

research institutions, NGOs, patient representatives, sponsors, government agencies and other stakeholders. ICMR Bioethics Unit, National Centre for Disease Informatics and Research (NCDIR), and Clinical Development Services Agency (CDSA) under the Translational Health Sciences and Technology Institute (THSTI) have further collaborated in organising four such events on November 30, 2017 at Ahmedabad, on December 21, 2017 at Visakhapatnam, on February 22, 2018, at Kochi and on March 8, 2018 at Guwahati. Many more dissemination programmes and trainings are being planned across the country during this year to reach out to people and create awareness. The Guidelines have also been made available on the ICMR website (www.icmr.nic.in) and on the NCDIR website (www.ncdirindia.org) and can be downloaded at no cost.

Clinical trials for marketing approval are regulated under The Drugs and Cosmetics Act and Rules (6) and biomedical and health research must follow the ICMR National Ethical Guidelines. There is therefore a need to harmonise and make sure that research participants whether participating in clinical trials, or basic or applied biomedical, health or socio behavioural research, are protected.

In our country, ethics is, unfortunately, still not part of the existing teaching curriculums in both the medical and non-medical streams. This influences both the quality of output in biomedical and health research and the protection of human participants for which the ethical conduct of research is essential. The ICMR National Ethical Guidelines document sets the standards for the ethical requirements to be followed in biomedical research in India. It is expected that all biomedical and health research in the country should follow this guidance which will go a long way towards improving the quality and outcomes of research.

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Benefit sharing in the revised Indian National Ethical Guidelines for Biomedical and Health Research Involving Human Participants

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Abstract

Though not an ethical principle per se, benefit sharing is still an important tool to achieve justice in international research.

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It comes back as a transversal issue through the revised Indian Ethical Guidelines for Biomedical and Health Research Involving Human Participants (hereafter referred to as "the Guidelines"). The guidelines invoke this principle with reference to the responsible conduct of research, ownership of biobanks and data repositories, informed consent process, community engagement, international collaborative research, and research in emergency or disasters, while using the phrase "maximization of benefit" instead of "benefit sharing". This approach may be seen as quite innovative, in that it sees benefit sharing (ie, maximisation of benefit) as a key ethical requirement. Unfortunately, it does not explicitly state that the principle is relevant to all research involving human participants, not only to specific situations such as biobanks,

research in emergencies and international collaborations; rather it appears to consider the risk of lack of benefit sharing as mainly related to international collaborations. Another important drawback is the frequent use of noncommittal language such as “could be considered” and “may be offered”. This suggests that the provisions with respect to benefit sharing are not mandatory and thus open to the discretion of different Ethics Committees. Therefore, for the Guidelines to become a positive model for other countries and ethics bodies, further elaboration of the principle and mode of implementation is needed.

Introduction

Middle-income countries (MICs) are playing an increasingly important role in biomedical and health research. From an ethics perspective, the eventual financial and other rewards of such research should always be fairly shared with research participants and their communities (1). For instance, if a clinical trial conducted in an MIC contributes to reaching positive conclusions regarding a new intervention, that intervention should become available to the community in which the trial was conducted (2). If human biological samples are collected from a vulnerable community during an infectious disease outbreak, any results from research conducted on those samples should be made available to the community using all possible “access mechanisms” (3).

These requirements are generally framed under the concept of “benefit sharing”. Even though not an ethical principle per se, benefit sharing is an important tool to achieve justice in international research (4). But unlike other ethical requirements that are widely accepted and adopted, such as independent ethics review of research protocols and informed consent procedures, benefit sharing is still poorly understood and implemented, including by many key research stakeholders, such as researchers, sponsors, regulators and, sometimes, ethics committees. Till date, there is no general, straightforward, transdisciplinary definition of benefit sharing in medical research. An unambiguous definition was proposed only for genetic resources, ie, the action of giving a portion of advantages / profits derived from the use of human genetic resources to the resource providers, in order to achieve justice in exchange, with particular emphasis on the clear provision of benefits to those who may lack reasonable access to resulting products and services (4).

