More considerations on post-trial obligations in the Declaration of Helsinki 2013

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Abstract

The problem of transitioning research participants to the appropriate health care when the study finishes is a global problem. The publication of a new version of the Declaration of Helsinki and its public discussion is a great opportunity to discuss it. My interpretation of the Declaration of Helsinki 2013 identifies two different types of post-trial obligations, namely, (1) access to care and (2) access to information after research. The intended beneficiaries of these obligations are individual participants of research studies. The Declaration identifies the sponsors, researchers and host country governments as the main agents responsible for complying with the post-trial obligations mentioned above. To justify this interpretation of the types, agents and beneficiaries of post-trial obligations, I first introduce a tentative classification of post-trial obligations. I then make a brief conceptual reconstruction of formulations of post-trial obligations in earlier versions of the Declaration and revise its main critiques. Finally I advance a critical analysis of the new formulation of post-trial obligations based on the discussion in the previous sections.

Keywords: post-trial access ethics, health care after research, right to health, information after research

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1. Introduction

The problem of transitioning research participants to the appropriate health care is a global problem.[1] It is not only a problem in low and middle income countries[2] but also affects a significant part of the population of high income countries. For example, in the US it primarily affects people uninsured or underinsured who participate in clinical research.[3] In the UK, it may affect ex-participants when the study intervention is not available in the National Health System (NHS) after the study is concluded, for example in cases of studies for rare genetic disordes[4] or "last-chance-drugs"[5]. However, as Sofaer et al. state, many researchers are unclear about their obligations after research and many research ethics committees (hereinafter RECs) do not know what to require of researchers.[6] Sofaer et al. also note that this situation may lead to a number of negative consequences, including lack of appropriate care for former research participants, unplanned costs to the health system and the loss of confidence in the research system.[7] To these negative consequences, there should be added the additional legal costs and the otherwise unnecessary delays in the provision of health care to the ex-participants generated by the litigation of former participants' claims to their right to health.[8]

These are sufficient reasons for trying to establish a better grasp of post-trial obligations of researchers, sponsors and other stakeholders involved in human health research.

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[1] National Research Ethics Service (NRES) (2012), "Care after research: a framework for NHS RECs", Health Research Authority (HRA), http://www.nres.nhs.uk/applications/guidance/guidance-and-good-practice/?1307152_entryid62=148568 , version 19 December. Spanish version, Sofaer, N., Lewis, P. and Davies, H. (Authors); Ignacio Mastroleo (trans.) (2012) " Atención después de la investigación: un marco para los comités de ética de investigación del National Health Service (NHS) (borrador versión 8.0)" Perspectivas Bioeticas, vol. 17, no. 33, pp. 47-70, http://philpapers.org/rec/SOFADD

[2] Cleaton-Jones, PE (1997) "An ethical dilemma. Availability of antiretroviral therapy after clinical trials with HIV infected patients are ended ", British Medical Journal, vol. 314, no. 7084, p. 887-888, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2126219/pdf/9093104.pdf ; Petryna, A. (2009) *When experiments travel: clinical trials and the search for human subjects overall,* Princeton: Princeton University Press, pp. 139-185.

[3] Sofaer, N., Lewis, P. and Davies, H. (2013) "Forthcoming practical framework for ethics committees on post-trial access to the trial intervention and healthcare", Journal of medical ethics, http://jme.bmj.com/content/early/2013/05/04/medethics -2013-101398.full.pdf + html; Kolata, G. and Eichenwald, K. (1999, June 22)."Stopgap medicine, a special report: for the uninsured, drug trials are health care", *New York Times* , http://www.nytimes.com/1999/06/22/business/stopgap-medicine-a-special-report-for-the-uninsured-drug-trials-are-health-care.html?pagewanted=all&src=pm; Sofaer, N. et al.(2009) "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" Journal of medical ethics, vol. 35, no. 3, pp. 183-188, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3044680/

[4] BBC News (2007, December 24) "Trial volunteers 'left in lurch'" http://news.bbc.co.uk/2/hi/health/7155572.stm

[5] Sofaer et al. (2013), op. cit.

[6] Sofaer et al. (2013), op. cit.

[7] Sofaer et al. (2013), op. cit.

[8] Wang, DWL and Motta Ferraz, OL (2012) "Pharmaceutical companies vs. the state: who is responsible for post-trial provision of drugs in brazil ", Journal of Law, Medicine & Ethics, vol. 4, no. 2, pp. 188-196, http://onlinelibrary.wiley.com/doi/10.1111/j.1748-720X.2012.00657.x/abstract

The publication of a new version of the Declaration of Helsinki (hereinafter DoH) and its current public discussion is an excellent opportunity to work in this direction.

As I argue in this paper, the DoH 2013 introduces two different types of post-trial obligations that can be distinguished by its different objects, namely, access to care after the research and access to information after the research.[9] The intended beneficiaries of these obligations are individual research participants, and the main agents required to comply with post-trial access provisions are sponsors, researchers and governments of host countries. In order to justify this interpretation of the types, the intended agents and beneficiaries of post-trial obligations, I first present a classification of post-trial obligations derived from a qualitative interpretation of the literature of post-trial access ethics. I then make a brief conceptual reconstruction of the formulations of post-trial obligations in previous versions of the DoH, and finally advance a critical analysis of the new formulation of post-trial obligations based on the discussion in the previous sections.

