

# Reasons Why Post-Trial Access to Trial Drugs Should, or Need not be Ensured to Research Participants: A Systematic Review

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**Background:** researchers and sponsors increasingly confront the issue of whether participants in a clinical trial should have post-trial access (PTA) to the trial drug. Legislation and guidelines are inconsistent, ambiguous or silent about many aspects of PTA. Recent research highlights the potential importance of systematic reviews (SRs) of reason-based literatures in informing decision-making in medicine, medical research and health policy. **Purpose:** to systematically review reasons why drug trial participants should, or need not be ensured PTA to the trial drug and the uses of such reasons. **Data sources:** databases in science/medicine, law and ethics, thesis databases, bibliographies, research ethics books and included publications' notes/bibliographies. **Publication selection:** a publication was included if it included a reason as above. See article for detailed inclusion conditions. **Data extraction and analysis:** two reviewers extracted and analyzed data on publications and reasons. **Results:** of 2060 publications identified, 75 were included. These mentioned reasons based on morality, legality, interests/incentives, or practicality, comprising 36 broad (235 narrow) types of reason. None of the included publications, which included informal reviews and reports by official bodies, mentioned more than 22 broad (59 narrow) types. For many reasons, publications differed about the reason's interpretation, implications and/or persuasiveness. Publications differed also regarding costs, feasibility and legality of PTA. **Limitations:** reason types could be applied differently. The quality of reasons was not measured. **Conclusion:** this review captured a greater variety of reasons and of their uses than any included publication. Decisions based on informal reviews or sub-sets of literature are likely to be biased. Research is needed on PTA ethics, costs, feasibility and legality and on assessing the quality of reason-based literature.

## Introduction

Special arrangements to ensure that research participants have post-trial access (PTA) to the trial drug can be crucial for participants worldwide who help test drugs unavailable through government-funded services (Kolata and Eichenwald, 1999; National Bioethics Advisory Commission Group, 2001; Macklin, 2004; BBC staff, 2007). With the increasing globalization of research, sponsors and researchers increasingly confront the issue of whether drug trial participants and/or their communities should, or need not be ensured PTA to the

trial drug or other possible benefits. A spectrum of views has been expressed by academics, participants, oversight agencies and industry organizations on this issue (Busse, 1997; National Bioethics Advisory Commission Group, 2001; PhRMA Group, 2001; Nuffield Council on Bioethics Group, 2002; Berkley, 2003; Fernandez *et al.*, 2003; Greenwood and Hausdorff, 2003; Macklin, 2004; Slack *et al.*, 2005; Shaffer *et al.*, 2006; Lavery, 2008; Sofaer *et al.*, 2009). International and national guidelines require PTA to the trial drug in at least some circumstances (CIOMS, 2002; The European Group on Ethics in Science and New Technologies to the

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European Commission, 2003; India Council of Medical Research, 2006; World Medical Association, 2008) and impose various procedural obligations, such as inclusion of information about PTA in literature for participants and in registries (UNAIDS Group, 2000; National Bioethics Advisory Commission Group, 2001; CIOMS, 2002; Nuffield Council on Bioethics Group, 2002; World Medical Association, 2004; World Medical Association, 2008); a recent literature assesses compliance. (Cohen *et al.*, 2008; Ciaranello *et al.*, 2009; Shah *et al.*, 2009). However, the guidelines conflict, change their stance on PTA (World Medical Association, 2004; Wolinsky, 2006; World Medical Association, 2008), and give little detail about when PTA to trial drugs should be ensured, for how long, and by whom. The US Code of Federal Regulations does not mention PTA (45CFR46, revised 2009). Some major sponsors of research are prohibited from funding PTA (NIH Group, 2005) or state that their remit excludes this (Wellcome Trust Group, 2004).

A systematic review involves an (as far as possible) exhaustive and reproducible search and evaluation of literature that meets pre-specified inclusion criteria to answer a focused question. The genre was developed in the late 1970s in social science, and later spread to medicine, where it was used with the aim of enabling maximally informed, minimally biased decisions. It was transferred, with similar intent, to non-clinical empirical research, including *empirical bioethics* (which uses qualitative or quantitative research to address empirical questions relevant to bioethics), and *philosophical* or *reason-based bioethics* (which employs reasoning to address bioethical questions) (Lemmer *et al.*, 1999; McCullough *et al.*, 2007; Strech *et al.*, 2008). While systematic reviews of the ‘vast literature [on research ethics]’ (Emanuel *et al.*, 2008: 4) have been advocated to help clinical researchers grasp its current status, and to improve decision-making in health care, there is only one systematic review of philosophical bioethics (McCullough *et al.*, 2007). It covers just seven articles and addresses an ethical question: the question of whether a specific clinical intervention is ethically justified. As we explain and argue elsewhere, systematic reviews that answer an ethical question are likely to mislead decision-makers, and more sweeping revisions of systematic review methodology than McCullough *et al.* propose are needed for systematic reviews of reason-based literature to be of use. In particular, a systematic review of philosophical bioethics should address the factual question of which reasons have been given when discussing the ethical question, and it should present detailed information on reasons. As we also

argue, decision-makers will still need literature that discusses the quality of reasons and their implications for the ethical question: a systematic review of reasons and literature assessing quality are each necessary parts of decision-makers’ dossier (Sofaer and Strech).

This systematic review addresses the question: ‘which reasons have been given for the views that former participants in a drug trial should, or need not, be ensured PTA to the trial drug?’ (*Ensuring PTA* here implies special arrangements when participants will otherwise lack PTA, but implies no verbal or written assurances to potential participants or participants.) A secondary question is: ‘how have these reasons been used to argue that post-trial access should, or need not, be ensured?’ In particular, what were the reasons taken to imply? Were the reasons endorsed? Were uses of reasons informed by previously published uses of the same reason? It is the first systematic review of reasons, and first systematic review of a large philosophical bioethics literature. This systematic review does not settle the question of whether former participants should, or need not be ensured PTA to the trial drug. However, as explained later and elsewhere, its usefulness to decision-makers and philosophers lies in aiding the identification of the strong reasons and their implications for ensuring PTA, and in setting the agenda for empirical and conceptual research to improve the information-base of decision-making (Sofaer and Strech, 2011).

## Methods

We included a publication, e.g. article, if and only if:

- (I) It included a reason why PTA should or need not be provided.
- (II) The PTA was for former participants in a drug trial.
- (III) The PTA was to a drug tested in the trial; and
- (IV) The publication was a peer-reviewed, published academic article or book; national-level report or working paper; or PhD thesis.

*Reason* in condition (I) covers reasons that support ensuring (PTA to the drug or other possible benefit), and reasons that were simply mentioned without being explicitly endorsed or rejected. PTA provision mentioned under condition (I) includes PTA-promoting actions e.g. the funding or affordable pricing of the drug post-trial, pre-trial planning about PTA and requiring such actions. We employed conditions (II) and (III) because of possible differences between

reasons for ensuring PTA to participants versus non-participants, and for providing the trial drug versus e.g. trial devices (Millum, 2009). Condition (IV) excluded laws, legal cases, case commentaries and guidelines because of the literature's extent and the difficulty of describing a reproducible search. Publications were not excluded explicitly based on language: we are together able to read in a number of languages and planned to employ translators if the search yielded promising publications that we could not adequately understand.

Reference librarians helped to select databases in science/medicine (Medline, LocatorPlus), law (Westlaw International) and ethics (ETHXWeb, JSTOR, Euroethics, Endebit), as well as thesis databases (Ethos-Beta Electronic Theses Online Service, WorldCat Dissertations; the latter is not limited to PhD theses). No database's index terms included *post-trial access* or synonym. For each database, we first searched with Boolean operations of keywords and of the database's relevant index terms, if any. On retrieving publications known to meet the inclusion conditions, we identified their index terms and keywords (including but not limited to ones referring to PTA), and sorted these into five content classes: access, clinical trials, drugs, ethics and research subjects. For our database-specific search terms and strings, please see table A1. Searches had no start-date but, where specifiable, a 2 October 2009 end-date. We next used bibliographic review and recommendations from authors of included publications to identify reports and books on research ethics, and hand-searched their tables of contents and indexes. Last, we searched in-text references, notes and bibliographies of included publications for promising titles (a 'snow-ball search') (Greenhalgh and Peacock, 2005).

Next, we worked independently through the resulting publication list to exclude publications based on their title, any abstract/extract and any index terms. Each author thus produced a list of publications that were candidates for meeting the inclusion conditions. One list had 134 publications, the other had 95; 93 were on both lists. After jointly resolving discrepancies to create one list of 121 publications, we each read the full text of each and selected those that met the above inclusion criteria. We repeated the process on the results of the snow-ball search until no further qualifying publications emerged. Figure 1 documents the search.

