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Justification, Coherence and Consistency of Provisions in the Revised Declaration of Helsinki

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Since the first version of the Declaration of Helsinki (DoH) was adopted in 1964, it has been revised nine times and numerous other bodies have promulgated ethics guidance documents. During this same period, scientific research with human subjects has dramatically increased in size, scope, and importance. If the DoH is to continue to play a significant role in regulating the research enterprise, it must convincingly convey a coherent, if highly general, view of the research enterprise and the basic normative requirements necessary to preserve its integrity and protect the rights and welfare of participants. In what follows, I argue that the emphasis in the DoH on detailed prescriptive requirements untethered from general justificatory grounds means that it is particularly dependent on readers to supply underlying normative justifications. Without these normative grounds, its provisions might appear inconsistent, unfounded, or arbitrary.

To make this argument, I provide a reading of several revised passages in the 2013 DoH. This reading draws on a normative framework that emphasizes a particular view of the proper division of labor between research and medical and public health systems and the threat that biased or poor quality research poses to those systems. It also treats various provisions of the DoH as helping to provide a public assurance to stakeholders that the research enterprise functions as a system of mutually beneficial social cooperation in which all parties are respected as free and equal contributors [1]. Although these commitments are not expressed within the DoH itself, this reading illustrates strengths and weakness of the new document and highlights areas for improvement.

Integrity of Scientific Information

The 2013 version of the DoH contains several changes that significantly expand the scope of requirements relating to the registration of research and the disclosure of findings. For example, the requirement for trial registration has been expanded from "every clinical trial" in the 2008 version to "every research study involving human subjects" (par. 35). With this expanded scope, this requirement now covers a wider range of research activities. For example, the 2008 wording would not cover sub-studies carried out within larger trials, such as biomarker studies, because these are not separate clinical trials. Such sub-studies are covered under the new language because they are research studies involving human subjects.

This expanded requirement also highlights a tension with the DoH. On the one hand, it claims to explicitly address only physicians. But to the extent that its requirements apply to every study involving human subjects, they would apply to research covered by non-physicians as well. Limiting the scope of the provisions to only research with human subjects that is conducted by physicians seems arbitrary, at best. Moreover, the requirement that research results be published has been expanded to include "publication and dissemination" and this obligation is now ascribed to sponsors as well as researchers, authors and editors (par. 36). The language of this paragraph has also been strengthened from "should" to "must" in several places, including the obligation to publish negative and inconclusive findings and to report conflicts of interest.

These concrete prescriptions assign potentially costly duties to a range of stakeholders and their requirements are not limited by disciplinary orientation or by the degree of risk posed to study participants. It is somewhat surprising, therefore, that the DoH does not contain an explicit statement of their normative grounding or justification. In particular, there have been a number of proposals recently to titrate the level of research oversight to risk as a way of reigning in what is criticized as costly regulatory overreach [2, 3]. The only explicit discussion of the "importance" of a "research objective" in the DoH is to state that it must outweigh the risks and burdens imposed on participants (par. 16, 2013). If a study poses little to no risk to participants, there is no independent ground stated in the DoH to justify requiring uniformly high oversight for it and risker or more burdensome studies.

The DoH would benefit, therefore, from an explicit statement that these requirements are justified because registration of studies and comprehensive reporting of all study data, including negative and inconclusive results, are necessary to ensure the

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reliability, relevance, and validity of scientific information. As the DoH states, the primary purpose of research involving human subjects is "to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments)" (par. 6). Reliable, relevant, and valid data are essential to the ability of the research enterprise to fulfill this purpose.

In modern health systems and health policy, many forms of research with human subjects contribute data on which clinicians, patients, researchers, institutions, policy makers, and others rely in making decisions that affect the health and welfare of individuals and groups and the allocation of scarce resources [4]. Because research data are the bedrock of evidence-based health systems and social policy, the quality and reliability of that information affects the health, welfare, and rights of the individuals who rely on those health systems to address their health needs. Even research that imposes little or no risk to study participants can generate data that is biased or of poor quality. Concerns about the quality of low risk studies have surfaced frequently in the context of postmarketing research, where decreased oversight removes incentives and safeguards against using biased evidence to advance marketing objectives, sometimes at the expense of patient health [5,6]. Similar concerns have emerged recently in biomarker studies as well [7,8].

Strengthening registration, publication and reporting requirements is justified by their contribution to ensuring the quality and reliability of research data. Ascribing obligations for registration, reporting, and dissemination of study findings to a broad range of stakeholders is also warranted because responsibility for ensuring the integrity of the research enterprise must be shared by all of the parities that assert some control over critical aspects of that process. The WMA may be uncomfortable stating moral requirements for stakeholders beyond physicians, but omitting the obligations of others would either cripple the document's ability to provide comprehensive ethical guidance across the lifecycle of research or it would lead to unfairly attributing to physicians responsibilities that vest in and must be discharged by other parties.

