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POST-TRIAL OBLIGATIONS IN THE DECLARATION OF HELSINKI 2013: CLASSIFICATION, RECONSTRUCTION AND INTERPRETATION

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ABSTRACT

The general aim of this article is to give a critical interpretation of post-trial obligations towards individual research participants in the Declaration of Helsinki 2013. Transitioning research participants to the appropriate health care when a research study ends is a global problem. The publication of a new version of the Declaration of Helsinki is a great opportunity to discuss it. In my view, the Declaration of Helsinki 2013 identifies at least two clearly different types of post-trial obligations, specifically, access to care after research and access to information after research. The agents entitled to receive post-trial access are the individual participants in 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 post-trial obligations, I first introduce a classification of post-trial obligations and illustrate its application with examples from post-trial ethics literature. I then make a brief reconstruction of the formulations of post-trial obligations of the Declaration of Helsinki from 2000 to 2008 to correlate the changes with some of the most salient ethical arguments. Finally I advance a critical interpretation of the latest formulation of post-trial obligations. I defend the view that paragraph 34 of 'Post-trial provisions' is an improved formulation by comparison with earlier versions, especially for identifying responsible agents and abandoning ambiguous 'fair benefit' language. However, I criticize the disappearance of 'access to other appropriate care' present in the Declaration since 2004 and the narrow scope given to obligations of access to information after research.

INTRODUCTION

The problem of transitioning research participants to the appropriate health care when a research study ends is a global one.[1] It is not only a problem in low and middle income countries (LMICs)[2] but also affects a significant part of the population of high income countries. For example, in the US it primarily affects uninsured or underinsured people 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

[1] N. Sofaer, P. Lewis & H. Davies. 2012. *Care After Research: A Framework for RECs*. UK: Health Research Authority. Available at: http://www.hra.nhs.uk/documents/2013/08/care-after-research.pdf [Accessed 22 Sep 2015].

[2] P.E. Cleaton-Jones. An Ethical Dilemma: Availability of Antiretroviral Therapy After Clinical Trials with HIV Infected Patients Are Ended. *BMJ* 1997; 314: 887; A. Petryna. 2009. *When Experiments Travel: Clinical Trials and The Global Search for Human Subjects*. Princeton: Princeton University Press: 139–185.

[3] G. Kolata & K. Eichenwald. 1999. Stopgap Medicine: A Special Report. For the Uninsured, Drug Trials Are Health Care. *The New York Times* 22 June; N. Sofaer et al. Subjects' Views of Obligations to Ensure Post-Trial Access to Drugs, Care and Information: Qualitative Results From The Experiences of Participants in Clinical Trials (EPIC) Study. *J Med Ethics* 2009; 35: 183–188.; N. Sofaer, P. Lewis & H. Davies. Forthcoming Practical Framework for Ethics Committees and Researchers on Post-Trial Access to The Trial Intervention and Healthcare. *J Med Ethics* 2014; 40: 217–218.

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System (NHS) after the study is concluded, for example in cases of studies for rare genetic diseases[4] or 'last-chance-drugs'[5]. However, readers encountering this topic for the first time should be aware that care after research may not be needed in many types of human health research (e.g. research with healthy volunteers or in patients with some acute or sub-acute diseases)[6] and that willingness to provide care after research when needed may be hindered by logistical and regulatory challenges, especially in the case of the post-trial provision of investigational study intervention. Therefore, as Sofaer et al. state, many stakeholders are unclear about their obligations after research and many research ethics committees (RECs) do not know what to require.[7] Sofaer et al. also note that this situation may lead to a number of negative consequences, including a lack of appropriate care for former research participants, unplanned costs to the health system and the loss of confidence in the research system.[8] 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' claiming their right to health.[9]

These are sufficient reasons for trying to establish a better understanding of the post-trial obligations of researchers, sponsors and other stakeholders involved in human health research. The publication of a new version of the Declaration of Helsinki in October 2013 and its current public discussion is an excellent opportunity to work in this direction. Accordingly, the general aim of this article is to give a critical interpretation of post-trial obligations towards individual research participants in the Declaration of Helsinki (DoH) 2013.

DoH 2013 introduces at least two clearly different types of post-trial obligations, specifically, obligations to provide access to appropriate care after research (in short, obligations of access to care after research) and obligations to provide access to relevant information after research (in short, obligations of access to information after research). Since I will only refer to these two types of obligations in the paper, the terms 'post-trial obligations' and 'post-trial access obligations' will be used interchangeably. The intended agents entitled to receive access 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 and agents of post-trial obligations in DoH 2013, I first present a classification of post-trial obligations derived from a qualitative interpretation of the literature of post-trial access ethics. Then, I make a brief reconstruction of the formulations of post-trial obligations in previous versions of the DoH. Finally, I advance a critical analysis of the new formulation of post-trial access obligations in paragraph 34 based on the discussion in the previous sections. Here, I will defend the view that paragraph 34 of 'Post-trial provisions' is an improved formulation of earlier versions in that it identifies responsible agents and abandons ambiguous 'fair benefit' language, but I criticize the disappearance of 'access to other appropriate care' present in previous versions of the Declaration since 2004 and the narrow scope given to obligations of access to information after research.