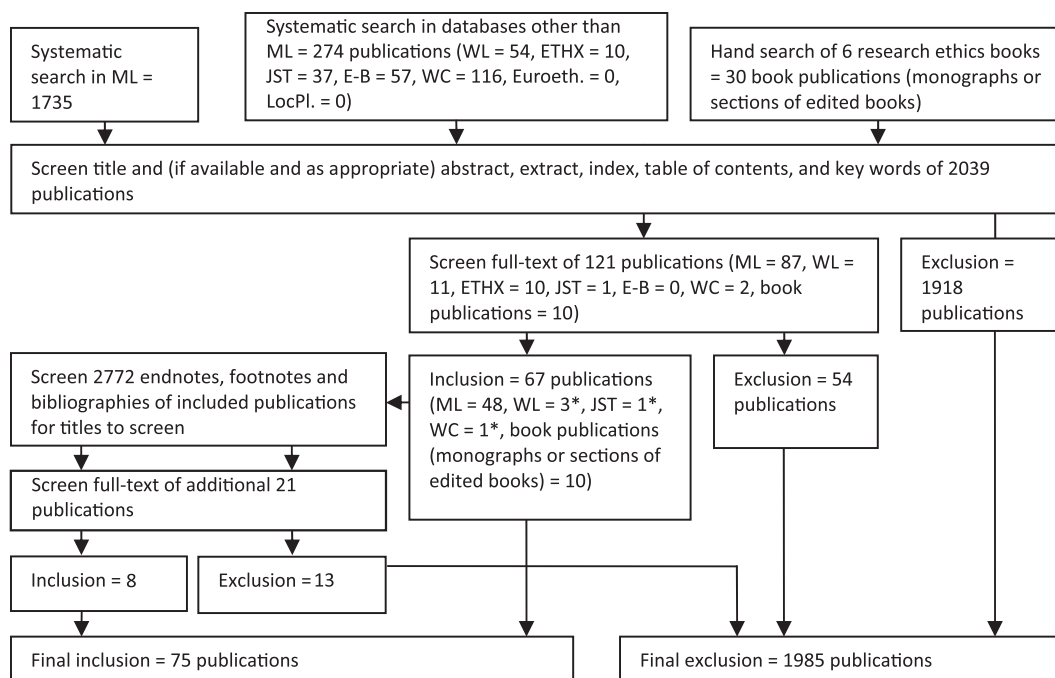
We distinguish here between the mention of a reason expressed by a specific passage in a publication (*Reason Mention*) from a *Type of Reason*, which may have different Reason Mentions in different publications. We

distinguish also between broad Types of Reason, e.g. **avoid exploitation**, and narrow Types of Reason, e.g. **avoid exploiting research participants**, or **avoid exploiting the host country**. In our analysis, each broad Type of Reason comprises several narrow types, and each narrow type falls under one broad type. Bold text indicates Types of Reason.

As we found no useful precedent for the systematic extraction and analysis of Reason Mentions, we developed a framework of narrow and broad Types of Reasons that best accommodated the reasons mentioned in the included publications. (For the development, details and limitations of our model for systematic reviews, see (Strech and Sofaer, How to write a systematic review of reasons, manuscript.) In brief, one author (NS) commenced extraction by identifying and numbering 10 publications already known to meet the inclusion conditions, and which illustrated a range of reasons and challenges to analysis. Both authors then independently extracted Reason Mentions from publication 1 and assigned each Reason Mention to a broad and a narrow type, assigning Reason Mentions to different narrow Types of Reason whenever it was suspected that the Reason Mentions might express different Types of Reason. (The narrow Types of Reason were thus very narrow.) Discrepancies between the resulting spreadsheets were identified, discussed and resolved. The process was repeated, for a total of nine publications, until coding additional publications resulted in no further changes to data types, and discrepancies between corresponding cells' contents were easily resolvable. N.S. then extracted and analyzed data from the remaining publications. D.S. checked the analysis. N.S. then identified and removed repeated Reason Mentions within each publication.

Last, N.S. used Excel to derive/calculate the results, which D.S. checked. We also conducted a sensitivity analysis, which aimed to see whether the difference in the number and variety of reasons captured by our systematic review versus the most comprehensive included publication was preserved when Types of Reason were more broadly individuated: we merged similar narrow Types of Reason, and recounted the numbers of reasons identified by our systematic review versus the most comprehensive publication. Table 1 shows which Types of Reason were merged (see the last note under the table).

Disagreements and problems that arose in the selection of publications and the data extraction and analysis were resolved by frequent discussion and not by deference to the second author; we did not need to appeal to a third person. Details of the types of data extracted and



**Figure 1.** Selection of publications. ML, Medline; WL, Westlaw; ETHX, ETHXWeb; JST, JSTOR; E-B, Ethos-Beta Electronic Theses Online Service; WC, Worldcat; Euroeth., Euroethics; LocPl., LocatorPlus; asterisks indicate number of publications that were not also retrieved by the systematic search in ML. Reasons for excluding 1985 publications: no content on research conducted on humans; or no content on clinical trials of drugs conducted on humans; or no content on whether PTA the trial drug should; or need not, be ensured to participants, their host community or country; or no reason for the view that PTA the trial drug should (or need not) be ensured to participants.

types of results are given in Strech and Sofaer, How to write a systematic review of reasons, manuscript).

## Results

### Publication Characteristics

Seventy-five publications were included (Supplementary Figure 1), published between 1991 and September 2009 inclusive. Nearly three-quarters (55, 73%) were published between 2002 and September 2009 inclusive. There was no book focusing on PTA. Publications used many different terms to refer to PTA.<sup>1</sup> Table 2 describes further characteristics of the included publications.

### Identity, Incidence and Implications of Reasons

The 75 publications together included 781 Reason Mentions, which we grouped under 36 broad and 235 narrow Types of Reason; when similar narrow types were merged to conduct the sensitivity analysis, there

were 202 narrow Types of Reason (Table 1). To generalize over the broad Types of Reason, reasons were based on considerations of morality, legality, interests and incentives, and/or practicality. Moral reasons belonged to two overlapping families: based on justice, or the roles of and relationships between stake-holders in research. Reasons classed under legality included reasons claiming that guidelines do (or do not) require ensuring PTA.

The most frequently mentioned broad Types of Reason were **avoid exploitation** (which had 97 Reason Mentions) and **stake-holder interests**: the interests of stake-holders in research such as participants, sponsors, governments of countries hosting research and society (86 Reason Mentions). A total of 14 (39%) broad Types of Reason had 5 or fewer Reason Mentions. The most-mentioned narrow Types of Reason were **avoid exploiting the host country** (23 Reason Mentions; mentioned only for ensuring PTA), and **if PTA is required, this will reduce the incentive to conduct research with consequent loss of potential benefits to potential research hosts** (23 Reason Mentions; mentioned only for the view that PTA need not be ensured),

**Table 1.** Broad and narrow Types of Reasons**1.1: MORAL REASONS BASED ON JUSTICE**

Avoid exploitation [97]

Avoid exploiting the host country [23] (1)

Avoid exploiting the host community [18] (1)

Avoid exploiting participants [19]

If avoiding exploitation requires PTA to be provided, then prior agreements should be required [8]

Research provides benefits other than PTA to the trial drug [6]

Fair level of benefits may but need not include PTA [9]

Requiring PTA may not suffice for providing fair level of benefits when the costs of participating in research are high or the benefits to the sponsor are great [3] (2)

Requiring PTA may not suffice for providing fair level of benefits because many trials do not yield a safe and effective intervention immediately or ever [1] (2)

Requiring PTA may not suffice for providing fair level of benefits when trial intervention is unsuccessful and no other benefits are provided [1] (2)

Avoid exploiting people (of unspecified identity) [13 for ensuring PTA, 2 for the view that PTA need not be ensured]

Rights [2]

Right to health care [1]

Participants' right that the terms of the research should be justifiable to them [1 unclear implication]

Autonomy [38]

A resource-poor community cannot give valid consent to hosting research unless there is a realistic plan to give it PTA [3]

The participant's consent is insufficiently informed because the participant was unable to predict what it will be like to lack PTA [1] (11)

The participant's consent is insufficiently informed because the consent form lacked an accurate account of PTA [2] (11)

The participant's consent is insufficiently informed because the participant has therapeutic misconceptions [2] (11)

