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TREATMENT NEEDS IN HIV PREVENTION TRIALS: USING BENEFICENCE TO CLARIFY SPONSOR-INVESTIGATOR RESPONSIBILITIES

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ABSTRACT

Some participants will get HIV-infected in HIV prevention trials, despite risk reduction measures. The subsequent treatment responsibilities of sponsor-investigators have been widely debated, especially where access to anti-retroviral therapy (ART) is not available. In this paper, we explore two accounts of beneficence to establish whether they can shed light on sponsor-investigator responsibilities. We find the notion of general beneficence helpful insofar as it clarifies that some beneficent actions will be obligatory where they can be dispensed without scuppering the trial. We find the notion of specific beneficence helpful insofar as it directs investigators to attend to the needs of trial participants; however the range of interventions that could be provided remains unhelpfully broad. We then examine accounts of the investigator-participant relationship to narrow the range of interventions that investigators should provide, concluding that health-care, and HIV infection, are appropriate foci. We conclude that when investigators are able to meet the ART needs of their participants (e.g. referral, assisted referral or direct provision) without sacrificing trial quality, they must do so. However, there is little of this explicit direction to be found in the account of specific beneficence itself, but rather it is found in accounts of the relationship that are compatible with beneficence.

INTRODUCTION

The question at the heart of this paper is: can beneficence assist to clarify the responsibilities of sponsor-investigators in relation to HIV infection in biomedical HIV prevention trials?

Some participants in HIV prevention trials will become infected with HIV through on-going risk behaviour despite access to counselling and HIV prevention measures.[1] The obligation of sponsor-investigators in relation to HIV infection in trials has been the subject of intense debate.[2] This debate is accentuated in settings where quality treatment for HIV infection (like Anti-Retroviral Treatment/ ART) may not be available to all who need it, either through the public health-care system or through donor programs like PEPFAR.[3] In such instances, it is difficult for stakeholders to work out the precise responsibilities of sponsor/investigators in relation to HIV infections acquired by trial participants. It has been claimed by some commentators that the principle of beneficence

[1] WHO-UNAIDS. Treating People With Intercurrent Infection in HIV Prevention Trials: Report From a WHO/UNAIDS Consultation, Geneva 17–18th July 2003. *AIDS* 2004; 18: W1–W12.

[2] R. Macklin. Standard of Care: An Evolution in Ethical Thinking. *Lancet* 2008; 72: 284–285; H.S. Richardson. Gradations of Researchers' Obligation to Provide Ancillary Care for HIV/AIDS in Developing Countries. *Am J Public Health* 2007; 97: 1956–1961; U. Schöklenk & R. Ashcroft. HIV Vaccine Trials: Reconsidering the Therapeutic Misconception and the Question of What Constitutes Trial Related Injury. *Dev World Bioeth* 2008; 7: ii–iv; C. Weijer & G. LeBlanc. The Balm of Gilead: Is the Provision of Treatment to Those Who Seroconvert in HIV Prevention Trials a Matter of Moral Obligation or Moral Negotiation? *J Law Med Ethics* 2006; 34: 793–808.

[3] B. Lo, N. Padian & M. Barnes. The Obligation to Provide Antiretroviral Treatment in HIV Prevention Trials. *AIDS* 2007; 21: 1229–1231.

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has not been appropriately specified and therefore cannot be helpfully applied to this debate.[4]

The aim of this paper is to develop such arguments further by exploring accounts of beneficence, and to establish whether beneficence can shed light on the responsibilities that sponsors and investigators have in relation to participants' HIV infection needs.