Responsiveness and Benefits

In several places, the 2008 DoH states that populations in which research is carried out should stand to benefit from the results of research. Paragraph 17 of the 2008 version reads, "Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research." Paragraph 33 of the 2008 version uses even broader language, "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."

Although the most direct result of research is new information and knowledge, research can also produce new interventions, improved infrastructure, and potentially lucrative financial rewards. If the core requirement for research in disadvantaged populations is that those populations benefit from participation, and if there are myriad benefits that can flow from research, then critics might wonder why research should be required to meet the responsiveness requirement at all [9].

The current revision of the DoH retains responsiveness as a requirement and eliminates this ambiguity:

Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research (par 20).

Although the responsiveness requirement will undoubtedly be subject to further criticism for vagueness, this language makes it clear that the primary consideration in evaluating research in vulnerable groups should be the relationship of the questions being investigated, and the knowledge that is expected to be generated, to the health needs or health priorities of that group.

The current version of the DoH does not contain a justification for this requirement, and some changes to the text obscure one potential justificatory ground. That is, in the 2008 version, the statement "Medical progress is based on research that ultimately must include studies involving human subjects" is followed immediately by the claim that "Populations that are underrepresented in medical research should be provided appropriate access to participation in research," (par 5, 2008). Although both claims are retained in the 2013 revision, the second now appears as an independent statement (par. 13), eight paragraphs after the former claim (par. 5). Separating these claims severs the natural justificatory link that was at least implied in the previous version.

The link that is more clearly implied in the 2008 version is that inclusion in research is necessary for vulnerable groups to share in medical progress. Excluding vulnerable groups from research stifles what is, if not the only, then the most efficient, avenue through which their distinctive health needs can be understood and addressed. If the fundamental purpose of research with human subjects is to produce the evidence necessary to improve standards of care and

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prevention, then exclusion from research creates or perpetuates evidence gaps. This means that health systems have fewer effective interventions for the distinctive health needs of excluded groups and that patients from these groups are exposed to elevated risk when they access those health systems [10].

Although the DoH is not explicit about the relationship between the requirements that have been discussed so far, there is a reading on which they can be seen as playing a crucial role in the social justification of research. On this view, the purpose of research is to produce a unique social good, namely, the information necessary to enable health systems to better understand and address the health needs of the people they serve [1, 4, 6]. This good is unique, because unlike other benefits that stakeholders seek from research participation, it often cannot be produced in any other way. Promoting access to research among underrepresented groups is thus necessary to promote equity in the capacity of health systems to meet the needs of the diverse communities that they serve. The responsiveness requirement, and the requirements relating to registration and publication are necessary to ensure that when individuals and groups participate in research, they have public assurance that they are helping to generate information that is likely to strengthen and improve the health systems on which they depend.

This kind of social justification is important because it legitimates social and individual support for the research enterprise as a collaborative undertaking [1]. In particular, medical and public health research require the support of diverse stakeholders, from researchers and institutions of scientific advancement, to public and private sponsors, participants, policy makers, and the community in whose name research is often conducted and whose interests it is supposed to advance. Many of these parties may contribute to the research endeavor for a variety of reasons. Some may seek profit, career advancement, access to medical care, prestige, or some mixture of these and other motives. These parochial motives alone cannot justify social support for the research enterprise, since not all parties seek the same parochial goals, there are often other means of advancing these ends, and because pursuit of these goals can sometimes come at the expense of other parties.

In contrast, research is often the only way to produce the evidence base necessary for health systems to effectively and efficiently meet the diverse health needs of the individuals that they serve. Because community members must rely on medical and public health services to address their basic health needs, ensuring equity in their capacity to fulfill this mission can be seen as a legitimate focus for social support and the use of social resources. When there is credible public assurance that the research system is designed to advance this goal, all of the necessary stakeholders can participate with the warranted belief that even if they each contribute in order to pursue some parochial interest, the system will not be coopted so as to siphon social support and social resources simply to advance the parochial interests of some at the expense of the others.

I am suggesting that it is useful to view the provisions discussed so far as helping to provide a public assurance to stakeholders that the research enterprise functions as a system of mutually beneficial social cooperation in which all parties are respected as free and equal contributors [1]. Because study participants are the most at risk of having their status as free and equal persons compromised in research participation, they require special assurance that their rights and welfare will be respected. Ethical principles that are traditionally viewed as forming the moral core of research ethics (such as informed consent, the minimization and justification of risk, and protections for confidentiality) can then be seen as special requirements necessary to ensure proper respect for study participants as free and equal.

The 2013 DoH contains a new provision that can be read as trying to ensure that participant interests are not compromised through research participation. It holds that, "Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured" (par. 15). If the legitimate social purpose of research is to generate a public good – the evidence base for effective and equitable health systems – then compensation for study-induced harms can be grounded in reciprocity. The DoH does not specify who bears this obligation and it would seem unreasonable to saddle researchers alone with it since other stakeholders who contribute to and benefit from the enterprise are better situated to effectuate it.

