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Four Faces of Fair Subject Selection

Abstract

Although the principle of fair subject selection is a widely recognized requirement of ethical clinical research, it often yields conflicting imperatives, thus raising major ethical dilemmas regarding participant selection. In this paper, we diagnose the source of this problem, arguing that the principle of fair subject selection is best understood as a bundle of four distinct sub-principles, each with normative force and each yielding distinct imperatives: (1) fair inclusion; (2) fair burden sharing; (3) fair opportunity; and (4) fair distribution of third-party risks. We first map out these distinct sub-principles, and then identify the ways in which they yield conflicting imperatives for the design of inclusion and exclusion criteria, and the recruitment of participants. We then offer guidance for how decision-makers should navigate these conflicting imperatives to ensure that participants are selected fairly.

Keywords: Clinical research ethics; justice in clinical research; fair subject selection; fair inclusion; fair opportunity; vulnerable populations

Main Text

The principle of fair subject selection is a requirement of ethical clinical research. However, this principle yields conflicting imperatives. Fair subject selection requires that vulnerable people receive special protections and perhaps also be excluded from participation (The National Commission for the Protection of Human Subjects of Clinical and Behavioral Research 1979, 10), but also that studies be inclusive of and even proactively target traditionally underrepresented groups (US Congress 1993; Emanuel, Wendler, and Grady 2000, 2704–5). It requires that people should have an opportunity to participate in potentially beneficial research (MacKay 2016), but also that those facing greater risks be excluded (Emanuel, Wendler, and Grady 2000, 2704–5). These types of tensions have been borne out in the case of research with pregnant women. Pregnant women have been excluded from research on the grounds that they are a vulnerable population or that participation is too risky (Coleman 2009; Lyerly, Little, and Faden 2008; Schonfeld 2013). However, scholars have argued quite convincingly that such exclusion is unjust, unfairly denying pregnant women as a class the benefits of knowledge gained from clinical research – i.e. safe and effective treatments – and unfairly denying individuals access to potentially beneficial clinical studies (Lyerly, Little, and Faden 2008). The principle of fair subject selection has thus been used to justify both the exclusion and inclusion of pregnant women in clinical research.

In this paper, we diagnose the source of this problem, arguing that the principle of fair subject selection is best understood as a bundle of four distinct sub-principles, each having normative force and each having specific, often conflicting implications for participant selection. *Fair inclusion* requires that the selection of participants be sufficiently inclusive to ensure that

the research in question is appropriately generalizable to clinically distinct populations. *Fair burden sharing* requires that the burdens of participation in ex ante net burdensome research be shared fairly. *Fair opportunity* requires that prospective participants be granted a fair opportunity to participate in research that is ex ante net beneficial. Finally, *fair distribution of third-party risks* demands that participants be selected to ensure a fair distribution of risks to bystanders.

We first provide an account of the ground and contours of the question of fair subject selection. We then map out these four sub-principles, explaining how each addresses a distinct dimension of this broader question. We then identify the different ways in which these sub-principles may yield conflicting imperatives. Finally, we offer guidance for how these conflicting imperatives should be navigated to ensure that participants are selected fairly.

1 The Benefits and Burdens of Clinical Research

Considerations of fairness arise most directly in cases where people cooperate to produce some set of benefits or goods. Principles of justice or fairness are necessary to determine how the benefits and burdens of such cooperative activity should be distributed. Speaking of *social* justice, John Rawls (Rawls 1999, 4) explains the role of principles of justice in the following 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.

Clinical research is similar to the broader system of social cooperation referenced by Rawls in that it too is a cooperative activity (Emanuel, Wendler, and Grady 2000, 2705).[1] Investigators, sponsors, and participants, among others, work together to produce clinically relevant, generalizable knowledge. As such, the cooperative practice of clinical research produces and distributes a number of benefits and burdens, and the choice of rules by which such research is carried out and its benefits and burdens distributed must be governed by principles of justice or fairness.

We focus here on a small part of this broader question: where participant selection influences the distribution of the benefits and burdens of research, in accordance with which principles should participants be selected to ensure a fair distribution of these benefits and burdens?

To make headway on this question, consider the many ways in which the distribution of the benefits and burdens of clinical research is tied to the selection of participants. First, clinical research may produce generalizable knowledge that can be used to improve people's health. Such knowledge is the principal benefit of clinical research and its distribution is often directly influenced by participant selection. In many cases, participant selection has implications for the generalizability – and so the value to various groups within society – of the knowledge produced

[1] We adopt the U.S. Food and Drug Administration's understanding of "clinical research", which includes any research with human participants that generates clinically relevant knowledge, for example clinical trials, and studies of natural history, epidemiology, and genetics (US Food and Drug Administration 2018).

by the study. For some types of research, human bodies and/or the environments they inhabit differ in clinically relevant ways, meaning that an intervention having a particular effect in one person may not have the same effect in another. In these cases, the distribution of the benefits of clinical research, here taking the form of generalizable knowledge, is influenced by the selection of participants. The selection of participants determines which groups of people will most benefit from the clinically relevant knowledge that is generated by the study.

Clinical research can also benefit individual participants. Participants may receive health benefits from participation, either because the intervention under evaluation proves to be more effective than the standard of care treatment or because participants receive superior medical care compared to nonparticipants. Participants may receive actionable test results, enabling them to take steps to protect or promote their health that they would have otherwise not taken. Participants may also simply have a preference to participate in research, regardless of whether they stand to benefit clinically, and the satisfaction of this preference arguably makes them better off in at least one respect. Finally, participants may also benefit financially from participating in clinical research by receiving payment for participation.

