RECIPIROCITY-BASED REASONS FOR BENEFITING RESEARCH PARTICIPANTS: MOST FAIL, THE MOST PLAUSIBLE IS PROBLEMATIC

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Keywords
clinical trials as topic, ethics, moral obligations, research subjects, access to healthcare, gift giving

ABSTRACT
A common reason for giving research participants post-trial access (PTA) to the trial intervention appeals to reciprocity, the principle, stated most generally, that if one person benefits a second, the second should reciprocate: benefit the first in return. Many authors consider it obvious that reciprocity supports PTA. Yet their reciprocity principles differ, with many authors apparently unaware of alternative versions. This article is the first to gather the range of reciprocity principles. It finds that: (1) most are false. (2) The most plausible principle, which is also problematic, applies only when participants experience significant net risks or burdens. (3) Seldom does reciprocity support PTA for participants or give researchers stronger reason to benefit participants than equally needy non-participants. (4) Reciprocity fails to explain the common view that it is bad when participants in a successful trial have benefited from the trial intervention but lack PTA to it.

INTRODUCTION
A central question in research ethics is whether and when participants in clinical research should be ensured extra benefits in addition to any needed to collect the data, safeguard participants from research-related risks, and fulfill morally optional promises that have been made, for example, to recruit sufficient participants. Various reasons have been given for the views that extra benefits should, or need not be ensured to trial participants and their communities. These reasons vary as to the persons or institutions to whom they apply and so as to their implications regarding who (if anyone) is obliged to ensure the benefits. In practice, research agents (e.g. researchers, funders) have supplied participants and their host communities with various benefits that are more or less related to health, including the trial intervention, food, and new healthcare or school buildings. Yet there

1 L. Belsky & H.S. Richardson. Medical Researchers’ Ancillary Clinical Care Responsibilities. BMJ (clinical research edn.) 2004; 328(7454): 1494–1496.
2 J.V. Lavery. 2008. The Obligation to Ensure Access to Beneficial Treatments for Research Participants at the Conclusion of Clinical Trials. In The Oxford Textbook of Clinical Research Ethics. E.J. Emanuel et al., eds. New York: Oxford University Press: 697–710; N. Sofaer & D. Streh. Reasons why Post-trial Access to Trial Drugs Should or Need Not Be Ensured to Research Participants: A Systematic Review. Public Health Ethics 2011; 4(2): 160–184; Nuffield Council on Bioethics. 2002. The ethics of research related to healthcare in developing countries. Nuffield Council on Bioethics: London; E.J. Emanuel et al. What Makes Clinical Research in Developing Countries Ethical? The benchmarks of ethical research. J Infec Dis 2004; 189(5): 930–937; C.V. Fernandez, E. Kodish & C. Weijer, Informing study participants of research results: An ethical imperative. IRB: Ethics and Human Research, 2003; 25(3): 12–19; D. Shalowitz & F. Miller. Disclosing individual results of clinical research: Implications of respect for participants. JAMA 2005; 294(6): 737–740.
3 Sofaer & Streh, op. cit. note 2, pp. 160–184; J. Millum. Post-trial Access to Antiretrovirals: Who Owes What to Whom? Bioethics 2009; 3: 145–154.
4 L. Heise, K. Shapiro & K.W. Slevin. Mapping the Standards of Care at Microbicide Clinical Trial Sites. USAID and Global Campaign for Microbicides 2008. Washington, DC; J.V. Lavery et al., eds. 2007. Ethical issues in international biomedical research: A casebook. New York, New York: Oxford University Press; C. Thiessen et al. Personal and Community Benefits and Harms of Research: Views from Rakai, Uganda. AIDS 2007; 21(18): 2493–501; R. Macklin. 2004. Double Standards in Medical Research in Developing Countries. Cambridge, UK: Cambridge University Press; N. Cass & A. Hyder. 2001. Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations. In Ethical and Policy Issues in benchmarks of ethical research. J Infec Dis 2004; 189(5): 930–937; C.V. Fernandez, E. Kodish & C. Weijer, Informing study participants of research results: An ethical imperative. IRB: Ethics and Human Research, 2003; 25(3): 12–19; D. Shalowitz & F. Miller. Disclosing individual results of clinical research: Implications of respect for participants. JAMA 2005; 294(6): 737–740.
3 Sofaer & Streh, op. cit. note 2, pp. 160–184; J. Millum. Post-trial Access to Antiretrovirals: Who Owes What to Whom? Bioethics 2009; 3: 145–154.
4 L. Heise, K. Shapiro & K.W. Slevin. Mapping the Standards of Care at Microbicide Clinical Trial Sites. USAID and Global Campaign for Microbicides 2008. Washington, DC; J.V. Lavery et al., eds. 2007. Ethical issues in international biomedical research: A casebook. New York, New York: Oxford University Press; C. Thiessen et al. Personal and Community Benefits and Harms of Research: Views from Rakai, Uganda. AIDS 2007; 21(18): 2493–501; R. Macklin. 2004. Double Standards in Medical Research in Developing Countries. Cambridge, UK: Cambridge University Press; N. Cass & A. Hyder. 2001. Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations. In Ethical and Policy Issues in

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Conflict of interest statement: No conflicts declared
is lack of clarity among research agents, research ethics committees and host communities about who owes what to whom, and why.

I will explore the common view that, because participants enable benefits for others (e.g. improved healthcare or health) those who benefit from the trial should reciprocate: benefit the participants in return. As formulated by the (now defunct) National Bioethics Advisory Commission, reciprocity concerns ‘what people deserve as a function of what they have contributed to an enterprise or to society.’ A key feature of reciprocity, as commonly understood in research ethics literature, is that its reason to benefit participants is that they have enabled benefit for others. Reciprocity seeks to address apparent imbalances in the distribution of costs and benefits. In this respect, appeals to reciprocity resemble appeals to avoiding exploitation and differ from appeals to supposed fiduciary duties of researchers or sponsors, or participants’ needs, or researchers’ capacity to meet these needs: unlike reciprocity principles, these other principles may apply irrespective of any benefits that participants may generate.

International Research: Clinical Trials in Developing Countries. Vol 2. Bethesda, MD: National Bioethics Advisory Commission: B1–B220; J. Ananworanich et al., Creation of a Drug Fund for Post-clinical Trial Access to Antiretrovirals. The Lancet 2004; 364(9428): 101–102; N. Sofae et al. Subjects’ Views of Obligations to Ensure Post-trial Access to Drugs, Care, and information: Qualitative results from the Experiences of Participants in Clinical Trials (EPIC) Study. J Med Ethics 2009; 35(3): 183–188; M.A. Lewis et al. The Termination of a Randomized Clinical Trial for Poor Hispanic Children. Arch Pediatr Adolesc Med 1994; 148(4): 364–367; J. Karbwang & J. Lazdins. 2007. Malarone testing in pregnant women in Thailand, in Ethical issues in international biomedical research: A casebook. J.V. Lavery et al., eds. New York, New York: Oxford University Press: 79–86; S. Giordano & M.G. Kiddugavu. 2007. Trading genes for toothbrushes: Research with the Aka Pygmy People in the Central African Republic, in Ethical issues in international biomedical research: A casebook. J.V. Lavery et al., eds. New York, New York: Oxford University Press: 171–183.