2. Classification of post-trial obligations

In this paper I propose a classification that distinguishes two general types of post-trial obligations that depend on their intended beneficiaries; either individual or collective. When it comes to individual beneficiaries the paradigmatic case is that of the participants in a research study, but it may be other individuals included such as the partner of the participant. In these cases, the main research ethics documents require a REC review of post-trial plans or arrangements that ensure responsible transition to the appropriate care and to disclose this information to potential participants during the informed consent process.[10] When it comes to a collective beneficiary, such as the host society of a research study or a particular community part of that society, the review of the local REC and informed consent from each individual participant are not sufficient because these decisions will affect members of a host society as potential participants of research and not only those actually involved. Therefore, some additional consultation is required with governing bodies of the host society that have the appropriate visibility and legitimacy to make decisions for all potential participant; for example, an agency of health technology assessment, the Ministry of Health and/or a national or regional REC.[11] In addition, I believe that the most appropriate way to address the normative discussion of post-trial obligations towards collective beneficiaries is from the point of view of the reasonable availability requirement and the

[9] For “object of obligation” I understand the following: if Mary promises Mike to take him to dinner, the object of Mary’s obligation is taking Mike to dinner. If Mary lends 100 GBP to Mike, the object of Mike’s obligation is to repay Mary 100 GBP.

[10] NRES (2012), op. cit., CIOMS-WHO (2002) *International Ethical Guidelines for Biomedical Research Involving Human Subjects,* Guideline 10, Spanish translation, http://www .cioms.ch / images / stories / CIOMS / guidelines / pautas_eticas_internacionales.htm ; World Medical Association (WMA) (2013), *Declaration of Helsinki of the WMA: Ethical Principles for Medical Research Involving Human Subjects,* paragraph 33, http:/ / www.wma.net/es/30publications/10policies/b3/index.html

[11] With regard to the lack of legitimacy and visibility of local RECs required to make certain decisions that affect all members of a host society as potential research participants see Katz, J. (1994) "Statement by committee member Jay Katz" in Advisory Committee on Human Radiation Experiments Final Report, http://www.hss.energy.gov/HealthSafety/ohre/roadmap/achre/jay_katz.html

responsiveness requirement to the needs and priorities of the host society. However there are other competing alternative normative frameworks that address this kind of obligations.[12]

However, in this paper I will focus exclusively on post-trial obligations towards individual research participants and will not address post-trial obligations towards collective beneficiaries. I made this choice for two practical reasons. Firstly, because the DoH 2013 addresses its post-trial access provisions as obligations towards individual participants of a research study. Secondly, because the case of post-trial obligations towards individual beneficiaries falls more clearly within the remit and legitimacy of local RECs. This makes the problem of post-trial obligations towards individual research participants more urgent. For example, based on a plausible interpretation of the DoH 2013, a local REC may require researchers of an oncology study to provide a post-trial intervention identified as beneficial in the study to the participants randomized to the placebo arm of a research study (e. g. added immunotherapy to standard therapy for children with high-risk of neuroblastoma)[13] or it may refuse to approve a research protocol that does not include the appropriate post-trial arrangements, as in the case of studies with anti-retrovirals for HIV/AIDS.[14]

With regard to the classification of post-trial obligations towards individual beneficiaries it is useful to distinguish at least another two types that can be clearly identified both in the DoH 2000, 2004, 2008 and in the recent literature post-trial ethics[15], namely, (1) obligations of access to care after research and (2) obligations of access to information after research. In turn, as will be explained in the reconstruction of the next section, it is useful to distinguish at least two subtypes of obligations of access to care after research that are present in the literature, namely (1.1.) the obligation of access to an intervention identified as beneficial in the study and (1.2.) the obligation of access to other appropriate care.

An uninsured research subject from US in a long-term diabetes study intuitively summarizes the concerns on which the first subtype of obligations of care after research

[12] CIOMS-WHO (2002) guideline 10, op. cit.. With regard to the obligations of reasonable availability see Glantz, LH, Annas, George J., Grodin, Michael A. and Mariner, Wendy K. (1998) "Research in Developing Countries: Taking "Benefit" Seriously" The Hastings Center Report, vol. 28, no. 6, pp. 38-42; Emanuel et al. (2008) "Addressing exploitation: reasonable availability versus fair benefits" in Exploitation and developing countries: The ethics of clinical research, Jennifer S. Hawkins and Ezekiel J. Emanuel (eds.), Princeton: Princeton University Press; Mastroleo, I. (2007) "Global Justice and biomedical research: the research required to post the host community," Bioethical Perspectives, year 12, no. 23, pp. 76-9, http://bit.ly/comunidad-anfitriona . With regard to the requirement of responsiveness see London, A. (2008) "Responsiveness to host community health needs" in Emanuel, E., Grady, C., Crouch, R., et al. (Eds.), *The Oxford textbook of clinical research ethics,* pp.737-744, New York: Oxford University Press; Macklin, R. (2011) "The 'Responsiveness Requirement' Defend" in *Post-trial access to trial drugs: Legal, ethical and practical issues,* workshop, http://ptaworkshop.files.wordpress.com/2012/01/responsiveness_requirement_defended.pdf

[13] Unguru, Y., Joffe, S., Fernandez, CV, and Alice, LY. (2013) "Ethical issues for patients-arm control after revelation of benefits of experimental therapy: a framework modeled in neuroblastoma", Journal of Clinical Oncology, vol. 31, no. 5, pp. 641-646, http://www.ncbi.nlm.nih.gov/pubmed/23295797

[14] Cleaton Jones (1997), op. cit..

