Guidelines and Guidance

The Ancillary-Care Obligations of Medical Researchers Working in Developing Countries

Participants in the 2006 Georgetown University Workshop on the Ancillary-Care Obligations of Medical Researchers Working in Developing Countries

Wherever medical resources are scarce and access to medical care is limited, as in most of the developing world, medical researchers face difficult issues about providing medical care beyond the purview of their research. In a vaginal microbicide trial enrolling sex workers in Benin, for instance, the researchers arranged for the sponsors to pay for the care of a participant with an extrauterine pregnancy unrelated to the microbicide [1]. In a study of tuberculosis preventive regimens for HIV-infected adults in Soweto, South Africa, all participants received free follow-up HIV care—except for antiretrovirals—as part of the protocol (personal communication, R. Chaisson). In these cases, working in partnership with local health care providers, researchers found ways to provide their study participants ancillary care: care that they needed, but that was required neither to successfully answer the scientific question nor to avoid or mitigate harm resulting from participation in the research [2,3]. The researchers' actions in these cases seem admirable, but are they typical? Are they required by the ethics of medical research? No one can say, as the issue of medical researchers' ancillary-care obligations has not been systematically examined and guidance is lacking. We aim to help rectify this lack of guidance by offering a suggested framework, focusing on the urgent context of ancillary-care needs in the developing world.

An Increasingly Pressing Issue

With the rise of multidrug-resistant and extensively drug-resistant tuberculosis, the scaling up of HIV prevention trials, the increasing prevalence of chronic diseases as the population of developing countries attains a greater average age, and the spread of immunosuppression resulting from the AIDS epidemic, ancillary-care challenges in developing countries will become more prevalent and more difficult. Yet there are also new opportunities, as such initiatives as the Global Fund to Fight AIDS, Tuberculosis and Malaria have enhanced the resources available for global health research and for the purchase of medicines and other therapies. Investigators, organizations, and companies doing medical research, both from host and sponsoring countries; those normally responsible for the study population's health care; research ethics committees and institutional review boards (generically, RECs); and the populations under study need guidance about the nature and extent of researchers' ancillary-care obligations.

The Guidelines and Guidance section contains advice on conducting and reporting medical research.

Summary Points

- Medical researchers, particularly those working in developing countries, as well as their sponsors, have some ancillary-care obligations.
- Ancillary-care obligations are positive obligations to provide care that participants need but that is required neither to successfully answer the researchers' scientific question nor to avoid or mitigate harm resulting from participation in the research.
- The ancillary-care obligations of such researchers and their sponsors are not limited to addressing the disease or condition that is the target of the research, nor do they center on that disease or condition.
- Existing guidelines for research do not adequately address ancillary-care obligations.
- Consideration of the "four P's" (positive obligation, planning, partnership, and practical steps: Box 1) and of "three questions" (of needs, alternatives, and the strength of obligation: Box 2) will help to address and direct the development of useful guidance.

Existing Guidance Unsatisfactory

Medical researchers working in developing countries clearly cannot meet all of the ancillary health needs of research participants, consistently with pursuing their scientific goals. Accordingly, some of the broad, positive declarations in existing research ethics guidelines ring hollow when applied to this issue. For instance, the Declaration of Helsinki states that "the health of my patient will be my first consideration" [4]. Physician–researchers who seek to follow this dictum will

Funding: The workshop from which this paper derives received generous funding from the Reflective Engagement Initiative at Georgetown University, with additional support from Georgetown University's Department of Philosophy, the Kennedy Institute of Ethics, and the PhRMA Foundation. These entities played no role in shaping the content either of the workshop or of the resulting paper. The views expressed here are those of the individual coauthors and do not represent the views of any of the organizations or institutions with which they are affiliated.

Competing Interests: See statement at end of article.