The participant's consent is insufficiently informed because investigators failed to ensure that the participant understood all relevant information [1] (11)

The participant gave informed consent to participating in research that would not give PTA [12]

To enrol in a trial is to assume the risk, and thus responsibility, of lacking PTA [2]

The stake-holders in the research agreed before the trial that there would be no PTA [2]

Host community fairly selected a package of benefits that excludes PTA [1]

The autonomy of the entity that hosts the research is paternalistically restricted when others choose which research-related benefits it will receive [9]

Offering PTA to potential participants may create or exacerbate therapeutic misconceptions [2]

Reciprocity [38]

Unspecified reciprocity [9] (12)

Reciprocity in return for assuming risk [6] (12)

Reciprocity to participants from researchers [5] (13)

Reciprocity to participants from society [5]

Reciprocity to participants from the sponsors [4] (13)

Reciprocity to participants from host country non-participants [3]

Reciprocity to the host community from researchers [1] (14)

Reciprocity to the host community from the sponsor [1] (14)

(continued)

Table 1. Continued

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Reciprocity to the host community from the world [2]
Reciprocity to participants from non-participants in the host country who have the same medical condition as participants [1]
Giving PTA to the successful intervention to former participants doubly disadvantages participants in unsuccessful trials, who received fewer benefits during the trial [1]
Distributive justice [23]
Unspecified distributive justice [1]
Equal access to healthcare for inhabitants of host and sponsor countries [1]
Inequalities between resource-rich sponsor and resource-poor host countries [3]
Providing PTA reduces financial inequalities between U.S. researchers and participants in resource-poor countries [1]
Prior agreements to provide PTA reduce inequalities in PTA between resource-rich and -poor countries [1]
If PTA is not guaranteed, there will be inequalities in PTA for participants who have, and participants who lack, health insurance [1]
Fair division of benefits and burdens of research between countries that host, and countries that sponsor, the research [4]
Fair selection of individuals to participate in research implies that if resource-poor country individuals will not benefit from the research, they should not participate [2]
If researchers and sponsors do not provide PTA, they risk failing to ensure that participants receive morally obligatory healthcare [1]
If benefits to the host community are negotiated between stake-holders in research, host communities will not receive fair benefits because their bargaining position is relatively weak [2] (18)
If benefits to the host community are negotiated between stake-holders in research, different host communities will receive different benefits [1] (18)
If PTA is required, the sponsoring government will bear an unjustly large proportion of the cost [1]
Providing PTA to former participants increases inequalities between participants and those who did not, or could not, participate [2]
Different standards [23]
Avoid using double standards for research conducted in different places [1]
Resource-poor country participants should receive the same post-trial benefits as resource-rich country participants [1]
Researchers should be held to a higher standard than physicians and business persons [1]
Pre-trial agreements are not generally used, so they should not be required [4]
PTA is not required to conduct research in resource-rich countries, so it should not be required to conduct research in resource-poor countries [2]
Pre-trial plans are not required to conduct research in resource-rich countries, so they should not be required to conduct research in resource-poor countries [2]
Pre-trial agreements are not required to conduct research in resource-rich countries, so they should not be required to conduct research in resource-poor countries [7]
International guidelines do not require PTA [4]
Clinical research should not be held to a higher standard than other international enterprises [1]
Physical health [22]
Participants' health need [16]
Host community's health need [2]
Urgent need to reduce huge burden of disease justifies pressing on with research without PTA [2]

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(continued)

Table 1. Continued

## Promising [13]

PTA was promised [1]

PTA was not promised [1]

Promise to provide PTA may be broken [11]

## Psychological health [10]

Lack of PTA may cause psychological harm to former participants [10]

## Non-maleficence [16]

Minimize possible harms [1]

Participants should not have worse health after the trial than during [10]

Participants should not have worse health care after the trial than during [1]

Participants should not have worse health after the trial than before [2]

Participants should not have worse health after the trial than if they had not participated [1]

Non-maleficence requires only that researchers and sponsors do not withhold any normally available effective treatment [1]

## Beneficence [9]

Unspecified beneficence [1]

Participants must benefit from the research [4]

Participants should continue receiving treatment for as long as they benefit from it [2]

Beneficence requires only that researchers and sponsors do not withhold any normally available effective treatment [1]

## Reward and recognition [9]

Reward for research participation [5]

Recognition of participants' contribution [3]

Pharmaceutical companies should show respect for participants [1]

## Compensatory justice [7]

Compensation for research-related harm [5]

Compensation for historic injustice [2]

## Avoid objectification [5]

Avoid objectifying the host community [1]

Avoid objectifying participants [3 for ensuring PTA, 1 for the view that PTA need not be ensured]

## Avoid abandonment [3]

Avoid abandoning participants [3]

## Fairness [5]

It is unfair to require sponsor to provide PTA when participation is low risk and benefits to sponsor are small [1]

Unspecified fairness [3 for ensuring PTA, 1 for the view that PTA need not be ensured]

## Responsiveness [4]

Responsiveness to host countries' needs [4]

## Access [4]

Former participants lack alternative access to care [4]

## Other justice [5]

Unspecified justice [4]

Priority to the sickest [1]

(continued)



**Table 1.** Continued

Charity [2]
Be charitable to former participants [2]
<b>1.2: MORAL REASONS BASED ON ROLE AND RELATIONSHIP</b>
Role [30]
Role of researchers
Researchers have a professional “commitment” to participants [1] (3)
Researchers bear a duty of care to participants [2] (3)
Researchers have moral fiduciary obligations to participants [1] (3)
Researchers are obliged not to disregard participants’ well-being [1] (3)
Researchers are responsible for former participants’ welfare [1] (3)
Because resource-rich countries have shirked their obligation to alleviate poverty in resource-poor countries, the role of researchers from resource-rich countries includes provision of fair benefits [1]
Researchers are not responsible for providing healthcare [5]
Researchers are not responsible for allocating resources between research and treatment [2]
Researchers’ and sponsors’ primary role is not to develop resource-poor countries [1]
Researchers are not responsible for funding development [1]
Researchers are obliged to be honest, but lack more substantial obligations to provide PTA [1]
Researchers’ primary role is to conduct research [1]
Researchers’ role is distinct from physicians’ role [1]
Role of government
Governments’ role includes deciding how to allocate resources between research and treatment [1]
Governments’ role includes providing health care [5]
Role of sponsor
Sponsor is not responsible for providing healthcare [2]
Sponsor is responsible for allocating resources between research and treatment [1]
Sponsors’ role is not to reduce inequalities between resource-rich and -poor countries [1]
Relationship [7]
Relationship between researchers and host community [1]
Participants entrust aspects of their health to researchers [3] (19)
Unspecified relationship between researchers and participants [2 for ensuring PTA, 1 for view that PTA need not be ensured] (19)
Concept of participant [4]
Subjects are victims [1]
Subjects are altruistic heroes [1]
Subjects are opportunists [1]
Subjects are willing contractors [1]
<b>1.3: INTERESTS AND INCENTIVES</b>
Stake-holders’ interests [86]
Participants’ interests
Participants’ interests: PTA to trial drug in participants’ interests [1]
Participants’ interests: treatment only during trial is better than no trial and no treatment [8]
Participants’ interests: even if trial will not provide PTA, participation buys time for future break-throughs [1]

(continued)



Table 1. Continued

Participants' interests: participants not harmed by trial [1]
Individual participant's interests: trial drug not indicated for former participant post-trial [6]
Participants' interests: PTA to trial drug may harm former participant [2]
Providing PTA to former participants increases inequalities between participants and those who did not, or could not, participate, and thus has the potential to increase tensions within host community [2]
Extent of sponsor's financial obligations depends on priorities of participants and host countries [1 unclear implication]
Host country's and community's interests
Host country's interests (unspecified) [1]
Host community's interests: research is unlikely to improve host community's health unless there is prior commitment to PTA [1]
Host countries do not lose benefits if research that would not benefit them is prevented [1]
PTA to trial intervention is one of several possible benefits to the community [1]
Host country's interests: country benefits from research even if it doesn't receive PTA [1]
Host community's interests may be better served by receiving benefit other than PTA [13]
Host country's interests: trial will not provide PTA but is necessary to provide access in the long-term [3]
Loss of potential benefits to host countries: even if there is no PTA immediately after the trial, price of intervention developed will eventually drop to the point that the host country can afford it [4]
Sponsor country's and society's interest
Sponsor country's interests: preventing the spread of infectious disease from resource-poor countries [1]
Society's interests: promote research [2]
Society's interests: better that product is developed to enable some people to have access than not to develop it [2]
Society's interests: trial without PTA will advance knowledge and thereby benefit society [1]
Society's interests: withhold successful drug from host community to prevent emergence of drug-resistant disease [3]
Sponsor's and share-holders' interests
Sponsor's interests: providing PTA enables collection of data that lengthens product's market-life [1]
Sponsors' interests: providing PTA improves drug company's public image [1]
If the sponsor does not provide PTA, it is possible that the research will be regarded as unethical, in which case the sponsor will not be able to obtain marketing approval for the product developed, with consequent loss of potential benefits to society [1]
If PTA is not guaranteed, activists may prevent pharmaceutical companies from recruiting further participants [1]
When pharmaceutical company funds PTA, this reduces share-holders' profits [1]
Researchers' interests
Researchers' interests: burden to researchers of providing PTA is too great [1]
Incentive [66]
Offer of PTA gives individuals an incentive to participate [2]
Offer of PTA gives communities an incentive to host research [1]
Giving PTA to the host population reduces the chance that individuals will be unduly induced to participate [1]