[15] NRES (2012), op. cit..

are based: “all of a sudden [they] just cut the cord, and you’re off on your own, you know. You come up with the three or four hundred dollars a month to keep this thing or just go ahead and die”.[16] Post-trial access to the study intervention in long-term diabetes study may be a fair example of an intervention identified as beneficial in the study. Anti-retrovirals in research studies testing a preventive intervention, such as preventive vaccines or microbicides, is the exemplary case of access to other appropriate care in post-trial ethics literature.[17] Finally, antibiotic treatment for opportunistic diseases (e.g. trimethoprim-sulfamethoxazol; trade name: Bactrim) could be either an example of access to a beneficial study intervention or appropriate care after research in contemporary research studies of anti-retrovirals for HIV/AIDS depending on the original desing of the study.[18]

In relation to the obligations of access to information after research, although the paradigmatic example is access to study results (either aggregated or individual), a relevant example in the literature is also access to information on adverse effects. In a series of focus groups on “subjects’ views of obligations to ensure post-trial access to drugs, care, and information”, several research participants from US complained about learning of adverse effects only from the media: “[...] these people took our drugs for us to see what was going on, and a year down the road we found out, oh, by the way, these might kill you. Hey, maybe we ought to call them and let them know!”.[19] Other participants pointed out that if the auto companies recalled their cars from market, the obligation of reporting adverse effects directly to the former participants seemed appropriate, even several years after the study had ended.[20]

The following table summarizes the classification of post-trial obligations to research participants presented above:

Post-trial obligations towards individual research participants	
1. Obligations of access to care after research	
1.1. Obligation of access to an intervention identified as beneficial in the study	1.2. Obligation of access to other appropriate care
2. Obligations of access to information after research	

Table 1. Classification of post-trial obligations towards individual participants

[16] Sofaer et al. (2009), op. cit., p.185.
[17] Schuklenk, U. (2001) “Helsinki Declaration revisions”, Indian Journal of Medical Ethics, vol. 9, no. 1 http://web.archive.org/web/20120307011426/http://www.ijme.in/091re029.htm
[18] Biehl, J. G. (2007) “Pharmaceuticalization: AIDS treatment and global health politics”, Anthropological Quarterly, vol. 80, no. 4, pp. 1083-1126.
[19] Sofaer et al. (2009), op. cit., p. 185.
[20] Sofaer et al. (2009), op. cit., p. 185.

A problem in DoH 2013 that motivated me to write this paper is that the phrase "access to other appropriate care" has disappeared from the formulation of post-trial obligations. This could be a significant loss. As I will argue, the obligation of access to other appropriate care cannot be inferred only from the concept of the obligation of access to beneficial intervention identified in the study, because it may be the case that a drug, treatment or essential healthcare service not included "in the study" is necessary to ensure responsible transition to the appropriate healthcare of research participants.[21]

In the next section, I will present a brief conceptual reconstruction of the formulations of post-trial obligations in the different versions of the DoH (section 3). I use my classification of post-trial obligations towards participants as an analytical tool for such reconstruction. I present this reconstruction in the hope that the revision of previous formulations of post-trial obligations in DoH will provide a common ground for discussion of the new formulation in DoH 2013.

3 Conceptual reconstruction of post-trial obligations in DoH 2000-2008

Before starting with the conceptual reconstruction I have to admit that in this paper I will not try to be exhaustive with respect to the many problems surrounding post-trial obligations.[22] In particular I will not go into details of plans or mechanisms for post-trial access[23], the review of the reasons given in the literature for or against access to care after research[24], or international regulations and laws dealing with post-trial access.[25]

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[21] I take the concept "responsible transition" from Christine Grady.

[22] An introduction to the topic meant for a wider audience can be found in Mastroleo, I. (forthcoming) "Introducción al problema de la continuidad del tratamiento beneficioso para los sujetos de investigación" en Jorge Alberto Álvarez Díaz (ed.) *Ensayos sobre ética de la salud*, Universidad Autónoma Metropolitana - Unidad Xochimilco, http://philpapers.org/archive/MASIAP

[23] Some of these mechanisms may be, for example: (1) researchers and their sponsors provide [X] using research funds or other sources, (2) researchers and sponsors pay for private insurance, contribute to a fund to pay for treatment of participants, or contribute to the costs of treatment of participants in governmental programs, (3) study participants are enrolled in more trials (treatment), (4) Participants are referred to the government health services that provide [X], possibly with the support and supervision of the researchers and / or sponsors.[...], (5) any combination of the above mechanisms. For example, sponsors may agree to provide [X] over a period of time and then the national governments may take over. These mechanism are taken from Millum, J. (2011) "Post-trial access to antiretrovirals: who owes what to whom?" Bioethics, vol. 25, no. 3, pp.. 145-154, http://www.ncbi.nlm.nih.gov/pubmed/19594728 . Millum (2011) also provides specific literature on particular cases where these mechanisms were tested. For a particular example of a combined mechanism of healthcare provision after research see also Bloch, C. (2009) "Circular No. 9 of the Ministry of Health of the Nation", Department of AIDS and STD, Ministry of Health of the Argentine Republic, http://es.scribd.com/doc/74882826/Circular-No-9-2009-SIDA-Protocolos-Bloch