CLASSIFICATION OF POST-TRIAL ACCESS OBLIGATIONS AND EXEMPLARY CASES

Classification

Before presenting the classification I have to state that in this paper I will not deal with many of the problems surrounding post-trial obligations. In particular I will not go into the details of supplying mechanisms of post-trial access[10], the reasons given in the literature for or against access to care after research[11], or the international regulations and laws of post-trial access.[12] However, I hope that the quoted references to the literature will be a relevant guide to anyone interested in these issues.

To start my classification, I propose a first distinction of post-trial access obligations into two general types: post-trial obligations towards individual agents and post-trial obligations towards collective agents. My intention is to focus only on post-trial obligations towards individ-

[4] BBC Staff. 2007. Trial Volunteers 'Left in Lurch'. *BBC News Online* 24 December. Available at: http://news.bbc.co.uk/2/hi/health/7155572.stm [Accessed 22 Sep 2015].

[5] Sofaer et al. 2014, *op. cit.* note 3.

[6] For a broader list of situations where post-trial access is unnecessary see Z. Zong. Should Post-Trial Provision of Beneficial Experimental Interventions Be Mandatory in Developing Countries? *J Medical Ethics* 2008; 34: 188–192

[7] Sofaer et al. 2014, *op. cit.* note 3.

[8] Ibid.

[9] D.W.L. Wang & O.L.M. Ferraz. Pharmaceutical Companies vs. the State: Who Is Responsible for Post-Trial Provision of Drugs in Brazil? *J Law Med Ethics* 2012; 40: 188–196.

[10] By 'supplying mechanisms' I understand the different mechanisms included in the plans or arrangements for supplying the objects of post-trial access obligations. J. Millum. Post-Trial Access to Antiretrovirals: Who Owes What to Whom? *Bioethics* 2011; 25: 145–154: 147.

[11] For a simplified version of the reasons for and against post-trial access to the study intervention see Sofaer et al. 2012, *op. cit.* note 1, pp. 5–7. This list is based on the systematic review of these reasons of N. Sofaer & D. Strech. Reasons Why Post-Trial Access to Trial Drugs Should, or Need not be Ensured to Research Participants: A Systematic Review. *Public Health Ethics* 2011; 4: 160–184.

[12] Sofaer et al. 2012, *op. cit.* note 1, pp. 7–10; S.M. Dainesi & M. Goldbaum. Provision of Investigational Drug After Clinical Research: Review of Literature, National and International Guidelines. *Revista da Associação Médica Brasileira* 2011; 57: 710–716.

ual agents without conflating them with obligations towards collective agents.[13] The rationale behind this distinction follows Grady's methodological steps, Grady states that 'it is both practically and ethically a different challenge' to comply with these obligations.[14]

One significant practical and ethical difference that could justify the difference between post-trial obligations towards individual and collective agents is the varying degree of responsibility and different roles of organizational actors (e.g. RECs, local health agencies, drug approval bodies) in reviewing post-trial arrangements for individual agent's needs (e.g. research participants) versus collective agent's needs (e.g. communities, population of host country). The exemplary case of post-trial access obligations towards individual agents is that of an individual research participant enrolled in a clinical trial. In this case, the most relevant and up to date research ethics guidelines require a REC review of post-trial plans or arrangements that ensure responsible transition to relevant information, to appropriate health care (either beneficial investigational drug and/or other appropriate care) and to disclose this information to potential participants during the informed consent process.[15]

However, when it comes to post-trial access obligations towards collective agents, such as the host society of a research study or a particular community which is part of that society, the review of a local REC and informed consent from each individual participant are not sufficient. These decisions will affect all members of the host society and not only those actually enrolled in a particular research. Therefore, there is a need for additional consultations with those host society's authorities –beyond the local REC– that have the appropriate legitimacy to take those decisions.[16] An open-ended list of such authorities will include the drug regulatory agency, the agency of health technology assessment, the Ministry of Health, the national or regional REC and/or other legitimate political authorities. This practical and ethical difference is just one of many, but is important enough to justify accepting the distinction between post-trial access obligations towards individual and collective agents at least as a working hypothesis.[17]

As stated above, in this paper I will focus exclusively on post-trial access obligations towards individual research participants. I made this choice for two practical reasons. First, because the formulation of DoH 2013 post-trial access provisions in paragraph 34 and its related paragraphs may be readily interpreted as obligations towards individual participants of a research study and not towards collective agents. Second, if post-trial obligations towards individual agents fall more clearly within the remit of responsibility and legitimacy of local RECs's reviews than obligations towards collective agents, then the problem of post-trial obligations towards individual research participants is more urgent for the everyday practice of local RECs. For example, based on a plausible interpretation of the DoH 2013, it is in the remit of a local REC to require provision of a post-trial intervention identified as beneficial in the study to the participants randomized to the placebo arm of a research study. Unguru et al. argue persuasively for this in the case of an oncology study of added immunotherapy to standard treatment for children with a high-risk of neuroblastoma.[18] However, the most plausible interpretation of requiring post-trial access to a beneficial study intervention does not entail that this responsibility falls over only one particular agent (i.e. the researcher). It requires all relevant agents to plan in advance for post-trial provisions and distribute the responsibilities accordingly.

[13] C. Grady. Challenge of Assuring Continued Post-Trial Access to Beneficial Treatment, *Yale J Health Poly L & Ethics* 2005; 5: 425–435: 427.

[14] Ibid.