Benefit sharing, considered at different levels, should include the research communities and society as a whole. At the community level it is especially relevant when the research is conducted with socially vulnerable and/or economically disadvantaged groups. For instance, in its commentary on guideline 2 (on research conducted in low-resource settings), the CIOMS guidelines state that when research is conducted in low-resource settings, “From the inception of research planning, it is important to ensure full participation of communities in all steps of the project, including discussions of the relevance of the research for the community, its risks and potential individual benefits, and how any successful

products and possible financial gain will be distributed, for example through a benefit-sharing agreement” (5:p. 5). Article 15 of the UNESCO Universal Declaration on Bioethics and Human Rights (6) states that the “benefits resulting from any scientific research and its applications should be shared with society as a whole and within the international community, in particular with developing countries;” provided that they do not “constitute improper inducements to participate in research.” Such benefits may take various forms, (eg, special assistance to those who take part in the research, access to quality healthcare, provision of products stemming from research, support for health services, access to scientific and technological knowledge, capacity-building facilities for research purposes, etc) (6). Emanuel and colleagues contend (1), in their framework for clinical research conducted in developing countries, that recruited participants and communities should “receive benefits from the conduct and results of research;” through fairly sharing “financial and other rewards of the research”. Unfortunately, the current Helsinki Declaration (7) omits an explicit reference to a fair level of additional benefits for the community (8, 9). The Good Clinical Practices (GCP) code of the International Conference of Harmonisation (ICH) is completely silent on the notion of benefit sharing (10). Even though not a guideline document for ethics, the ICH GCP code is a *de facto* guide for national legislators and funding agencies assessing, reviewing and prioritising research; thus, principles and standards that are not addressed in the ICH GCP are very likely to go underfunded or poorly implemented (11). In the absence of a national or international legislation enforcing it, it is entirely up to the research sponsors and funders to decide how far they wish to go in applying the principle of “benefit-sharing” (11-13).

Benefit sharing in ICMR’s revised national guidelines

In 2017, the Indian Council of Medical Research (ICMR) issued the revised National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, applicable to all biomedical, social and behavioural science research for health conducted in India and involving human participants, their biological material and data (14)*.

As a principle

“Benefit sharing” is not mentioned as a principle as such in the guidelines. However, the Statement of General Principles lists the “principle of maximization of benefit”, and strongly suggests incorporating the concept of benefit sharing such that “due care is taken to design and conduct the research in such a way as to directly or indirectly maximize the benefits to the research participants and/or to the society” (1.1.8). It is noteworthy that the 2006 version of these Guidelines mentioned both the “principles of the maximization of the public interest and of distributive justice”, whereby “the research or experiment and its subsequent applicative use are conducted and used to benefit all human kind and not just those who are socially better off but also the least advantaged; and in particular, the research participants themselves and

or the community from which they are drawn" (15:p. 6). The phrase "benefit sharing" is not adopted in either version of the Guidelines, but the proposed formulation seems more focused and straightforward, and is complemented by the principle of reciprocity (invoked under the heading "Public Health Research"), which requires that "individuals or communities, who have borne a disproportionate share of burden or risks for the benefit of others be given some form of benefit. The benefit should be context specific, such as protection from further exposure, access to food, healthcare, clothing and shelter, communication or compensation for lost income" (14:sec 8.1, p 95). Importantly, in both versions of the Guidelines, the chapter on General Ethical Issues includes a specific provision on "ancillary care," ie, "participants may be offered free medical care for non-research-related conditions or incidental findings if these occur during the course of participation in the research, provided such compensation does not amount to undue inducement as determined by the EC" (2.7.1).

As a transversal issue

"Benefit sharing" often comes through the document as a transversal ethical issue, differently worded in different sections.

First, it is stated in relation to distributive justice that "plans for direct or indirect benefit sharing in all types of research with participants, donors of biological materials or data should be included in the study, especially if there is a potential for commercialization. This should be decided a priori, in consultation with the stakeholders, and reviewed by the Ethics Committee (EC)" (2.4.4). This reflects the general approach of the 2006 Guidelines (15). Interestingly, the "post-trial access of research benefits to participants and their communities" is mentioned elsewhere as an example of contemporary ethical issues under debate in biomedical and health research (3.1.2), even though it was already covered extensively in the previous version (15:p 30).