5 National Bioethics Advisory Commission (NBAC). 2001. Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Bethesda, MD: National Bioethics Advisory Commission: 59; The central concept of reciprocity was developed to a high degree of sophistication in political philosophy, e.g. A. Buchanan. Justice as Reciprocity versus Subject-Centered Justice. Philos & Public Aff 1990; 19: 227–252; J. Rawls. 1972. A theory of justice. Cambridge, MA: Harvard University Press; J. Rawls. 1993. Political Liberalism. New York: Columbia University Press; and the concept of gratitude in ethics, e.g. F.R. Berger. Gratitude. Ethics 1975; 85: 298–309. Before the concept of reciprocity entered debates on obligations to ensure post-trial access in an article by Gostin in 1991. L. Gostin. Ethical Principles for the Conduct of Human Subject Research: Population-Based Research and Ethics. Law Med Health Care 1991; 19: 191–201. Also relevant are discussions of political obligation, e.g. A.J. Simmons. Associative Political Obligations. Ethics Int Aff 1996; 106: 247–273; and special obligations, e.g. S. Keller. Four theories of filial duty. Phil Quart 2005; 56: 254–274; N. Kolodny. Which Relationships Justify Partiality? The Case of Parents and Children. Philos Public Aff 2010; 38: 37–75. Ignacio Mastroleo’s PhD thesis (2012), which I have not read due to my inability to read Spanish, discusses reciprocity and reciprocity-based arguments for PTA to the trial intervention in the light of literature on political obligation and special obligations.

for others. Reciprocity supplies a reason for researchers to benefit participants that does not depend on the contingent psychology of researcher or participant, unlike reasons based on participants’ actual expectations of benefits or researchers’ emotional engagement or friendship with participants.

There is a striking variety of reciprocity principles in the PTA literature, literature discussing whether research participants should have post-trial access (PTA) to the trial drug.6 These principles are not presented as descriptions of tendencies to benefit benefactors or principles of courtesy, but as principles of justice, which apply to people or institutions whether or not they wish to reciprocate. Yet it is false that whenever one person causes events that benefit a second, the second person has reason to benefit the first. A judge who presides over a murder enquiry, and thereby receives much publicity, benefits from the accused, but has no reason to benefit the accused. Furthermore, unless one is so unlucky as to benefit seldom from others, a moral obligation to benefit all those who benefit us, even if unintentionally and indirectly, and even when we could not have refused those benefits, is implausible: at most, we owe our benefactors gratitude.7 So, at most, a qualified reciprocity principle is true.

Despite the many appeals to reciprocity, the discussions of the formulation or persuasiveness of reciprocity principles are few; they are also extremely brief,8 with two exceptions, one devoted to an application of a specific reciprocity principle.9 This article supplies the missing characterization, comparison and critique of reciprocity principles. It argues, of some common reciprocity principles, that they must be rejected. It argues, of the one identified as the most plausible, that it is difficult to justify, and explores its implications for whether participants should have PTA to the trial drug, even when this was not promised to them, and whether researchers and

6 Sofae & Strech, op. cit. note 2.
7 This discussion mirrors one in the philosophy of law. One answer to the question of why we are morally obliged to obey the law is that we have benefited from the fact that others have obeyed it. Nozick famously objected that if my neighbours have set up a radio station to which I enjoy listening, I am not obliged to contribute to the radio station. R. Nozick. 1974. Anarchy, State and Utopia. New York: Basic Books.
8 Sofae & Strech, op. cit. note 2; Millum, op. cit. note 3; National Bioethics Advisory Commission. 2001. Ethical and policy issues in international research: Clinical trials in developing countries. Bethesda, MD: National Bioethics Advisory Commission; D. Cooley. Distributive Justice and Clinical Trials in the Third World. Theor Med Bioeth 2001; 22(3): 151–167; M. Merritt. Bioethics, Philosophy and Global Health. Yale J Health Policy Law Ethics 2007; 7: 273–317; A. Wertheimer. 2011. Rethinking the ethics of clinical research: Widening the lens. New York: Oxford University Press.
9 Wertheimer, op. cit. note 8, pp. 277–279; M. Merritt & C. Grady. Reciprocity and Post-trial Access for Participants in Antiretroviral Therapy Trials. AIDS 2006; 20(14): 1791–1794.
society have a stronger reason to benefit participants over equally needy (or even needier) non-participants.

**BACKGROUND: OBJECTIONS TO RECIPROCITY AS A REASON FOR BENEFIT-SHARING**

While most authors in the PTA literature who invoked reciprocity thought it supported PTA to the trial drug for participants, a few objected to reciprocity-based arguments for PTA. A good starting-point to identifying and evaluating various reciprocity principles is to determine whether the objections succeed against all such principles.

**Lack of voluntary agreement**

Joe Millum appears to claim that one person must benefit another only if both are voluntarily engaged in the benefit-generating enterprise:11

\[\ldots\] if I hire you to clear the path, then I owe you fair compensation for doing so; and if you are so hired and bring along a friend to assist you, you ought to share the payment you receive with her. What makes the difference \ldots\ is that the other people are voluntarily engaged in the enterprise that generates the benefit, either by commissioning it to be done or by taking part in doing it.12

He points out: ‘Though HIV/AIDS patients \ldots outside of the study may benefit from research on their condition, they are not voluntary partners in the research enterprise, and so need not reciprocate.’ (p. 7) He concludes that the general public need not reciprocate to participants.

In Millum’s example, the payment for path-clearing was presumably agreed before path was cleared. Millum does not consider whether reciprocity ever requires participants in a voluntary enterprise to give benefits, which were not pre-agreed, to other participants in the enterprise. If I have hired you to clear the garden path for a specific fee, should I give you extra when it turns out that you cleared the poisoned ivy of which neither of us was aware? Again, suppose that you have consented to participate in my study based on my paying you £50. Am I morally obliged to give you benefits in addition to those we agreed, should it turn out that your participation, either alone or with others, yields enormous benefits for non-participants, whether anticipated or not? Millum’s example suggests that the answers are ‘no’ but this seems too quick, because it is precisely in question whether reciprocity grounds researchers’ obligations to participants to provide benefits that were not pre-agreed. At most, therefore, Millum refutes appeals to reciprocity in support of social obligations to participants.

**Costs for non-participants**

Supplying a scarce drug to ex-participants may mean that there is none left for non-participants. When these non-participants would otherwise have received the drug based on a national decision about whom to prioritize, Merritt and Grady reject the following the reciprocity principle: ‘In return for participants’ contributions to the social good that ART [Anti-Retroviral] trials produce, it seems fitting for their country to offer them priority for post-trial access to ART’; see also Merrit. One reason for their rejection is:

\[\ldots\] reciprocity does not obligate the recipient of a benefit to make a contribution or sacrifice disproportionately greater than the one to which it is a response. Yet the postponement of nonparticipants’ access to urgently needed life-saving treatment may be a loss vastly disproportionate to the temporary research-related risks and burdens that ART trial participants typically assume. (p. 1792)

This objection regards the relative size of the benefit that participants provide to non-participants relative to the reciprocal benefit that non-participants are supposed to provide in return. The second reason is ‘\ldots non-participants would be asked to give up in the name of reciprocity the very benefit [ART for HIV] they are supposed to have received through participants’ activities’. (p. 1792)

There are several objections here. One is that non-participants have not benefited from participants and so need not benefit participants. This is a version of the

11 This is a charitable interpretation of Millum. A strict interpretation is that, for Millum, reciprocity applies whenever ‘people are voluntarily engaged in the enterprise \ldots’ Such a reciprocity principle is false. If you and I decide to plant seeds together, and you enjoy the resulting flowers, you do not owe me any benefits as a result. Millum must mean, more precisely, that if I have agreed to pay you in return for clearing the path, I owe you the pay that we agreed.

12 Millum, op. cit. note 3, pp. 6–7.

13 Wertheimer, op. cit. note 8.

14 Millum, op. cit. note 3, p. 1791; Merritt and Grady’s objection is similar to ‘objections from outsiders’ to the view that parents (for example) may give greater weight to the interests of their children than to those of equally needy (or needier) others. The objection is that the relationship does not justify privileging the child when the opportunity cost to others, such as needier children, is high. However, Merritt and Grady do not contest the view that researchers may give greater weight to the interests of participants than to those of equally needy non-participants: they contest only the view that society should, as a way of reciprocating to participants, prioritize participants’ access to ART post-trial.

