Protections for clinical trials in low and middle income countries need strengthening not weakening

The latest revision of the Declaration of Helsinki weakens protections for trial participants in low and middle income countries. Rafael Dal-Ré and colleagues argue that this is a step in the wrong direction.

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Debate over how to ethically balance the risks and benefits generated by clinical research has been ongoing for over 25 years. This is especially challenging for clinical research conducted by entities from high income countries in poorer countries. In particular, there is concern that funders and investigators from high income countries may exploit participants in low and middle income countries (LMICs). People living in impoverished communities with limited access to adequate healthcare may be more willing to accept the risks and burdens of trial participation than those with better access to resources, while their relative lack of power undermines their ability to claim a fair share of the benefits that result from the trials.

The World Medical Association’s Declaration of Helsinki was established to guide the ethical conduct of medical research. Successive revisions to the declaration, which sees its 50th anniversary this year, have provided increasing protection for research participants in LMICs. The 2008 version specified that research participants are entitled to share in the benefits that result from the studies in which they participate, including access to interventions identified as beneficial in the study or to “other appropriate care or benefits” (table 1\(^\dagger\)). This change was made in recognition of the fact that many trials conducted in LMICS were failing to provide any benefits to trial participants in those countries. For example, a review of trials conducted between 2004 and 2007 in tuberculosis (n=23), malaria (n=67), and HIV/AIDS (n=222) in developed (58%) and developing countries (42%), found that only 1.3% mentioned post-trial provisions.\(^5\) Unfortunately, the 2013 version of the declaration omits reference to “other appropriate care or benefits” and limits the scope of possible benefits to interventions “identified as beneficial in the trial.” This ignores the fact that many trials do not result in an effective intervention. We argue that the provisions need strengthening.

Promoting justice and fairness in trials

To fulfil the principle of justice,\(^6\) vulnerable research participants should not be enrolled in studies that pose significantly greater risks than the benefits they offer. The Helsinki declaration initially focused on the risks and benefits to participants. The original 1964 version stated that the enrolment of patients in clinical trials must be justified by its therapeutic value for the patient, and revisions in 1975 added the requirement that the risks to participants should be minimised. However, it became clear that these requirements do not preclude external funders and investigators from conducting trials in LMICs that benefit only, or primarily benefit, people in high income countries.

In an attempt to counter this concern the Council for International Organisations of Medical Sciences (CIOMS) introduced the “reasonable availability” requirement into its 1993 ethical research guidelines.\(^7\) This requirement mandates that products identified as effective during a trial should be made reasonably available to the participants and the host community at the completion of the trial. Reasonable availability was added to the 2000 version of the Helsinki declaration, although it was limited to study participants and did not cover the host community (table 1\(^\dagger\)). Although this addition increases the protections for trial participants in LMICs,\(^8\) it is not sufficient to protect vulnerable individuals from exploitation because of the low chances that a trial will result in a successful treatment.\(^9\)

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**Likelihood of benefit**

The development of a new medicine requires the successful completion of a stepwise process involving a number of trials. Phase I trials, typically conducted in healthy volunteers to assess safety, are followed by phase IIa trials of “proof of concept” and phase IIb trials for “dose finding” in participants with the condition of interest. Phase III pivotal studies for efficacy are conducted in a larger number of participants to ensure the intervention results in the clinical outcome of interest. Data show that medicines approved by the US Food and Drug Administration needed a mean of 3.7 pivotal trials, with 2.7 yielding significant positive results and the remainder inconclusive or negative results.16

The process of bringing new medicines successfully to market is long and risky (table 2). Only 11% of new molecular entities starting phase II trials are eventually marketed.17 Thus, for instance, when conducting a phase IIb trial the chances of success are very limited. Only 34% of products will end up with an appropriate dose to be tested in phase III,18 with 81% of failures being due to an unfavourable efficacy or safety profile.19 Thirty per cent20 of all new medicines starting phase III fail to conclude it, of which 52% do not show the expected efficacy and 35% do not show an acceptable safety profile.21 Even if the phase III trial is successful (that is, the new drug is submitted to regulatory agencies for approval), participants in a phase IIb trial must wait an average of 3.5 years for the eventual marketing authorisation.22 The median length of the clinical phase (I, II, and III) for new drugs approved during 2005-09 was shortest for HIV drugs (3.6 years) and longest for immunological agents (7 years).23

In short, in the best scenario, participants in a phase IIb trial have little more than 10% chances of having contributed to a new product that will be marketed after more than 3.5 years after the conclusion of their study. Is it fair to ask participants (and their community) to wait at least 3.5 years to gain benefit (being treated with the new drug if still needed) for their participation in the trial, acknowledging that in some 90% of cases this will never happen? Sometimes participants in a phase III trial of a chronic condition are able to join a follow-up extension study until the medicine is marketed,24 but this is not common and there are many non-chronic conditions for which this is not possible.

Since most trials with investigational medicines yield negative results, the reasonable availability requirement implies that the participants of these trials are not entitled to any benefits, despite the fact that they are exposed to risks and burdens.

