to crowding. But, fulfilling this imperative of fair inclusion may require including in studies persons who are already burdened, or who would face greater burdens than others in the context of the study (Loo 1982, 105-106). Thus Loo (1982, 109) notes, investigators must decide whether to include autistic children in laboratory studies on the effects of crowding, individuals who are hypothesized to be most negatively affected by such conditions. Investigators must also decide whether to carry out field research on the effects of crowding, which would involve studying people currently exposed to such conditions, namely, people who are more likely to be socio-economically disadvantaged and racial or ethnic minorities (Loo 1982, 113-114). In the context of clinical research, investigators may need to include participants with co-morbidities to ensure that the findings are generalizable to those who are likely to be end users of the intervention. However, participants with co-morbidities are likely to face higher risks than other participants.

For similar reasons, fair inclusion may also conflict with fair distribution of third-party risks. For example, fair inclusion in the context of research on anti-poverty interventions may require the inclusion of participants who are ethnic or racial minorities. However, as Warwick (1982, 114) notes, the results of such research may be used to blame the victims of socio-economic injustice. As an

example, Warwick (1982, 114) points to Daniel P. Moynihan's (1965) study, *The Negro Family: The Case for National Action* (and the social scientific studies it relied on), which, in his words, concluded that "the Negro family (as it was then called) suffers from instability, a propensity to produce illegitimate children, and a matriarchal structure" and that "experience in this family setting…has harmful effects on all children." Warwick (1982, 114) points to the criticisms of psychologist William Ryan (1967, 463), who argued that the report encouraged "(no doubt unintentionally) a new form of subtle racism…and seduces the reader into believing that it is not racism and discrimination but the weaknesses and defects of the Negro himself that accounts for the present status of inequality between Negro and white."

Finally, fair opportunity or fair burden sharing may conflict with fair distribution of third-party risks whenever the former principles favor the inclusion of people whose inclusion would unfairly distribute risks among third parties. For example, in a proposed controlled human infection study to evaluate a candidate Zika vaccine, investigators suggested that healthy men be excluded from participation on the grounds that they are more likely than women to transmit the virus to their sexual partners (Durbin and Whitehead 2017). While the inclusion of these men would be favored by fair burden sharing, it is thus disfavored by fair distribution of third-party risks.

One might think that fair opportunity and fair burden sharing may yield conflicting imperatives. However, this would be a mistake. Fair burden sharing applies in cases where the study is ex ante net burdensome whereas fair opportunity applies in cases where the study is ex ante net beneficial. Since, for any prospective participant a study will either be ex ante net burdensome or ex ante net beneficial, these principles do not yield conflicting imperatives regarding the enrollment of particular individuals. Investigators may face challenges with respect to subject selection, however, in cases where a study is ex ante net beneficial for some prospective participants, but not all (MacKay and Saylor 2020, 17).

How should investigators navigate these conflicting imperatives? Elsewhere, Katherine Witte Saylor and I provide a decision-procedure investigators may use to address these conflicts in the case of clinical research with competent adults (MacKay and Saylor 2020, 16). We argue first that it is permissible for investigators to tolerate some unfairness in the selection of participants, when this unfair treatment satisfies the following conditions (MacKay and Saylor 2020, 13):

A. The unfair treatment is expected to significantly advance the realization of one of the investigator's purposes;
B. There is no less unfair treatment by which the investigator may significantly advance the realization of their purpose that would not result in undue burdens on them; and
C. The purpose of the investigator is more valuable than the purposes frustrated by the unfair treatment and outweighs any wrong associated with the unfair treatment.

This set of conditions, we suggest, expresses the claim that participant selection that is unfair in some dimension is permissible when it is necessary for the fulfillment of some valuable purpose, and this purpose is more valuable than the purpose the unfair treatment would frustrate and the wrong associated with the unfair treatment (MacKay and Saylor 2020, 13).[10]

We argue next that the purpose of producing knowledge that fairly benefits members of society is sufficiently valuable to decide a number of the above-mentioned conflicts in favor of fair inclusion (MacKay and Saylor 2020, 13). More specifically, investigators should favor fair inclusion

[10] This test of permissible unfair treatment is drawn from work I've done elsewhere on the ethics of discrimination – another context in which agents face difficult questions regarding the permissibility of treating individuals in prima facie unfair ways. In this work, I show that the above test summarizes the insights of prominent liberty-based accounts of discrimination and is also consistent with the tests employed by U.S. and Canadian courts to determine when otherwise permissible treatment is justified (MacKay 2018).