15 Merritt, op. cit. note 8, pp. 273–317.
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objection regarding relative sizes. The other objection is about the type of reciprocal benefit: if the reason why participants should receive treatment is that their participation led to treatment for non-participants, but non-participants didn’t receive treatment then non-participants need not give up their treatment to treat participants.

Merritt and Grady’s notion of the benefit that participants enable for others is surely too limited: non-participants may benefit from care that has resulted from medical research, even though the participants in this trial have not enabled this. Furthermore, non-participants’ receipt of benefits may support obligations to reciprocate to participants that may be discharged by benefiting participants in any specific trial. However, let’s grant that reciprocity doesn’t support diverting scarce ART from non-participants, who would otherwise receive ART, to ex-participants. Still, as Merritt and Grady note, their objection allows that some other reciprocity principle, or in other circumstances the particular reciprocity principle they consider, might support obligations for researchers or society to give participants PTA to the trial drug.

RECIROCITY PRINCIPLES AND THEIR RATIONALES

The reciprocity principles in the PTA literature, shown in Table 1, are a good starting point for exploring who (if anyone) must reciprocate to whom, and why, and with what, and so for identifying the most plausible reciprocity principles. To aid comparison, I present each as an instance of:

[Reciprocity Principle] If person P1 performs action A1 that produces (potentially produces) (is reasonably expected to produce) benefit B1 for person P2 at t1 (possibly: and produces benefit B0 for P1) in context C, then P2 has a moral obligation to perform action A2 at t2, where t2 is later than t1, such that (it is reasonable for P2 to expect that):

a. A2 will result in benefit B2 for P1, and
b. B2 (minus B0) bears relation R to B1 (A1).

Bracketed phrases show alternative or additional phrasing. The Reciprocity Principle attempts to generalize over the different published reciprocity principles; different substitutions of the variables correspond to making different substantive assumptions and result in different reciprocity principles. For the sake of simplicity, the Reciprocity Principle is insufficiently general: (1) P1 and P2 are individuals, but some authors think that reciprocity requires benefiting communities that host research (host communities) because of the public goods they help to create.17 (2) The Reciprocity Principle omits any explicit mention of P2’s capacity to reciprocate, which Sidgwick points out affects our intuitions as to the size of reciprocal benefit.18 (3) The Reciprocity Principle also omits a relation between P1 and P2, an exclusion which I argue below is justified.

I will call the obligations that the Reciprocity Principle refers to as reciprocal obligations and the benefits (B2) they support reciprocal benefits. We are interested in instances when P1 is a participant in a trial and B1 is a benefit from that trial or clinical research. In this article, I will argue of one specific instance of the Reciprocity Principle that it is the most plausible reciprocity principle.

WHY ACCEPT A RECIPROCITY PRINCIPLE?

Table 1 shows that most publications which mentioned a reciprocity principle gave no rationale for it, perhaps because the authors wrongly considered the principle self-evident. I will next argue that the rationales fail; so, absent a self-evident reciprocity principle, another rationale must be supplied.

Some publications suggested that the need to ‘compensate’ participants justifies reciprocity to participants,19 although without interpreting ‘compensation’. It seems to me impossible to find an interpretation which results in a viable rationale. A first possible interpretation is that something like the following justifies the Reciprocity Principle when P1 is a participant: Compensation for Research-related Harm: If a participant suffers research-related harm, they should receive compensation.

However, the argument is invalid: the Reciprocity Principle supports obligations even to participants who have not suffered research-related harm. Put slightly differently: why should harmed participants have to benefit others in order to be owed benefits according to the Reciprocity Principle?

Compensation might instead be for injustice preceding the trial, perhaps perpetrated by colonial powers where research now takes place. Even if there was such injustice, it is unclear why its rectification requires provision of research-related benefits to participants in particular and also how such provision achieves rectification. Also, as before, why should participants have to benefit others in order to be owed compensation for past injustice?

17 S. Berkley. Thorny Issues in the Ethics of AIDS Vaccine Trials. Lancet 2003; 362(9388): 992.
18 Wertheimer, op. cit. note 8, p. 278.
19 S. Harth & Y. Thong. Aftercare for Participants in Clinical Research: Ethical Considerations in an Asthma Drug Trial. J Med Ethics 1995; 21: 225–227; R. Ashcroft. After the Trial is Over: What are the Sponsor’s Obligations? SciDev.Net 2005; May: 3.
Table 1.

Please note:
- The quotations supporting the interpretations and full citations are available from the author (neema@alum.mit.edu).
- Some of the authors below did not endorse the PTA principle that they mentioned.
- Regarding the coding in Table 1:
  - Where a publication mentioned reciprocity more than once, the characterization of the reciprocity principle was based on all the mentions.
  - Some characterizations are based on text not included in the quotation such text is available from the author (neema@alum.mit.edu).
  - I have been careful to fill in cells only if the information is given in the statement of a reason based on reciprocity. So if, for example, A2 is named as the sponsor in the same passage as the quotation with the reciprocity reason, but in a reason that appears to be distinct, I have entered ‘not specified’ in A2.

| Publication | Code for reciprocity principle | Rationale for reciprocating | P1 | A1 | B1 |
|-------------|--------------------------------|-----------------------------|----|----|----|
| Ashcroft 2005 (see note 19) | reciprocity in return for assuming risk | compensation | participants | risk assumption | not specified |
| Ashcroft 2005 | reciprocity to participants from researchers | compensation | participants | unspecified actions that ‘contribute significantly to researchers’ objectives’ (my italics) | the furthering of ‘researchers’ objectives’ |
| Ballantyne 2006 (see note 22) reporting NBAC’s discussion of the implications of reciprocity (NABC 2001) | giving PTA to the successful intervention to former participants | not specified | participants | risk assumption | not specified |
| Berkley 2003 (see note 17) | reciprocity to the host community from the world | not specified | ‘Communities participating in AIDS prevention and treatment trials’ | ‘contributing knowledge that is a global public good’ (my italics) | ‘contributing knowledge that is a global public good’ (my italics) |
| Carse & Little 2008 (see note 22) | Unspecified reciprocity | not specified | participants | risk assumption | not specified |
| Chang 2002 (see note 22) reporting NBAC’s discussion of reciprocity NABC 2001 | reciprocity in return for assuming risk | compensation | participants | risk assumption | sacrifice |
| Neema Sofaer | | | | | |
| Cooley 2001 (see note 8) | unspecified reciprocity | not specified | participants | not specified (‘create’ ‘benefits’ (my italics)) | not specified (‘create’ ‘benefits’ (my italics)) |
| Gostin 1991 (see note 5) | reciprocity to the host community from researchers | not specified | participants | risk assumption | ‘substantial benefit’ to sponsors and researchers ‘industry [sponsors] may benefit financially from government subsidies in the development of the product’ |
| Gostin 1991 | reciprocity to the host community from the sponsor | not specified | ‘Third world populations’ | being ‘used to create a health benefit for mankind’ (my italics) | ‘a health benefit for mankind’ |
| Grady 2005 (see note 9) | reciprocity to participants from society | not specified | participants | risk assumption | ‘the good of society and the advancement of science’ |
| Harth & Thong 1995 (see note 19) | reciprocity to participants from society | compensation reward | participants | risk assumption | ‘benefit of society as a whole’ |
| Hutt 1998 (see note 22) | unspecified reciprocity | fairness | participants | risk assumption | benefits of research, including marketed drug |
| Lavery 2008 (see note 2) reporting and elaborating on Ashcroft 2005 | Reciprocity to participants from sponsors | Not specified or, possibly, ‘gratitude’, depending on interpretation of Lavery | participants | risk assumption | ‘enormous economic benefit’ for sponsors; ‘contribution to research’ |
| Li 2000 (see note 22) | reciprocity in return for assuming risk | not specified | participants | risk exposure | not specified |
### Researcher and Sponsor Responsibilities

- **Researchers**: Not specified, but Ashcroft mentions ‘responsibilities to research participants that extend beyond the research period’.
- **Sponsors**: Not specified, but Ashcroft mentions ‘responsibilities to research participants that extend beyond the research period’.
- **Research Participants**: To share in the benefits of research.