[15] Council for International Organizations of Medical Sciences (CIOMS). 2002. *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (revised in 2002). Geneva: CIOMS, guidelines 5, 10, and Appendix 1; World Medical Association (WMA). 2013. *Declaration of Helsinki of the WMA: Ethical Principles for Medical Research Involving Human Subjects*, paragraph 34, 'Post-trial provisions'. Available at: http://www.wma.net/en/30publications/10policies/b3/index.html [Accessed 22 Sep 2015]; Sofaer et al. 2012, *op. cit*. note 1 includes an explicit definition of 'responsible transition'.

[16] With regard to the lack of legitimacy of local RECs required to take certain decisions see J. Katz. 1994. Statement by Committee Member Jay Katz. In *Advisory Committee on Human Radiation Experiments Final Report*. Available at: https://bioethicsarchive.georgetown.edu/achre/final/jay_katz.html [Accessed 22 Sep 2015].

[17] Consequently, ethical research on post-trial obligations towards collective agents should follow the discussion on reasonable availability requirement, responsiveness and fair benefit sharing in its various interpretations. On reasonable availability see L.H. Glantz et al. Taking Benefits Seriously in Developing Countries. *Hast Cent Rep* 1998; 28: 38–42; I. Mastroleo. Justicia Global e Investigación Biomédica: La Obligación Post Investigación hacia la Comunidad Anfitriona. *Perspectivas Bioéticas* 2007; 23: 76–79, http://philpapers.org/rec/MASJGE-2 [Accessed 22 Sep 2015]; on the responsiveness requirement see A. London. 2008. Responsiveness to Host Community Health Needs. In *The Oxford Textbook of Clinical Research Ethics*, E. Emanuel et al., eds. New York: Oxford University Press: 737–744; on fair benefit sharing see E. Emanuel. 2008. Benefits to Host Countries. In *The Oxford Textbook of Clinical Research Ethics Princeton*, E. Emanuel et al., eds. New York: Oxford University Press: 719–728.; R.C. Hughes. Justifying Community Benefit Requirements in International Research. *Bioethics* 2014; 28: 397–404; D. Schroeder. 2014. Sharing of Benefits. In *Handbook of Global Bioethics*, H.A.M.J. ten Have & B. Gordijn, eds. Dordrecht: Springer: 203–223; O. Zvonareva et al. Engaging Diverse Social and Cultural Worlds: Perspectives on Benefits in International Clinical Research from South African Communities. *Dev World Bioeth* 2015; 15: 8–17; For an alternative view on research and global health see B. Pratt & B. Loff. A Framework to Link International Clinical Research to the Promotion of Justice in Global Health. *Bioethics* 2014; 28: 387–396.

[18] Y. Unguru, S. Joffe, C.V. Fernandez & L.Y. Alice. Ethical Issues for Control-Arm Patients After Revelation of Benefits of Experimental Therapy: A Framework Modeled in Neuroblastoma. *J Clin Oncol* 2013; 31: 641–646.

Paragraph 34 of DoH 2013 clearly states that 'post-trial provision' is a joint responsibility of various agents; the most salient being sponsors, researchers and host country governments, as I will argue.

It would be also the responsibility of the local REC to refuse approval for a research protocol that does not include appropriate care after research arrangements for participants with persisting health needs and no access to roughly equal or best therapeutic alternatives outside the trial, as in the exemplary case of studies with anti-retrovirals for HIV/AIDS in South Africa in the 1990s.[19]

With regard to post-trial access obligations towards individual agents it is useful to introduce a second distinction to the current classification, based on the object of the obligations[20], specifically, (1.) obligations of access to care after research and (2.) obligations of access to information after research. These objects of post-trial obligations can be clearly identified in previous versions of DoH and in the recent literature on post-trial ethics.[21] In turn, as I will explain in the next section, it is also useful to introduce a further distinction of two subtypes of obligations of access to care after research: (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. To avoid ambiguity in the phrase 'intervention identified as beneficial in the study', I will understand that it makes reference only to the *investigational* beneficial study intervention.

The following table 1 below summarizes these last distinctions:

Table 1. Classification of post-trial access 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 (in short, access to beneficial study intervention)	1.2. Obligation of access to other appropriate care
2. Obligations of access to information after research		

Exemplary Cases

To complete my classification, I will present some historical examples of each obligation. This section should not be regarded as a case study since it lacks the in-depth and detailed explanation needed for each case. The value of including exemplary cases here is just to improve the understanding of the classification presented in the above section and the use of some terms such as 'study intervention', 'beneficial', 'other appropriate care', etc. by attaching an appropriate historical reference taken from the current literature on post-trial obligations.

An uninsured research subject from the US in a long-term diabetes study illustrates the ethical concerns regarding (1.), obligations of access to care after research.[22] This case captures the two basic practical conditions that presuppose the requirement for access to care after research for individual research participants: (a) a relevant unmet health need or health-related quality of life deficit and (b) no access to roughly equal or best therapeutic alternative outside the trial.

The (1.1.) obligation of access to an intervention identified as beneficial in the study is captured in the research ethics literature by the case of Jay Weinstein, a firefighter diagnosed with chronic myelogenous leukemia (CML).[23] By 1999, his disease was in its final phase. Then Weinstein became a participant in a preliminary study that was testing imatinib, the investigational intervention of that research study. The one therapeutic alternative 'that could save him was a bone marrow transplant, but that required a donor, and he did not have one'.[24] Imatinib was identified as beneficial for Weinstein and he continued taking it once the research study was over.[25]

The (1.2.) obligation of access to other appropriate care can be illustrated by two exemplary cases. In trials testing a preventive HIV/AIDS intervention, such as a vaccine or microbicide, access to safe and effective anti-retroviral after research for participants infected

[19] Cleaton-Jones 1997, *op. cit.* note 2.