(continued)

Table 1. Continued

Requiring PTA would comprise a disincentive to conduct research [16] (10)
Requiring PTA would comprise a disincentive to conduct small, exploratory studies [1] (10)
If pre-trial commitment to funding PTA is required, this will reduce the incentive to conduct research because funders are unwilling to commit to funding PTA prior to receiving research results and consequent public pressure to provide PTA [1]
If PTA is required, this will reduce the incentive to conduct research, with consequent loss of potential benefits to potential research hosts [23]
Progress occurs in multiple steps, so requiring PTA to be provided immediately may reduce the research conducted and thereby cause loss of potential benefits to host countries [2]
If PTA is required, research will not be conducted in resource-poor contexts whose infrastructure precludes PTA, with consequent loss of potential benefits to the neediest potential research hosts [1]
Offer of PTA may unduly induce individual to participate [8]
Offer of PTA may unduly induce population to host research [1]
Trust [6]
Ensuring PTA helps maintain participants' trust in research [1]
Ensuring PTA helps maintain potential participants' trust in research [3]
If PTA is not provided, former participants may lose trust in research and may consequently have less incentive to participate again [1]
Expectations [2]
Participants expect that they will have PTA [1]
Communities that host research expect that the intervention that they help to develop will be used to improve their health [1]
<b>1.4: PRACTICAL REASONS</b>
Stake-holders' competence [43]
Researchers' competence
Researchers are able to advocate for PTA [8]
Researchers and sponsors cannot do more than advocate for PTA [1]
Researchers lack skills and experience to negotiate fair benefits [1]
Researchers lack skills and experience to provide PTA [1]
Researchers lack resources to provide PTA [3]
Researchers lack funding to provide PTA [1]
Researchers lack (unspecified) power to ensure PTA [2]
Researchers lack power to ensure PTA because lack power over drug funding by foreign aid [1] (4)
Researchers lack power to ensure PTA because lack power over drug funding by host countries [1] (4)
Researchers are unable to influence host country's health policy [1]
Researchers lack power over health policy [3] (4)
Researchers lack power over host country's health policy [1]
Researchers and sponsors lack power to ensure PTA because PTA depends on many factors their beyond control [1]
Researchers lack power over drug approval in host countries [1] (4)
Researchers lack power to ensure PTA because they lack power to approve drugs [1] (4)
Sponsor's competence
Sponsor lacks resources to deliver PTA [2]
Sponsors lack power to make unilateral decisions about PTA [3] (5)
Sponsors have limited power over priorities of agencies providing health care [1] (5)

(continued)

Table 1. Continued

Sponsor lacks power to ensure PTA because lacks power over drug funding by host countries [1] (5)
Sponsor lacks power to ensure PTA because lacks power over drug funding by foreign aid [1] (5)
Sponsor lacks power to ensure PTA because lacks power to approve drugs [3] (5)
Sponsors lack legal power over drug approval process in sponsor and host countries and so cannot guarantee reasonable availability [1] (5)
Sponsor lacks power to make unilateral decision at the start of the trial to give PTA [1 for ensuring PTA, 2 for view that PTA need not be ensured] (5)
Logistical obstacles [46]
Lack of host country infrastructure makes PTA unlikely unless PTA is guaranteed [1] (7)
Unspecified logistical obstacles to implementing PTA [20]
Difficult to locate former participants in need of treatment [4]
Lack of host country infrastructure makes it difficult to provide PTA [4] (7)
Lack of host country infrastructure means that even if sponsor supplies intervention post-trial, former participants are unlikely to benefit [2] (7)
Administration of intervention post-trial must be supervised [1]
Unrealistic to expect researchers to provide PTA [4] (8)
Unrealistic to expect sponsors to provide PTA [2] (8)
Funders unwilling to guarantee to fund PTA before knowing study results [3]
Difficult to co-ordinate stake-holders to provide PTA [2]
Further research may be needed after showing effectiveness and safety before drug can be provided [3]
Research funders have not funded negotiations with host regarding benefits [1]
Cost [30]
Drug company sponsors profit from the research [3]
Pharmaceutical company sponsors make large profits from the research [1]
The sponsor's revenue from marketing a successful drug covers the cost of providing PTA [1]
Cost of funding PTA is high [5] (15)
Cost of funding PTA to sponsor may be too high [3] (15)
Whether a trial is ethical does not depend on whether sponsor can afford to provide PTA [1]
The higher the cost of PTA, the lower the chance that PTA will be provided [2]
Cost of funding PTA to the sponsoring government may be too high [1]
The sponsor needs to recoup the cost of developing the intervention [4]
If PTA is provided, then less research can be conducted [4 unclear implications]
Extent of sponsor's financial obligations depend on research type [1 unclear implication]
The lower the cost of PTA, the stronger the reason to provide it [1 unclear implication]
Safety and/or effectiveness [21]
Trial drug is effective [1] (9)
Trial drug is safe and effective [1] (9)
Trial drug is ineffective [2] (6)
Trial drug is not safe and/or not effective [3] (6)
Further research may be needed to show effectiveness and/or safety [6]
Many trials do not yield a safe and effective intervention immediately or ever [1] (6)
Purpose of research [13]
The purpose of research includes providing PTA to beneficial interventions [1]
The purpose of research is to develop interventions to improve the health of the population on which the intervention was tested [3]

(continued)

Table 1. Continued

The primary purpose of research is not to further international distributive justice [1]
The purpose of research is distinct from the purpose of health care [4]
The purpose of research is not to further social justice in resource-poor countries [1]
The purpose of research is to obtain regulatory approval for the trial intervention in sponsor's country [1]
The purpose of research is to produce generalizable knowledge to improve health (of unspecified individuals) [1 for ensuring PTA, 1 for the view that PTA need not be ensured]
Efficiency [5]
It is more efficient to treat former subjects than non-participating community members [1]
Requiring PTA encourages scientists to combine studies, and thereby to reduce the number of participants [1]
Researchers may be inefficient healthcare providers [2]
Maximize the amount of research conducted and thus the potential health benefits from research [1]
Science [4]
Obligation to maximize the scientific value of the trial and so to maintain the control group after the end of the trial [4]
Context of research [3]
Resources for providing PTA are scarce [2 unclear implications]
Limited motivation of researchers and sponsors to provide PTA [1 unclear implication]
<b>1.5: LEGAL REASONS</b>
Legality [31]
PTA is required by guideline [8]
Researchers have legal fiduciary obligations to participants [2]
International guidelines do not require PTA [4]
PTA not required by US legal code [1](17)
Research funder forbids use of its funds for PTA [3]
It is illegal for researchers to provide health care outside of a clinical trial [1]
It is illegal for sponsor to provide health care outside of a clinical trial [4] (16)
It is illegal for sponsor to provide a non-approved trial intervention post-trial [1] (16)
Difficult to interpret guideline or ethical principle that requires PTA [4]
Intellectual property rights may make it impossible for researchers to guarantee PTA prior to trial [2]
PTA is not required by guideline (17)

Notes: • This table lists all the mentioned reasons why PTA should or need not be ensured, including those that were rejected, or neither rejected nor endorsed. Given that reasons will in any case need to be appraised, it better aids the decision-maker to err on the side of comprehensiveness. • Finer-grained data is available on request. • No colour background: reason used just for the view that PTA should be ensured; number in square brackets with no colour background is number of reason mentions used for the view that PTA should be ensured. • Grey background: reason used just for the view that PTA need not be ensured or with unclear implications; number in square brackets with grey colour background is number of reason mentions used for the view that PTA need not be ensured. • Red background: some reason mentions were for the view that PTA should be ensured and some for the view that it need not be ensured, or implications for PTA were left unspecified. • Note that, for many broad Types of Reason, the number after the broad type (e.g. Avoid exploitation) is more than the sum of numbers after the narrow types because, for colourless or grey reasons the number given excludes the few reason mentions with unclear implications. • Round parentheses: reasons followed by the same number in parentheses were merged in the sensitivity analysis.