### Various Actions Including Advocacy

- Researchers and sponsors: Various actions including advocacy (researchers and sponsors), ensuring that post-trial interventions are in place (researchers); possibly, depending on interpretation of ‘fall squarely’, financing PTA (sponsors and researchers).
- Researchers: Presumably, the successful trial intervention, if any; benefits [participants] helped to create.
- Researchers: ‘[Make] the product more widely available to the local population’ (p. 199).

### Pharmaceutical Companies

- Sponsors: Provide ‘ongoing access’ to marketed drug.

### Researcher and Sponsor Benefits

- Researchers and sponsors: Benefits including advocacy; possibly, trial drug if successful or ‘alternative community benefits suggested by local leaders’.
- Researchers: ‘The product [of research]’ (p. 199).
- Sponsors: ‘Benefits [participants] helped to create’.

### Societal Benefits

- Society: ‘Ongoing access’ to the trial drug.
- Society: PTA to healthcare, which includes the trial drug.

### Proportionality Between PI’s Burdens and Benefits

- Proportionality between PI’s burdens and benefits: ‘It would be unjust if the populations which bear significant burdens of research were to reap the fewest rewards’.

- Y: Appropriate recognition, ‘fair share of the gains’.

### Footnote

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Table 1. Continued

| Publication | Code for reciprocity principle | Rationale for reciprocating | PI | AI | BI |
|-------------|--------------------------------|----------------------------|----|----|----|
| Macklin 2004 (see note 4) reporting NBAC’s discussion of reciprocity (NABC 2001) | reciprocity to participants from society | not specified | participants | assumption of risk and inconvenience | ‘generate findings necessary to advance knowledge and develop new medical interventions’ According to Macklin, even the participants in an unsuccessful trial make a contribution. |
| MacPherson 2004 (see note 22) | reciprocity in return for assuming risk | not specified | participants | risk assumption | sponsors’ ‘anticipated’ . . . ‘long-term financial profit’ |
| Merritt 2007 (see note 8) | reciprocity to participants from researchers | not specified | participants | assumption of ‘risks and burdens of research’ | ‘producing generalisable knowledge’ (my italics) |
| Merritt & Grady 2006 (see note 9) reporting and criticizing NBAC’s position (NABC 2001) | reciprocity to participants from host country non-participants | not specified | participants | not specified; ‘contributions to . . . social good’ (my italics) | ‘contributions to . . . social good’ (my italics) |
| Millum 2009 (see note 3) commenting on others’ appeal to reciprocity | reciprocity to participants from researchers | not specified | participants | not specified | provide benefits to others |
| Millum 2009 (see note 1) commenting on others’ appeal to reciprocity | reciprocity to participants from host country non-participants | not specified | participants | not specified | not specified |
| Millum 2009 (see note 3) commenting on others’ appeal to reciprocity | reciprocity to participants from non-participants in the host country who have the same medical condition as participants | not specified | participants | not specified | not specified |
| NBAC 2001 (see note 5) | unspecified reciprocity | not specified | participants | make ‘essential contribution’ to ‘success’ of the research | ‘newly proven intervention’ |
| Sachs 2009 (see note 22) | reciprocity in return for assuming risk | not specified | participants | risk assumption | not specified |
| Shah, Elmer & Grady 2009 (see note 22) | reciprocity in return for assuming risk | not specified | participants | risk assumption | research findings |
| Zong 2008 (see note 20) | reciprocity to participants from researchers reciprocity to participants from society | reward | participants | contribute to ‘others and society’ | ‘researchers . . . acquire useful knowledge and develop new interventions’ (my italics) |
| P2                | A2                                  | B2                                                                 | Information on R? Y/N (information) |
|-------------------|-------------------------------------|----------------------------------------------------------------------|-----------------------------------|
| sponsors          | not specified                       | ‘financial obligations’, ‘sustainable benefit to host nations’      | Y (‘sponsors’ ethical and financial obligations’ are increasing function of probability and severity of harm to participants and financial profit for sponsors) |
| researchers, and sponsors whom researchers represent | not specified | address participants’ medical needs | N |
| host-country population that did not participate in the trial | not specified | giving priority to participants over non-participants in allocating scarce ART | Y when reporting NBAC’s position: according to NBAC reciprocity is ‘what people deserve as a function of what they have contributed to an enterprise or to society’ |
| researchers sponsors | provision of benefits | possibly, post-trial access to ART | Merritt and Grady: Y. Reciprocity requires neither the provision to participants by non-participants of benefit larger than that which participants have enabled for non-participants, nor the provision of the very benefit that the trial was supposed to enable for non-participants |
| ‘people with HIV/AIDS’ | not specified | not specified | Y (‘what [participants] are owed reflects their relative contribution’ AND In order to show that ART is an appropriate return for participation in a particular HIV/AIDS trial a number of factors must be assessed . . . Most importantly, the amount of compensation that participants are owed will depend on the size of the contribution they make and the extent of the benefit (broadly understood) generated by the research . . . This will clearly vary between trials, but we can note two key points. First, whatever the final distribution of benefits, no one should be made worse off by fulfilling their duties of reciprocity. This follows from the point of reciprocity: it is an appropriate response to benefits received . . . Second, the amount might be more or less than the cost of providing ART: there is no reason to expect a priori that what someone is owed for her contribution to a particular piece of HIV/AIDS research will be equivalent to a lifetime of treatment.’ AND ‘Likewise, the extent of duties of reciprocation depends on the size of the benefit generated by the particular trial, which will vary. Thus how much is owed will differ from trial to trial. In some cases it may be that ART need not be given at all in order to discharge the duties; in other cases, ART may be appropriate, but for a limited period of time. It is not possible to determine exactly what is owed without looking at the details of particular research projects.’) |
| not specified, though various beneficiaries of research are named | not specified | not specified | as row above |
| not specified | not specified | Post-trial access to the trial drug ART | Y (Proportionality: ‘an interaction is reciprocal just in case if one party benefits then the other party benefits proportionately’) |
| sponsors researchers | not specified | ‘opportunity to benefit from findings of the trial’ | N |
Compensation might also be payment for participants’ services; indeed, some authors’ rationale for the Reciprocity Principle appeals to the need to ‘reward’ participants.\textsuperscript{20} However, the implied argument is either circular or unsound. It is circular in that the principle that we should reward those who benefit us (or some subset thereof) is too close to the principle that we should reciprocate to such people to justify it. It is unsound because, at most, it is a principle of courtesy that we should reward all those who have benefited us, while reciprocity is supposed to be a principle of justice.

**WHO SHOULD RECIPROCATE AND TO WHOM?**

Table 2 shows that reciprocity has been thought by authors of the PTA literature to apply between various P1-P2 pairs, and that these pairs differ as to whether or not there is an agreement, e.g. contract or consent form that specifies the terms of the relationship. The question is whether an agreement between P1 and P2 makes it more (or less) plausible that P2 has reciprocal obligations to P1. I will argue that the Reciprocity Principle’s plausibility doesn’t depend on whether P1 and P2 have an agreement.

When there is no P1-P2 agreement, as in the case of members of the public and participants, it is hard to defend reciprocal obligations. These members may have been unaware that by accepting benefits, for example, by taking a newly marketed drug, they were thereby assuming obligations; in addition, in cases such as incapacitating medical emergencies, they could not have refused the benefits. The question also arises why members of society have reciprocal obligations to research participants that they appear lack to other high-risk workers who collectively provide social benefits e.g. motorway tunnel constructors. Furthermore, when there is an agreement between P1 and P2, it is unclear why reciprocity should give a moral reason to provide benefit that is *in addition* to pre-agreed benefits, a moral reason that has no counterpart in a commercial relationship.\textsuperscript{21} The question also arises whether the *appearance* of a reciprocal obligation can be explained away in terms of expectations, friendship or physical proximity between researcher and participant. In any case, the Reciprocity Principle doesn’t seem any more plausible whether P1 and P2 have, or lack an agreement; indeed, the Reciprocity Principle seems in need of clarification and justification in either case.