[20] 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 USD to Mike, the object of Mike's obligation is repaying Mary 100 USD.

[21] Sofaer et al. 2012, *op. cit.* note 1.

[22] '[. . .] 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', Sofaer et al. 2009, *op. cit.* note 3, p.185.

[23] G. Kolata. 2005. Slowly, Cancer Genes Tender Their Secrets. *The New York Times* 27 December; R. Macklin. The Belmont Principle of Justice: An Idea Whose Time Has Come. *APA Newsletter on Philosophy and Medicine* 2006; 5(2): 4–5.

[24] Kolata 2005, ibid.

[25] The complete history of post-trial provision for Jay Weinstein was not found in the literature. However, Carolyn Blasdel, a clinical research nurse working with one of the principal investigators of imatinib trials, Dr. Brian Drucker, was contacted through email and provided a detailed explanation of general post-trial arrangements of imatinib study: 'The original Phase I clinical trial for imatinib started in 1998. At the time, nobody knew if it would work since the drug had never been tried in humans, and there were no provisions for continuing imatinib beyond the length of the study. As the trial was ending, Novartis [the sponsor of the trial] decided to provide free imatinib for the Phase I trial participants as long as they were on imatinib. These original Phase I patients are still getting imatinib provided free by Novartis. Later trials Phase II and III have also provided drug for many years, the studies have been continued as extension studies, primarily to provide drug for the patients who were responding. One of the early Phase III studies did end recently and patients were individually transitioned either to having their drug provided by insurance or to Novartis' patient assistance program.' (Blasdel 2012, May 23rd, personal communication, edited).

during the trial has been the exemplary case discussed in post-trial ethics literature.[26] In therapeutic research studies of anti-retrovirals for HIV/AIDS, access to antibiotic treatment for opportunistic diseases, when not available in the host community, can be identified as an example of access other appropriate care after research.[27]

As stated in the introduction, one of the problems in DoH 2013 that motivated me to write this paper is that the terms referring to (1.2.) the obligation of access to other appropriate care, have disappeared from the formulation of post-trial obligations. This has been considered in the literature a significant loss in protection.[28] 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 other essential health care service not included in the study is necessary to ensure responsible transition to the appropriate health care of research participants.[29]

Finally, with respect to (2.) the obligations of access to information after research, although the paradigmatic example is access to individual study results and aggregated outcome, a relevant example in the literature is also access to information on adverse effects. In a series of focus groups on post-trial access to drugs, care, and information, several research participants from the US complained about learning of adverse effects only from the media.[30] Other participants pointed out that if auto companies were able to recall their defective cars from both the market and clients who had bought them, the obligation of reporting adverse effects directly to the former participants seemed appropriate, even several years after the study had ended.[31] This considerations points to the responsibilities not only of researchers and sponsors but also to those of regulatory agencies of host governments and their adverse event reporting system.[32] This coincides with the list of agents responsible for complying with post-trial provisions in paragraph 34 of DoH 2013, namely, researchers, sponsors and host country governments.

In the next section, I will present a brief reconstruction of the development in the formulations of post-trial obligations in the different versions of the DoH.

RECONSTRUCTION OF POST-TRIAL OBLIGATIONS IN DoH 2000–2008

My objective in this section is to present the development of the wording or linguistic formulation of post-trial access obligations in the evolving DoH, correlating these changes with the most salient arguments and positions in the literature. My aim is not to make a historical reconstruction, but rather a conceptual reconstruction using the classification presented in the previous section.

The first formulation of (1.), obligations of access to care after research appears for the first time in 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 only refers in my classification to (1.1.) the obligation of access to an intervention identified as beneficial in the study. 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.

The main changes in the wording between the classification in Table 1 and the original formulation in paragraph 30 are the substitution of the phrase 'access to [. . .] prophylactic, diagnostic and therapeutic methods' for 'access to an intervention' and 'best proven' for 'beneficial'. In particular, the latter is a substantive change so it justifies making a clarifying consideration. Access to 'beneficial' intervention implies that access to an investigational intervention is regarded by sound clinical evaluation as the best choice for the former individual research participant to continue treatment at a time when the investigational intervention may not have shown sufficient evidence of safety and efficacy to be licensed for a particular indication – so the intervention is not 'proven' from the point of view of sound statistical evaluation of the research data. As in the case in imatinib trials, where the condition of the participant was life-threatening (i.e. chronic myelogenous leukemia) and there was no roughly equal or better therapeutic alternative with a better effectiveness and safety profile than imatinib, available clinical evidence was considered enough to establish the investigational intervention as 'beneficial' for Jay Weinstein, the New York firefighter mentioned above. What is important

[26] U. Schuklenk. Helsinki Declaration Revisions. *Indian J Med Ethics* 2001; 9: 29; Millum 2011, *op. cit.* note 10.

[27] J.G. Biehl. Pharmaceuticalization: AIDS Treatment and Global Health Politics. *Anthropol Quart* 2007; 4: 1083–1126: 1112.