THE *PRIMA FACIE* PRINCIPALIST APPROACH IN THIS PAPER

Commentators have observed that there has not been enough principled argument about the controversial issue of sponsor-investigators' responsibilities to trial participants.[5] Our concern in this paper is thus with ethical principles rather than an exploration of the practical anthropological question of what stakeholders' opinions are on this matter.[6] We do not reject the value of consultation with relevant stakeholders, like participating communities, on operationalising treatment decisions,[7] however, substantive ethical decisions are not best achieved by consensus.[8] For example: in Germany in the 1940s, the majority of citizens may have agreed that Nazi policy was best. That consensus did not make the policy right. So it is necessary to determine, through reasonable application of principles, what is right. Some have argued that involving stakeholders in a structured decision-making process via large consultative meetings will elucidate the core obligations, especially when 'norms and standards' are considered.[9] However, without prior clarification of such norms, this approach only reassigns the difficult struggle with norms and standards to consultative meetings. Canvassing people's opinions on this matter may be morally respectful, but is not necessarily morally definitive;[10] and some ethical responsibilities will exist regardless of how stakeholders feel about them.

The theoretical model underpinning this exploration is the 'four principles' approach (as expressed in the work of Beauchamp and Childress).[11] This approach is a well-known and widely utilized theoretical standard in this field. It is pragmatically useful, and has metaethical merit (that is, there are good philosophical reasons for following this normative framework). The four principles are: respect for autonomy, non-maleficence, justice and beneficence. The four principles approach is a *prima facie* model of deontology, which means one is obliged to act based on each of the principles unless they conflict with other stronger obligations based on competing principles, or conflicting interpretations of the same principle. For instance, there may be defensible, yet competing, *prima facie* duties, based on the principle of beneficence, such as: for sponsor-investigators to offer benefits to entire communities, or otherwise to research participants alone. In such cases, one has to specify the principle in relation to the context under consideration. By examining the most reasonable specification of the principle in the context, one can determine one's actual, as opposed to *prima facie* or immediately apparent, duty.[12] Because Beauchamp and Childress's exposition of the four principles is general, one may need to specify the principles by reference to accepted theories derived from these principles. The four principles approach is therefore a coherent model for integrating otherwise seemingly discrete theories: for instance, one can understand beneficence through the lens of multiple interpretations (Utilitarian and Humean, say). In the four principles approach, one must determine which interpretation is most meaningful and helpful. It is this task we turn to below.

BENEFICENCE

To date, beneficence-based arguments on this issue have been rejected as poorly specified and unconvincing.[13] Yet, as one of the four principles, beneficence deserves equal consideration. We will turn, therefore, to examine the ethical principle of beneficence, in the context of treatment needs in HIV prevention trials.

Beneficence is one of the four *prima facie* principles in bioethics, and as such should always be practiced unless there are over-riding reasons not to do so. It has been defined as contributing to the welfare of other persons.[14] While there is agreement on this simple definition, there is disagreement as to whether or not we have an obligation (duty) to contribute to others' welfare, or if beneficence is supererogatory (morally praiseworthy, or 'nice' to do, but with no entailment of a duty to perform such an act). Those who subscribe to the latter interpretation see beneficence as less morally compelling than the other principles. The most notable example of the interpretation of beneficence as supererogatory is Council for International Organizations of Medical Sciences (CIOMS) guideline 21 which states: 'Although sponsors are, in

[4] Weijer & LeBlanc, *op. cit.* note 2.
[5] Ibid.
[6] W.D. Ross. 2002. Introduction. In *The Right and the Good*, 2nd ed. P. Stratton-Lake, ed. Oxford: Oxford University Press.
[7] UNAIDS/AVAC. 2007. *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials.* Geneva: UNAIDS.
[8] G.E. Moore. 1996. *Ethics*. London: Oxford University Press.
[9] D. Tarantola et al. Ethical Considerations Related to the Provision of Care and Treatment in Vaccine Trials. *Vaccine* 2007; 25: 4863–4874.
[10] C. Grady et al. Research Benefits for Hypothetical HIV Vaccine Trials: The Views of Ugandans in the Rakai District. *IRB* 2008; 30: 1–7.
[11] T.L. Beauchamp & J.F. Childress. 2001. *Principles of Biomedical Ethics*. Oxford: Oxford University Press.
[12] Ibid.
[13] Weijer & LeBlanc, *op. cit.* note 2.
[14] Beauchamp & Childress, *op. cit.* note 11.