What might trigger obligations to reciprocate?

In PTA literature, the action (A1) that triggers the reciprocal obligation is often the participant’s assumption of or exposure to risk or burden,\textsuperscript{22} sometimes, ‘sacrifice’,\textsuperscript{23} or contributions to researchers’ objectives, research, medical knowledge or social good\textsuperscript{24} and, once, participants’ ‘essential contribution’ to the trial’s ‘success’.\textsuperscript{25} (p. 60) The concepts are left unexplained. Authors assume that the feature of the action that triggers the obligation is its causal relation to creating benefit for others. However, authors do not explain whether the action must cause benefit (as distinct from e.g. having the capacity to benefit), the type of benefit, and whether it suffices to *try* to reciprocate.

I will argue that the action that most plausibly triggers a reciprocal obligation is an individual’s exposure to substantial risk or burden through participating in clinical research, given that clinical research as a whole creates large social benefits. Furthermore, because not all participation carries substantial risk or burden, reciprocity supports social or researchers’ obligations to participants less frequently than its proponents have thought.

\textsuperscript{20} Harth & Thong, *op. cit.* note 19, pp. 225–228; Z. Zong. Should Post-trial Provision of Beneficial Experimental Interventions be Mandatory in Developing Countries? *J Med Ethics* 2008; 34(3): 188–192.

\textsuperscript{21} Wertheimer, *op. cit.* note 8.

\textsuperscript{22} Lavery, *op. cit.* note 2, pp. 697–710; Macklin, *op. cit.* note 4, Gostin, *op. cit.* note 5, pp. 191–201; Merritt, *op. cit.* note 8, pp. 273–317; Harth & Thong, *op. cit.* note 19, pp. 225–228; Ashcroft *op. cit.* note 19, p 37; A.J. Ballantyne. 2006. *Exploitation in HIV/AIDS International Clinical Research* [thesis], Melbourne: Monash Centre for Human Bioethics. Available at: http://trove.nla.gov.au/work/25425628?versionId=30643993 [Accessed 25 May 2013]; A.L. Carse & M.O. Little. 2008. Exploitation and the Enterprise of Medical Research. In *Exploitation and Developing Countries: The Ethics of Clinical Research*. J.S. Hawkins and E.J. Emanuel, eds. Princeton & Oxford: Princeton University Press: 206–245; E. Chang. Fitting a Square Peg into a Round Hole: Imposing Informed Consent and Post-trial Obligations on United States Sponsored Clinical Trials in Developing Countries. *South Calif Interdiscip Law J* 2002: 339–340; C. Grady. The Challenge of Assuring Continued Post-trial Access to Beneficial Treatment. *Yale J Health Policy Law Ethics* 2005; 5(1): 425–435; L.E. Hutt. Freebies for Subject 641: a Discussion of the Ethical Prospect of Providing Drug Trial Subjects with Post-trial Access to the Drug Tested – a Canadian Perspective. *Health Law J* 1998; 6 Spec No: 169–187; R. Lie. 2000. Justice and international research. In *Biomedical research ethics: Updating international guideline*. R. Levine, S. Gorovitz, and J. Gallagher, eds. Geneva: CIOMS: 27–40; C.C. Macpherson. Research Sponsors’ Duties to Developing World Host Nations: the ongoing WMA Discussion of Possible Revisions to the 2000 Declaration of Helsinki (paragraph 30). *Dev World Bioeth* 2004; 4(2): 173–175; B. Sachs. Going from Principles to Rules in Research Ethics. *Bioethics* 2009. DOI: BIOT1744 [pii]10.1111/j.1467-8519.2009.01744.x [doi]; S. Shah, S. Elmer & C. Grady. Planning for Posttrial Access to Antiretroviral Treatment for Research Participants in Developing Countries. *Am J Public Health* 2009; 99(9): 1556–1562.

\textsuperscript{23} E. Chang. Fitting a Square Peg into a Round Hole: Imposing Informed Consent and Post-trial Obligations on United States Sponsored Clinical Trials in Developing Countries. *South Calif Interdiscip Law J* 2002: 339–340, p. 352.

\textsuperscript{24} Harth, *op. cit.* note 2, pp. 697–710; Macklin, *op. cit.* note 4; Merritt, *op. cit.* note 8; pp. 273–317; Merritt & Grady, *op. cit.* note 9, pp. 1791–1794; Ashcroft, *op. cit.* note 19.

\textsuperscript{25} National Bioethics Advisory Commission, *op. cit.* note 5, p. 60.
Making an essential contribution

Participants can be said to make an essential contribution to their trial in two senses. The first is that, without the contribution of the specific participant, the trial could not happen. This is false in most trials, although true of trials for rare diseases where the number of participants needed to achieve statistical significance is the number of individuals worldwide who meet the trial’s inclusion conditions. It seems implausible that reciprocity should apply so rarely, particularly when what would make the difference as to whether reciprocity supports benefits is facts about supply and demand of participants.

The second sense is that the trial couldn’t happen without the contribution of a group of participants, each of whom meets the inclusion conditions. This is true of all trials but compatible with individual participants’ being replaceable. With ‘essential contribution’ thus understood, every participant makes an essential contribution. A reciprocity principle that applies to all participants may be what proponents of reciprocity have in mind, but seems implausibly broad: it supports reciprocal benefits even for persons who participate for purely self-interested reasons and who in fact benefit greatly. While such a broad principle is more plausible if it is understood as extremely weak, reciprocity could not do the work of justifying the costly post-trial access to trial interventions that many of its proponents expect of it. Thus, I reject the view that a participant’s (or participants’) essential contribution to research, whether narrowly or broadly construed, grounds reciprocal obligations.

Assuming risk

Risk assumption refers to independent events the PTA literature doesn’t distinguish: (1) Intention to perform an act knowing that this entails being exposed to a probability of harm.27 (2) Being exposed to a probability of harm.28 Possibly also: (3) Being harmed. One can assume a risk, albeit unknowingly, and consequently suffer harm.

We can eliminate interpretation 3 because there is a principle of justice, distinct from any reciprocity principle, which requires compensation for participants with research-related harm. The question is whether even participants who aren’t harmed should be given benefits, and whether harmed participants should be given benefits in addition to any compensation for research-related harm.

Risk and probability in 1 and 2 should presumably be understood as net: if the participant intends to obtain net benefits, or is exposed to a chance of a net benefit, it is unclear he/she should receive benefits in addition to any pre-agreed; perhaps the same is true if the net risks are minor. If so, it’s correct to include B0 (the benefit the participant has already enjoyed) in the Reciprocity Principle and to hold that there are no reciprocal obligations to participants who do not bear net risks.

One might object that if participation generates huge benefits for others, e.g., billions for commercial sponsors, it is implausible that there should be no reciprocal obligations to participants who have not borne net risks. However, one can explain away any intuition that there are with a prohibition against exploiting participants. Avoidance of exploitation requires that participants should receive a fair share of the benefits arising from

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26 To defend my claim that there is no agreement between participants and non-participants: participants who benefit their compatriots or global society are like the person who clears the garden path without having undertaken to do so on a formal basis.

27 Some reciprocity principles in the PTA literature suggest that participants’ morally relevant property is that they intentionally assume risk, e.g., ‘Because research participants accept some risk for the good of society and the advancement of science, certain things are owed to them in return.’ The U.S. National Bioethics Advisory Committee described this as ‘justice as reciprocity.’ C. Grady, op. cit. note 22, pp. 425–435., p. 430; see also Merritt, op. cit. note 8, pp. 273–317.