Participation in clinical research should not only be construed as a benefit to participants, however. In addition to the time and effort that participation involves, clinical research can also be harmful or burdensome to individual participants. Participants may be worse off if the intervention under study proves to be less effective than the standard of care treatment, or if it proves to be more harmful than beneficial. In addition, clinical research often imposes risks and burdens to participants that are unrelated to the intervention under study – e.g. blood draws to collect data and risks to privacy.

Finally, clinical research may be harmful for third parties, and the selection of participants may influence the distribution of these harms. Research with members of identifiable groups may sometimes result in stigmatization and discrimination affecting nonparticipants. In addition, some studies of infectious disease may pose a risk of infection to third parties, and if participants differ in terms of the risk of infection they pose to others, participant selection has implications for third-party risks.

The selection of participants therefore has implications for the distribution of the benefits and burdens of clinical research. How should participants be selected to ensure that these benefits and burdens are distributed fairly?

2 Four Faces of Fair Subject Selection

In this part of the paper, we identify four sub-principles that should govern the selection of research participants. We provide a general definition of each, recognizing that each requires further development in future work. We discuss each sub-principle in turn.[2]

2.1 Clinically Relevant Knowledge: Fair Inclusion

As we note above, there are cases where participant selection has implications for the generalizability of the clinically relevant knowledge that is produced. Where people differ in ways that are relevant to the disease or intervention under investigation, the generalizability of the resulting knowledge will depend on the nature of the participants enrolled in the study. If

[2] As a shorthand, we shall speak of "investigators" as bearing the principal responsibility to select participants fairly. However, we hold that the requirement of fair subject selection applies to all agents who make decisions regarding participant selection.

intervention A or disease X behaves differently in one group of people (whether due to differences in genetics, sex, co-morbidities, environment, health behaviors or other factors) compared to a reference group, then a trial that only enrolls the latter type of people will not produce clinically relevant knowledge for the former – or at least not knowledge of the same quality. In these types of cases, studies yield benefits for only a restricted category of people.

Complete exclusion or underrepresentation of certain populations is a problem of fairness since it means that members of these populations are not experiencing the benefits of clinical research to the same extent as others. This is particularly worrisome in the case of publicly funded research, since members of different populations, in some cases defined by age, race, and sex, do not benefit equally from a government project.

To ensure that the benefits of clinical research in the form of clinically relevant knowledge are shared fairly within a population, there must therefore be *fair inclusion* of clinically distinct populations.

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

The principle of fair inclusion is 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)."

Fair inclusion is also prominent in scholarly discussions regarding participant selection (Corbie-Smith, Moody-Ayers, and Thrasher 2004, 1362; Emanuel, Wendler, and Grady 2000,

2704; Kass and Lyerly 2018, 91–92; King 2018, 128; Meltzer and Childress 2011, 379–80; Friedman Ross and Nelson 2018, 84–86; Weijer 1996, 340–41). As we note above, scholars have argued for decades that pregnant women must not be excluded from clinical research to ensure that it yields knowledge that is generalizable to them (Institute of Medicine (US) 1994; Lyerly, Little, and Faden 2008). Researchers have also argued that arbitrary upper age limits too often lead to exclusion of the elderly from research on conditions such as heart failure that primarily affect people as they age (Cherubini et al. 2011). Similarly, scholars and advisory committees have decried the exclusion of complex patients with common comorbidities that are likely to have direct impacts on relevant study outcomes, such as the co-occurrence of kidney disease with diabetes or cardiovascular disease, the co-occurrence of multiple psychiatric conditions, and higher-risk, complex cancer patients (Jin, Pazdur, and Sridhara 2017; Maini et al. 2018; Wong et al. 2018). Finally, commentators have argued that genomic research needs to proactively target a much more diverse range of participants if it is to yield knowledge that is relevant to populations that are not of European ancestry (Popejoy et al. 2018).

The precise content of fair inclusion will depend on answers to questions in the realm of health research priority setting.[3] The underlying idea is that sponsors of research have a duty to fund and carry out research that fairly benefits people and that this duty has implications for participant selection. For example, if principles of priority setting imply that governmental sponsors of research such as the National Institutes of Health ought to produce clinically relevant knowledge that does not disproportionately favor members of a particular racial group, then it

[3] Fair priority setting may also need to encompass issues of compensatory justice in cases where particular populations have been unfairly excluded from research in the past (Kass and Lyerly 2018, 92). For discussion of this question, we thank Elana Jaffe.

follows that governments have an obligation to ensure that participant enrollment is sufficiently inclusive to produce knowledge that is truly generalizable across racial groups.

Providing an account of health research priority setting is of course beyond the scope of this paper; however, Leah Pierson and Joseph Millum (2018) have recently made significant progress on this problem. Of interest for our purposes, Pierson and Millum (2018) argue that different types of funders – governmental, multilateral, nonprofit, and for-profit – have different special duties that are relevant to decisions regarding which populations they should benefit. If Pierson and Millum are correct on this point, it would follow that the demands of fair inclusion may vary by sponsor-type.

A further question concerns fair inclusion's appropriate site of application. The principle of fair subject selection is commonly understood to apply to particular studies. However, to satisfy fair inclusion, it may not be necessary to ensure that *all* studies are inclusive of diverse populations, only that research portfolios as a whole are sufficiently inclusive.[4] Sponsors may therefore satisfy fair inclusion by requiring individual studies to be inclusive, or by funding multiple studies that together provide knowledge relevant to clinically distinct groups.