**Table 2.** Characteristics of publications included in this systematic review

Features of publication	<i>n</i> (%) of publications
Content type <sup>a</sup>	
Philosophy discussion <sup>b</sup>	62 (83)
Policy critique <sup>c</sup>	26 (35)
Informal philosophical review <sup>d</sup>	18 (24)
Policy review <sup>e</sup>	18 (24)
Opinion piece <sup>f</sup>	4 (5)
Case study of PTA <sup>g</sup>	2 (3)
Commentary <sup>h</sup>	2 (3)
Empirical study <sup>i</sup>	2 (3)
Discussion of PTA legal case <sup>j</sup>	1 (1)
Publication type	
Article	55 (73)
Sections with distinct author groups in edited books	9 (12) <sup>k</sup>
Report	5 (7)
Journal-published letters	3 (4)
Journal-published news article	1 (1)
Monograph	1 (1)
PhD thesis	1 (1)
PTA discussed in relation to which trials?	
All	57 (76)
HIV/AIDS <sup>l</sup>	18 (24)
Mental health	1 (1)
Genetics	1 (1)
Published in 2004 (the most prolific year)	13 (17)
Publications whose main topic was not PTA	47 (63)
Publications concerning only research conducted by resource-rich in resource-poor countries	58 (77)
English-language publications <sup>m</sup>	75 (100)
Characteristics of 55 articles included	
Field of journal	
Medicine	18 (33)
Bioethics	17 (31)
Law	12 (22)
Public health	4 (7)
Science	2 (4)
Articles published online at <a href="http://www.scidev.net">www.scidev.net</a>	2 (4)

<sup>a</sup>Publications were assigned more than one content type where appropriate.

<sup>b</sup>Discussion of whether there are PTA obligations.

<sup>c</sup>Assessment of PTA regulations, guidelines and/or policies.

<sup>d</sup>Publication that mentioned >12 narrow types of reasons that met the inclusion conditions.

<sup>e</sup>Review of regulations, guidelines and/or policies regarding PTA.

<sup>f</sup>Expression of mere opinion about whether there are PTA obligations.

<sup>g</sup>Description of trial in which PTA was an issue.

<sup>h</sup>Commentary on another publication included in this review.

<sup>i</sup>Publication reporting empirical study, not necessarily of PTA.

<sup>j</sup>Discussion of legal case in which PTA was an issue.

<sup>k</sup>The 9 sections occurred in a total of three edited books.

<sup>l</sup>The HIV/AIDS publications concerned AZT, ART or vaccine research.

<sup>m</sup>See 'Limitations' section.

followed by **avoid exploiting participants** (19 Reason Mentions; mentioned only for ensuring PTA), and **avoid exploiting the host community** (18; mentioned only for ensuring PTA). Most (210, 89%) narrow Types of Reason had five or fewer Reason Mentions.

Reason Mentions classed under **avoidance of exploitation** concerned the exploitation of the host country (23 Reason Mentions<sup>2</sup> (Crouch and Arras, 1998; Glantz *et al.*, 1998; Benatar, 2000; Lie, 2000; Cooley, 2001; National Bioethics Advisory Commission Group, 2001; Chang, 2002; Kottow, 2002; Orentlicher, 2002; Page, 2002; Participants in the Conference on Ethical Aspects of Research in Developing Countries, 2002; Lo and Bayer, 2003; Lavery, 2004; Macklin, 2004; Page, 2004; Participants in the 2001 conference on ethical aspects of research in developing countries, 2004; Emanuel, 2008; Wertheimer, 2008)), participants (19 Reason Mentions in 15 publications (Cleaton-Jones, 1997; McLean, 1997; Crouch and Arras, 1998; Emanuel, 1998; National Bioethics Advisory Commission Group, 2001; Brody, 2002; Nuffield Council on Bioethics Group, 2002; Orentlicher, 2002; Macklin, 2004; Ballantyne, 2005; Grady, 2005; Benatar and Fleischer, 2007; Hawkins and Emanuel, 2008; Lavery, 2008; Zong, 2008)), the host community (18 Reason Mentions in 13 publications, (Gostin, 1991; Annas and Grodin, 1998; Glantz *et al.*, 1998; Page, 2002; Participants in the Conference on Ethical Aspects of Research in Developing Countries, 2002; Macklin, 2004; Participants in the 2001 conference on ethical aspects of research in developing countries, 2004; Yearby, 2004; Basu *et al.*, 2006; Gbadegesin and Wendler, 2006; Emanuel, 2008; Lavery, 2008; Siegel, 2008)), or an unspecified group (16 Reason Mentions in 8 publications, (Crouch and Arras, 1998; Participants in the Conference on Ethical Aspects of Research in Developing Countries, 2002; Macklin, 2004; Ashcroft, 2005; Ballantyne, 2006b; Lavery, 2008; Siegel, 2008; Sachs, 2009)). Publications agreeing that avoiding exploitation is sometimes or always a reason for ensuring PTA differed as to whether avoiding exploitation requires providing PTA in particular, (McLean, 1997; Annas and Grodin, 1998; Crouch and Arras, 1998; Glantz *et al.*, 1998; Benatar, 2000; Chang, 2002; Kottow, 2002; Page, 2002; Lo and Bayer, 2003; Basu *et al.*, 2006; Benatar and Fleischer, 2007) or a fair level of benefits that may but need not include PTA<sup>3</sup> (Brody, 2002; Orentlicher, 2002; Participants in the Conference on Ethical Aspects of Research in Developing Countries, 2002; Lavery, 2004; Participants in the 2001 conference on ethical aspects of research in developing countries, 2004; Ballantyne,

2005; Ballantyne, 2006a; Carse and Little, 2008; Emanuel, 2008; Siegel, 2008).

Reciprocity is the notion that, because one party (X) benefits another (Y), Y is obliged to benefit X in return. Reason Mentions classed under **reciprocity** differed as to the identity of X (participants or the host community) and of Y (the sponsor, researchers, society, the world, any host country non-participant or host country non-participants who have the same medical condition as participants). Eight of the 12 possible combinations of X and Y were mentioned. Some **reciprocity** Reason Mentions differed also regarding why participants/communities may be entitled to benefit, e.g. because they assumed risk (Lie, 2000; Chang, 2002; Macpherson, 2004; Ashcroft, 2005; Merritt, 2007; Carse and Little, 2008; Sachs, 2009; Shah *et al.*, 2009) or were used to create benefit for mankind (Gostin, 1991).

**Role** Reason Mentions collectively reflected conflicting views regarding various role-related obligations, powers, and limits to the powers of researchers, sponsors and governments. For example, many reasons for the view that PTA need not be ensured appealed to researchers' or sponsors' lack of influence on health policy or on the drug approval process. A key conflict regarded whether researchers have the same role as doctors (implying that researchers should ensure PTA) or different role (implying that researchers need not ensure PTA); reasons appealing to the **purpose of research** or to the **relationship** between researchers and participants/communities were similarly polarized.

Although **logistical obstacles** were most often left unspecified, a broad range was mentioned. Such obstacles were almost without exception taken to imply that PTA need not be ensured. Concerns about the **safety and/or efficacy** of the trial drug were only used to argue for the view that PTA need not be ensured in specific cases or against the view that PTA should always be required.

Fourteen **non-maleficence** Reason Mentions appealed to the view that participants should not be worse off after the trial, but completed 'not be worse off after the trial than ... with respect to ...' differently. For most such Reason Mentions (11, 76%), participants should not be worse off than *during* the trial; for two (14%), than *before* it; for one (7%), than *if they had not participated*. For most (13, 92%), the relevant respect was health, whereas for one (7%) it was health care.

Publications endorsing<sup>4</sup> a narrow reason for a conclusion agreed about whether the reason was for ensuring PTA or for the view that PTA need not be ensured. The most frequently endorsed reasons<sup>5</sup> included ones used just for ensuring PTA (**avoid exploiting**

participants, participants' health need), and others used just to argue that PTA need not be ensured (**host community's interests may be better served by receiving benefit other than PTA**).