Citation: Participants in the 2006 Georgetown University Workshop on the Ancillary-Care Obligations of Medical Researchers Working in Developing Countries (2008) The ancillary-care obligations of medical researchers working in developing countries. PLoS Med 5(5): e90. doi:10.1371/journal.pmed.0050090

Abbreviations: REC, research ethics committee; UNAIDS, Joint United Nations Programme on HIV/AIDS

encounter difficulties when their participants in a medically underserved area develop health needs that outstrip the research team's resources or plans; for example, when a rural participant in a study of vitamin A deficiency is found to have cancer treatable only at the tertiary-care hospital in the capital of the neighboring country. Taking the Helsinki dictum directly to generate ancillary-care obligations would yield an unreasonably expansive requirement. Ethics guidelines that more specifically address ancillary-care issues are rare. It is more common for guidelines to cover the adjacent but distinct issues of post-trial availability or "trial-related" adverse events [5,6]. An example of sound, but fragmentary, guidance on ancillary care may be found in Joint United Nations Programme on HIV/AIDS (UNAIDS) Guideline 16, which calls for "a comprehensive care package" for participants of HIV vaccine trials to be agreed upon on a basis of "host/community/sponsor dialogue" [7]. This view is also taken by the Nuffield Council on Bioethics [8].

One of the most explicit statements about ancillary care is the statement in the Commentary to the Council for International Organizations of Medical Sciences' Guideline 21 that "although sponsors are, in general, not obliged to provide health care services beyond what is necessary for the conduct of research, it is morally praiseworthy to do so" [5]. This guidance might be interpreted either as implying that there is no moral obligation to provide ancillary care or simply as indicating that the moral obligation belongs to people other than the research team. We agree that these obligations may well be best discharged by seeing to it that participants get care from others. This means that being familiar with local health care resources will itself sometimes be morally obligatory, and not merely praiseworthy.

Dialogue and planning are crucial, but cannot fruitfully proceed in a vacuum. As both our experience and anecdotal evidence suggest, many researchers and research sponsors working in developing countries, as well as their local collaborators and the populations under study, strongly feel a need for clearer guidance about ancillary care. Leaving the moral burden of assessing ancillary-care claims and the logistical burden of planning for them in the hands of individual principal investigators is unfair, unduly exposing them to controversy and to charges of unethical behavior. It is also inefficient and unlikely to ensure that ancillary care is always provided when it should be.

Whose Responsibility?

Although principal investigators and members of their research teams are on the front lines of ancillary care, ancillary-care obligations also fall upon the sponsors (funders) of medical research. It seems unreasonable to assume that researchers who carry out their ancillary-care obligations by tending to the urgent ancillary needs of their research participants are hijacking resources that ought to be devoted solely to research purposes. As we argue below, tending to these needs is an integral and necessary part of ethical research with human beings. Research sponsors should support principal investigators and their research teams in carrying out their front-line ancillary-care obligations, whether by supplementing study budgets or by reinterpreting or easing restrictions on providing care that is not "study-related." Sponsors should not simply respond to requests that reach them to provide support for ancillary care, but should require that, in any research proposal, due attention be paid to defining and costing appropriate ancillary-care implications.

A Middle Position on Ancillary-Care Obligations

Companies and individuals doing medical research in developing countries who are able to alleviate the dire effects of medical scarcity there have some obligation to address the unmet health needs of their study participants, but how far does this obligation extend? On one side, we reject expansive arguments that would analyze medical researchers' obligations directly in terms of duties to remedy global injustice. On the other side, we reject a narrow understanding according to which medical researchers, being scientists first and foremost, owe study participants no ancillary care, only that medical care needed to bring the research study safely to completion.