general, not obliged to provide health-care services beyond that which is necessary for the conduct of the research, it is morally praiseworthy to do so'.[15]

There are two accounts under which beneficence moves from being supererogatory to become an obligation. Beauchamp and Childress define these two interpretations of beneficence: the first account, characterized by the work of Singer, is referred to as general beneficence.[16] The second account is specific beneficence.[17]

General beneficence

This account construes beneficence as maximizing benefits, expressed as the maxim: if one can do something beneficial without sacrificing anything of comparable moral significance, it ought to be done.[18] This definition calls for an understanding of beneficence as a *duty* that one has an obligation to follow *provided that nothing of comparable moral significance* is being sacrificed by acting beneficently. An analogy can illustrate this interpretation: if one purposefully ignores a drowning person, whom one could easily save, one has done more than simply failed to do something good; one has abdicated a moral duty to save a life. In contrast, a person who risks her life to save the life of another, while doing something beneficent, has done something supererogatory – beyond the call of duty. Hence, depending on the comparable cost attached to the beneficent act, (as well as the relative weight of any other competing principles), beneficence can be either obligatory or supererogatory. While the above examples are of rescuing others, beneficence would require not only rescuing those who are in danger, but would furthermore require simply assisting, in whatever way, those whom one can help (without morally comparable sacrifice) irrespective of whether or not they are in danger. This interpretation of beneficence is much broader in scope than it is usually construed in research ethics. It goes beyond that expressed in the Belmont Report,[19] in that it implicitly sees benefits as being anything – not just those things that are research-related.[20]

It has been argued by some commentators that beneficence is too far-reaching to helpfully apply to the problem of sponsor-investigators' responsibilities in resource-poor trial contexts, and could create a ceaseless series of demands on researchers.[21] It is true that investigators working in an impoverished community will, on a daily basis, face the needs of people involved (and uninvolved) in the trial, and will be aware that there are some needs they could meet. Anecdotally, some investigators report that their conscience does not allow them to ignore some of those needs, although *in toto* they are overwhelming. However, according to the prior definition, charitable actions are only morally obligatory if nothing of comparable moral significance is being sacrificed which includes important research not taking place, or the researcher being unable to function because of charity fatigue.

Therefore, this account of general beneficence is partially helpful in the matter at hand, by directing sponsor-investigators to provide proportionately low-cost interventions that serve the interests of the beneficiaries. However, on such an account, it is not clear that the interventions should necessarily be treatment provision, when a capable actor could provide a range of other goods such as literacy training, or poverty alleviation. At first glance, there appears to be nothing inherent in the principle of beneficence that leads to the conclusion that treatment for health problems or even for the condition under study (ART) is the most logical focus.

It also appears not to help with the question of 'who' should be the recipient of investigators' beneficent acts. This account directs that when one can prevent something bad from happening without morally important sacrifice, one must help. This is, however, a general obligation: one has it to everyone. There is nothing that limits this duty of beneficence to trial participants alone. On these grounds, when ensuring treatment for participants' relatives or friends can be done without sacrificing the trial, it must also be done.

In summary, this account of beneficence clarifies that beneficent acts are not always praiseworthy and in some instances will be obligatory, namely, where there is a legitimate need that one can reasonably meet without sacrificing anything of comparable significance, one ought to do it. However, it does not necessarily follow that these interventions be limited to health-care, and on this account, it does not focus attention on trial participants alone.

[15] Council for International Organizations of Medical Sciences (CIOMS). 2002. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva: CIOMS. Available at: http://homepage.vghtpe.gov.tw/~mre/goodexp/Fercap-Survey/CIOMS-2002-Guidelines.pdf [Accessed 01 Feb 2007].

[16] P. Singer. 1999. *Practical Ethics*. Cambridge: Cambridge University Press.

[17] Beauchamp & Childress, *op. cit.* note 11.

[18] Singer, *op. cit.* note 16.

[19] National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research. 1979. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. Elkridge: United States Department of Health, Education, and Welfare.