28 Other reciprocity principles mentioned in the PTA literature suggest merely that participants’ morally relevant property is that they are exposed to risk, e.g., ‘The challenge (of whether there is a general obligation to ensure PTA) is indeed difficult. One might try to say that the trial participants are exposed to risk . . . But that does not show that a trial in which there is an appropriate risk : benefit ratio, as there should be . . . is morally wrong.’ Lie, op. cit. note 22, p. 30.
their interaction with researchers and sponsors. It is no shortcoming of reciprocity that it (as distinct from a non-exploitation principle) does not support additional benefits for participants who do not bear net risks, when participation generates massive benefits for others.

In any case, however risk assumption is interpreted, the Reciprocity Principle does not apply to all participants: not to one who, through participation in clinical research, intends to obtain net benefit, is not exposed to a probability of harm, and reaps net benefit. The lingering questions are whether intention to assume risk (interpretation 1 of risk assumption) is necessary for there to be reciprocal obligations and, if not, whether understanding A1 as being exposed to a probability of harm (interpretation 2) results in an implausibly wide interpretation of the Reciprocity Principle.

Sacrifice

The Reciprocity Principle applies to fewer participants when A1 refers to sacrifice rather than to risk assumption, for two reasons: (1) assumed risks can be small, whereas large risks are essential to sacrifice; and (2) a participant can bear significant risk without intending this (say, because he/she was misinformed about the risk or misunderstood), whereas intention seems central if not essential to sacrifice.

The Shorter Oxford English Dictionary’s most pertinent definition of ‘sacrifice’ is ‘To permit injury or ruin to the interests of (a person) for the sake of some desired object’.29 Charitably interpreting this, there is sacrifice in ethical research when: (1) The participant intends to permit injury . . . to his/her own interests,30 and (2) The participant permits this for the sake of another’s good (whether or not the other’s good obtains), and (3) The possible harm is at least large: either the probability or the harm must be at least large.

The definition seems too wide: it counts as a sacrifice a case when a participant assumes a substantial risk in order to improve others’ health, but receives net benefits from participation. Perhaps this is not absurd: we think that soldiers make a sacrifice when they fight intending thereby to protect us, but survive and receive net benefits (e.g. through salary, enhanced status). However, some

| Table 3. Scope of Reciprocity Principle compared with A1 as sacrifice versus risk assumption |
|-------------------------------------|-------------------------------------|
| **Upper left**                      | **Upper right**                     |
| Participant ‘permit[s] injury or ruin to the interests of [him-/herself]’ | Participant ‘permit[s] injury or ruin to the interests of [him-/herself]’ |
| Participant is injured or his/her interests are ruined | Participant receives net benefits |
| **Lower left**                      | **Lower right**                     |
| It is not the case that participant ‘permit[s] injury or ruin to the interests of [him-/herself]’ | It is not the case that participant ‘permit[s] injury or ruin to the interests of [him-/herself]’ |
| Participant is injured or his/her interests are ruined | Participant receives net benefits |

might prefer to say that such participants or soldiers merely intended to make a sacrifice.

Sacrifice versus risk assumption

Table 3 shows that the Reciprocity Principle applies more narrowly when A1 is a sacrifice than when it is risk assumption: it applies in the latter, but not former case when the participant does not intend to permit injury but suffers injury. There is sacrifice in just the cells on the upper right and upper left31 or just the upper left cell (as I think), but risk assumption in all the cells except lower right. Risk is assumed, but there is no sacrifice, in variants of the upper left and upper right cells in which ‘moderate harm’ substitutes ‘injury or ruin’.

What follows if A1 is making a sacrifice? The Reciprocity Principle supports reciprocal benefits for some participants, but not for the participant who assumes no risk but does assume a large burden for society’s sake, such as enrolling in a long trial involving some discomfort. However, while this exclusion seems against the spirit of the Reciprocity Principle, that spirit can be accommodated by broadening the OED definition of sacrifice to, for example: ‘To permit injury or ruin to the interests of (a person) or assume a substantial burden for the sake of some desired object’. Nonetheless, the Reciprocity Principle does not support benefits for participants who have a purely self-interested motive or believe that, at most, they will suffer little harm. In line with common morality, an interpretation of the Reciprocity Principle with A1 as making a sacrifice supports the view that an agent’s intentions affect others’ obligations to him or her. While this interpretation of the Reciprocity Principle might seem too narrow for some, those who accept it can still say that those who don’t intend to assume significant risks but suffer injury are still owed benefits, but as compensation for research-related injury.

One might think that the Reciprocity Principle is most plausible when it applies to participants who intend to

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29 C.T. Onions, Ed. 1978. *The Shorter Oxford English Dictionary on Historical Principles*. Oxford: Oxford University Press.

30 The definition appears to require the intention to permit injury or ruin but it is unclear if this is essential to sacrifice. On the one hand, it seems possible to sacrifice oneself without intending to sacrifice oneself or even to bear net costs: we can say that a conscript has sacrificed his life for his country even if he did not intend to risk his life, let alone die. On the other hand, it seems odd to say that a participant made a sacrifice, at least, a sacrifice for others as in the definition above, if he enrolled just for personal gain, but turned out to experience significant net costs.

31 Assuming the SOED’s definition of sacrifice.
assume large health risks for others’ benefit. If justice requires the provision of reciprocal benefits, it is surely to such heroes. An implication is that, assuming that few participants have purely altruistic motives for participation, the Reciprocity Principle supports reciprocal benefits for few participants. Another implication is that in even fewer cases does it support reciprocal obligations for researchers: presumably few participants sacrifice themselves for researchers’ sakes. Even when the Reciprocity Principle supports reciprocal obligations, competing principles can still override it. Thus, if A1 is making a sacrifice, it is plausible that in only a few cases, at most, will there be reason, all things considered, to give participants reciprocal benefits.

Is the Reciprocity Principle too narrow when A1 is making a sacrifice? It seems so: it has different implications for participants in the same trial who bear the same substantial net risk, when only one intends thereby to help others; yet both seem entitled to reciprocal benefits. Similarly, British soldiers who fought in WWII have benefited me. Some wanted to save the free world for future generations, and so presumably intended to benefit persons like me. However, others fought only because they would otherwise have been shot, or even because they relished killing. Nonetheless, I don’t have a stronger reason to benefit the altruistic soldiers only.

I am arguing that the Reciprocity Principle is more plausible when A1 is not (1) Intention to perform an act knowing that this entails being exposed to a probability of harm, but (2) Being exposed to a probability of harm, when the probability of harm is a substantial, net risk. An additional, practical consideration against interpreting the Reciprocity Principle to apply depending on the participant’s intention is the difficulty in ascertaining a participant’s intention and so in concluding whether there are reciprocal obligations.

If the Reciprocity Principle is most plausible when A1 is being exposed to a substantial net risk, any benefit that participants have derived through participation should be subtracted from the risk of participation.32 One might object that reciprocity will then never support PTA to the trial drug where taking the trial drug during the trial has saved the participant’s life; however, this seems an acceptable implication, given that other reasons (e.g. health need, non-abandonment) may support PTA. One might also object that participants who aren’t owed reciprocal benefits because they didn’t assume large net risks might nonetheless be owed benefits because they have enabled the sponsor to profit hugely from their participation; however, as mentioned previously, a non-exploitation principle can accommodate this intuition.