### Attitudes Taken to Reasons

Most reasons were clearly accepted or rejected at most or all Reason Mentions. However, several common<sup>6</sup> broad reasons were exceptions, including **cost** (clear attitude expressed in 20 of 30 Reason Mentions, 66%) and **distributive justice** (18 of 23, 78%).

Reasons were rejected on various moral and empirical bases. For example, publications mentioning **if PTA is required, this will reduce the incentive to conduct research with consequent loss of potential benefits to potential research hosts** differed as to whether requiring PTA would reduce the research conducted (Cooley, 2001; Nuffield Council on Bioethics Group, 2002; Macklin, 2004). Those who thought it would disagreed about whether this was a reason why PTA need not be ensured. One publication denied this on the grounds that a reduction in research would not mean a loss of benefits for communities who would have hosted the research without receiving its benefits (Glantz *et al.*, 1998). Another denied it because it is good to prevent exploitative research (Chang, 2002).

### Spectrum and Incidence of Conclusions

Three-quarters of the publications (56, 75%) took a stance on whether PTA should, or need not, be ensured, and a quarter (19, 25%) on whether ensuring PTA should be required (Supplementary Table 1). Of all the conclusions drawn by publications, the most common conclusion was that PTA should sometimes be provided (45 publications, 60%), although some publications (10, 13%) concluded PTA should always be provided and one (1%) that there is no obligation. Of those concluding PTA should sometimes be provided, some thought that products/services likely to be beneficial should be provided, but not necessarily PTA to the trial intervention, e.g. (Participants in the Conference on Ethical Aspects of Research in Developing Countries, 2002).

Among publications considering whether PTA should be required (19 publications, 25%), the most common conclusion was that it should not (16, 84%). Sixteen (21%) expressed conclusions about pre-trial obligations to discuss, plan or enter into agreements regarding PTA; 13 (17%) endorsed such an obligation. No publication distinguished these obligations' scope,

and publications differed about whether such actions should be required. Six (8%) endorsed an obligation to advocate for ensuring PTA or to refer participants to treatment or other trials (Crouch and Arras, 1998; National Bioethics Advisory Commission Group, 2001; Nuffield Council on Bioethics Group, 2002, 2005; Pace *et al.*, 2003; Carse and Little, 2008). Four (5%) claimed Research Ethics Committees (Institutional Review Boards) should approve only research with appropriate PTA arrangements, though without defining *appropriateness*.

Nearly half (25, 45%) of publications claiming that PTA should be provided sometimes or always did not specify an agent obliged. Publications concluding there is a PTA-related obligation identified, collectively and individually, various agents who have the obligation; exceptions were obligations to advocate for ensuring PTA or to refer participants to other care or research, collectively attributed only to researchers and sponsors, and to approve research only if it has appropriate PTA arrangements, attributed only to RECs. It is our opinion that some but not all publications referencing several agents claimed that responsible agents should collaborate, but we did not systematically collect data on responsibilities to collaborate.

Many conclusions that PTA should be provided did not contain all of the following information: who should fund, provide or receive the trial drug, and/or for how long.

### Reasons Endorsed and Conclusions Drawn by Individual Publications

Supplementary Table 2 gives, for each publication, the reasons that were clearly for ensuring PTA or for the view that PTA need not be ensured, and that were clearly endorsed or rejected by the author, and the publication's conclusion. Publications varied widely in the number of narrow reasons mentioned, including those presented in a third party's voice (range: 1–67) (table available on request from the corresponding author). The average number of narrow Types of Reason mentioned by informal philosophy reviews (Glantz *et al.*, 1998; Hutt, 1998; Lie, 2000; National Bioethics Advisory Commission Group, 2001; Chang, 2002; Nuffield Council on Bioethics, 2002; Orentlicher, 2002; Page, 2002; Macklin, 2004; Ashcroft, 2005; Grady, 2005; Ballantyne, 2006a; Carse and Little, 2008; Emanuel, 2008; Lavery, 2008; Zong, 2008; Millum, 2009) was 24, compared to this review's 235. The most comprehensive included publication, an informal review, (Lavery,



2008) reported 22 broad and 59 narrow Types of Reason (58, when narrow types were broadened in the sensitivity analysis). Among the reasons it did not mention were, for example, **host community's interests may be better served by receiving benefit other than PTA.**

### Use of Relevant Literature

Publications collectively referenced<sup>7</sup> 20 regulations, guidelines or recommendation-containing reports (*instruments*), most commonly CIOMS's guidelines (12 or 16% of publications mentioned a version of CIOMS's guidelines (CIOMS, 1982; CIOMS, 1983; CIOMS, 1993; CIOMS, 2002)), NBAC's (National Bioethics Advisory Commission Group, 2001) (11 or 15% of publications) and NCOB's reports (Nuffield Council on Bioethics Group, 2002) (9 or 12% of publications). Over half of instrument-referencing publications (28/51, 55%) referenced one or more of these three. Over two-thirds (14, 67%) of instruments were referenced by just one publication.

Of the 55 articles included in this systematic review, the most-referenced articles were the early Glantz *et al.*<sup>8</sup> (10 publications, 13%), (Cooley, 2001; National Bioethics Advisory Commission Group, 2001; Nuffield Council on Bioethics Group, 2002; Orentlicher, 2002; Page, 2002; Participants in the Conference on Ethical Aspects of Research in Developing Countries, 2002; Macklin, 2004; Participants in the 2001 conference on ethical aspects of research in developing countries, 2004; Gbadegesin and Wendler, 2006; Emanuel, 2008) and Crouch and Arras (Crouch and Arras, 1998) (9, 12%) (Cooley, 2001; Kottow, 2002; Orentlicher, 2002; Page, 2002; Macklin, 2004; Ballantyne, 2006b; Gbadegesin and Wendler, 2006; Emanuel, 2008; Siegel, 2008). Both these early papers argue that avoiding exploitation requires ensuring PTA and neither reference any theory of exploitation or reflect on the nature of exploitation. Many later authors citing these publications accepted that it was important to avoid exploitation but argued that this did not require ensuring PTA. These all cited Wertheimer, whose theory of exploitation implies their view (Wertheimer, 1999; Wertheimer, 2008); most reflected on the nature of exploitation.

Nearly two-thirds of publications mentioning a **reciprocity** reason (13/21, 62%) mentioned just one combination and either did not reference any publication mentioning a **reciprocity** reason (7/21, 33%) (Gostin, 1991; Harth and Thong, 1995; Hutt, 1998; Lie, 2000; Berkley, 2003; Macpherson, 2004; Carse and Little, 2008) or referenced just one (6/21, 29%) (Chang, 2002; Grady, 2005; Ballantyne, 2006b; Zong, 2008;

Sachs, 2009; Shah *et al.*, 2009). Few of these publications (5/21, 24%, 2 of which shared an author) discussed the formulation and persuasiveness of **reciprocity** reasons (Cooley, 2001; National Bioethics Advisory Commission Group, 2001; Merritt and Grady, 2006; Merritt, 2007; Millum, 2009).

Authors mentioning reasons based on nonmaleficence, rights, autonomy or (with few exceptions) the role of sponsors or researchers, relationships, the purpose of research (Nuffield Council on Bioethics Group, 2002; London, 2005), or distributive justice (Macklin, 2004) failed to acknowledge alternative formulations of the reason or reflect on the reason. None of the 30 **cost** Reason Mentions distinguished the (very different) marginal cost of producing a drug, the cost of discovery/development and gaining approval, and this cost combined with that of failed discovery/development; few distinguished the various cost-components of PTA such as drug, skilled labor, and equipment, (e.g. Gbadegesin and Wendler, 2006). Few publications distinguished the implications of the reasons they mentioned for PTA for participants in the trial *versus* for non-participants, (e.g. Millum, 2009).

## Discussion

Our systematic review found many (36) broad Types of Reason, based on considerations of morality, legality, interests and incentives, and/or practicality, for the views that PTA to the trial drug should, or need not be ensured for participants. It identified a greater variety of reasons compared to all publications including informal philosophy reviews, as confirmed by sensitivity analysis.

While this systematic review does not settle the question of whether PTA to the trial drug should, or need not be ensured to trial participants, it has various direct and indirect uses for decision-makers such as policymakers, regulators, Institutional Review Boards (Research Ethics Committees) and designers of research protocols. Its list of reasons (Table 1) is the best guard currently available against failing to identify infrequently published or only inadequately presented reasons that are nonetheless strong. On the one hand, if the publishing world is working well, infrequently published reasons will be a distraction. On the other hand, the most frequently published reasons may simply be the best publicized, perhaps due to conflicts of interest that induce authors to endorse weak reasons and to ignore or reject strong reasons. In the absence of evidence either way, a

systematic review is crucial in that it gives even such reasons an equal voice, prior to identification of the strong ones.