2.2 Harms to Participants: Fair Burden Sharing

To generate benefits for one population in the form of clinically relevant knowledge, it is often necessary to impose burdens on research participants. Participation in clinical research

[4] Relatedly, Alex John London and Jonathan Kimmelman (2019) have recently argued that in order to ensure the ethical treatment of participants, it may be necessary to evaluate particular studies as components of a broader research portfolio, not in isolation.

often involves risks to participants' health and privacy. It can also be time-intensive, taking participants away from activities that they prefer or to which they have obligations (e.g. work or childcare). Burdens arise from the planned activities of research and also from unexpected adverse events, and individuals may differ in their ability to manage them. Since clinical research is a social practice from which all members of society benefit, the burdens of this practice must be shared fairly. Since the burdens of participation are directly allocated to participants in ex ante net burdensome research, this is another dimension of fair subject selection.

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

Fair burden sharing is widely recognized as a requirement of fair subject selection in the research ethics literature and regulations and its content has been further specified in a number of ways (Meltzer and Childress 2011, 377–78; Weijer 1996, 336–38). First, scholars have argued that the burden of participation in ex ante net burdensome research should be borne by those best placed to bear the burdens in question (Emanuel, Wendler, and Grady 2000, 2704). For example, according to *The Belmont Report* (The National Commission for the Protection of Human Subjects of Clinical and Behavioral Research 1979, 9):

> 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 or select only "undesirable" persons for risky research. 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 burdens on already burdened persons.

The prospective participants best placed to bear the burdens of participation are those who are not already burdened, for example, by socio-economic disadvantage or illness, but also those for whom participation would simply be less risky (Emanuel, Wendler, and Grady 2000, 2704).

Scholars have also argued, second, that it is unfair to ask people to participate in ex ante net burdensome research if the risks of participation are unacceptably high (London 2007, 110; Rid and Wendler 2011, 165). The underlying idea is that in the context of a cooperative project it is unfair to ask some individuals to bear excessive burdens for the purposes of benefitting others. As Rawls (1999, 3) puts it, "[justice] does not allow that the sacrifices imposed on a few are outweighed by the larger sum of advantages enjoyed by many." For example, Annette Rid and David Wendler (2011, 165) argue that there are limits to the level of risk it is acceptable to ask people to bear for the benefit of others, and that to determine this level of risk, reviewers should adopt the perspective of "social arbiters." Such arbiters must "(1) carefully consider the risks and prospective benefits for all affected parties, ensuring that the risks to individuals are not excessive and proportionate to the benefits to them and/or society, (2) give everyone's claims fair consideration, and (3) treat like cases alike across different areas of policy." Participants may only therefore be asked to face those levels of risk that are consistent with a "fair consideration" of participants' interests and the interests of those who may benefit from the research (Rid and Wendler 2011, 165). For particular studies, Rid and Wendler suggest, there is thus a level of acceptable risk above which it would be unfair to ask participants to face. Alex John London (2007, 110) argues similarly that risks to research participants are 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." The interests of

community members must be treated fairly and with equal concern, and this places limits on the level of risk individuals may be asked to bear in order to benefit others.

2.3 The Benefits of Participation: Fair Opportunity

Clinical research may also benefit participants. These benefits may be health-related, preference-related, or financial. Where participation is ex ante net beneficial, the selection of participants raises a direct question of fairness: how should the opportunity to participate be allocated?

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

Scholars ground fair opportunity on the idea that people are moral equals, and so their interests deserving of equal consideration. When deciding how to allocate the good of participation in ex ante net beneficial research therefore, investigators must recognize that all who meet the scientific requirements of the study have a prima facie equal claim to participate (Emanuel, Wendler, and Grady 2000, 2704–5; MacKay 2016, 674). Treating prospective participants equally is particularly important when the research is publicly funded since citizens have a claim to the benefits of public projects. However, even in the case of privately funded research, investigators must treat prospective participants in a way that recognizes their equal moral status, just as private for-profit companies may not discriminate against people seeking employment or wanting to purchase their goods or services.

Fair opportunity is also widely recognized in the research ethics literature and regulations (Lyerly, Little, and Faden 2008, 6–7; MacKay 2016; Meltzer and Childress 2011, 378–79; Weijer 1996, 338–40). The Belmont Report (The National Commission for the Protection of

Human Subjects of Clinical and Behavioral Research 1979, 9), as quoted above, specifies 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." Commentators have also argued in favor of opening up net beneficial studies to broader populations. For example, as we note above, scholars have argued for the inclusion of pregnant women in many studies to ensure that they have access to the direct benefits of participation (Lyerly, Little, and Faden 2008, 6–7). Similarly, the American Society of Clinical Oncology has moved to examine common exclusion criteria in part to improve access to prospectively beneficial trials (Unger et al. 2019). Having HIV is a common exclusion criterion in prospectively beneficial cancer treatment trials because of perceived risk of research-related harms, but management of HIV has progressed so significantly that it may no longer be justifiable to deny people with well-managed HIV access to trials (Jin, Pazdur, and Sridhara 2017).

While scholars largely agree on the requirement that prospective participants have a fair opportunity to participate in ex ante net beneficial clinical studies, there are a number of remaining questions to be addressed. First, does fair opportunity merely require that investigators not favor or disfavor prospective participants in the design of inclusion and exclusion criteria for illegitimate reasons? Or does it also require that prospective participants have a roughly equal ability to participate in research, that is, that they do not face obstacles to participation based on their socio-economic status or geographic location? Call the former principle *formal* fair opportunity and the latter *substantive* fair opportunity (MacKay 2016, 677).

There are also questions regarding the factors that should be considered when determining if a study is net beneficial or net burdensome. There is consensus that the health

benefits of the experimental intervention should count as benefits, but there is disagreement on whether either ancillary care, payment, or simply the satisfaction of participants' preferences to participate should be counted as benefits (Wertheimer 2013). The answers to these questions will have important implications for which studies are net beneficial for participants, and so fall under fair opportunity, and which studies are net burdensome, and so fall under fair burden sharing. Additionally, although any study is either ex ante net beneficial or net burdensome for a given individual, studies may not be either ex ante net beneficial or ex ante net burdensome for all participants, since participants may vary in terms of personal preferences or individual characteristics – e.g. disease stage or access to alternatives. We discuss these complications further below.