[24] For a simple version of the reasons for and against post-trial access to the study intervention see NRES (2012), op. cit., pp.54-59. This list is based on the systematic review of these reasons of Sofaer, N and Strech, D. (2011) "Reasons why post-trial access to trial drugs should, or need not be ensured to research participants: a systematic review", Public Health Ethics, vol. 4, no. 2, pp. 160-184, http://phe.oxfordjournals.org/content/4/2/160.full.pdf+html

[25] "Guidelines, legislation and position statements from other bodies" in NRES (2012), op. cit .; Dainesi, SM and Goldbaum, M. (2011) "Fornecimento após or investigational drug clinical research fim da - da Revisão literature and give Diretrizes nacionais and internacionais" Revista da Associação Brasileira

However, I hope that the respective references to the literature will be relevant to anyone interested in these issues.

My objective in this paper is to show the development of the formulations of post-trial obligations in DoH, using the classification presented above as an analytical tool for interpretation. Even if contested and certainly not definitive, my interpretation can be a useful analytical tool for other researchers and decision makers in the multidisciplinary field of research. For instance, they might use this conceptual analysis to cope with the intricacies of the language of DoH, design ethnographic research to test the limits of the classification in practice or to build their own interpretation based on my classification.[26] That being said, the first formulation of what I considered above (1) obligations of access to care after research appears in the DoH 2000:

> 30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study (WMA 2000).

This formulation of the post-trial obligations only refers to a single type of obligation of access to care after research, the one we called in table 1 (1.1.) obligation of access to an intervention identified as beneficial in the study. However, DoH 2000 makes no mention either of (1.2.) the obligation of access to other appropriate care or to (2) obligations of access to information after research.

At the time, this first formulation of post-trial obligations was regarded as an innovation in the protection of individual participants but was also criticized for not taking into account access to other appropriate care in trials of HIV vaccines; for example access to anti-retrovirals. As Schuklenck states in a paper written in 2001:

> The revised version of the Declaration includes a note on post-trial availability of drugs to the trial subjects: [...]. If implemented by trial sponsors, it means that those who made the development and testing of a new drug possible, because they volunteered as research subjects, will be provided any drug successfully tested. Unfortunately, this will not help prevent deaths in preventive vaccine trials. For example, people infected during HIV vaccine trials will not be provided post-trial with the best proven AIDS treatments. Ongoing UNAIDS-backed trials accept HIV infections of trial participants (for instance those resulting from a research subject's therapeutic misconception) as inevitable, but refuse to provide to these HIV-infected trial subjects essential AIDS medication. The revised version of the Declaration is silent on this matter. Since trial subjects need only be provided with drugs “identified by the study”, and preventive vaccine trials will not identify treatments, the Declaration does not require that subjects infected during a

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Health, vol. 57, no. 6, pp. 710-716, http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0104-42302011000600021

[26] I thank Patricia Kingori and Salla Sariola for pointing me out some of the uses my classification may have.

> vaccine trial be provided essential medication. The consequences will be particularly disastrous for research subjects affected by AIDS.[27]

What Schuklenk states can be interpreted as a problem with the formulation of the DoH 2000 that incorrectly limits obligations of access to care after research to only a subtype, namely, access to beneficial interventions "identified by the study". This is a problem because it could be argued that the scope of obligations of access to care after research is wider. Also, that its width corresponds with the human right of research participants to access essential healthcare even when it is not "identified by the study" as with anti-retrovirals in the case of preventive HIV vaccine trials. It could be argued that Schukelnk position and my classification of post-trial obligations assume that there is a justifcatory relationship between access to essential levels of the right to health and post-trial obligations. This is not shared by everyone working on research ethics. However, this will be discussed in more detail in the next section of this paper.[28]

In response to this kind of criticism and controversy generated, the WMA introduced a note of clarification on the formulation of paragraph 30 in 2004, in which new conceptual elements were presented:

> Note of clarification on paragraph 30 of the WMA Declaration of Helsinki. The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review (WMA 2004).

Among the new elements, the formulation of post-trial obligations in the note of clarification on paragraph 30 introduces the concept of "post-trial access" for the first time within the Declaration. Also, it includes for the first time the operational obligation that arrangements concerning post-trial obligations must be described in the study protocol for REC consideration and revision. With reference to the types of post-trial obligations, the note includes a new requirement in response to the arguments mentioned above; namely, what I have identified in my classification as (1.2.) obligation of access to other appropriate care. However, there is still no mention in DoH 2004 of (2) obligations of access to information after research. Finally, it is necessary to highlight the easing of the language in which post-trial obligations are expressed from "be assured of" in DoH 2000 to "identify" in 2004.[29]

WMA notes of clarification on paragraph 30 and on paragraph 29 in 2002 concerning the use of placebo were both harshly criticized in what was called "The Battle of

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[27] Schuklenk, U. (2001) "Helsinki Declaration revisions", Indian Journal of Medical Ethics, vol. 9, no. 1 http://web.archive.org/web/20120307011426/http://www.ijme.in/091re029.htm

[28] For a more detailed explanation of the relationship between post-trial obligations and the right to health see Mastroleo, I. (2012a) "The requirement of continuity of beneficial treatment to research subjects," pp. 147-226, Ph.D. thesis, University of Buenos Aires, https://bitly.com/NNc5nB

[29] I thank Florencia Luna for pointing out this to me.