[20] There is, anyway, something potentially arbitrary about 'research-related' benefits, as the latter is open to ad-hoc definition. Commonly accepted 'research-related' benefits such as the building of permanent clinics rather than the use of temporary structures, are not always strictly necessary to the research. Similarly, treatment in prevention trials is not strictly necessary but if it is written into the protocol, it will then be defined as a 'research-related' benefit.

[21] Weijer & LeBlanc, *op. cit.* note 2.

Specific beneficence

Beauchamp and Childress outline concerns about the self-limiting device inherent in accounts of general beneficence and argue that it could be too demanding. [22] Furthermore, they assert that the more widely we generalize obligations of beneficence, the less likely we may be to meet our primary responsibilities. These primary responsibilities are to those with whom we have relationships.

We will now turn to specific beneficence as outlined in Beauchamp and Childress's account in their overview of beneficence.[23] In keeping with the four principles model outlined above, the principle of beneficence can be further specified with reference to contextual facts and other theories, in order to practically apply it.

Specific beneficence means one should assist those with whom we have special relationships and meet our responsibilities to those whom we are close or indebted.[24] The kinds of relationships Beauchamp and Childress are thinking about here are, for example, in friendships and families and those relationships that arise because of 'special commitments, such as explicit promises and roles with attendant responsibilities'.[25] In particular they defend a reciprocity-based justification of specific beneficence (while acknowledging that this does not account for the full range of obligations of beneficence). Specific beneficence, as it is here understood derives from Hume's assertion that as people benefit from society, so too should they contribute to society. Beauchamp and Childress thus understand that many obligations of beneficence are justified by 'implicit arrangements underlying the give and take of social life', but that obligations of specific beneficence 'arise from implicit and explicit commitments, such as promises and roles'.[26]

Their account is justified by reference to theories that are compatible with beneficence such as the account of fiduciary responsibilities given by Miller and Weijer.[27] Such accounts of specific beneficence justify, for instance, intuitions that one has a greater duty to assist one's family than strangers, or that a doctor has more obligation to treat a patient than a stranger, all other things being equal.

According to their model of specific beneficence, one party (X) has an obligation of beneficence to another specified party (Y) when the following conditions are met:

a. Y is at risk of loss or damage to life, health or some other major interest;
b. X's action is needed (singly or in concert with others) to prevent this loss or damage;
c. X's action (singly or in concert with others) has a high probability of preventing it;
d. X's action would not present significant risks, costs or burdens to X; and
e. The benefit that Y can be expected to gain outweighs any harms, costs or burdens that X is likely to incur.

If all the criteria are met, there is an obligation to assist. In the absence of all these criteria being met, there is no obligation but it remains morally praiseworthy to perform the beneficent action.

Presumably the line between a supererogatory and obligatory beneficent action may be difficult to determine; however, some important considerations may be:

a) The level of suffering of the recipient of the beneficent action (the greater the suffering, the greater the duty to respond beneficently);
b) The reliance of the recipient on the agent for assistance (the greater the reliance, the greater the duty to respond beneficently);
c) The likelihood of successfully being beneficent (the greater the likelihood, the greater the duty to respond beneficently);
d) The capacity of the agent to afford and implement beneficent action (the greater the capacity, the greater the duty to respond beneficently); and
e) The costs involved in dispensing the beneficence (the higher the costs, the lower the duty to respond beneficently. The benefit to the recipient should outweigh the costs to the respondent).

Applied to the issue at hand, if party X is a sponsor from a resourced setting and party Y is a trial participant from a setting where treatment options are wholly inadequate, then let us consider that:

a. HIV infection, morbidity and awareness of impending death gives rise to a high level of suffering;
b. Participants are dependant on researchers to acquire treatment for them;
c. ART would prolong life and afford a higher quality of life;
d. Sponsors and researchers can finance and provide ART to participants; and
e. The financial expense of acquiring ART, and the demands of dispensing ART and managing participants are outweighed by benefits to infected participants.