Second, it is stated under "post research access and benefit sharing" that benefit sharing should be modulated at different levels: "the benefits accruing from research should be made accessible to individuals, communities and populations whenever relevant" (2.11). Some concrete suggestions are provided as to how the principle may be translated into practice, which were already present in the Guidelines of 2006: "Sometimes, more than the benefit to the individual participant, the community may be given benefit in an indirect way, by improving their living conditions, establishing counselling centres, clinics or schools, and providing education on good health practices" (2.11).

A third level of benefit sharing appears, as in the previous Guidelines, with respect to "collaborative research," "international collaboration in biomedical and health research," and "research undertaken with assistance and/or collaboration from international organizations" (3.8.1), where scientific benefits should be fairly shared with local researchers: "the

participating centres should function as partners with the collaborator(s) and sponsor(s) in terms of ownership of samples and data, analysis, dissemination, publication and intellectual property rights (IPR) as appropriate. There must be free flow of knowledge and capacity at bilateral/multilateral levels" (3.8.1.); "Indian participating centres should function as partners with the collaborator(s) and sponsor(s) in terms of ownership of samples and data, analysis, dissemination, publication and IPR related to research in India, as may be considered appropriate" (3.8.3); and "researchers and EC members should be trained to understand and recognize ethical perspectives that reflect India's best interests" (3.8.3). It notes that the need for "an ethical framework based on equality and equity" to guide such collaborations is due to the "different levels of development in terms of infrastructure, expertise, social and cultural perceptions, laws relating to IPR, ethical review procedures, etc." (3.8.3)

The collection, storage and export of biological samples, always subject to ethics review, is a fourth area related to benefit sharing. The Guidelines state: "if there is exchange of biological material involved between collaborating sites, the EC may require appropriate Memorandum of Understanding and/or Material Transfer Agreements (MTA) to safeguard the interests of participants and ensure compliance while addressing issues related to confidentiality, sharing of data, joint publications, benefit sharing, etc."; "any research involving exchange of biological material/specimens with collaborating institution(s) outside India must sign an MTA justifying the purpose and quantity of the sample being collected and addressing issues related to confidentiality, sharing of data, joint publication policy, IPR and benefit sharing, post analysis handling of the leftover biological materials, safety norms, etc." (3.8.1.). The Guidelines explicitly address benefit sharing issues in relation to biological materials, biobanking and datasets: "biological materials and/or data have potential commercial value, but the participants' contribution and their share in this benefit is very often not known to them", thus the informed consent document should "emphasize this aspect, with necessary clauses for clarity about benefit sharing", and "describe whether donors, their families, or communities would receive any financial or non-financial benefits by having access to the products, tests, or discoveries resulting from the research" (11.4.5). Also, "the benefits accrued, if any, should be returned to the communities from where the donors were drawn in community-based studies; and to the maximum extent possible, benefits should be indirect or in kind".

Fifth, the Guidelines clearly recognise that issues related to benefit sharing should be considered and reviewed by ECs, by looking at "how the benefits of the research will be disseminated to the community". They also clarify that "post research plan/benefit sharing" is one of the elements that should be reviewed by an EC "if research on biological material and/or data leads to commercialization"; and that in human genetic testing research, the consent form may include explanations/details on "issues related to ownership rights, IPR concerns, commercialization aspects, benefit sharing" (sec 7).

Finally, specific issues related to post-research benefit (which is a specific way to implement benefit sharing) arise when research is conducted during humanitarian emergencies and disasters. The Guidelines state that in such situations, “sponsors and researchers should strive to continue to provide beneficial interventions, which were part of the research initiative, even after the completion of research and till the local administrative and social support system is restored to provide regular services”(12.6). Research conducted in emergency/disaster and involving a foreign researcher/institution, should also provide benefit by helping “in developing the capacity of local researchers and sites, and provide key learning points to the policy makers and the community (12.9.5).

Discussion

The new Guidelines comprehensively cover “traditional” issues in bioethics, such as the informed consent process and independent ethics review, as well as various “contemporary issues,” such as the “use of underprivileged and vulnerable groups as participants,” “research on emerging technologies,” and post-trial access of research benefits to participants and their communities (3.1.2). The last point already present in the 2006 document, goes beyond the requirement of post-trial access “for the participants” only. It encompasses the requirement to implement benefit sharing at community level also, ie, the moral obligation to make any newly-developed therapeutic, preventive or diagnostic intervention promptly and routinely available to all those in need in the community that hosted the research.