Helsinki".[30] After this clash of ethical views, a new version of the DoH was published in 2008:

> 33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits (WMA 2008).

The main improvements in this new formulation are the following. It mentions for the first time that participants are entitled to be informed of "outcomes" leading to what I have identified as a case of (2) obligation of access to information after research. It simplifies the construction of "prophylactic, diagnostic and therapeutic procedures" with the term "intervention". It retains access to interventions identified as beneficial in the study and to other appropriate care, which were present already in the note of clarification in 2004 and which are both considered necessary to ensure access to essential healthcare after research for all participants.

However this new formulation of post-trial obligations has also received justified criticism.[31] The most important is that it presents post-trial obligations in terms of the entitlement of participants to benefit sharing and the inclusion for the first time in the DoH of the concept of access to other appropriate benefits.

Both modifications can be read as inspired by the "fair benefits approach"[32]; an ethical framework primarily developed by a group of members of the Department of Bioethics of the NIH Clinical Center.

The most obvious consequence of formulating post-trial obligations in terms of entitlements is to leave undetermined which agents are responsible for meeting the obligations for the right to "share any benefits". But this was already a problem in the formulations of DoH 2000 and 2004. The more subtle implication is that the 2008 formulation was engineered to dilute the requirement of provision of appropriate healthcare after research to the former participants present in DoH 2000 and 2004, at least under the intended interpretation of the fair benefits approach. This is possible since paragraph 33 puts at the same level access to care after research with access to "other appropriate benefits", neither granting any special status to access to healthcare

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[30] Wolinsky, H. (2006) "The Battle of Helsinki" EMBO reports, vol. 7, no. 7 pp. 670-672, http://www.nature.com/embor/journal/v7/n7/full/7400743.html

[31] Mastroleo, I. (2008) "El principio de acceso posinvestigación en la revisión 2008 de la Declaración de Helsinki" Perspectivas Bioeticas, vol. 13, no. 24-25, pp. 140-157, http://bit.ly/acceso-helsinki-2008 ; Zong, Z. (2008) "Should post-trial provision of beneficial experimental interventions be mandatory in developing countries?", Journal of Medical Ethics, vol. 34, no. 3, pp.. 188-192, http://jme.bmj.com/content/34/3/188.full.pdf

[32] The participants in the 2001 conference on ethical aspects of research in developing countries (hereinafter Emanuel et al.) (2002). "Fair benefits for research in developing countries", Science, vol. 298, pp. 2133-2134, http://www.sciencemag.org/content/298/5601/2133.summary ; Emanuel et al. (2004) "Moral standards for research in developing countries from 'reasonable availability' to 'fair benefits'", The Hastings Center Report, vol. 34, no. 3, pp.. 17-27, http://www.ncbi.nlm.nih.gov/pubmed/15281723 ; Emanuel et al.(2008) "Addressing exploitation: reasonable availability versus fair benefits" in Exploitation and developing countries: The ethics of clinical research, Jennifer S. Hawkins and Ezekiel J. Emanuel (eds.), Princeton: Princeton University Press.

nor making any specific distinction between these categories. So, if access to care after research is just another "fair benefit", there is no independent moral obligation to provide care after research to the research participants beyond what the relevant parties may agree.

The ethical approach of Emanuel et al. assumes that the level of fair benefits must be calculated by a negotiation among the participants, the community and the sponsor; focusing on "a broad range of burdens and benefits [...] rather than making any one type of benefit into a moral litmus test" (i.e. access to essential healthcare after research).[33] Among the "broad range of benefits" the authors include the development of capabilities in research infrastructure, training of researchers and improving training for ethics committee members as they indirectly benefit the participants and, therefore, should fall within the balance of the "fair benefits" received. If we recall the case of the uninsured American participant in a long-term diabetes study presented in the first section, it would be morally valid for researchers and sponsors within the fair benefits approach to "cut the rope" (interrupt the intervention identified as beneficial in the study) based on the reasoning that the participant has received "fair benefits" during the study, and that he and the host country authorities have consented to conduct the research. Again, this is possible because the main thesis of Emanuel et al. is that post-trial access to the interventions identified as beneficial or other appropriate care that participants may still need should not function as a moral requirement or limit for conducting research.[34]

Perhaps Emanuel et al.'s normative commitments could be made more clear by showing that the interpretation of fairness behind the fair benefits approach is one of "ideal market transactions":

> "a fair distribution of benefits at the micro-level is based on the level of benefits that would occur in a market transaction devoid of fraud, deception, or force in which the parties have full information. While this is always idealized—in just the way economic theory is idealized—it is the powerful ideal informing the notion of fairness of micro-level transactions. Importantly, this notion of fairness is also relative; it is based on comparisons to the level of benefits for other parties interacting in similar circumstances. Just as the fair price in markets is based on comparability, so too is the determination of fair benefits (to avoid exploitation) based on comparability".[35]