In the above hypothetical case, beneficence is not supererogatory, because all the criteria which render beneficence a duty can be met. However, if any of these points were to be different, beneficence would *not* be an obligation. If, for example, the finances required to provide

[22] Beauchamp & Childress, *op. cit.* note 11.
[23] Ibid.
[24] Ibid.
[25] Ibid: 173.
[26] Ibid: 175.
[27] P.B. Miller & C. Weijer. Fiduciary Obligation in Clinical Research. *J Law Med Ethics* 2006; 34: 424–440.

ART to trial participants formed a disproportionate amount of the trial budget;[28] or researchers will not be working in the host-country by the time participants actually need ART; or researchers do not have the medical competencies to directly dispense ART to patients, then point (d) cannot be met and the beneficent action then becomes supererogatory. If we were to insist that it is still sponsors-investigators' duty to give ART when this is not possible, important research may not take place, which would be contrary to the spirit of beneficence, as the general public would not benefit from advances in scientific knowledge.

In the above hypothetical example, the trial setting was construed as having no treatment options for participants. Some might argue that this is no longer the contemporary problem for HIV vaccine trials. That is, it is more likely that prevention trials will take place in settings where treatment options are available but of variable quality. Can these conditions, for specific beneficence as a duty, give helpful direction about the responsibilities of researchers in relation to these more contemporary treatment problems?

Applied to the issue at hand, if party X is a sponsor from a resourced setting and party Y is a trial participant from a setting where treatment options are available but variable in quality, let us consider that:

a) HIV infection entails suffering;
b) Investigators can undertake capacity-building and technical assistance for ART service providers to whom they will refer infected participants;
c) ART ranks highly among the interventions that successfully offset suffering and death; and
d) Costs to sponsor-investigators in terms of money, and staff time are not so demanding that they imperil the scientific quality of the trial.

Also, in another setting where HIV treatment options are available and reliable, condition (a) will be met, that is, HIV infection entails suffering and condition (c) will be met because ART ranks highly among the interventions that successfully offset suffering and death. Condition (b) can be fulfilled by investigators locating and partnering with providers, referring participants to them, and following them up. Condition (d) will be met if 'costs' to sponsor-investigators, in terms of staff time spent against partnership-formation, referral and monitoring, are not so excessive as to undermine the trial.

To apply this account of specific beneficence to the problem of ART in prevention trials, investigators have to consider the most appropriate context-dependant response (that is, referral, assisted referral or direct provision) and consider if the costs can be borne. This will require them to be able to assess costs like staff down-time, financial costs in relation to the overall budget and impact on the scientific quality of the research.[29] They will also do well to explicitly assess the services available prior to trial initiation, a point made eloquently by previous writers.[30]

Condition (d) is most likely to be fulfilled when there are treatment options available and the action needed from researchers is partnership. Condition (d) is least likely to be fulfilled when there are no treatment options and the action that is needed from researchers is that they pay for and provide treatment (particularly where treatment is needed long after the trial is over and researchers are not AIDS clinicians). Research ethics committees have a critical role to play in establishing whether or not researchers have done enough to assess treatment options available to participants and if researchers will take appropriate action based on this assessment (e.g. partnering where providers exist).

So, this account of specific beneficence appears to be promising:[31] like the former account, it can give rise to moral duties (as opposed to commendable actions) and it appears to be applicable to the case under consideration here. Nevertheless, there are a number of limitations in its ability to clarify the duties of sponsor-investigators in relation to treatment needs of trial participants. Like the former account, there still remains an array of proportionately low-cost interventions that offer benefits to participants, therefore on this account, if trial participants present with non-medical needs, which can be met without morally relevant sacrifice (e.g. the trial) investigators must assist.

Assertions that researchers should treat the needs of participants when a four-stage test can be passed suffer from similar problems. It has been asserted that researchers should treat participants' medical problems when four conditions can be met, namely, that A is in a position to help B; A has the capability to help B; the burden on A would not be unreasonable; and B would not be taking unfair advantage of A.[32] However, it follows logically that when this four-stage test can be passed in relation to any conceivable need or problem experienced by a trial participant, sponsor-investigators must assist.