[28] R. Dal-Ré, P. Ndebele, E. Higgs, N. Sewankambo & D. Wendler. Protections for Clinical Trials in Low and Middle Income Countries Need Strengthening Not Weakening. *BMJ* 2014; 349: g4254. The authors defend also that the loss of the reference to other appropriate benefits is a significant loss, a position I criticize in I. Mastroleo. Strengthening Protections for LMICs Is Not Straight Forward: A Response to Dal-Ré and Collaborators. *BMJ* 2014; electronic letter to the editor, 14 July, http://www.bmj.com/content/349/bmj.g4254/rr/760699 [Accessed 22 Sep 2015].

[29] I take the concept 'responsible transition' from Christine Grady as quoted in Sofaer et al. 2012, *op. cit.*, note 1, p. 3.

[30] '[. . .] 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!', Sofaer et al. 2009, *op. cit.* note 3, p. 185.

[31] Ibid., p. 185.

[32] Ibid., p. 187.

to distinguish here is that there are two appropriate levels of evidence needed for two different practical questions. On the one hand, what is the appropriate level of evidence to consider that an investigational intervention is proved by a study? On the other, what is the appropriate level of evidence to consider an investigational intervention beneficial for a participant that may still have unmet health needs? Confusing 'statistical evaluation of the research data' to determine that an investigational intervention is proved with clinical evaluation of a single participant to determine that is beneficial would be a mistake.[33] This present study only tries to highlight one frequent confusion in the literature. Analyzing in detail how to establish that an investigational intervention is beneficial and how should this information be used to make post-trial access determinations is beyond the scope of this article.

Paragraph 30 of DoH 2000 generated two controversies. First, whether post-trial access obligations should or should not be interpreted as necessary conditions for approval of a research study. Second, paragraph 30 was criticized for not taking into account access to essential health care after research in particular trials; for example access to anti-retrovirals in preventive trials of HIV vaccines. As Schuklenk 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 vaccine trial be provided essential medication. The consequences will be particularly disastrous for research subjects affected by AIDS.[34]

[33] P. Ferrari Andreotti & F. N. Moura Viana. 2011. Point of View of the National Agency for Health Surveillance [ANVISA] Regarding the Issue: Guarantee of Access to Post-Clinical Trial Medications. In *Guarantee of Access to Post Clinical Trial Drugs*. Sao Paulo: Brazilian Association of Clinical Research Organizations (ABBRACRO). Available at: https://es.scribd.com/doc/260373252/ABRACRO-2011-Guarantee-of-Acces-to-Post-clinical-Trial-Drugs [Accessed 22 Sep 2015].

[34] Schuklenk 2001, *op. cit.* note 27, p. 29.

What Schuklenk states can be interpreted in terms of the classification presented in the previous section as an objection to the formulation of 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'. I propose that the assumed scope of post-trial access obligations to care after research in the discussion corresponds with the scope of the human right of research participants to access essential health care even when the specific form of such care they require is not 'identified by the study', as with anti-retrovirals in the case of preventive HIV vaccine trials. This normative threshold may not be shared by everyone working in the research ethics field and will be discussed in more detail at the end of this section. However, at this point, it is enough for the reconstruction to expose the normative commitments to the reader.

During 2004, in response to Schuklenk's objection and the general controversy generated, the WMA issued a note of clarification on the formulation of paragraph 30, in which new terms and concepts were introduced:

> 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 terms 'post-trial access' and 'identified as beneficial in the study' for the first time in 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 review. 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.) the 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 'should be assured of' in paragraph 30 to just 'identify' in the note of clarification. With regard to this last change of terms, what seems to be at stake again is whether this requirement should or should not be interpreted as a condition for approval of clinical trials.

In any case, WMA's note of clarification on paragraph 30 was harshly criticized by both critics and supporters of

post-trial obligations.[35] 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 the 'outcome of the study' 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'.[36] It retains access to interventions identified as beneficial in the study and access 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 health care after research for all participants.

However, this new formulation of post-trial obligations has also received justified criticism.[37] The most important is that presents post-trial obligations in terms of the entitlement of participants to benefit sharing and that it includes for the first time in the DoH the concept of access to other appropriate benefits. As I will now discuss, both modifications are consistent with the main thesis of the 'fair benefits approach' that post-trial obligations should not be a necessary condition for approval of research studies.[38]

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 arising from 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 linguistic formulation was engineered to dilute the requirement of provision of appropriate health care after research to the former participants present in DoH 2000 and 2004, at least under one intended interpretation of the fair benefits approach. By quoting different kinds of access as 'examples' of benefit sharing, paragraph 33 presents access to care after research (beneficial investigational intervention or other appropriate care) at the same level with access to 'other appropriate benefits', neither granting any special priority to access to healthcare nor making any specific distinction between these categories. So, if access to care after research is just another 'fair benefit' this implies that there is no independent moral obligation to provide care after research to the research participants beyond what the relevant parties may agree.