In my view, the main problem with the fair benefits approach is that market fairness is the only kind of fairness that takes into account. As noted by Reidar Lie, to determine the fairness of research studies is not analogous to determining the fair price of a product or service through negotiation between the parties, as you are supposed to do in a flea market or when bargaining with a plumber. At the very least, the unjust background conditions of the participants and the relevance of the knowledge for the society should also be considered.[36] To this critique, you can add London's arguments

[33] Emanuel et al (2004) op. cit., p. 26.
[34] Emanuel et al. (2008), op. cit., p. 299.
[35] Emanuel et al. (2008), op. cit., p. 294.
[36] Lie, RK (2010) "The fair benefit approach revisited," Hastings Center Report, vol. 40, no. 4, p. 3, http://www.thehastingscenter.org/Publications/HCR/Detail.aspx?id=4765

that Emanuel et al. sustain a minimalist interpretation of ethical principles with possibly severe consequences.[37]

My personal disagreement with the fair benefit approach interpretation of post-trial obligations is that healthcare of former participants is considered as a benefit at the same level as the training of REC members and researchers, and improving infrastructure. On one hand, training REC members and researchers or improving clinical facilities are necessary costs in order to produce generalizable knowledge. So it seems unfair to charge these costs into the actual participants account instead of into the account of all the potential beneficiaries of the knowledge generated. On the other hand, healthcare (either a study intervention or other appropriate care after research) is a good that has priority over other possible benefits since it affects the exercise of the basic moral capabilities of ex-participants. The principle of fair equality of opportunity tries to capture this requiring an essential range of right to health provisions to any democratic society.[38] Furthermore, the main documents on human rights require an essential level of right to health to both democratic and non-democratic countries.[39] At this point two clarifications may be useful. Firstly, that essential level of right to health is wider than access to access to essential healthcare services or treatments. Secondly, That grounding post-trial obligations in ex participants right to health does not deny, as happens in other basic principles of research ethics, that there could be ethically justified exceptions to post-trial obligations. It neither denies that the right to health, as most human rights, can only be fully achieved progressively. Nevertheless, accepting exceptions and the principle of progressive realization of human rights does not render the right to health meaningless or void. Progressive realization implies core obligation to provide essential levels of the right to health, anti-discriminatory measures targeting vulnerable groups, and rules out deliberately regressive measures.[40]

Finally, the category of “other appropriate benefits” in the DoH 2008 formulation is so loose that, in practice, it can be used not only by crooked researchers but also by authoritarian or corrupt governments to advance their own agendas instead of the interest of their communities; for instance trading the use of potential research subjects

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[37] London, A. (2005) “Justice and the human development approach to international research”, Hastings Center Report, vol. 35, no. 1, pp.. 24-37, http://repository.cmu.edu/cgi/viewcontent.cgi?article=1399&context=philosophy . London also states that the interpretation of ethical principles advocated by the fair benefits approach is consistent with a state of affairs where the middle and low income countries free to “work” in research that promotes the health interests of high-income countries, while research sponsors use their considerable bargaining power to capture most of the benefits generated by the collaboration in London, A. and Zollman, K. (2010) “Research at the auction block: problems for the fair benefits approach to international research”, Hastings Center Report, vol. 40, no. 4, pp.. 34-45, http://repository.cmu.edu/cgi/viewcontent.cgi?article=1397&context=philosophy

[38] For the first statement see Daniels who extends Rawls theory of justice to the right to health in Daniels, Norman (2008) *Just health: meeting health needs fairly*, Cambridge: Cambridge University Press. I try to throughout my PhD dissertation and I called it the model of democratic reciprocity. See especially Mastroleo (2012a), op. cit., pp. 145-226.

[39] International Covenant on Economic, Social and Cultural Rights (ICESCR) (1966) "UN Treaty Collection: International Covenant on Economic, Social and Cultural Rights", https://treaties.un.org/Pages/ViewDetails.aspx?src=TREATY&mtdsg_no=IV-3&chapter=4&lang=en

[40] I would like to thank Dev Kevat for his discussing right to health and post-trial obligations with me.

for a soccer stadium to gain wider popularity. Or even technology and infrastructure for military purposes. So, as NBAC states, making post-trial benefits "responsive to the health needs of the participants provides an additional way to ensure that research participants are exploited" neither by helicopter research nor by governments of host countries.[41]

Perhaps someone may think that this criticism of the fair benefits approach is aspirational. However, there are good clinical practice guidelines and regulations of post-trial obligations consistent with this interpretation of the right to health, and they have been incorporated into the research ethics monitoring system of different democratic societies such as Argentina, Brazil and the UK.[42] Unfortunately, to my knowledge, there is neither available a systematic survey of compliance of post-trial obligations in these or other countries nor a review of post-trial access arrangements required by RECs based on these good clinical practice guidelines and regulations inspired by DoH.

Finally, someone may object that grounding post-trial obligations on the right of health of ex-participants does not explain why investigators or sponsors have an obligation to realize that right. Usually this obligation rests on the state. But in non-ideal situations, states fail to realize the right to health. And it could be argued that researchers and sponsors should not be obliged to make up for the moral failures of the state..[43] An appropriate answer would need to develop a paper of its own, but I will try anyway to attempt a short response. As Zimmerman states:

> "The claim, unqualified, that no one should be said to be obligated to make up for the moral failures of another is surely far too sweeping. Just consider a case where all that is needed to prevent a child from dying is the donation of one dollar. There are one hundred people present who can each give one cent; you can give one dollar without any hardship whatsoever; none of the others gives money to the child; and you give one cent, smugly assuring yourself that, in doing your part, you've done your duty. The child dies, of course". Zimmerman (1996:259).