The account of specified beneficence described above cannot wholly address questions of 'what' interventions should be provided to beneficiaries. One is left to consider how best one can select (in a non-arbitrary way) those

[28] Richardson, *op. cit.* note 2.

[29] Ibid.

[30] L. Belsky & H.S. Richardson. Medical Researchers' Ancillary Clinical Care Responsibilities. *Br Med J* 2004; 328: 1494–1496; Richardson, *op. cit.* note 2.

[31] Beauchamp & Childress, *op. cit.* note 11.

[32] R. Brownsword. The Ancillary-Care Responsibilities of Researchers: Reasonable but Not Great Expectations. *J Law Med Ethics* 2007; 35(4): 679–691.

beneficial interventions one should provide to persons in the relationship in question.

That is, three questions need careful thought, namely: (i) Why is there a duty to respond to the *heath-care needs* of trial participants, rather than other needs that a beneficent actor in a special relationship could respond to? (ii) Why is there a duty to respond to the *HIV infection* of trial participants when there may be a range of health-care problems facing participants? (iii) Why is there a duty to attend to *ART needs* specifically, when participants could need a broad range of care for their infection?

It appears there is little in these accounts of beneficence that can easily answer these questions. One could attempt to answer these questions by turning to ideas that are compatible with the principle of specific beneficence. It could be argued however that turning to these ideas is an *ad hoc* attempt to get the principle of beneficence to do more than it can. It could be counter-argued that this is an effort to further specify beneficence in a way that allows one to foreground interventions in a principled manner, and that turning to other theories to specify and apply a principle is exactly what the four principles approach encourages. It is thus fitting that we at least attempt to respond to the apparent ambiguities that arise from an application of the principle of beneficence with reference to compatible theories.

On the first question: why respond to health-care needs? It would seem that health-care is an appropriate focus because the relationship between investigator and participant centres on health. It has been previously argued that a fiduciary relationship is established when 'one party entrusts another with discretionary power over the legal, economic, or other practical interest of a beneficiary, and the other party undertakes, expressly or impliedly, to exercise that power'.[33] This definition is compatible with Beauchamp and Childress' understanding of a specific, reciprocal obligation of beneficence as outlined above. By practical interests, Miller and Weijer argued that the interests must relate in a 'discernable and actual way to the welfare of the beneficiary'.[34] Applied to the investigator-participant relationship, it has been argued that the interests that are engaged are the participants' *medical interests*.[35] Therefore, in health-care research, it is health-care matters that are at the heart of the relationship, and that health protection is entailed by the duty of care between investigators and participants. This account of the relationship between researcher and participant helps to narrow the range of matters about which researchers should care, to *health matters.*

On the second question: why HIV? It appears that HIV is an appropriate focus in HIV prevention trials, because HIV is a health condition entrusted to researchers when participants permit researchers to test their HIV status.[36] It has been argued that participants give permission for researchers to collect information and samples from them, and researchers accept responsibility for responding to this information using their specialized knowledge.[37] In this way, participants entrust a narrow range of their health-care to researchers. Researchers come to have some responsibility for these conditions.[38] Researchers work out what limited aspects of participants' health have been entrusted to them by examining which conditions are revealed by tests and interventions in the research protocol and for which participants gave their informed consent.[39] HIV falls within the scope of what is entrusted to researchers.[40] It follows therefore, that HIV is a legitimate focus. However, investigators in prevention trials will also explicitly diagnose other medical conditions such as hypertension, or diabetes.

On the third question: why attend to ART needs? Beneficial interventions for HIV could potentially include interpersonal problem-solving skills, treatment for opportunistic infections and prevention of mother-to-child transmission. However, ART ranks highly among interventions that will offset suffering and death (a factor in considering whether or not one is duty bound to perform a beneficent act); and it is also potentially one intervention that a health researcher *may* be in a position to dispense or leverage.