Similarly, the new paragraph 34 holds that, "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." This duty is ascribed to multiple stakeholders and the more general language of benefit sharing from the 2008 version has been replaced with specific emphasis on participants who need access to study interventions.

On the reading I have been proposing, this provision fits into a larger view of the proper division of labor between research and medical and public health systems. The social function of research is to generate the evidence necessary to improve the standard of care and prevention and it falls to medical and public health systems to provide access to this improved care on a large-scale basis. When research is contemplated in places where this division of labor may not

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take place, requiring strong assurance that research is relevant to health needs or priorities of the less-advantaged increases the likelihood that information and interventions will later be integrated into the health systems that serve those populations. However, the time horizon for the process of integrating new findings or interventions into health systems can be protracted. The requirement in paragraph 34 ensures that there is some meaningful continuity in the care that is provided to participants whose health depends on access to study interventions until the responsibility for providing access to an improved standard of care can be effectively discharged within the regular health system.

Critics may counter that even if these conditions are met, there is no guarantee that host communities will receive a fair level of benefit from hosting research. After all, most studies do not vindicate successful interventions. Three brief points about this objection are worth considering. First, it is not at all clear what a fair level of benefit is for hosting a research study and the most prominent accounts of this matter are underdeveloped, at best, and internally inconsistent at worst [11]. Second, rigorously designed and well-executed trials that produce negative findings do contribute to the evidence base necessary to improve the standard of care – if they are published. Granted, this is not an immediate benefit to communities. But compliance with the requirements discussed above increases the prospect that host communities will have access to the long-term benefits that come from increased understanding and the eventual development of interventions that can bridge health gaps.

Third, there is a genuine concern that studies might be carried out in ways that divert local resources from other health priorities, consume scarce resources, or otherwise burden members of communities that already suffer from problems rooted in poverty and deprivation. These are legitimate concerns and it would strengthen the DoH if it contained a statement to the effect that research conducted in resource scarce environments must mitigate the prospect of these deleterious effects and should make positive contributions to strengthen the capacity of local health systems.

Reasonable Risk

In the previous section I suggested that standard research ethics requirements regarding informed consent and the reasonableness of risk can be seen as helping to provide public assurance to potential participants that their moral status and their interests will be respected in the course of research participation. The 2013 revision of the DoH includes a new provision in paragraph 17 that adds to this assurance, namely, that "Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher." However, other revisions are somewhat puzzling.

The 2013 DoH retains language from the 2008 version to the effect that physicians must not be involved in research unless they are confident that the risks have been "adequately assessed and can be properly managed." The 2008 version then states that, "Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results" (par. 20, 2008). The claim that studies must be stopped when findings of benefit or lack thereof are conclusive seems to follow directly from the scientific purpose of research and from concern for the welfare of study participants. Once there is conclusive proof that risks of an intervention outweigh its benefits, or its beneficial effects have been confirmed, the study question has been answered and there is no longer a social purpose that justifies exposing participants to study-related risks.

The language form the 2008 version may strike readers as too simplistic since, for example, it may be difficult in practice to know when the results of a single study represent "conclusive proof." The new version retains this language, however, and reads, "When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study" (par. 18, 2013). If the risks of participation are found to outweigh potential benefits or there is conclusive proof of definitive outcomes, on what basis would a trial be continued? Where the 2008 version states a condition for stopping studies based on confirmation of risks and benefits, the proposed revision opens the possibility that studies could continue after these issues have been conclusively established without providing substantive guidance about how clinicians should make such decisions. Moreover, continuing a study once "risks are fond to outweigh the potential benefits" seems to undermine any public assurance to participants that their interests will not be knowingly compromised through study participation.

To avoid inconsistency, either the old language should have been retained or the new language should have been be clarified. For example, it might be revised to say that as evidence mounts to indicate that potential benefits do not outweigh risks or that confirms beneficial results, physicians must assess whether to continue, modify or immediately stop the study.

Conclusion

I have tried to provide a reading of the 2013 DoH that integrates some of its key provisions within a coherent, general view of the research enterprise and the central ethical challenges that it has to address. Although this analysis draws heavily on normative foundations not explicitly stated

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in the DoH, it is clear that those concerns are not alien to the document. This analysis highlights ways in which many proposed changes increase the coherence and comprehensives of the document while indicating particular areas where difficulties and inconsistencies remain. Because the DoH is not explicit about these foundational issues, however, it is vulnerable to appearing inconsistent, unfounded, or arbitrary to readers who approach it with different interpretive starting points.

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From Justifying Inclusion to Justifying Exclusion of Study Populations: Strengths and Limitations


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Since the 2000s, international ethical guidelines for human subjects research increasingly emphasize that exclusion from research participation must be justified. Despite increased use of inclusive selection requirements for the choice of study populations, it has so far not been evaluated what the moral strength of these requirements is and who should ensure that study populations are inclusively selected.

Methods

We analysed inclusive selection requirements or statements on justifying the exclusion of study populations in ethical guidelines on human subjects research.

Results

We found that most ethical guidelines focus on inclusive selection requirements

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