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

Finally, as we note above, clinical research may be harmful for third parties (Kimmelman 2005; Eyal et al. 2018; Shah et al. 2018), and the selection of participants may influence how these harms are distributed. First, research with members of identifiable groups may result in stigmatization and discrimination affecting nonparticipants (Hausman 2008). For example, research on the prevalence of drug abuse or psychiatric disorders in certain identifiable groups could lead to stigmatization of, or discrimination against, nonparticipant members of those groups. Although it can be difficult to track cases of manifested stigmatization or discrimination, fears of such harms are significant and well documented. In a highly publicized case, members of the Havasupai Tribe suffered psychological harm due to their concerns about stigmatization after their genetic material, collected primarily for a diabetes study, was used for studies of schizophrenia, ethnic migration and population inbreeding (Garrison 2013). In a survey of

prospective research participants moreover, the majority were concerned that genetics research could contribute to racial discrimination (Goldenberg et al. 2011).

Second, clinical research may impose health-related risks on nonparticipants (Eyal et al. 2018; Shah et al. 2018). For example, controlled human infection studies, which involve the deliberate exposure of healthy research participants to infectious agents, often pose a risk of infection to third parties. Since participants may differ in terms of the risk of infection they pose to others, the selection of participants may influence whether and how this risk is distributed among nonparticipants.

Since the selection of research participants plays a role in the creation and distribution of these third-party risks, an additional sub-principle is necessary to ensure their fair distribution.

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

The two considerations we mention above in our discussion of fair burden sharing seem relevant here. First, fair distribution of third-party risks would seem to require the allocation of third-party risks among people who are most able to bear them, that is, people who are not socio-economically disadvantaged, ill, or who lack access to health care (Kimmelman 2007, 488). Second, just as there is a level of risk that it would be unfair to ask participants to bear, it is also reasonable to think that there is a level of risk that it is unfair to expect third parties to bear.[5]

[5] Indeed, Jonathan Kimmelman (2007, 488) argues that when risks to bystanders are greater than minimal, bystanders should be directly informed of the risk and perhaps even provided with the opportunity to consent to their imposition. Holly Fernandez Lynch (Unpublished, 2019) offers an excellent exploration of where the threshold of unacceptable risks to non-consenting bystanders should be set in her paper, "Establishing the Ethical Threshold for Research Risks to Nonconsenting Bystanders."

Since the selection of participants influences the distribution of risks to third parties, investigators must select participants in a way that ensures these risks are distributed fairly. This may mean excluding certain participants from a controlled human infection study, for example, if their enrollment would impose risks of infection on third parties who are already ill or socio-economically disadvantaged; or excluding certain participants whose inclusion would impose unacceptably high risks on nonparticipants.

Fair subject selection is thus a multidimensional requirement, including four distinct sub-principles: fair inclusion, fair burden sharing, fair opportunity, and fair distribution of third-party risks. To select subjects fairly, investigators must comply with these sub-principles when designing inclusion and exclusion criteria, and when recruiting participants. Table 1 presents each sub-principle along with its principal implications for participant selection:

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 groups with characteristics relevant to the disease or intervention.
Fair Burden Sharing	Burdens of participation in clinical research must be fairly shared.	Select participants best able to bear the burdens of research and exclude prospective participants facing unacceptably high risks.
Fair Opportunity	Prospective participants must be granted a fair opportunity to participate in clinical research that is expected to be net beneficial.	Do not exclude people unfairly from research studies and make reasonable efforts to enhance people's ability to participate.
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.

As we note above, further work is needed to fully specify the content of these sub-principles. We set this task aside here, addressing another important question in the next two parts of the paper: what should investigators do when these principles yield conflicting imperatives?

3 Identifying Conflicting Imperatives

To answer this question, it is important to first systematically identify the ways in which the four sub-principles may yield conflicting imperatives. We do so here before formulating and defending a decision procedure investigators may follow to navigate these conflicts.

First, fair inclusion is likely to conflict with fair burden sharing. Compliance with fair burden sharing may lead investigators to exclude people who would face unacceptably high risks or who are less able to bear the risks of research than others. However, fair inclusion may *require* that such people be included in cases where the reasons they face such burdens are also clinically relevant. For example, because of disease-relevant differences in genetics, clinical presentation, environment, and lifestyle, fair inclusion requires research on preventing and treating cardiovascular disease in low-income African American participants with multiple comorbidities. However, many of these prospective participants are already burdened in society, so asking them to bear additional burdens of research participation may be unfair.

For similar reasons, fair inclusion is also likely, second, to conflict with fair distribution of third-party risks. The latter principle may require the exclusion of prospective participants

whose inclusion would impose risks unfairly on third parties, but the inclusion of these participants may be required by fair inclusion. For example, the real-world effectiveness of infectious disease treatment is often best studied in the populations and locations where the disease is endemic because of local population differences in genetics or immunity from prior infections; fair inclusion therefore indicates targeting participants in endemic regions (Selgelid and Jamrozik 2018). However, if a study involves controlled infection with a pathogen and measures taken to prevent its spread outside the study are inadequate (for example, if local sanitation infrastructure is inadequate to kill pathogens spread via sewage), nonparticipants could be put at risk of infection. In these cases, fair distribution of third-party risks may imply that the study be performed in non-endemic regions where the risk of infection to nonparticipants is lower.[6]