In summary, we have seen that accounts of beneficence may give rise to duties to help others,[41] or those we are in special relationships with,[42] particularly when the action will not present morally relevant sacrifice. However, there is nothing inherent in the account of general or specific beneficence to conclude unequivocally that investigators should focus on health-care concerns, or even HIV infection. To draw these conclusions, it is necessary to turn to other accounts that explicitly attempt to characterize the relationship between investigators and participants, such as Miller and Weijer,[43] who argue it is a fiduciary relationship around health matters and Richardson and Belsky,[44] who argue that it is a substantive but limited fiduciary relationship where researchers are entrusted with discrete health-care concerns. Indeed, the latter authors argue that the model for working out when

[33] Miller & Weijer, *op. cit.* note 28, pp. 427–428.
[34] Ibid: 428.
[35] Ibid.
[36] Richardson, *op. cit.* note 2.
[37] H. Richardson & L. Belsky. The Ancillary-Care Responsibilities of Medical Researchers: An Ethical Framework for Thinking about the Clinical Care that Researchers Owe their Subjects. *Hastings Cent Rep* 2004; 34: 25–33.
[38] Belsky & Richardson, *op. cit.* note 31.
[39] Ibid.
[40] Richardson, *op. cit.* note 2.
[41] Singer, *op. cit.* note 16.
[42] Beauchamp & Childress, *op. cit.* note 11.
[43] Miller & Weijer, *op. cit.* note 28.
[44] Richardson & Belsky, *op. cit.* note 38.

researchers are responsible for treating these discrete conditions supports conclusions mounted on the basis of beneficence.[45] More specifically, Richardson argues that responsibilities to treat HIV with ART in prevention trials will be high when the following conditions (among others) are met: namely that participants would suffer/ be badly off if their HIV infection was not treated; where there are no reliable alternatives for care, thus making them dependant on sponsor-researchers; and where the costs of financing treatment are reasonably low in relation to the overall trial budget.[46]

JUSTICE

Of course, beneficence is only one out of four principles in the adopted normative framework. In this approach, a principle is binding unless outweighed by another principle. It is not the purpose of this paper to explore justice-based arguments in detail; however, in order to avoid a charge of bias such arguments should not be overlooked. Justice is a broad principle with multiple interpretations therefore it requires specification. Some difficulties with justice-based arguments have been outlined previously.[47] In this section, we consequently turn briefly to consider another conception of justice which is reciprocity. Reciprocity calls for providing something in return for contributions that people have made.[48] Applied to the case at hand, it would be argued that something is owed to trial participants who acquire an infection because they undergo some risk and considerable inconvenience in participating in a trial.[49] Reciprocity is a helpful concept because it limits researchers' focus to trial participants, and not the community or world at large.

However, one is grateful to the contributions not just of those trial participants who become infected, but also to those that do not.[50] Without uninfected participants, it is difficult to draw conclusions about efficacy in prevention trials. Taking the principle of reciprocal justice seriously would mean both infected and uninfected participants deserve equal contribution of thanks. Yet it seems impossible to do this fairly: if we provide ART to infected participants, it seems unfair to give commensurate financial compensation to uninfected participants. Some may argue that the commitment to provide HIV treatment will be offered to all, like the *ex-ante* benefit of health insurance; and thus all participants benefit equally. However, this hardly seems to be equal or fair in reality: to be offered a hypothetical benefit is not the same as being offered a tangible benefit.

Furthermore, researchers rely on the goodwill and buy-in of other research stakeholders, like participating communities. Without such parties, trials would be impossible. Researchers should, in other words be 'grateful to' such parties, and on the account of reciprocal justice presented here, such parties are also deserving of thanks. Considering these facts leads, then, to the net of justice seemingly being spread far too wide for us to be able to come up with a practical, actual duty based on justice.