Here, it will be useful to reconstruct the main thesis of the fair benefit approach. The ethical approach of Emanuel et al. assumes that the level of fair benefits must be calculated by a negotiation between 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', for example access to the beneficial study intervention or to other essential health care after research.[39] Among the 'broad range of benefits' the authors include the development of capabilities in research infrastructure, the training of local researchers and the education of 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, it would be a morally valid reason for researchers and sponsors within the fair benefits approach to discontinue care after research based on the argument that the participant has received enough 'fair benefits' during the study, and that he and the host country authorities had consented to conduct the research under conditions that did not include the participant's health needs. This is possible because the main thesis of Emanuel et al. is that what has been identified as obligations of access to care after research should not function as a moral limit for conducting research.[40]

[35] H. Wolinsky. The Battle of Helsinki: Two Troublesome Paragraphs in the Declaration of Helsinki Are Causing a Furore over Medical Research Ethics. *EMBO Reports* 2006; 7: 670–672. The other 'troublesome paragraph' that Wolinsky mentions is the 'Note of clarifications on paragraph 29' about the use of placebo issued by WMA in 2002.

[36] Nevertheless, by simplifying the construction of 'prophylactic, diagnostic and therapeutic procedures' with the term 'intervention' the reference of the term 'intervention' was obscured for the general public since DoH does not include definitions of its terms.

[37] Z. Zong. Should Post-Trial Provision of Beneficial Experimental Interventions Be Mandatory in Developing Countries? *J Medical Ethics* 2008; 34: 188–192; I. Mastroleo. EI Principio de Acceso Posinvestigación en la Revisión 2008 de la Declaración de Helsinki. *Perspectivas Bioéticas* 2008; 24–25: 140–157, http://philpapers.org/rec/MASEPD-2 [Accessed 22 Sep 2015]; Mastroleo 2014, *op. cit.*, note 29.

[38] Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries. Fair Benefits for Research in Developing Countries. *Science* 2002; 298: 2133–2134; Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries. Moral Standards for Research in Developing Countries: from 'Reasonable Availability' to 'Fair Benefits'. *Hast Cent Rep* 2004; 34: 17–27; E. Emanuel & Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries. 2008. Addressing Exploitation: Reasonable Availability versus Fair Benefits. In *Exploitation and Developing Countries: The Ethics of Clinical Research*. J. Hawkins & E. Emanuel eds., Princeton: Princeton University Press: 286–313.

[39] Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries 2004, *op. cit.* note 40, p. 26.

[40] Emanuel et al. 2008, *op. cit.* note 40, p. 299.

Perhaps Emanuel et al.'s normative commitments could be made more clear by showing that the underlying interpretation of fairness 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.[41]

The main problem with the fair benefits approach's commitment to market fairness is that it is the only kind of fairness that it takes into account. As noted by Reidar Lie, one of the original authors of the fair benefit approach, who later revised his position, establishing the fairness of research studies is not analogous to establishing the fair price of a product or service through negotiation between the parties, as one is supposed to do in a flea market or when bargaining with a plumber. At the very least, the 'background conditions of injustice' and the relevance of the knowledge for the society should also be considered.[42]

To Lie's objection, one can add London's arguments that Emanuel et al. sustain a minimalist interpretation of ethical principles with possibly severe consequences.[43] London also states that the interpretation of fairness advocated by the fair benefits approach is consistent with a state of affairs where participants from low and middle income countries are 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.[44]

My disagreement with the fair benefit approach interpretation of post-trial obligations is twofold. First, health care for former participants is considered to be a benefit at the same level as the training of REC members and researchers, and improving infrastructure. However, training REC members and researchers or improving clinical facilities are necessary costs in order to conduct a clinical trial and produce generalizable knowledge. So it is unfair to discount all these costs against the actual participants benefit account instead of the benefit account of all the potential beneficiaries of the knowledge generated. Second, health care (either a beneficial study intervention or other appropriate care after research) is a good that has ethical priority over other possible benefits because it affects the exercise of the basic moral capabilities of ex-participants. For instance, in Daniel's theory of just health, the principle of fair equality of opportunity tries to capture this, requiring an essential range of right to health provisions to any democratic society.[45] Furthermore, the main human rights treaties require an essential level of the right to health for both democratic and non-democratic countries.[46]

At this point one clarification may be useful. Defenders of the fair benefit approach may be against the right to health interpretation of post-trial obligations because it might be used as a necessary condition for approval of research proposals. However, grounding post-trial obligations in research participants right to health does not deny that there could be ethically justified exceptions, as happens in other basic principles of research ethics such as informed consent. Neither does it deny that the right to health, as most human rights, can only be fully achieved progressively. However, it does reverse the burden of proof towards researchers, sponsors and the rest of potential beneficiaries to argue for these exceptions. Access to care after research, even of an investigational study intervention, should be the rule not the exception and RECs should have to evaluate whether the reasons given by researchers and sponsors to discontinue care after research are ethically applicable to a particular research protocol.[47]

Finally, some may object that any alternative to the fair benefit approach is aspirational. In response, I would simply point out that there exist sound good clinical practice guidelines and regulations of post-trial obligations consistent with this interpretation of care after research and the right to health, and have been incorporated into

[41] Ibid., p. 294.
[42] R.K. Lie. The Fair Benefits Approach Revisited. *Hast Cent Rep* 2010; 40: 3.
[43] A.J. London. Justice and the Human Development Approach to International Research. *Hast Cent Rep* 2005; 35: 24–37.
[44] A.J. London & K.J. Zollman. Research at the Auction Block. *Hast Cent Rep* 2010; 40: 34–45.
[45] N. Daniels. 2007. *Just health: meeting health needs fairly*. New York: Cambridge University Press. I apply this framework to post-trial access obligations in I. Mastroleo. La Obligación de Continuidad de Tratamiento Beneficioso hacia los Sujetos de Investigación. PhD dissertation in Philosophy, Buenos Aires: University of Buenos Aires: 185–194, available online in *JOSHA*; 2015, http://dx.doi.org/10.17160/josha.2.5.57 [Accessed 22 Sep 2015].
[46] International Covenant on Economic, Social and Cultural Rights (ICESCR). 1966. *UN Treaty Collection: International Covenant on Economic, Social and Cultural Rights*. Available at: https://treaties.un.org/Pages/ViewDetails.aspx?src=TREATY&mtdsg_no=IV-3&chapter=4&lang=en [Accessed 22 Sep 2015].
[47] Sofaer et al. 2012, *op. cit.* note 1, p. 5.