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[41] National Bioethics Advisory Commission (NBAC) (2001) *Ethical and policy issues in international research: clinical trials in developing countries*, Report and Recommendations of the National Bioethics Advisory Commission, vol. 1, p. 60, http://bioethics.georgetown.edu/nbac/clinical/Vol1.pdf. This is a strategic or prudential argument that relies on the moral argument based on the right to health. A purely strategic analysis that supports post-trial care after research as a second -best alternative could be found in Wertheimer, A (2010) *Rethinking the ethics of clinical research: widening the lens*, Oxford University Press, pp. 317-318.

[42] NRES (2012), op. cit.; Mastroleo, I. (2012b) "Guías para los comités de ética de investigación del Reino Unido sobre atención de la salud después de la investigación: un comentario crítico sobre la traducción al español del borrador versión 8.0", Perspectivas Bioéticas, vol. 17, no. 33, pp. 71-81, http://philpapers.org/archive/MASGPL ; Oliveria Cezar, D. (2012) *Pesquisa com medicamentos: aspectos bioéticos*, Rio Grande do Sul: Saravia, base don (2009) "Obrigação de fornecimento do medicamento após a conclusão de pesquisa" tesis de doctorado en derecho, orientador: Judith Hofmeister Martins Costa, Universidade Federal do Rio Grande do Sul.

[43] I would like to thanks Annetta Rid for presenting this objection to me in written. I have altered and paraphrased some of the original wording for the sake of space and it may not be an exact representation of the more complex original objection.

This general consideration about moral obligations can be translated to the case of obligations to care after research in order to reply the non-ideal objector. I will make to assumptions for the sake of the argument. First, that under ideal conditions (full compliance of the members of the host society, including the functionaries of the state in charge of provisions of the right to health) the sponsors and researchers' obligation of care after research towards participants would be discharged just referring the latter to the available health services available whatever they are. Second, that researchers and sponsors have not responsibility whatsoever for the failure of the state to realize the right to health to essential levels. So the sponsors and researchers are willing to do their part (referring ex-participants to the state's health service), but they feel no responsibility for the outcomes under the actual circumstances even if this means that former participants would receive only symptomatic care and no access to treatment for their health needs. Unfortunately, it can be argued against the non-ideal objector that these considerations don't get researchers and sponsors off the moral hook. Not even if they argue that they have already paid taxes and provided fair benefits during the trial. Because, as Zimmerman shows in his example, moral obligations in non-ideal conditions tend to increase before getting too onerous for the agent to comply with and giving him a moral excuse: in the case of saving a child your obligation multiplies a hundred times because of non-compliance and still we tend to see the results as intuitively fair. So If the state or any other member of the society is not doing its part in a fair arrangement (i.e. non-ideal or partial compliance), that increases the burden of the members who do comply with fair arrangements up to the point that the cost are too much to comply with. This increment is also a background injustice from the point of view of ideal or full compliance. But assuming that the costs to researchers, sponsors and the rest of the society doesn't reach the critical point of "too much", the fair distribution of background injustice seems to prioritize the former participants, as well as the dying child in Zimmerman example, because its unfairness is deeper and more urgent.

4 Review of post-trial obligations in DoH 2013

In October 19th 2013 the WMA adopted the latest version of the DoH which replaces the 2008 version. In this version, currently in force, the main paragraph of post-trial obligations is formulated as follows[44]:

> Post-Trial Provisions. 34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process (WMA 2013)

This paragraph introduces what I called in the first section (1.1.) the obligation of access to beneficial intervention identified in the study. In turn, a case of (2) obligation of

[44] Post-trial operational obligations are also included in paragraph 26 (Informed Consent) and paragraph 22 (Scientific Requirements and Research Protocols) "In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions" WMA (2013).

access to information after research is contained in paragraph 26 under the heading of informed consent:

> [....] All medical research subjects should be given the option of being informed about the general outcome and results of the study (WMA 2013)[45]

I think that DoH 2013 formulation is an improved version of paragraph 30 of the DoH 2008: (a) the language of the contentious fair benefit approach in which post-trial obligations were presented was removed[46]; (b) the ethical requirement has been reformulated in terms of post-trial access provisions based on the health needs of participants; (c) it explicitly identifies the main agents responsible for post-trial obligations (the "sponsors" , "researchers" and "governments of the host countries"), whose absence was one of the main criticisms in the formulations of post-trial obligations since DoH 2000; (d) it requires that plans or arrangements for post-trial provisions be disclosed to the participants during the informed consent process for the first time in DoH.[47]

However, it is also necessary to point out the main points where it is possible to improve this formulation. First, I think it would have been justified to include governments of countries funding research studies as agents responsible for post-trial obligations. Reviewing the literature on post-trial access mechanisms, it is possible to identify not only the governments of the host countries, but also to the governments of the founding countries as responsible agents for care after research provision, at least in publicly sponsored research.[48] For example, it has been proposed that US governmental agencies that usually finance multicentre trials (Center of Disease Control (CDC), National Institutes of Health (NIH), etc.) could ensure care after research by coordinating and expanding government aid programs like the President's Emergency Plan For AIDS Relief (PEPFAR) to countries where clinical trials are conducted[49] or introducing new programs to meet post-trial obligation exclusively. Identifying governments of funding countries as part of those responsible for post-trial access