However, since post-trial access is only applicable to studies that actually result in, or contribute to, the development of a new therapeutic, preventive or diagnostic intervention it represents only one of the possible forms that benefit sharing can take. Other benefit sharing measures have been proposed in the literature, such as access to quality healthcare for the research community, upgrade/support for the local health services, capacity-building for research and routine care purposes, etc. (16).

Since it is not mentioned explicitly, it may seem that the Guidelines do not consider benefit sharing as a central ethics principle. However, it seems to us that the principle of “maximization of benefit” may and should be read as a translation of the concept of “benefit sharing”. Rather than minimising the importance of the principle, the alternative wording emphasises the moral obligation to make the best effort to design the best (maximal) possible benefit sharing measures for each research study, based on the characteristics of the research, of the community and of any other contextual determinants. The emphasis on this principle is reiterated by the Guidelines as they underscore distributive justice as a privileged approach to build an ethical framework for research. However, the failure to use the most commonly used/accepted phrase of “benefit sharing” entails a risk that readers fail to recognise the central role given to benefit sharing (or maximisation of benefit) in the ethics review of a research protocol.

In addition to being spelt out as a principle, benefit sharing (maximisation of benefit) is a transversal issue that comes back throughout the document, with reference to the responsible conduct of research, ownership of biobanks and data repositories, the informed consent process, community engagement, international collaborative research, and research in emergency or disasters. When it comes to international collaboration in research, the Guidelines extend the concept of benefit sharing as follows: from the relation *research group-to-community*, where the research group is morally compelled to share direct and indirect benefits with the community, to the relation *international research group-to-Indian researchers*, where the international research group is morally compelled to support Indian peers to build their skills, expertise and research infrastructure. This is in line with the view of different authors—such as the NIDIAG group, which argued that transnational health research consortia should promote global health equity, among other things by advocating for an equal participation of researchers from low- and middle-income countries on platforms that govern regulation, agenda, and financing of global clinical research (17).

Quite surprisingly, however, benefit sharing (maximisation of benefit) does not explicitly appear in a few specific chapters, including those on behavioural research and on clinical trials (even if there are a few sparse mentions of post-trial access or obligations). We may assume that these cases are covered by the general principle of “maximization of benefit”, and by the general statement that ECs should always look at “how the benefits of the research will be disseminated to the community” (14: p 40). It would have been much clearer if benefit sharing had been explicitly mentioned under these headings, and especially under clinical trials, where issues like post-trial access to communities, upgrade of local infrastructures and capacity building are undoubtedly very relevant (16, 18-19). This may have been better (but still insufficiently,) addressed in the 2006 version of the Guidelines, which stated under the heading “Specific principles - Drug trials” that “after the clinical trial is over, if need [sic] the drug is found effective, it should be made mandatory that the sponsoring agency should provide the drug to the patient till it is marketed in the country and thereafter at a reduced rate for the participants whenever possible. A suitable *a priori* agreement should be reached on post trial benefits” (15: p 35).

On a more positive note, the Guidelines include a specific provision that “participants may be offered free medical care for non-research-related conditions or incidental findings if these occur during the course of participation in the research” (2.7.1). This is a very important point that challenges the common view that medical research should not be mixed with healthcare and clinical issues, and that researchers’ responsibilities are limited to meeting specific research objectives. By reiterating the call for the provision of “free medical care for non-research-related conditions or incidental findings”, the Guidelines make, to the best of our knowledge, a unique and brave statement that the researchers (and sponsors) have greater responsibilities toward the participants

not limited to the act of providing and receiving medical data and/or biological samples.