The benefit that participants’ actions cause

We need not benefit mountain climbers just because they have borne substantial risk, so must ask in what context assumption of substantial net risk leads to reciprocal obligations. I will argue that the Reciprocity Principle is most plausible when the person bears substantial risk through participating in the clinical research enterprise which, as a whole, provides substantial social benefits. Mountain climbing does not benefit society.33

Whether or not soldiers should receive reciprocal benefits does not depend on whether their commander makes mistakes that caused the loss of the battle: it depends on something like the soldier’s contribution or assumption of risk. So, if two participants in research bear the same substantial risk, it seems implausible that one should be owed reciprocal benefits when his trial succeeds in showing that the intervention is safe and effective but the other not, just because of differences in the trial design, which participants could not control. For the Reciprocity Principle to be a principle of justice, then, the benefit cannot be the product of the participant’s trial or of that trial and other trials that investigate the same intervention. A weaker reason for this is that, if participants in unsuccessful trials were never owed reciprocal benefits, the Reciprocity Principle would tend to disadvantage the already disadvantaged, as participants in unsuccessful trials tend to benefit less from participation than those in successful trials.34

For the Reciprocity Principle to be most plausible, ‘benefit’ must be understood to mean that an individual’s participation always produces benefit. If B1 is the benefit from the entire research enterprise, participants produce benefit just by participating. This results in an intuitively plausible interpretation of B1, in that if we think participants are owed reciprocal benefits, it is because they have participated in risky research, and not in any specific trial. If the Reciprocity Principle applies to participants because of the benefit they actually produce, we can omit the parenthetical phrase in the Reciprocity Principle: ‘If individual P1 performs action A1 that produces (alternatively: has the potential to produce) benefit B1 for agent P2 at t1 . . . ’ An implication of setting B1 as the benefit from the entire research enterprise is that, if the enterprise were to stop producing social benefit, the Reciprocity

32 I set aside the question of which of the items that seem to be benefits, such as financial payments, should be counted as such when interpreting the Reciprocity Principle. There are obviously difficulties in giving a plausible account of what it is to subtract benefit enjoyed from risk assumed.

33 We will later ask whether the Reciprocity Principle is true of all enterprises that create social benefits, or only specific enterprises e.g. clinical research or national defence.

34 The reason is weaker because one might accept the Reciprocity Principle as a prima facie principle that tends to disadvantage participants in unsuccessful trials and which, in such cases, is overridden by a principle to avoid exacerbating disadvantage.
Principle would not support benefits for any participant. This is an implication that I accept.

The size and type of benefit that participants are owed back

The intuitive thought is that reciprocity ‘is an appropriate response to benefits received’. What is an appropriate response to persons who, through participation, benefit others?

It is easier to say when the benefit is not proportionate. To thank one’s parents and to leave forever without any provision for their wellbeing is to provide inappropriately little; this is particularly so if they cannot care for themselves. Similarly, a researcher reciprocates inappropriately little if he gives chocolates to a participant with serious, unaddressed health needs when participation has involved a huge sacrifice.

Wertheimer points out that Sidgwick claimed that:

there is no accepted principle by which to determine what one party owes another . . . In some contexts, we may adopt for pure procedure account and let market or contractual agreements dictate the answer . . . In other contexts . . . we may think of reciprocity as imperfect procedural justice, where there is a (to be determined) independent criterion of what one party owes the other. So we may think that A owes B more than $5/hour . . . even if they agree on that wage.

Wertheimer notes that intuitions depend on:

. . . at least three factors: (1) the degree [represented by B1] to which [e.g. the researcher] benefits from the interaction with [e.g. the participant]; (2) the degree to which [e.g. the participant] has sacrificed or benefited from the interaction [represented by B0 and A1, which can be an act of sacrificing]; (3) [the capacity of the beneficiary] to reciprocate [possibly captured by R].

While the Reciprocity Principle holds between individuals, participants collectively benefit a group of people and any reciprocal benefits must be divided between participants. Thus, which benefits are appropriate for an individual participant depends, minimally, on the size of the social benefits created and size of the group of participants who have each borne a substantial net risk, and perhaps also the participant’s average or actual contribution.

Social benefit is benefits for individuals and so the questions to address are which benefits count and which individuals count. The benefit from research could be conceived as licensed interventions, improved population health and/or mental security from knowing that there are effective interventions should we need them. The benefits that matter are the latter two, but they are also harder to measure, which one must take into account if reciprocity is to be a principle of practical justice.

The beneficiaries of research can be variously understood. I am not diabetic but, should I develop diabetes, I would need diabetes drugs. Am I a beneficiary of the research and an appropriate substitute for P2? Supposing that I, a non-diabetic in London, am an appropriate substitute, what about a remote non-diabetic inhabitant of a Pacific island who will not have access to the drug for the next two generations? It seems implausible that the latter has any obligation to reciprocate, presumably because the sense in which she can benefit from the medical advance is so weak.

Nonetheless, there are some plausible constraints on the size of B2. First, reciprocity does not apply when non-participating members of the host society who reciprocate would have to give up precisely what they were supposed to gain from the trial, namely, an effective treatment. Second, B2 (the reciprocal benefit) need not be larger than B1 (the benefit that participants enable or provide). Perhaps we can say something stronger: B2 need not approach the size of B1; otherwise, I could never reciprocate sufficiently to my domestic cleaner who happened to save my life. Third, the greater the net risk to the participant, the larger the reciprocal benefit should be: B2 should increase with net risk. This seems more plausible than the position that every participant who bears greater than a specified net risk should have the same reciprocal benefit. While providing reciprocal benefits to participants unduly induce people into becoming participants, reciprocity should be understood as giving a prima facie reason, which can be overridden by competing considerations.

WHICH IS THE MOST PLAUSIBLE INSTANCE OF THE RECIPROCITY PRINCIPLE?

The most plausible instance of the Reciprocity Principle, which I will call Net Instance, applies only to persons who bear substantial risk through participating in clinical research, which as a whole, provides substantial social

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35 Millum, op. cit. note 3, p. 7. Millum is one of the few commentators to question reciprocity-based arguments. Similarly, commenting just on benefit size, Sachs writes ‘an interaction is reciprocal just in case if one party benefits then the other party benefits proportionately’ (my italics). Sachs, op. cit. note 22, p. 6.

36 Wertheimer, op. cit. note 8, p. 277.

37 Ibid.

38 It would seem absurd, for example, to implement, on the basis of applying Reciprocity Principle, a global tax that this person’s society should pay in order to benefit ex-participants, at least while the product is not available, based on a moral obligation to reciprocate to those who enable clinical research.

39 Merritt & Grady, op. cit. note 9, pp. 1791–1794.

40 Wertheimer, op. cit. note 8.
benefits. Net Instance does not discriminate between participants in successful and failed trials: both are conceived as providing the same benefit, in that both enable clinical research that, as a whole, yields enormous benefits. It is compatible with view that reciprocity and compensation for research-related harm are distinct: it applies when a participant bears net risks for the benefit of others, even when the participant is not harmed. Net Instance becomes decreasingly plausible as the size of the reciprocal benefit \( B_2 \) approaches the size of the benefit provided \( B_1 \).

Participants in the same trial may bear different risks, and the reciprocal benefit \( B_2 \) depends on the risk borne. So, Net Instance may require different benefits for different participants, in particular, for active-arm versus placebo-arm participants; in some trials, the active-arm may be riskier; in others, the placebo-arm. This will make it hard to apply Net Instance, all the more because the risk is knowable, at best, only after the trial. Approximations using e.g. average predicted risk may be necessary if Net Instance is to be used to support e.g. a global tax that funds benefits for participants.

**WHAT NET INSTANCE IMPLIES**

It is difficult to be precise about Net Instance’s implications without criteria for a participant who bears significant net risk or burden, or knowing which participants meet the criteria. Nonetheless, Net Instance implies that not all participants should receive reciprocal benefits: only those who are exposed to significant net risk or burden.\(^{41}\)

Some commentators have argued that reciprocity or non-exploitation does not require the provision to participants of PTA to the trial drug in particular: at most, to provide (\( B_1 \)). My argument suggests this is a slight oversimplification. Net Instance requires PTA to the trial drug when, but only when, the participant has borne significant net risks or burdens and, without PTA, will not be in sufficient health to enjoy the reciprocal benefit owed to him/her. Net Instance requires, for example, PTA for participants with advanced HIV in an HIV drug trial in a resource-poor country whose only access to HIV drugs is through the trial and who have borne substantial net risks or burdens through participating. The specification of ‘only’ is a tricky business. To illustrate: does reciprocity support HIV drugs to ex-participants whose only way to access to HIV drugs is to sell their children into slavery?