when it conflicts with fair opportunity, and they should favor fair inclusion over fair burden sharing at least in cases where the latter is interpreted to require the selection of participants best able to bear the burdens of research. In cases of clinical research with competent adults, and where the research in question does not pose unacceptable risks to participants, investigators should realize fair inclusion, even if this implies selecting participants who are less able to bear the burdens of research (MacKay and Saylor 2020, 13-14). The goal of producing knowledge that fairly benefits members of society, we suggest is great enough to justify denying some prospective participants a fair opportunity to participate in ex ante net beneficial research, and to ask already burdened people to participate in ex ante net burdensome research. For example, in the above-mentioned case of a study evaluating a promising treatment for prostate cancer, it would be permissible to aggressively recruit prospective participants with co-morbidities to ensure that the study will fairly benefit patients with these co-morbidities even if this involves turning away some number of prospective participants without them who would likely benefit from participation. Such recruitment satisfies conditions A and B, and it satisfies C since the goal of generating knowledge that fairly benefits members of society is more important than the goals of particular individuals in participating in a study.

In cases where the research would pose unacceptable risks to participants however, we favor fair burden sharing over fair inclusion; and also argue that conflicts between fair inclusion and fair distribution of third-party risks should be decided in favor of the latter sub-principle (MacKay and Saylor 2020, 13-15). Including people likely to face high risks in a study, we suggest, does not satisfy C, since participation involves threatening these participants' basic interests and is also deeply unfair, involving the sacrificing their basic interests for the benefit of others (MacKay and Saylor 2020, 15).

This way of navigating the above-mentioned conflicting imperatives, we conclude, implies the following decision procedure for investigators (MacKay and Saylor 2020, 16):

1. Design inclusion criteria to answer the scientific question in a way that fairly benefits members of society (fair inclusion).
2. Design exclusion criteria to exclude prospective participants for whom the risk of participation is unacceptably high (fair burden sharing).
3. Revise exclusion criteria to exclude prospective participants whose inclusion would result in an unfair distribution of risks to third parties (fair distribution of third-party risks).
4. Among potential participants meeting inclusion criteria and not meeting exclusion criteria, set and meet goals for enrollment of potential participants to ensure research fairly benefits members of society (fair inclusion).
5. Consistent with step 4, fairly extend the offer of participation to all prospective participants satisfying inclusion and exclusion criteria (fair burden sharing and fair opportunity).

This decision-procedure, we suggest, offers a promising way for investigators to navigate conflicts among the four sub-principles; however, it is also limited to *clinical research* with *competent adults* (MacKay and Saylor 2020, 16). With respect to cases of pediatric clinical research, we note that it may not be permissible to select participants less able to bear the burdens of research in order to realize fair inclusion and so that this is a question deserving of further research (MacKay and Saylor 2020, 17). In addition, it's not clear whether this decision procedure is applicable in the context of other forms of research in which investigators are likely to face similar conflicting imperatives. One might argue that clinical research is distinct in that the knowledge it produces is clinically relevant, thus offering future patients the prospect of health benefits. Different forms of social scientific research, by contrast, may not offer people the prospect of such benefits and so it may be harder to argue that conflicts between fair inclusion and fair burden sharing, for example, should be decided in favor of the former sub-principle. For example, political science survey research with members of disadvantaged communities may be necessary to understand the political beliefs and preferences of

members of these groups; but may also expose these participants to significant risks if they live in countries with high levels of political violence and weak norms of free political speech and thought (Desposato 2016, 12). It may be difficult to justify this research in cases where the outcome of the research is only knowledge, not an intervention that is likely to improve people's lives. While our account offers a helpful starting point for thinking about the navigation of the above-mentioned conflicting imperatives in non-clinical research, one should not think it is directly applicable to these contexts.

One might also question our basic approach to the problem of conflicting imperatives, namely, that it is a good idea to specify a priority ranking that is applicable in different contexts. G. Owen Schaefer (2020) argues that the relative moral importance of the conflicting imperatives depends on factors that are particular to a study – e.g. its social value, the quality of its design, and the risks and benefits involved. He argues instead that investigators should adopt a "context-sensitive approach that does not presuppose which sub-principles of fair subject selection will take priority in a given case (Schaefer 2020, 20)." Elise Smith and Charles Dupras (2020) arrive at a similar conclusion, arguing that there is too much scientific uncertainty regarding risks and benefits in clinical research for the decision-procedure to be helpful for members of Institutional Review Boards. Further research is therefore necessary to determine whether such a decision-procedure is a good idea for resolving conflicting imperatives in the context of research, and, if so, what such a procedure would look like in different types of social scientific research.