Ethics committees as key actors to ensure benefit sharing

The Guidelines give a central role to the Indian ethics committees, entrusting them with full legitimacy and power to require that the ethics principles articulated in the guidelines are translated into procedures and practices. The ECs are the gatekeepers of the concrete measures that will be taken by researchers and sponsors to protect the research participants, their communities, and (in case of international projects) the local researchers. Importantly, the ECs can and should give due consideration to cultural and local sensitivities and set extra requirements when needed. When it comes to benefit sharing (maximisation of benefit), the ECs can and should check if a research protocol is giving due consideration to the best possible measures for sharing benefits with the research participants, the research community (eg in terms of improved access to food, healthcare, clothing and shelter, compensation for lost income, access to the findings of the research...), and the local researchers (eg in terms of opportunities for training, building research skills and networks, gaining decision-making power in international research...). This is very important, since guidelines, checklists and templates from most ECs and Institutional Review Boards (IRBs) do not include "benefit sharing" among the issues to be checked/reviewed (20, 21). This may result in insufficient protection of communities that host medical research programmes and can in the worst case (but not unlikely) scenario, favour conditions for the exploitation of socially disadvantaged groups, such as those reported in the biomedical and bioethics literature (22-26), including cases from India (27-29).

Unfortunately, there is a serious drawback to the enhanced role given to ECs, ie, the language used in the Guidelines is often quite noncommittal, such as "could be considered" and "may be offered". This suggests that the propositions with respect to benefit sharing are not mandatory and thus open to the discretion of the different ethics committees. In addition, a thorough assessment of the adequacy of benefit sharing measures is a complex issue that depends on the nature of the research, the needs and vulnerabilities of the concerned community, and the characteristics of the research sponsor. Not all the ECs and EC members will necessarily be aware of the ethical relevance of such issues, nor will they be ready for this additional task. Specific training and sensitisation activities may be needed to successfully translate this important ethics requirement into routine review practices.

This is especially (but not only) important in collaborative research: research protocols will most likely also undergo ethics review in the country of the sponsor, where the concerned EC will not necessarily focus on benefit sharing measures. The Guidelines explicitly state that "a mechanism for communication between the ECs of different participating centres should be established" and that "in case of any conflict, the decision of the local EC based on relevant facts/guidelines/

law of the land shall prevail" (3.8.2). Therefore, when it comes to benefit sharing, it is especially relevant that the Indian ECs are able to take on their role of gatekeeper, and when needed also inform and educate their peers abroad.

A model approach towards benefit sharing

The approach of the new Indian Guidelines to sharing benefits with research communities, that is, a transversal ethics requirement that should be implemented (and maximised) in all research, and the adequacy of which must be verified by the ethics reviewers, could be seen as a positive model to be implemented in other countries and by other bodies. This approach does not imply that benefit sharing measures are "mandatory" in any research, but rather that the researchers should either describe them or explicitly justify why they are absent.

However, before this may happen in practice, some important improvements are needed. First, the phrase "benefit sharing" should be used instead of "maximization of benefit", for consistency with other ethics guidelines, for reader friendliness and for clarity. Second, it should be explicit that this transversal requirement is relevant to *all research involving human participants, data and samples*, and not only to specific situations like biobanks, research in emergencies and international collaborations. Third, the document gives the impression that the risk of lack of benefit sharing, and thus of exploitation in research, is mainly or only related to international collaborations, ie research conducted in India by foreign researchers and sponsors. While the potential for exploitative practices may surely be magnified in externally-sponsored research (as already stated in the 2006 document), we note that the possibility of exploitative practices is real, and should not be neglected, also in the absence of interests from abroad.

Lastly, the Guidelines are quite complex and not easy to read, thus they are not adequate to be used as a practical manual. For instance, somebody reading only the chapter on clinical trials will not learn about benefit sharing and would ignore or neglect this requirement: he/she would have to read the whole document to understand that ECs should always look at "how the benefits of the research will be disseminated to the community" irrespective of the kind of research and including clinical trials. To make the Guidelines a practical tool, there should be a pathway to implementation and practical guidance, to help ethics reviewers translate the principles into a handy guidance for the review processes. This may be achieved, for instance, by developing standardised training modules for new members of the ECs, and by proposing some model review templates that may be adopted by ECs for the different kind of research. For instance, with reference to the topic covered in this paper, such templates would always include a field on "benefit sharing" to guide the ethics reviewer to systematically check against each protocol whether measures for benefit sharing are needed, and if so, whether they are included, and adequate.

Conclusions

The approach of these Guidelines to research benefit sharing (maximisation of benefit) is quite innovative, in that it sees it as a transversal ethics requirement that should always be implemented for the benefit of local communities and local researchers. However, some important improvements are needed before they may be used as a handy guidance by Indian ECs or proposed as a model for other countries and ethics bodies.

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