Fair inclusion may also, third, conflict with fair opportunity. To satisfy fair inclusion, it may be necessary to prioritize the recruitment of clinically distinct populations – i.e. to engage in a form of affirmative action for members of these groups. For example, in order to improve diversity in genomic databases, precision medicine initiatives are attempting to oversample from groups who have been historically underrepresented in these types of databases (Sankar and Parker 2017). But prioritizing the enrollment of under-represented groups in this way may prevent the fulfillment of fair opportunity, necessitating the exclusion of some eager volunteers who would otherwise be able to benefit from participation. Full compliance with fair

[6] Another case where fair distribution of third-party risks might conflict with fair inclusion is in HIV cure studies in low-resource settings, where patients stop taking antiretroviral drugs as part of the study. Sexual partners outside the study face transmission risks, and in settings with poor access to medical care, third parties are at elevated risk compared to high resource settings (Shah et al. 2018).

opportunity, by contrast, may result in insufficient participation of clinically relevant subpopulations.

Fourth, fair burden sharing may conflict with fair distribution of third-party risks. The prospective participants favored by fair burden sharing – e.g. those best able to bear the burdens of research – may also be those whose inclusion would distribute third-party risks unfairly. 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 to transmit the virus to their sexual partners than women (Durbin and Whitehead 2017). The inclusion of these men would thus be favored by fair burden sharing but disfavored by fair distribution of third-party risks. The reverse may also be true under certain circumstances. Prospective participants least able to bear the burdens of research may also be those whose inclusion would be favored by fair distribution of third-party risks.

Fifth, fair opportunity may conflict with fair distribution of third-party risks. Fair opportunity requires that all prospective participants have a fair opportunity to participate in ex ante net beneficial studies; however, fair distribution of third party-risks may require the exclusion of prospective participants whose inclusion would unfairly distribute third-party risks. For example, members of identifiable groups may want to access the direct health benefits of participating in a particular clinical study, but their inclusion may impose risks of stigmatization or discrimination on nonparticipant members of their group.

Might fair opportunity also conflict with fair burden sharing? No. These principles address mutually exclusive types of research. Fair opportunity deals with research that is ex ante net beneficial for participants whereas fair burden sharing deals with research that is ex ante net burdensome. If participation is not ex ante net beneficial, there are no *opportunities* to be shared;

if participation is ex ante net burdensome, it makes no sense to talk of sharing *burdens*. In principle therefore, these sub-principles do not yield conflicting imperatives.

Things will of course be more complicated in practice since studies will rarely be ex ante net beneficial or ex ante net burdensome for all prospective participants. First, if benefits are understood widely to include payment or the satisfaction of a preference to participate in a meaningful activity, then studies that are ex ante net burdensome from a clinical perspective may nonetheless be ex ante net beneficial on balance for some potential participants. Second, even if benefits and burdens are understood more narrowly to simply involve the clinical harms and benefits of participation in a study, there may still be cases where prospective participants differ such that the same study is ex ante net beneficial for one participant but ex ante net burdensome for another, for example, because the latter participant has a co-morbidity that makes participation riskier.

Still, regarding the enrollment of individual prospective participants, fair opportunity and fair burden sharing do not yield conflicting imperatives. Since participation for individual prospective participants is either ex ante net beneficial or ex ante net burdensome, there won't be cases where *both* sub-principles apply, creating the possibility for conflicting imperatives. The decision procedure we develop below, moreover, provides investigators with guidance for studies in which participation for some prospective participants is ex ante net beneficial but ex ante net burdensome for others.

4 Navigating the Conflicting Imperatives

Given these conflicting imperatives, there may be studies in which investigators will not be able to adhere to all four requirements. On the assumption that each requirement has

normative force, participants will be selected unfairly in these studies. How should investigators resolve these conflicts when they arise? In what follows, we propose a principled approach to navigating these conflicting imperatives.

To make headway on this question, we appeal to another context in which agents face difficult decisions regarding the permissibility of treating people in prima facie unfair ways: the ethics of discrimination. Discrimination involves treating members of a particular socially salient group worse than non-members because of their membership in that group. While most would recognize that discriminatory treatment is prima facie unfair, there are cases in which it is nonetheless justifiable. More specifically, MacKay (2018) has recently provided an account of permissible discrimination that summarizes the insights of prominent liberty-based accounts of discrimination, and that is largely consistent with the tests employed by U.S. and Canadian courts to determine when otherwise discriminatory treatment is justifiable. According to MacKay's (2018, 57) account, discriminatory treatment is permissible if:

1. The discriminatory treatment is expected to significantly advance the realization of one of the discriminating agent's purposes;
2. There is no less discriminatory means by which the discriminatory agent may significantly advance the realization of its purpose that would not result in undue burdens on it; and
3. The purpose of the discriminating agent is more valuable than the purposes frustrated by the discriminatory treatment.

On this account therefore, treating agents may discriminate against individuals when the discriminatory treatment is more or less necessary to significantly advance a morally valuable purpose. While such treatment is prima facie unfair, it is permissible when necessary to facilitate

the realization of a goal that is more valuable than the purposes the treatment would frustrate (MacKay 2018, 57–58).

MacKay's account explains why certain forms of discriminatory practices are permissible. For example, while it is widely recognized as unfair for employers to discriminate against potential employees on the basis of factors such as race, sex, gender identity, and religion, MacKay's account (2018, 58) explains why it is permissible for churches and religious schools to favor members of the faith when hiring people to perform clerical or educational roles. Such institutions have a morally important purpose of practicing the faith in question, hiring a member of the faith into a clerical position is necessary to realize this purpose, and this purpose is more valuable than the purposes frustrated by the differential treatment – i.e. a non-member's interest in occupying the position in question. It can also explain why it may be permissible for selective colleges to favor applicants who are racial minorities. While such favoring is discriminatory, giving minority candidates a relative advantage over non-minority candidates on grounds of race, it is justifiable when necessary for colleges to secure the educational benefits of having a diverse student body (MacKay 2018, 60).