the research ethics monitoring system of different democratic societies such as Argentina, Brazil and the UK.[48]

The conceptual reconstruction of this section has tried to correlate the changes in the different formulations of post-trial obligations in DoH from 2000 to 2008 with some of the most salient arguments in research ethics literature from the position of a defender of the right to health. In the next section, I present a critical interpretation of the linguistic formulation of post-trial obligations in DoH 2013.

INTERPRETATION OF POST-TRIAL OBLIGATIONS IN DoH 2013

In October 2013 the WMA adopted the current version of the DoH which replaces the 2008 version. In this version, the only one recognized by the WMA with normative force, the main paragraph of post-trial obligations is formulated as follows[49]:

> 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 classification of the first section (1.1.) the obligation of access to beneficial intervention identified in the study. The case of (2), obligation of 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)

I will defend the view that DoH 2013 improves the formulation of the obligation of access to beneficial intervention identified in the study by comparison with paragraph 33 of the DoH 2008. First, the ambiguous reference to benefit sharing entitlements has been modified.[50] This includes removing the reference to 'other appropriate benefits' introduced in DoH 2008 by the controversial fair benefit approach interpretation of post-trial obligations. I understand and share one of the main viewpoints of the defenders of the fair benefit approach, namely, that other basic needs of research participants or host societies should be taken into account besides health needs.[51] However, the reference to 'other appropriate benefits' in the DoH 2008 was so loose that it was open to being used by unscrupulous parties as a 'blank check'.

Second, the ethical requirement has been reformulated in terms of post-trial access provisions based on the health needs of individual participants. This closely follows NBAC's recommendation that making post-trial benefits 'responsive to the health needs of the participants provides an additional way to ensure that research participants are not exploited' neither by helicopter research nor by corrupt governments authorities of host countries.[52] However, this might not be enough and, as I will argue below, there is still a need to do more research about how to implement post-trial access requirements.

Third, paragraph 34 explicitly identifies the main responsible agents for post-trial obligations (the 'sponsors', 'researchers' and 'governments of the host countries') whose absence was one of the main criticisms in the previous formulations of post-trial obligations in DoH since 2000 version.[53] I explicitly stated 'main responsible agents' because I believe that the formulation should be interpreted as an open ended list. As I will argue, the agents identified are the most salient in the literature of post-trial obligation but not the only ones.

Fourth, I believe that the formulation of paragraph 34 amounts to progress because it requires for the first time in DoH that plans or arrangements for post-trial provisions be disclosed to the participants during the informed consent process. Here, I will not argue in detail against the objection that the provision of access to appropriate care after research is necessarily an undue inducement. On this point, I follow the opinion in the literature which rejects the relevance of such arguments at least when research studies meet standard ethical requirements of responsiveness, social value, risk and benefit assessment,

[48] Sofaer et al. 2012, *op. cit.* note 1; Dainesi & Goldbaum 2011, *op. cit.* note 12; S. Colona & I. Schipper. 2015. *Post-Trial Access to Treatment: Corporate Best Practices*. Amsterdam: Centre for Research on Multinational Corporations (SOMO). Available at: http://www.somo.nl/publications-en/Publication_4169/at_download/fullfile [Accessed 22 Sep 2015].

[49] References to obligations related to post-trial provision in para. 34 are also included in para. 22 (Scientific Requirements and Research Protocols) 'In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions'; in para. 26 (Informed Consent) 'In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of [. . .] post-study provisions [. . .]'. There's also a mention to '[. . .] interventions that result from the research.' in para. 20 (Vulnerable groups and individuals) WMA 2013, *op. cit.* note 16.

[50] For arguments against fair benefit approach see previous section.

[51] J.V. Lavery et al. 'Relief of Oppression': An Organizing Principle for Researchers' Obligations to Participants in Observational Studies in the Developing World. *BMC Public Health* 2010; 10: 384.

[52] 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. Bethesada, MD: NBAC: 60, Available at: http://bioethics.georgetown.edu/nbac/clinical/Vol1.pdf [Accessed 22 Sep 2015].

[53] D. Schroeder & E. Gefenas. Realizing Benefit Sharing–The Case of Post-Study Obligations. *Bioethics* 2012; 26: 305–314: 310.

etc..[54] More benefits or inducements are not necessarily undue inducements, though they might be. It is important to bear in mind that the conceptual rejection of post-trial provisions as necessarily an undue inducement relies heavily in the existence of a sound scientific and ethical evaluation of the protocol by RECs and host country health authorities. It neither rules out the possibility of some questionable post-trial arrangements that RECs and drug regulatory agencies should forbid in otherwise sound protocols, nor the possibility of post-trial provisions being an undue inducement where sound evaluation is missing.