In any case, hopefully at most a minority of cases will have this structure and so Net Instance will usually not support PTA to the trial drug in particular. In other words, Net Instance usually implies at most the participants should receive benefit, not that they should receive post-trial access to the trial drug in particular, but it does in cases in which participants will not be in a position to derive any benefit unless kept alive or healthy by the trial intervention.\(^{43}\) So, reciprocity cannot explain the common intuition that there is something wrong when sick patients get better as a result of participating in a successful trial and then lack PTA to the trial intervention: first, even when Net Instance does support reciprocal benefits, sometimes it does not support PTA in particular and, second, some such participants do not bear net risks.

Providing reciprocal benefits to participants may have costs for non-participants. Realizing this has led some to argue that the principle of reciprocity does not apply in some circumstances.\(^{44}\) The question arises of the implications of Net Instance for prioritizing participants over needy non-participants, and for prioritizing participants over equally needier non-participants.

By way of background: at one extreme, ensuring e.g. PTA to participants incurs no costs because no special arrangements are necessary. At the other extreme, the costs are extremely high: when the participants are numerous and young, and suffer from a chronic condition that needs expensive, life-long treatment; when local infrastructure must be improved to ensure PTA; and when researchers cannot outsource PTA provision.

Ensuring PTA may incur costs for non-participants via various mechanisms. Arrangements to ensure PTA may result in reduced access to, or quality of, healthcare for the local community if they draw the trial drug from a limited national stock of the intervention,\(^{45}\) or use local labor, equipment or facilities. Many arrangements will have financial costs, for example, costs of the intervention, monitoring and training, and costs in terms of time and energy, during or after the study. These costs may lead to reduction in the scientific knowledge acquired in the current study\(^{46}\) or acquired through further research.

\(^{41}\) I make the plausible assumption that some participants do not assume substantial net risks and benefits.

\(^{42}\) C. Pace, F.G. Miller & M. Danis. Enrolling the Uninsured in Clinical trials: an Ethical Perspective. *Crit Care Med* 2003; 31(3 Suppl); S121–5; D. Orentlicher. Universality and its Limits: When Research Ethics Can Reflect Local Circumstances. *J Law, Med Ethics* 2002; 30(3): 403–410; E.J. Emanuel. 2008. Benefits to Host Countries. In *The Oxford Textbook of Clinical Research Ethics*, E.J. Emanuel et al., eds., Princeton & Oxford: Princeton University Press: 719–728; J.S. Hawkins & E.J. Emanuel. 2008. Introduction: Why Exploitation? In *Exploitation and Developing Countries: The Ethics of Clinical Research*, J.S. Hawkins and E.J. Emanuel, eds. Princeton & Oxford: Princeton University Press: 1–20; Lavery, *op. cit*. note 1, pp. 697–710.

\(^{43}\) And, of course, any reason that the Reciprocity Principle gives to researchers to ensure PTA might be defeated by other reasons.

\(^{44}\) Merritt & Grady, *op. cit*. note 9, pp. 1791–1794; M. Merritt. Moral Conflict in Clinical Trials. *Ethics* 2005; 115(2): 306–330.

\(^{45}\) Merritt & Grady, *op. cit*. note 9, pp. 1791–1794.

\(^{46}\) Resources used for PTA might otherwise be have used to improve data collection in the current study.
that would have been conducted with the resources that are instead used to ensure PTA.

Reduced ability to acquire scientific knowledge may mean that future persons who would have benefited from the interventions developed do not benefit, or that they benefit later than they would have done otherwise. Possibly, the future population that would have derived benefit is more numerous and needier than the participants and each member would have benefited to a greater extent. So, compared with not ensuring PTA to participants, ensuring it may be less efficient – sometimes considerably less efficient – in terms of improving health.

Special arrangements to ensure PTA may also have personal and professional costs: costs for researchers with ambitions other than staying on with the participants to ensure that they have appropriate care (when PTA must be ensured and cannot be outsourced). In addition, any legal or felt obligation to ensure PTA in the present study may give the sponsor or researchers disincentives to conduct research that ultimately lead again, via reduction in scientific discoveries, to failure to realize health benefits. They may also have financial costs for any shareholders in the entity that sponsors the research, costs which may be passed onto the consumers of the developed medical products.

To return to the questions for prioritizing participants over non-participants (whether equally needy or needier): Net Instance implies that sometimes there is a stronger prima facie reason to benefit a participant who has borne a substantial net risk or burden through participating, than to benefit an equally needy non-participant. Net Instance, if true, can therefore help to justify the common view that researchers have special obligations to participants that they do not have to non-participants. However, without further specification and information on how to balance reciprocity against competing considerations, it is impossible to determine whether Net Instance implies that sometimes there is a stronger prima facie reason to benefit a participant who has borne a substantial net risk or burden through participating, over a needier non-participant.

That Net Instance is the most plausible version does not imply that it is viable. There are outstanding questions as to why society has reciprocal obligations to participants that it appears not to have to high-risk road workers, who also enable large social benefits, and why researchers may have reciprocal obligations to provide benefits that were not pre-agreed and have no counterpart in commercial life.47 If Net Instance were justified, but only in the context of research, this would strengthen and broaden the view called ‘research exceptionalism’, that ‘research merits stringent regulation despite the fact that it is no riskier than many other activities which we do not regulate stringently’.48 Even if Net Instance is defensible, a deeper analysis is needed to determine how to trade off Net Instance, which supports benefits just for the participant, and principles that more strongly support benefits for the needier non-participant than for the less needy participant.

**CONCLUDING REMARKS**

Reciprocity is commonly invoked to support PTA for participants to the trial intervention, without explaining reciprocity, yet the most general reciprocity principle is obviously false. Through comparing and critiquing reciprocity principles, this article has found: (1) Reciprocity cannot explain the common intuition that it is bad when participants who have benefited from participating in a trial that turns out to be successful then lack PTA to the trial intervention. (2) Reciprocity supports PTA for participants seldom: at most when participants have borne a significant net risk or burden, PTA to the trial intervention is necessary to keep them in sufficient health to enjoy the benefits owed to them, and there are no defeating reasons. So, contrary to popular belief, reciprocity cannot support a policy of PTA for all participants in a successful trial. (3) Reciprocity is most plausible when the participant experiences significant net risks or burdens, whether or not the participant intended this or is consequently harmed or could be replaced, and enables benefit to others through participating in research, given that, as a whole, research benefits society. (4) This version of reciprocity is both narrower and wider than those that proponents of reciprocity endorse. It is narrower in that it applies only when the participant is exposed to significant net risks or burdens. It is wider in that it applies even when a trial is badly designed, and so cannot benefit anyone, or the trial intervention is shown to be unsafe or ineffective. It is also hard to justify: this article provides at most skeptical and qualified endorsement.

This article has therefore undermined several common views in research ethics and regulation, the press and the public mind. It comprises necessary groundwork for addressing major outstanding questions: the nature of social obligations to research participants, whether researchers have special obligations to participants, and whether participants should be given priority in the allocation of a successful trial intervention over equally needy, or needier non-participants.

**Acknowledgements**

Table 1 contains published and unpublished data from a systematic review I conducted with Daniel Strech. I am extremely grateful to

47 Wertheimer, op. cit. note 8.

48 J. Wilson & D. Hunter. Research Exceptionalism. *Am J Bioeth* 2010; 10(8): 45–54, p. 45.
David Hunter, Penney Lewis, Ignacio Mastroelo and Leif Wenar for their insightful comments on this article and to David Hunter and Leif Wenar for comments on a long manuscript from an extract of which this article was developed. I undertook part of this work as a Caroline Miles Visiting Scholar at the Ethox Centre, University of Oxford. I received valuable feedback from audiences at talks I gave at the World Congress of Bioethics, Rotterdam (28 June 2012), and The Ethox Centre, University of Oxford (30 June 2012). I am grateful to the Wellcome Trust Research Fellowship in Biomedical Ethics for funding.

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