Adopting MacKay's account to the context of fair subject selection, we suggest that it is permissible for investigators to tolerate some unfairness in the selection or participants, when this unfair treatment satisfies the following conditions:

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.

These three conditions express the general claim that investigators may engage in unfair subject selection when the unfair treatment in question is necessary to fulfill their important goals, and these goals are more valuable than the goals that the unfair treatment would frustrate and any wrong associated with the unfair treatment.

Perhaps the most morally important purpose of investigators, we suggest, is the production of knowledge that fairly benefits members of society. It is widely held that the central goal of clinical research, considered as a morally justified practice, is to produce socially valuable, clinically relevant knowledge (Emanuel, Wendler, and Grady 2000, 2701). However, the goal of producing knowledge that fairly benefits members of society goes beyond this, requiring that investigators and other relevant decision-makers ensure that studies are sufficiently inclusive to produce knowledge that is generalizable to clinically distinct groups. Government funders of research, and those investigators who carry out publicly-funded research, clearly have a duty to realize this goal for they are bound by duties of distributive justice (Pierson and Millum 2018, 10). Indeed, as we note above, the National Institutes of Health Revitalization Act of 1993 requires investigators to ensure that their studies are sufficiently inclusive. Multilateral research funders such as the World Health Organization and World Bank also have a duty to realize this goal since their central purpose lies in helping states realize justice in the international order (Pierson and Millum 2018, 11). Non-profit and for-profit research funders also arguably have a general duty to realize this goal, though as Pierson and Millum (2018, 12–14) argue, they also have special obligations – e.g. duties to specific populations in the case of non-profits, and duties to shareholders in the case of for-profits – that may outweigh this general duty and so permit

them to deviate from realizing the goal of producing knowledge that fairly benefits all. Even for these latter sponsors however, while realizing this goal may not always be morally binding on them, this does not diminish the value of the goal in question.

The moral importance of this goal, we suggest, gives investigators and other decision-makers reason to decide some of the above-mentioned conflicts in favor of fair inclusion. To produce knowledge that fairly benefits all members of society, after all, investigators will need to ensure that their studies are sufficiently inclusive. Consider first the conflict between fair inclusion and fair opportunity. These sub-principles yield conflicting imperatives since fair inclusion requires prioritizing the enrollment of members of clinically relevant groups whereas fair opportunity requires granting all prospective participants a fair opportunity to participate. This conflict, we suggest, should be decided in favor of fair inclusion. First, while adhering to fair inclusion may involve the frustration of the interests of some individuals in participating in research that is ex ante net beneficial, the goal of producing knowledge that fairly benefits members of the public is far more important. Depending on the results of the research, fulfilling this goal may lead to significant health benefits for clinically distinct populations. This goal is also, second, sufficiently morally important to outweigh the wrong associated with denying certain prospective participants the opportunity to participate in the study. While investigators have a duty to treat prospective participants fairly, people do not have a right to participate in particular studies, and participation in particular studies is far less important to people's life plans than other spheres of public life where concerns regarding equality of opportunity are prominent – e.g. access to health care or access to employment. For these two reasons, we suggest that condition C of the above account is satisfied, implying that it is permissible for

investigators to limit fair opportunity when doing so is necessary to ensure particular studies are sufficiently inclusive.

This line of argument also supports favoring fair inclusion over fair burden sharing in at least some types of cases. Recall that fair burden sharing has two requirements: (1) select participants best able to bear the burdens of research, and (2) exclude prospective participants facing unacceptably high risks. Considering (1) first, we suggest that the goal of ensuring that studies fairly benefit all members of society is more morally important than the purposes that would be realized by excluding or disfavoring prospective participants simply because they are less able to bear the burdens of participation than others, and also outweighs the wrong associated with not fulfilling this dimension of fair burden sharing. In cases where prospective participants consent to participate in research, and where they do not face risks that are unacceptably high, investigators should favor fair inclusion over this first dimension of fair burden sharing.

First, prospective participants who are less able to bear the burdens of research may be said to have an interest in not participating in burdensome research. But, mere adherence to fair inclusion should not be understood to frustrate this interest in cases where participation is voluntary. The only interest that is frustrated by full compliance with fair inclusion is that of not being asked to participate in burdensome research. However, any such interest seems of no moral weight, if it can be said to exist at all. Compliance with fair inclusion is thus morally more important than the interests of prospective participants that would be frustrated by such compliance, namely, the interest in not being asked to participate in burdensome research.

Compliance with fair inclusion also outweighs the unfairness of enrolling people less able to bear the burdens of research. While there is admittedly some unfairness in cases where a

collective burden is disproportionately borne by those less able to bear it, the wrong of this unfairness is mitigated in cases where those bearing the burden do so voluntarily, as in the case of competent adults' participation in ex ante net burdensome research. That is, when members of a community must shoulder some collective burden, it is morally worse if decision-makers simply allocate this burden disproportionately to those less able to bear it, than if those less able to bear the burden disproportionately volunteer to bear it. Moreover, the degree of unfairness that is involved in such cases seems easily outweighed by the importance of fair inclusion.

Consider an analogy. Suppose that in the context of a blood services system that relies on voluntary donations, the majority of donors are less able to bear the burdens of donation. Compared to others, they live further away from clinics, are socio-economically disadvantaged, have less free time, and have certain health conditions that mean they face slightly higher risks from the donation process. This pattern of contribution is arguably unfair since those best able to bear the burdens of donation are not doing their fair share in a collective endeavor. But supposing that these donations are necessary to maintain an adequate blood supply, should the blood services system remedy this unfairness by turning these voluntary donors away? No. In our view the moral importance of ensuring an adequate blood supply vastly outweighs the unfairness associated with the pattern of contribution.