Having acknowledged that DoH 2013 paragraph 34 represents a positive change, it is also necessary to point out the main elements where it is possible to improve its 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 supplying mechanisms, it is possible to identify not only the governments of the host countries, but also the governments of the funding countries as responsible agents for care after research provision, at least in publicly sponsored research.[55] For example, it has been proposed that US governmental agencies that usually finance multicenter 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[56] or by only introducing new programs that meet post-trial obligation. Identifying governments of funding countries as among those responsible for post-trial access provision can be justified on global justice and human rights compliance grounds. A global tax on international research has been proposed and could be used for implementing this kind of global justice considerations.[57] In addition, identifying governments of funding countries as agents responsible for research studies overcomes the objection that certain governmental agencies financing research, such as the NIH, are not allowed to finance health care for participants after research. Clearly this prohibition does not apply to the country or society financing research as a whole, for example the US.

Second, it is regrettable that the reference to 'other appropriate care' contained in the versions 2004 and 2008 of DoH is missing. As stated above, the phrase 'access to other appropriate care' conceptually avoided the criticism that DoH 2000 did not take into account access to essential health care after research for research participants, such as in HIV preventive vaccine trials. If the host countries have a system of universal health coverage, then 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 universal health care coverage is not present everywhere and for everyone, even in high-income countries. And when it is present, its scope varies widely depending on the condition addressed by the study. By deleting 'access to other appropriate care' DoH 2013 left unprotected part of the right of former participants to access essential health care after research, namely, when they need other appropriate essential care not identified in the study such as in prevention HIV/AIDS trials.

However, according to Jeff Blackmer, executive director of the Canadian Medical Association's ethics office and a member of the committee who made the changes, the phrase access to other 'appropriate care or benefits' from DoH 2008 was deleted as 'a response to African physicians who protested that some community leaders were pressuring locals to enroll in clinical trials in order to secure the facilities that came along with them'.[58]

However, deleting the reference of 'access to other appropriate care' from DoH 2013 is just a way to avoid dealing with the basic ethical problems, namely, the interference of 'community leaders' or other responsible authorities in research participants informed consent process and the negligence or incapacity of RECs and host country authorities to deal with this situation. With or without the reference to 'other appropriate care or benefit' the facilities and economic incentives will be present if the trials are hosted in LMICs. Moreover, DoH 2013 paragraph 34 avoids this problem, if one actually exists, at the cost of the health needs of potential research participants, the most vulnerable party. As pointed out by Paul Ndebele, director of the Medical Research Council of Zimbabwe in Harare, educating the local authorities seems to be one of the ethical ways forward.[59] More empirical research on how to best implement post-trial requirements is another path we should follow as well.

Finally, restricting the obligation of access to relevant information after research only to the 'general outcome 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

[54] R. Macklin. 2004. *Double Standards in Medical Research in Developing Countries*. New York: Cambridge University Press: 124–127; E.J. Emanuel, X.E. Currie & A. Herman. Undue Inducement in Clinical Research in Developing Countries: Is it a Worry? *Lancet* 2005; 366: 336–340.; Sofaer et al. 2012, *op. cit.* note 1, p. 6 'Compromising judgment'.

[55] Millum 2011, *op. cit.* note 11.

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

[57] A.J. Ballantyne. How to Do Research Fairly in an Unjust World. *Am J Bioeth* 2010; 10: 26–35.

[58] H. Ledford. Edits to Ethics Code Rankle. *Nature* 2014; 515: 174.

[59] Ibid.

former participants could also be included, for example, measures to improve the welfare of participants based on the research results,[60] the group they were randomized to in the research study,[61] appropriate incidental findings, newly detected adverse effects or the withdrawal of the drug from the market for safety reasons.[62]

CONCLUSIONS

In the previous section, I defended the view that DoH 2013 paragraph 34 of 'Post-trial provisions' is an improved formulation compared to earlier versions, especially in so far as it identifies responsible agents and abandons ambiguous 'fair benefit' language. However, I criticize two points, namely, the disappearance of 'access to other appropriate care' present in the Declaration since 2004 and the narrow scope given to obligations of access to information after research.

All these considerations, as well as the classification and reconstruction of the previous sections, were inspired by a personal 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.[63] However, I believe that readers who do not share this conception of democratic fairness will find the analytical work in this paper useful to further develop their own conceptions of post-trial access obligations.

The analysis I presented is also inspired in a dynamic conception of human ethical improvement, as exemplified by the conceptual reconstruction of section three where linguistic formulations of post-trial obligations have changed in relation to new experience available and the discussion of the most appropriate justification of the ethical principles governing research in human health. Our current understanding of how principles of research ethics should be is far from complete. So therefore it is to be 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. The change in the linguistic formulations of post-trial obligations is an expression of our work to found and propagate the most appropriate ethical principles for research with humans.

[60] E.J. Emanuel. Reconsidering the Declaration of Helsinki. *Lancet* 2013; 381: 1532–1533.

[61] Unguru et al. 2013, *op. cit.* note 19; Sofaer et al. 2009, *op. cit.* note 3.

[62] Sofaer et al. 2009, ibid, Sofaer et al. 2012, *op. cit.* note 1.

[63] This normative idea of democratic society is present for example in J. Rawls. 1993. *Political Liberalism*. New York: Columbia University Press; C.S. Nino. 1998. *The Constitution of Deliberative Democracy*. New Haven: Yale University Press.

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