One version of the expansive position holds that, the world being pervasively unjust, medical researchers from the developed world and their sponsors have a duty to do all they can to address all of the ancillary-care needs they encounter [9,10]. There are four objections to this position. First, there is no reason why those engaged in non-exploitative medical research—and there are better safeguards in place today to prevent exploitation in research than there were a decade ago—should bear a greater part of the burden of addressing global injustice than does any other citizen of the developed countries. Second, medical research in general, and in particular much of the medical research conducted in developing countries, is directed towards easing people's health burden, which, in the developing world, is severe. Meeting all encountered ancillary-care needs would strain budgets and monopolize the scarce time of trained personnel. Unlimited ancillary-care demands would impose heavy costs on medical research and would very likely have an inhibitory effect. Therefore, imposing this level of cost on the research enterprise is ethically unreasonable. Third, if researchers working in developing countries addressed all or even most of their participants' unmet health needs via their research studies, that might unduly tempt people to enter these studies. While ethical concern with undue inducement is sometimes exaggerated, this expansive position on ancillary care would distort the incentives of potential study participants in an inappropriate way [11]. Fourth, were researchers to take on the full range of unmet local health needs, they would often be taking on health care responsibilities that appropriately belong to the host government or local organizations.

While this expansive position is therefore not acceptable, there is a broad consensus that ancillary-care obligations are not nil [1,7,8]. Four strong arguments demonstrate that medical researchers and their sponsors have positive ancillary-care obligations. (1) Due Concern for Welfare: Due concern for the welfare of those with whom one interacts arguably requires addressing one's research participants' serious medical needs when one has the capacity to do so and they lack other recourse [4]. (2) Rescue: Especially when these needs are urgent, a duty of rescue may come into play [12]. (3) Justice: While it is not up to medical researchers or their sponsors to remedy global injustice in the provision of health care, they do encounter many who suffer from injustices and have some obligation to do their part in

alleviating this suffering, where they are competent to do so [13]. (4) Entrustment: While these first three considerations potentially apply to those who are not research participants as well as to those who are, there is considerable consensus that ancillary-care obligations are specially owed to research participants. One way of thinking about this special obligation is to take it that, by entering a study or clinical trial, research participants automatically entrust certain aspects of their health into the researchers' care [2,3].

Each of these arguments—from welfare, rescue, justice, and entrustment—demonstrates the existence of strong, positive ancillary-care obligations. Given the reasons against the expansive position on ancillary care, these positive obligations are limited. Concretely working out the extent and limits of these obligations requires considerably more work [14,15], but here we make a start.

Unrelated Conditions Covered; "Target" Conditions Not Privileged

Whichever arguments supporting researchers' ancillary-care obligations are accepted, it is clear that these obligations extend to diseases and conditions unrelated to what is under study. The implications of justice are not restricted to the target disease alone; neither are the implications of due concern for welfare, rescue, or what is effectively entrusted to researchers by consenting to participate in certain procedures.

By the same token, none of these arguments specially privilege ancillary care for a study's target disease or condition. In emphasizing the importance of considering ancillary care for other diseases or conditions, we depart from, and seek to go beyond, the approach implicitly taken both by a World Health Organization/UNAIDS consultative body concerning the ethical considerations related to providing care and treatment in vaccine trials [14] and by the recently published UNAIDS document on HIV prevention trials [16]. The former body, in particular, relied on the unfocused argument from justice that we criticized above, as well as similarly broad appeals to beneficence and to reciprocity ("…the ethical principles of justice as equality, reciprocity and beneficence might be used to justify access to care and treatment for trial participants for conditions targeted by the vaccine candidate…" [14]). These arguments get some traction; but they are not, in their nature, confined to medical needs arising from a study's target disease or condition.

Doing justice, in this context, is complicated. It requires being sensitive to whether it is fair to give study participants priority over others in need of treatment [17]. Whether reciprocity demands post-trial treatment depends on what benefits participants may have gotten during a trial. Most generally, while maximizing benefit to those participants who are in need may require providing them with necessary care, participants in other trials may have needs that are more urgent than those arising from the target disease or condition.

While talk of a "target disease" tends to suggest interventional trials, ancillary-care obligations also arise in observational and epidemiological studies [18]. For example, in Kenya, a non-interventional study of pregnant women investigated the effect of maternal infection or immunity to various parasitic diseases (such as malaria and schistosomiasis) on their babies. Relying on published studies of women visiting antenatal clinics in this area, a 30% HIV prevalence rate was expected among study participants. On this basis, it was calculated that administering single-dose nevirapine (then otherwise difficult to obtain) would prevent 11–20 HIV infections among the babies born to study participants (personal communication, L. Higgs). Due concern for the babies' welfare gave these researchers and research sponsors compelling moral reasons for providing nevirapine as ancillary care for this non-target disease.