Although the immediate need of an adequate blood supply is perhaps greater than that of sufficiently inclusive research, we think that the latter goal is sufficiently analogous to the former to also outweigh the unfairness associated with already burdened populations voluntarily participating in ex ante net burdensome research. Indeed, we think that investigators ought to include such prospective participants even when doing so serves no goal other than fully enrolling a study. Note however, that because our arguments turn on participants' consensual

participation in research, this conclusion may not extend to the case of research with children and persons with cognitive disabilities. In this latter type of case, it's not clear to us that the degree of unfairness is indeed outweighed by the importance of fair inclusion.

We suggest therefore that with respect to competent adults, the first dimension of fair burden sharing should be understood to imply that investigators must avoid targeting prospective participants who are less able to bear the burdens of research but should instead advertise the opportunity to participate as widely as possible. This course of action recognizes that participation in burdensome clinical research is a collective burden that should be shared widely, and also prevents investigators from taking advantage of people's vulnerability to increase enrollment. The only time investigators should target such people is when doing so is justified by either the need to fulfill the principles of fair inclusion or fair distribution of third-party risks. Investigators should thus adhere to fair inclusion, even if it means enrolling competent adults in ex ante net burdensome research who are less able to bear the burdens of research.

The situation is different, however, with the second requirement of fair burden sharing, namely, that prospective participants be excluded if they face unacceptably high risks. Recall that the underlying idea here is that there is a certain level of risk that it would be unfair to ask prospective participants to bear for the purposes of benefitting others. As London (2007, 110–11) argues, such levels of risk are inconsistent with an equal regard for the basic interests of prospective participants and those of the beneficiaries of clinical research. Fair inclusion may conflict with this requirement of fair burden sharing since it may require the inclusion of individuals who would face such risks.

In these types of cases, investigators should adhere to the imperative of fair burden sharing, not fair inclusion. First, while the goal of producing clinically relevant knowledge that

benefits all is weighty, fulfilling this goal in these types of cases would involve violating the "basic interests" of those prospective participants who would face unacceptably high risks. Such interests, London (2007, 109) claims, "are interests that each individual has in being able to cultivate and to exercise those fundamental human capacities that are constitutive of what the philosopher John Rawls refers to as our two moral powers: the capacity to formulate and to pursue a life plan based on a conception of the good and to regulate our conduct with others on the basis of principles of right." By enrolling prospective participants who would face such risks, investigators enable the frustration of individuals' most fundamental interests, interests which liberal societies have a fundamental duty to protect and promote (Rawls 1999). Doing so would also, second, constitute highly unfair treatment of the participants in question, involving a failure to treat their interests with equal concern. Note too that we may not set aside the basic interests of people even if they consent to treatment that does so. Thus, we do not allow people to waive the basic rights and liberties that protect their basic interests, nor do we allow them to face unacceptably high risks in order to benefit others. While we permit people to donate their blood, we do not permit them to donate their hearts.

For these reason, condition C of the above framework is not satisfied and so investigators may not enroll prospective participants who would face unacceptably high risks. While enrolling these prospective participants would further a morally important purpose, it would treat these participants unfairly and it would also frustrate the realization of a purpose that is of equal – if not greater – moral importance: the protection of people's basic interests. As the Declaration of Helsinki states, "while the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects (World Medical Association 2013)."

This line of argument also gives us reason to favor the analogous dimension of fair distribution of third-party risks over fair inclusion. Recall that the former principle also forbids the imposition of risks on third parties that are unacceptably high. Fair inclusion may require that investigators enroll prospective participants in studies whose inclusion would impose such risks on others. Just as investigators may not ask prospective participants to face risks that are inconsistent with an equal regard for their basic interests and the interests of potential beneficiaries, so too they may not simply impose such risks on non-consenting third parties. Indeed, the level of risk to third parties that meets the threshold of "unacceptably high" is no doubt a fair degree lower than the level that meets this threshold for participants since third parties do not consent to participation (Hausman 2007). The underlying intuition here is that there may be levels of risk it is fair to ask people to undergo, but that it may be unfair to simply impose on them. It may be fair to ask my neighbor to donate one of his kidneys to me, but not to simply dump pollutants on his property that expose him to the same level of risk as a kidney donation.

What about the second dimension of fair distribution of third-party risks, namely, the requirement that risks be borne by third parties best able to bear them? Suppose that fair inclusion demands that investigators include people whose inclusion will impose risks on third parties who are ill or socio-economically disadvantaged. Suppose further that these risks do not meet the threshold of "unacceptably high," but do meet a threshold such that they are not negligible. Should investigators include these prospective participants or not?

This is a challenging question. Consider first that this type of case is different from the case above where prospective participants less able to bear the burdens of research volunteer to bear such burdens; in this case, people are non-consensually exposed to risks, and so the

unfairness in question is morally worse (Hausman 2007). Consider second that although the risks in question are not unacceptably high, they will be risks borne by people less able to bear them – e.g. people who are ill or socio-economically disadvantaged. This is important if we think that the interests of those who are worse off in society have special moral weight. Conducting studies that are sufficiently inclusive is of course an important goal, but so is protecting the interests of persons who are worse off in society.

For these two reasons, we are skeptical that condition C is satisfied in studies where compliance with fair inclusion requires an unfair distribution of risks to third parties. It's not clear that compliance with fair inclusion is morally more important than the need to protect the interests of worse off nonparticipants or outweighs the unfairness of the distribution of risk. We admit however, that this question requires further attention.