Therefore, while it has some intuitive appeal, the principle of reciprocity does not easily assist with the first of our two questions: 'who' is deserving? Likewise it does not clearly assist with the second question of 'what' kinds of helpful actions one should engage in. Clearly, investigators can express their gratitude to those participants who become infected by providing, or ensuring treatment. However, presumably some other expression of gratitude might suffice. The principle of reciprocity, then, while intuitively appealing and of some assistance, does not offer complete answers to concerns about how best to limit one's duties in terms of who or what.

It appears therefore, that justice arguments also suffer from specification challenges. It is possible to try to limit justice by turning to concepts like partial entrustment,[51] to show that it is healthcare conditions diagnosed in trials that should be the focus of justice-based interventions. Indeed Richardson concludes that their partial entrustment model supports conclusions mounted on the basis of justice.[52] One of the factors for working out when researchers are responsible for the treatment needs of their participants is that of compensating participants for risks and burdens assumed in a trial, which resonates strongly with notions of reciprocal justice. However, critics might argue that the relationship between justice and partial entrustment is merely one of convenience.

SUMMARY

Some participants are likely to become infected with HIV during the course of HIV prevention trials, despite risk reduction measures. The subsequent responsibilities of sponsor-investigators have been widely debated, especially where access to antiretroviral therapy (ART) is not available. It has been alleged that the principle of

[45] Richardson, *op. cit.* note 2.
[46] Ibid.
[47] C. Slack et al. Provision of HIV Treatment in HIV Preventive Vaccine Trials: A Developing Country Perspective. *Soc Sci Med* 2005; 60: 1197–1208.
[48] R. Macklin. Changing the Presumption: Providing ART to Vaccine Research Participants. *Am J Bioeth* 2006; 6: W1–W5.
[49] Ibid.
[50] Weijer & LeBlanc, *op. cit.* note 2.
[51] Richardson & Belsky, *op. cit.* note 38.
[52] Richardson, *op. cit.* note 2.

beneficence has not been appropriately specified and as such remains unhelpful in relation to this challenging problem.[53]

In this paper, we explored two accounts of beneficence, to establish whether they can shed light on sponsor-investigator responsibilities. We found that the notion of general beneficence is helpful insofar as it clarifies that some beneficent actions will be obligatory where they can be dispensed without scuppering the whole trial.

We found the notion of specific beneficence helpful insofar as it directs investigators to attend to the needs of trial participants specifically, however the range of potential interventions that researchers could assist with remains unhelpfully broad.

Based on the notion that it is the relationship between investigators and participants that gives rise to duties of specific beneficence, we turned to accounts of the investigator-participant relationship and the concomitant responsibilities that arise there-from, in order to consider if the range of interventions that investigators should provide could be limited in a non-arbitrary way.

We concluded that healthcare is an appropriate focus because the relationship between researcher and participant centres on health,[54] and that HIV is also an appropriate focus because HIV is a health condition entrusted to researchers when participants permit them to test their HIV status.[55] We concluded that ART is also a legitimate focus because it relieves suffering and death. As such, when investigators are able to meet the ART needs of their trial participants (referral, assisted referral or direct provision) without sacrificing the quality of the trial, it must be done. However, we concede that there appears to be little of this explicit direction to be found in the account of specific beneficence itself, but rather in accounts of the relationship that appears compatible with beneficence. This attempt to consider other theories that may be compatible with beneficence is done here in a preliminary manner in the hope that it will encourage further deliberation.

[53] Weijer & LeBlanc, *op. cit.* note 2.
[54] Miller & Weijer, *op. cit.* note 28.
[55] Richardson, *op. cit.* note 2.

Recent international ethical guidelines,[56] that address researchers' obligations to HIV infection acquired in biomedical HIV prevention trials, maintain that researchers *must ensure access* to comprehensive care for HIV infection, including ART for participants. This is asserted to rest in part on the principle of beneficence. We hope that this paper provides something of an elucidation of this principle in relation to this complex concern, and demonstrates that this assertion is not as simple as it first appears.

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[56] UNAIDS. 2007. *Ethical Considerations in Biomedical HIV Prevention Trials*. Geneva: UNAIDS.