Specifying the Principles

A second set of issues deserving of greater scholarly attention concerns the content of the sub-principles themselves. The four sub-principles, as formulated above and in the research ethics literature, are rather vague, and further work needs to be done to specify each in greater detail to

ensure that it is action guiding for investigators and sponsors of research. For example, consider fair inclusion. As I note above, the precise content of this sub-principle depends on the development of an account of research priority setting. For example, the question of which groups of children to include in a study evaluating an educational intervention designed to improve math outcomes requires an answer to the question of which groups of children with respect to whom there is an obligation to improve numeracy outcomes. Unfortunately, to my knowledge, with the exception of Pierson and Millum's (2018) recent work on health research priority setting, very little scholarly work has been done on this issue.

Consider fair opportunity next. Fair opportunity surely requires that investigators not treat prospective participants for ex ante net beneficial research differently on the basis of arbitrary factors. But does it require more than this? For example, does fair opportunity also require that investigators and sponsors take positive steps to ensure that prospective participants have a fair chance to participate in ex ante net beneficial research, for example, to ensure that they are not disadvantaged by factors such as geography, language, or socio-economic factors (MacKay 2016, 677)? Might government sponsors of research have stronger obligations in this regard compared to private sponsors?[11] While such a substantive conception of fair opportunity may impose significant demands on investigators and sponsors of research, more formal conceptions of equality of opportunity are often understood to be stepping-stones to more substantive conceptions (Cohen 2009, 14-24).

Similarly, what does fair opportunity imply in the context of what Iyer, Hendriks, and Rid (2020) call "high-demand" trials, that is, when "more individuals are eligible and interested in enrolling in a given trial than there are available slots?" For example, should investigators conduct a

[11] Thanks to Danielle Bromwich for raising this point.

lottery, prioritize those who have previously participated in research on grounds of reciprocity, or perhaps prioritize those most likely to benefit from participation (Iyer, Hendriks, and Rid 2020, 36-37)? In other words, which factors are non-arbitrary when it comes to the selection of prospective participants for ex ante net beneficial studies?

Finally, while research ethicists are increasingly discussing the need to consider risks to third-parties when determining the permissibility of studies (Hausman 2007; Shah et al. 2018), much work remains to be done unpacking the sub-principle of fair distribution of third-party risks. In particular, scholars must think very carefully about which levels of risk it is fair to impose on non-consenting third parties. This question arises in the context of clinical research, where third parties may be exposed to infectious agents, but also arises in many different forms of social scientific research. For example, Joshua R. Gubler and Joel S. Selway (2016, 177) describe a study in which investigators wished to determine the impact of crosscutting identities on prejudice in Chennai, India. The investigators decided to sample from members of the lower castes living in urban slums on the grounds that members of this group provided the strongest test of their theory of the impact of crosscutting identities. However, Gubler and Selway (2016, 177) note that the study also imposes risks of discrimination on third party members of this group. They worry that members of the upper castes will use the study's results to argue that caste prejudice is simply a phenomenon of the lower castes and so that programs designed to increase access to jobs for members of the lower castes are not necessary (Gubler and Selway 2016, 177). An account of fair distribution of third-party risks is necessary to determine if it is permissible to carry out the study as designed, given the possibility of harms to bystanders.

Conclusion

A good deal of scholarly work thus remains to be done on the requirement of fair subject selection. Research ethicists must think carefully about how to navigate the conflicting imperatives of the four sub-principles, and also about how to further specify these sub-principles so that they are action-guiding for investigators and sponsors of research. My hope is that this chapter provides scholars with a solid conceptual foundation for carrying out these important tasks.

In closing, I would note that work is also necessary to address conflicts between the imperatives of fair subject selection, other requirements of ethical research, and valuable goals related to research.[12] For example, there may be cases where fair inclusion favors the participation of people who may be less able to give valid informed consent – e.g. people with cognitive disabilities. Similarly, in the case of phase 1 studies with healthy volunteers, Ana S. Iltis (2009) identifies a tension between the need to avoid undue influence and the need to fairly distribute the burdens of participation. By keeping payments low to avoid undue influence, Iltis (2009, 71-74) argues, investigators inevitably target and recruit members of socio-economically disadvantaged groups. In addition, recruiting sufficient numbers of an under-represented group may be an expensive exercise, perhaps requiring investigators with fewer resources to devote to other studies. Further work is necessary to provide investigators and sponsors of research with principles to adjudicate these challenging conflicts.

[12] Thanks to Joseph Millum for raising this point.

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