**How to balance benefits and risks**

Ethicists and experts therefore argued that research guidelines need to go beyond reasonable availability to protect participants and host communities in LMICs.7 10-22 In 2001, a group of experts from Western and African countries convened in Malawi and developed the fair benefits framework.23 As well as requiring that external sponsors conduct trials in LMICs only when they are designed to address health problems of the host community, it suggests that it is the level of benefit and not the type of benefit that is important and expands the options beyond the trial intervention. This framework expands the benefits that might be provided to participants and host communities to include ancillary health services, training of healthcare staff, or development of research and medical care capacity.24 For example, a series of five HIV/AIDS trials in South Africa provided education on HIV to the host communities.25 Another group conducting intervention trials in Bangladesh, India, Malawi, and Nepal provided various benefits, including essential equipment and drugs and training of local health providers in newborn care.26 Investigators conducting public health interventions in Asia provided emergency transport and access to acute healthcare services.27

It is clear that including a broader range of benefits increases the chances that participants and host communities will receive sufficient benefits and justice. As a result, in 2002, the CIOMS guidelines27 expanded beyond the reasonable availability requirement to include possible provision of treatments for conditions unrelated to the trial. Similarly, the 2004 clarification of the Helsinki declaration included the possibility of providing participants access to “other appropriate care,” and this was broadened in 2008 to allow for the provision of “other appropriate care or benefits” when needed to address the potential for exploitation (table 1).

**Current problems**

Although these expansions help to reduce the potential for exploitation, they remain limited in two important ways. Firstly, the requirements are limited to study participants and do not include the host community, despite the fact that host communities provide important support for research studies and can be exposed to burdens for the benefit of others.28 Secondly, they do not describe what level of appropriate care or benefits should be provided to address the potential for exploitation. Unfortunately, rather than tackling these deficiencies, the 2013 revision removed the provision for other appropriate benefits. The process for the revision included consultation with many stakeholders, including four expert conferences, extensive discussion with representatives from Africa and Asia, and issuing a draft revision for public comment.29 The draft included the following addition to paragraph 20: “Consideration should also be given to ensuring that the community receives a fair level of additional benefits.”30 This requirement built on the earlier advances of expanding the range of potential benefits that can be provided and also clarified that the level of benefits that is provided must be fair. However, this clause was deleted from the final approved version after Indian and South African Medical Associations expressed concern that allowing funders and investigators to provide a broader range of benefits to LMICs would increase the potential for coercion and undue inducement.31

Since coercion involves threatening to harm individuals physically, psychologically, financially, or in other ways if they decline to enrol in research,32 we do not believe that expanding the range of benefits that could be provided to people in LMICs will increase the potential for coercion. In contrast, undue inducement involves offering individuals benefits that cloud their judgment to the extent that they may enrol in trials contrary to their interests and better judgment. Rather than dealing with this concern by reducing or eliminating the provision of other benefits, a better approach would be to ensure that research trials do not pose excessive risks and that they offer participants sufficient benefits.33 This would ensure that enrolment would not be contrary to participants’ interests and also reduce the potential for exploitation. The Helsinki declaration should specify that external funders, host investigators, and research ethics committees are responsible for ensuring that trials in LMICs do not pose excessive risks and offer a fair level of benefits to participants and host communities, based on the risks and burdens they face and the extent to which others benefit from their involvement in the research.
When a trial of an experimental medicine is being discussed between the external sponsor and the host country stakeholders—investigators, research ethics committees, health authorities, and community representatives—it is impossible to foresee whether the product will eventually reach market. Since trial participants (and their community) will have little or no benefit from the “knowledge and practices” derived from the conduct of many trials, a requirement for fair benefit will help to ensure that those in LMCs are not exploited.\(^7\)\(^{23}\)

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Key messages

The 2013 Declaration of Helsinki fails to assure justice and fairness for participants and host communities in international trials in low and middle income countries.

Limiting benefits solely to drugs and vaccines identified as successful within a trial will often mean participants and their communities receive no benefit.

The declaration should be revised to allow a broader range of benefits and specify that the level of benefits should be fair.

In the meantime, funders, host investigators, and research ethics committees should recognise the option of providing a broader range of benefits to ensure that individuals living in low and middle income countries are not exploited.

Tables

| Table 1 | Changes relating to benefits for clinical trial participants and communities in Declaration of Helsinki, 2000 to 2013 |
|---------|--------------------------------------------------------------------------------------------------------|
| Edinburgh, 2000 | Note for clarification, 2004 | Seoul, 2008 | Fortaleza, 2013 |
| 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 | 14. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits | 22. In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions |
| 17. 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 | 20. 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 |
| 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 | 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 | 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 |
| 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 | | |
Table 2 | Data on clinical development of new medicines

| Phase I | Phase II | Phase III |
|---------|----------|-----------|
| Success rates (%) | 54 | 34 | 70 |
| Average cycle time (years) | 1.5 | 2.5 | 2.5 |
| Probability of success to market from key milestones, 2006-08 (%) | 5 | 11 | 66 |

Causes of failure: 2011-12 (%):

| Efficacy | 59 | 52 |
| Safety | 22 | 35 |
| Other | 19 | 13 |

Median No of participants, 2000-10:

| Standard medicine | 1708 |
| Orphan medicine | 438 |

Median review time for a drug application during 2001-10 was 322 days for the Food and Drug Administration and 366 for the European Medicines Agency; 91% of submissions are successful.