This line of argument also gives us reason to favor fair distribution of third-party risks over fair opportunity. These sub-principles may yield conflicting imperatives in cases where fair opportunity requires extending an opportunity to enroll to certain prospective participants, but where their inclusion may result in an unfair distribution of risk to third parties. Given our argument that fair distribution of third-party risks should take precedence over fair inclusion, and given our argument that the imperatives of fair inclusion are of greater moral importance than those of fair opportunity, it follows that fair distribution of third-party risks should take priority over fair opportunity.

Finally, fair distribution of third-party risks may conflict with fair burden sharing. There may be cases where either the inclusion of prospective participants best able to bear the burdens of research results in an unfair distribution of risks to third parties, or where the prospective participants whose inclusion satisfies fair distribution of third-party risks may result in an unfair

sharing of burdens. With respect to the former type of conflict fair distribution of third-party risks should take priority. The reasons that this principle takes priority over fair inclusion and fair opportunity apply here as well. With respect to cases where fair distribution of third-party risks may favor the inclusion of people who would face unacceptably high risks, fair burden sharing takes priority. Investigators should not enroll prospective participants facing unacceptably high risks simply because their inclusion is consistent with the fair distribution of risks to third parties. Prospective participants should not be exposed to unacceptably high risks for any reason.

Is it permissible, though, to enroll prospective participants who are less able to bear the burdens of research, in order to satisfy fair distribution of third-party risks? Investigators may face this decision in the unlikely scenario where if to adequately enroll a study, they must decide to either enroll prospective participants whose inclusion unfairly distributes risks to third parties or enroll prospective participants who are less able to bear the burdens of research. In this type of scenario, we suggest that investigators should prioritize fair distribution of third-party risks. For the reasons we state above, acting in accordance with the latter principle is of great moral importance, whereas ensuring that only those best able to bear the burdens of research enroll is of very weak moral importance. Indeed, as we argue above, this dimension of fair burden sharing is not sufficiently important to justify either excluding or even disfavoring competent prospective participants who are less able to bear the burdens of research.

To sum up, we have provided an account of how the five conflicts among the sub-principles should be adjudicated. Fair inclusion should take priority over fair opportunity and fair burden sharing, except with respect to the enrollment of prospective participants who would face unacceptably high risks. Fair distribution of third-party risks should take priority over fair inclusion, fair opportunity, and fair burden sharing, except with respect to the enrollment of

prospective participants who would face unacceptably high risks. This way of resolving these conflicts yields the following decision procedure:

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. Design 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).

Step 5 expresses the judgment we introduce and defend above that fair burden sharing should not be interpreted to justify excluding or even disfavoring prospective participants less able to bear the burdens of research. On this interpretation therefore, the requirements of fair burden sharing nicely align with the requirements of fair opportunity. Since (1) fair opportunity demands that all persons have a fair opportunity to participate in research, and (2) fair burden sharing demands that the burden of participation be shared widely, these two principles imply the same course of action: advertise the possibility of participation to all members of society who satisfy steps 1-4 and refrain from targeting particular populations. This alignment saves investigators from having

to determine whether, for each prospective participant, the study is either ex ante net beneficial or net burdensome, and whether fair opportunity or fair burden sharing should apply. Moreover, if benefits to participants are understood in a wide sense to include payment and preference satisfaction, it also saves investigators from having to make difficult value judgments to determine if participation is net beneficial or net burdensome for particular participants – e.g. weighing the benefit of the satisfaction of an altruistic preference against certain health risks.

We hope this decision procedure offers investigators a useful way to navigate the above-mentioned conflicting imperatives in an ethical way. We would also recognize that the general problem of prioritizing conflicting imperatives is a challenging one, and that revisions may be necessary for application to particular forms of clinical research. For example, as we note above, our arguments in support of prioritizing fair inclusion over the first dimension of fair burden sharing apply largely to research with competent adults, and so this prioritization may need to be revised in cases of research with children or incompetent adults.

Conclusion

The principle of fair subject selection often yields conflicting imperatives. In this paper, we have explained why this is so, arguing that fair subject selection is best understood as a multi-dimensional principle containing four distinct sub-principles, each with normative force, and each with its own set of implications. We have also identified the ways in which these sub-principles may yield conflicting imperatives and have provided decision-makers with a procedure to navigate them when they arise.

We conclude by noting that considerations of fairness are not the only legitimate considerations relevant to participant selection. Investigators have a duty to respect participants,

and so secure informed consent and take steps to protect vulnerable participants. Investigators may also have scientific reasons to exclude certain prospective participants. In certain circumstances moreover, these non-fairness considerations may conflict with the fairness considerations we outline above. For example, complex patients are routinely excluded from research for scientific reasons, but these exclusions conflict with the imperative of fair inclusion. Similarly, children and people with limited education, language barriers, or cognitive disabilities are also excluded because of consent or predicted retention/completion challenges, but this also conflicts with fair inclusion and fair opportunity.

Providing an account of how these fairness and non-fairness considerations should be balanced is beyond the scope of this paper. However, we would note that the account of permissible unfair treatment that we introduce above provides the tools necessary to address these conflicting imperatives. On this account, investigators may treat prospective participants unfairly, either to realize certain scientific goals or to adequately respect participants, when such treatment is necessary to realize these goals, and the value of these goals is sufficient to outweigh the unfairness of the treatment in question. Further work is of course necessary to carefully think through whether and when these non-fairness considerations outweigh fairness considerations and vice versa. However, we would note that this account requires investigators to discharge a justificatory burden when deciding whom to exclude. Just as investigators may not satisfy one sub-principle of fair subject selection at the expense of another without justification, neither may investigators select participants unfairly in order, for example, to further certain scientific goals without adequate justification.

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