Our finding that the most-endorsed reasons included ones used just for ensuring PTA and others just for the view that PTA need not be ensured provides a salutary warning against considering only reasons that PTA should be ensured, or only reasons that PTA need not be ensured. Given the challenges to locating this particular literature, the list of publications included (Supplementary Figure 1) obviates the need for decision-makers to hire hundreds of hours of skilled labor to locate relevant publications. Furthermore, because our review describes the search and selection process in detail, decision-makers can check that the list is complete with much less effort than we exerted. Our summary of positions taken by individual publications (Supplementary Table 2) may aid decision-makers who are interested in specific publications but who cannot access them or lack the time or analysis skills to extract the reasons endorsed, attitudes taken to these and conclusions drawn.

This systematic review may also aid decision-making indirectly, by identifying research whose results should enable better-grounded decisions. Unlike the included informal reviews, (Glantz *et al.*, 1998; Hutt, 1998; Lie, 2000; National Bioethics Advisory Commission Group, 2001; Chang, 2002; Nuffield Council on Bioethics, 2002; Orentlicher, 2002; Page, 2002; Macklin, 2004; Ashcroft, 2005; Grady, 2005; Ballantyne, 2006a; Carse and Little, 2008; Emanuel, 2008; Lavery, 2008; Zong, 2008; Millum, 2009) this systematic review identifies all the empirical or ethical points of dissent. Its identification of stark differences between publications on matters of fact shows that multi-disciplinary research is urgently needed to understand the costs,<sup>9</sup> feasibility, legality and effects of requiring PTA, and any tendency of PTA offers to potential participants to boost recruitment or to reduce the quality of informed consent.

We consider decision-makers' need for our systematic review strong, on the assumptions that the need for a systematic review increases with the literature's size, the variety of fields or literary genres, the barriers to retrieving and assessing the literature, the differences between the perspectives of decision-makers and those affected by their decisions; and the inconsistency and incompleteness of guidance. Admittedly, a systematic review makes more demands on decision-makers than an informal review, but its advantages justify these demands. The first systematic review of a large reason-based literature and the first of how reasons were used, this systematic review comprises a starting-point for future

systematic reviews of reasons relevant to decision-makers.

This systematic review has further implications for policymaking. It suggests the need to scrutinize key guidance documents that assume that avoiding exploitation requires ensuring PTA, (CIOMS, 2002) because it shows that the mature literature rejected the view that avoiding exploitation requires PTA, e.g. (Brody, 2002; Orentlicher, 2002; Participants in the Conference on Ethical Aspects of Research in Developing Countries, 2002; Lavery, 2004; Participants in the 2001 conference on ethical aspects of research in developing countries, 2004; Ballantyne, 2005; Ballantyne, 2006a; Carse and Little, 2008; Emanuel, 2008; Siegel, 2008). Moreover, various findings suggest that, for practical purposes, decision-procedures will be needed to set guidelines on PTA (Daniels, 2008), because authors may fail to reach agreement: (i) The most-endorsed reasons included ones used just for ensuring PTA, and others used just for the view that PTA need not be ensured, suggesting that disagreement will persist; further discussion is needed, however, to determine if disagreement is intractable. (ii) Some publications (14, 19%) expressed no view about any PTA-related obligation. (iii) Like some prominent instruments, (UNAIDS Group, 2000; National Bioethics Advisory Commission Group, 2001; CIOMS, 2002; World Medical Association, 2008; 45CFR46, revised 2009) some publications claiming PTA should sometimes or always be provided (25, 45%) did not specify an agent obliged.

The systematic review is of interest also to philosophers who seek to understand whether PTA should, or need not be ensured. First, it reduces the chance that they, as well as decision-makers, will fail to identify the strong reasons and their implications for ensuring PTA. Second, the systematic review aids the identification of reasons relevant to determining whether there are obligations, such as ensuring PTA to trial results (Fernandez *et al.*, 2003), providing ART to participants who seroconvert in HIV vaccine trials (Berkley, 2003; Slack *et al.*, 2005), or providing participants with care for non-trial conditions<sup>10</sup> (Richardson and Belsky, 2004; Richardson, 2007). Third, its identification of inter-publication differences in the naming, formulation and implications of moral reasons suggests that conceptual research is needed. For example, the differences identified in authors' use of terms for concepts such as exploitation and reciprocity suggests that research is needed on how to distinguish such concepts. This systematic review should facilitate this task, in that it presents a list of very finely individuated reasons, and so simplifies the task into one of deciding which of these to merge. Last, it

raises the question of whether publications' focus on exploitation is justified or is a serendipitous result of the focus of much-referenced publications, guidelines and reports (CIOMS, 1982; CIOMS, 1983; CIOMS, 1991; CIOMS, 1993; Crouch and Arras, 1998; Glantz *et al.*, 1998; National Bioethics Advisory Commission Group, 2001; CIOMS, 2002). This focus differs from that of participants whose views are reported in the limited empirical literature (Kass and Hyder, 2002; Shaffer *et al.*, 2006; Sofaer *et al.*, 2009). Such conceptual research may also inform policy.

## Quality

Decision-makers will need a distillation of the best reasons and their implications, and guidance on how to weight reasons, neither of which this systematic review provides. There is need for research to construct a suitable measure of quality and determine how best to distil. For the reasons given above, distillation should occur only after a systematic review such as this one has captured all the published reasons and how they have been used. The systematic review remains an essential ingredient of decision-makers' brief for the reasons above and because of decision-makers' need to check the distillation and its legitimacy.

While we did not collect data on the quality of reasons, our impressions suggest scope for improvement. A small number of publications seemed excellent e.g. (Merritt and Grady, 2006; Lavery, 2008). However, the authors of many interpretations of reasons did not express awareness of some or any interpretations. Some reasons were presented unclearly and many were discussed only briefly or not at all. There has been minimal or no influence on the PTA literature of analyses of social or distributive justice, autonomy or just health care (Dworkin, 2000; Daniels, 2008) or distinctions in economics between types of cost. Some publications appear unaware of theories of exploitation such as (Wertheimer, 1999; Wertheimer, 2008). The three most frequently-referenced instruments require PTA sometimes, (CIOMS, 1982; CIOMS, 1983; CIOMS, 1993; National Bioethics Advisory Commission Group, 2001; CIOMS, 2002; Nuffield Council on Bioethics Group, 2002) yet others impose more demanding obligations (The European Group on Ethics in Science and New Technologies to the European Commission, 2003). Differences in instruments referenced may explain why some (11) **legality** Reason Mentions were used for the view that PTA should be ensured and others (18) for the view that PTA need not

be ensured. While some inter-publication differences regarding the interpretation, implications or persuasiveness of **exploitation**, **reciprocity**, **role** and **responsiveness** appeared grounded in awareness of different interpretations of reasons or their implications, we cannot rule out that other differences are due to lack of imagination compounded by ignorance of relevant literature. We believe that, in general, systematic review of reasons will improve authors' awareness of the need to consider reasons' alternative interpretations and implications.

Furthermore, many publications omitted to indicate the strength of reasons relative to that of other reasons or to establishing the conclusion in the absence of defeating reasons. Some reasoning appeared invalid. For example, some reasons why PTA need not be ensured showed, at most, why *specific agents*, e.g. sponsors, need not ensure PTA.

No included publication described its search, let alone a reproducible, exhaustive one (McCullough *et al.*, 2004). Some variation in publications' number of narrow reasons mentioned (range: 1–67) was justified: one excellent publication scrutinized one reason, explicitly stating there may be other reasons it would not consider (Merritt and Grady, 2006). Yet, other publications asserted conclusions based on inadequate discussion of fewer reasons than had at the relevant time been published, e.g. (King, 1997; Brody, 2002; Kottow, 2002; Basu *et al.*, 2006; Benatar and Fleischer, 2007).

## Recommendations

We recommend that authors be aware of a broader range of relevant literature, including regulations, guidelines and recommendation-containing reports, and that they acknowledge when insufficient evidence limits the strength of factual reasons regarding e.g. cost (Guyatt *et al.*, 2008). Authors should carefully consider and state each reason's implications, if any, for participants versus non-participants (Millum, 2009) and for whether it requires PTA in particular or, rather, a package of possible benefits that need not include PTA, (Participants in the 2001 conference on ethical aspects of research in developing countries, 2004) and also any all-things considered conclusion. Further research should address which inter-publication differences are legitimate. As existing comparative legal analyses are of small samples of instruments, (Nuffield Council on Bioethics Group, 1999; National Bioethics Advisory Commission Group, 2001; Macklin, 2004; Lavery, 2008; Zong, 2008) we recommend the

examination of a larger sample. The field would benefit from a book-length, interdisciplinary discussion. Implementing these recommendations may increase inter-publication agreement and improve PTA policy.