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[45] The DoH 2013 draft version contained a similar sentence on paragraph 34 on post-trial provisions. See WMA (2013), *Declaration of Helsinki of the WMA: Ethical Principles for Medical Research Involving Human Subjects,* Draft for public consultation, http://www.wma.net/es/20activities/10ethics/10helsinki/15publicconsult/DoH-draft-for-public-consultation_plain.pdf

[46] For aguments against this ethical approach see previous section and Lie (2010), op. cit., London (2005), op. cit., London and Zollman (2010), op. cit., Mastroleo (2008), op. cit.

[47] I won't deal here with the arguments that state the provision of access to appropriate health care after research can function as an undue inducement. On this point generally follow the opinion of Macklin, R. (2004) *Double standards in medical research in developing countries,* Cambridge: Cambridge University Press, pp.. 124-127, and NRES (2012), "Compromising judgment", op. cit., both of which discard the relevance of such arguments at least when research studies meet standard ethical requirements of responsiveness, social value, risk and benefit assessment, etc.. In some cases, however, there may be some questionable post-trial arrangements that should be evaluated carefully by the REC such as offering a 50% discount to participants on a new drug for allergies.

[48] Millum (2011), op. cit.

[49] Lo, B., Padian, N. and Barnes, M. (2007) "The obligation to Provide antiretroviral treatment in HIV prevention trials", AIDS vol. 21, no. 10 pp. 1229-1231, http://www.ncbi.nlm.nih.gov/pubmed/17545698

provision can be justified on global justice grounds and human right's compliance.[50] Furthermore, a global tax on international research has been proposed for implementing this kind of global justice considerations.[51] In addition, identifying governments of funding countries as agents responsible for research studies overcomes the objection that certain governmental agencies (e.g. NIH) are not allowed to finance healthcare for participants after research, as this prohibition does not apply to the country or society financing research as a whole (e.g. the US).

Second, it is regrettable that the reference to "other appropriate care" contained in the in versions 2004 and 2008 of DoH is missing. As stated in the previous section, this was introduced in order to avoid the criticism that DoH 2000 didn't take into account access to essential healthcare after research for research participants, such as in HIV preventive vaccine trials. Usually, if the host countries have a system of universal health coverage, referring former participants to the national health system as a mechanism of access to care after research is usually sufficient to meet post-trial obligations. However this healthcare system is not present everywhere and for everyone, even in middle and high-income countries, and when it is, its scope varies widely depending on the condition addressed by the study. As stated in the first section of the paper, with the new formulation of post-trial obligations it could be argued that the DoH 2013 left unprotected part of the right to health of former participants to access essential healthcare after research, namely, when they need other appropriate essential care not identified by the study.

Third, restricting the obligation of access to information after research only to the "general outcomes and results of the study" seems insufficient. As discussed in the examples taken from the literature of post-trial access ethics, other information relevant to the health of former participants could also be included, for example, measures to improve the welfare of participants based on the research results[52], the group they have been randomized in the research study[53], newly detected adverse effects or the withdrawal of the drug from the market for safety reasons[54].

All these suggestions are inspired by a conception of democratic fairness in modern societies, understanding democratic in the normative sense of societies that design their institutions and establish relations based on ethical principles and human rights.[55] However, this view is also compatible with a dynamic conception of human ethical improvement, as exemplified by the conceptual reconstruction of section three where

[50] Mastroleo (2012a), op. cit.
[51] Ballantyne, A. (2010) "How to do research fairly in an unjust world", The American Journal of Bioethics, vol. 10, no. 6, pp. 26-35. Ballantyne's proposal has been defended and contended in the same issue of AJOB by various authors. See for example MacDonald, C. and Walton, N. (2010). "The perverse consequences of a proposed global tax on research", The American Journal of Bioethics, vol. 10, no. 6, pp. 46-47.
[52] Emanuel, E. (2013) "Reconsidering the Declaration of Helsinki", The Lancet, vol. 381, no. 9877, pp. 1532-1533.
[53] Unguru et al. (2013), op. cit ., Sofaer et al. (2009), op. cit ..
[54] Sofaer et al. (2009), op. cit ..
[55] This idea of democratic is society present in the theory of justice of John Rawls and others. Rawls, J. (1993) *Political liberalism*, Columbia University Press; Nino, C. S. (1996) *The constitution of deliberative democracy,* Yale University Press

linguistic formulations of post-trial obligations have changed in relation to new experience available and the discussion of the most appropriate justification of ethical principles governing research in human health. Our current understanding of what principles of research ethics should be is far from complete. Therefore it is expected that new formulations and changes in DoH will occur. It is through public debate and argumentation that ethical principles governing research on human health are established. In turn, these lead to moral and institutional obligations of participants, researchers, sponsors, and the rest of the global society that benefit from the research enterprise. These obligations do not exist in an ideal world and are not inscribed in the DNA of researchers and sponsors. Therefore, the change in the linguistic formulation of post-trial obligations is merely an expression of our work to find the most appropriate ethical principles.

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