## Limitations

We did not assess quality because the methodology of quality assessment poses substantial challenges and has yet to be developed. However, in order to answer our secondary research question on how reasons have been used, we did collect data on whether Reason Mentions referenced appropriately. Unfortunately, such data is inadequate even as a partial indicator of quality: possibly, lack of an appropriate reference is in some genres not an indicator of low quality, as our finding that some informal reviews written by prominent authors give few or no references (Ashcroft, 2005) may suggest. Furthermore, it was conceptually and practically difficult to decide when a reason was original (and thus to conclude that no reference was necessary) and, in some cases, also to decide when a reference was appropriate. The data nonetheless gave some indication of authors' breadth of awareness of relevant literature and guidelines.

A further limitation of this systematic review is that it may fail to capture the perspectives of participants, industry, regulators and some lawyers: our particular inclusion conditions were not met by empirical literature reporting participants' views, industry grey literature, laws, guidelines, cases or commentaries. Nonetheless, some of their reasons were captured vicariously through publications' attribution of reasons to other parties or when publications reasoned e.g. that PTA should be provided because guidelines so require. Our systematic review also gives some indication of instruments' influence on the literature.

We may have missed some qualifying publications. Databases' index terms did not include *post-trial access* or synonym, and were applied inconsistently. Although we searched for and within books on research ethics, we did not search systematically for these. Databases did not provide abstracts for some publications, which we screened based on title and keywords alone. Although we did not exclude publications based on language, our database selection created bias in favor of English-language publications and this may explain why all the publications included were written in English. We contacted some, but not all authors of qualifying publications for help in identifying others. Neither author was blinded as to publications' identity:

one (N.S.) knew much literature too well to be blinded. Selection of publications was consensus-based; possibly, independent scoring, or coding by others, might select different publications (McCullough *et al.*, 2007). Our operational definition of *informal philosophy review* did not capture some publications that seemed to be informal philosophy reviews. However, an operational definition was necessary; ours was justified (the operational definition and justification are available on request from the corresponding author); and we rest our finding about the relative comprehensiveness of our systematic review on the maximum number of reasons mentioned by any publication, as calculated in the sensitivity analysis, not on the average number of reasons given by informal philosophy reviews.

There were also limitations to our assignment of Reason Mentions to Reason Types. (1) Because we decided to assign Reason Mentions to Reason Types based not just on the words used to express the reasons, but also on the meaning of those words, it is possible that different reviewers would make different assignments. Our analysis is nonetheless valid because reviewers assigned types independently, checked for discrepancies, and were able to resolve all discrepancies. (2) Differences in referencing conventions and with establishing originality made it difficult to decide when an appropriate reference was (not) given where one was necessary.

Our sum of Types of Reasons had additional limitations. (1) Types could be made narrower or broader; some broad types cover diverse narrow types; and there may be similarly good reasons to class a narrow Type of Reason under different broad types. In response: (i) our sensitivity analysis shows that our systematic review mentions a much greater variety of reasons than any publication included, whether Types of Reason are individuated narrowly or broadly. (ii) Narrowly-individuated narrow Types of Reason are meaningful and homogenous and their assignment to broad types was obvious and well-justified. (iii) When deciding how broad the broad Types of Reason should be, we faced a trade-off between having few but heterogeneous broad types versus impractically many, but more natural broad types. Given the practical aims of this article, we allowed some heterogeneity. (2) We summed the number of Reason Mentions that were used to support slightly different types of conclusions. However, we gave qualitative results where more appropriate. We note also that classical systematic reviews face the analogous problem that the studies reviewed addressed slightly different research questions. (3) We did not exclude, from the sum of Reason Mentions,

reasons mentioned by the same author in different included publications. However, removal of such repeated reasons would make little difference to the sum. (4) The difference between the number of narrow Types of Reason identified by our systematic review and the most comprehensive informal review is slightly exaggerated because our systematic review used some narrow types such as **unspecified logistical obstacles**. However, there were only 12 unspecified types (0.5% of the narrow Types of Reason).

This systematic review presented data on the frequency with which Types of Reason were mentioned in order to identify reasons on which attention has focused, and neglected reasons. However, this data should be presented with caution. Research is needed to determine if decision-makers assume that the more common reasons are the stronger ones; if so, authors of future systematic reviews targeted at decision-makers should consider not presenting data on how frequently (or infrequently) reasons are mentioned.<sup>11</sup>

## Supplementary Data

Supplementary data are available at *PHE* Online.

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## Conflict of Interest

N.S. is currently collaborating with the UK's National Research Ethics Service to write its guidance on post-trial access. N.S. owns shares in pharmaceutical companies with a total value of under \$600 on 13 July 2010.

## Notes

1. The terms are listed in a table available from the corresponding author.
2. In this sentence as elsewhere, counts of reasons exclude repeats of reasons in the same publication.
3. Publications agreeing, that a fair level of benefits may but need not include PTA, with the latter view were on average more recent.
4. Sometimes or always.
5. Endorsed >10 times and endorsed by >95% of commentators that mentioned the reason.
6. >22 Reason Mentions.
7. References were counted only if they were references given when mentioning reasons why PTA should, or need not be ensured.
8. Publications that referenced Glantz *et al.*, but not when mentioning a qualifying reason, are excluded from this count.
9. This will require the identification an appropriate, measurable concept of cost, as well as empirical research.
10. A result tangential to this article is that, for the above reasons, systematic reviews may be an important research tool for philosophical bioethicists. However, systematic reviews of philosophical literature pose various conceptual and methodological challenges (McCullough *et al.*, 2007) (see also p. [complete once paper has been type-set]).
11. The issue of whether to include frequency data is discussed in greater length in (Sofaer and Strech, 2011; Strech and Sofaer, How to write a systematic review of reasons, manuscript.)

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## Appendix A

**Table A1.** Search terms and strings

Database	Search string
Medline	<p>Focus on ethics:            (("Ethics"[Mesh] OR "Human Rights"[Mesh] OR "ethics"[Subheading])) AND            (((((((("Health Services Accessibility"[Mesh]) OR ("Continuity of Patient            Care"[Mesh]))) OR ("Drugs, Investigational/supply and distribution"[Mesh])) OR            ((post-trial provision))) OR ((post-trial obligations))) OR ((post-trial access))) OR            ((post-trial benefits))) OR ((post-trial responsibility))) OR ((follow-up)))) AND            (((("Clinical Trials as Topic"[Mesh]) OR ("Biomedical research"[Mesh])) OR            ("Human experimentation"[Mesh]))))</p> <p>Focus on developing countries:            (((("Vulnerable Populations"[MeSH Terms]) OR ("Developing            Countries"[Mesh]))) AND (((("Patient Advocacy"[MeSH Terms]) OR            ("Ethics"[Mesh] OR "Human Rights"[Mesh] OR "ethics"[Subheading])))) AND            (((((((("clinical trials as topic"[Mesh]) OR ("Human Experimentation"[Mesh]))            OR ("Biomedical Research"[MeSH Terms])) OR ("Drugs, Investigational/supply            and distribution"[Mesh]))) OR ("Research/organization and            administration"[Mesh])))</p> <p>Disjunction of terms used to refer to PTA in included publications: <sup>a</sup>            "post-trial provision" or "post-trial obligation" or "post-trial obligations" or            "post-trial access" or "post-trial access" or "post-trial benefit" or "post-trial benefits"            or "post-trial responsibility" or "post-trial responsibilities" or "prior agreements"</p>
Westlaw	"post-trial access"
JSTOR	"post-trial obligation"
Scidev.net	"post-trial responsibility"
LocatorPlus	"post-trial obligations"
Euroethics	"reasonable availability" "post-trial provision" "Post-trial follow-up" "after the trial" and research and drug
ETHXweb	post-trial
Ethos-Beta Electronic Theses Online Service	post-trial (any field) and (ethics (any field) or bioethics (any field))
WorldCat Dissertations	"post-trial access" (keyword) "after research" (keyword) "post-trial" (keyword) exploitation and "clinical research"

<sup>a</sup>These terms also included *post-trial followup*, *after participation* or *aftercare*, but we excluded them from the search string because the resulting searches were insufficiently specific.