Some ancillary-care needs can be readily foreseen and planned for. In certain areas of the world, for example, researchers studying children with malaria will know to expect that a significant percentage of these children will also be infected with schistosomiasis and that carrying out study procedures might well reveal this comorbidity. They should arrange for any children they diagnose with schistosomiasis to receive antihelminthic agents. In some cases, diagnosis

Box 1. Three Questions for RECs Assessing Human Studies in Developing Countries

1. Needs: What ancillary-care needs, if any, are likely to be encountered?
   - What is the health burden of the host population (locally endemic diseases, local disease prevalence and incidence, etc.)?
   - Are the study procedures likely to reveal concurrent diseases or conditions that will need to be addressed?
2. Alternatives: Can identified ancillary-care needs be met by the existing local health system?
   - What existing health care facilities and opportunities, especially for treatment of locally endemic conditions, are reasonably accessible to study participants?
   - To what extent is the existing local health infrastructure already overburdened and local trained medical personnel scarce?
3. Obligations: How strong is the responsibility of researchers and their sponsors to address the ancillary-care needs they identify in this study?
   - How severe or acute are the likely ancillary-care needs, and what would be the consequences, for individual study participants, were these needs to go unmet?
   - Is the identification of ancillary-care needs in this study likely to be integral or incidental to carrying out study procedures?
   - What is the duration of the study and how extensive are the proposed interactions between researchers and study participants?
   - Is the research study part of a broader set of studies that these researchers or their sponsors are conducting, or aim to conduct, with this host population?
   - What are the foreseeable costs of providing ancillary care, in funds, personnel time, and potential interference with the study's scientific aims?
   - What is the nature and identity of investigators' and funders' institutions, and to what extent would they be able to support the provision of ancillary care?

Box 2. Four Guidance Points on Ancillary-Care Obligations ("The Four P's")

1. **Positive duty:** Researchers and research sponsors, especially those working in developing countries, have some positive moral obligation to provide some ancillary care to their study participants (or to see to it that their participants receive such care).
2. **Planning:** Researchers and research sponsors, especially those working in developing countries, consequently should develop plans, both in general and for each protocol, for meeting the ancillary-care obligations that may be expected to arise. They should also take account of the unpredictable nature of ancillary-care needs and plan accordingly.
3. **Partnership:** These ancillary-care plans should be developed in dialogue and partnership with the host community, in ways that maintain respectful interaction, avoid displacing or disrupting local health care structures, and represent the population of potential study participants, community advisory boards, and the local medical community.
4. **Practical provisions:** Where they have foreseeable ancillary-care obligations, researchers and research sponsors should take definite practical steps towards meeting these obligations. This might mean hiring a physician with certain competencies as part of the local study team; setting aside a certain line item or percentage of the budget; or forming partnerships with those who can provide drugs or with development agencies that can aid in improving the local infrastructure.

of ancillary conditions is not only foreseeable, but integral to a study's design. For instance, a trial of a drug to treat cryptosporidial diarrhea in children might first administer HIV tests to the children and then stratify them on the basis of their HIV status [19]. The protocol of such a trial should include a plan for the ongoing management or referral of the children identified as being HIV infected.

Review by Research Ethics Committees

Because research protocols, especially those involving developing-country participants, should outline how they will address participants' ancillary-care needs [16], RECs reviewing these protocols should assess the investigators' stated plans for meeting anticipated ancillary-care needs. Research studies and their contexts vary so radically, and in ways that affect ancillary-care obligations, that protocol-by-protocol review is essential. An observational study involving only a single assessment of each participant, for instance, raises very different issues than a long-term interventional trial. Existing RECs are a well-established mechanism for ethics review of research studies. Examination of ancillary-care issues should be integral to their review. Because the issue of ancillary care has not been explicitly raised until recently, it is not known to what extent RECs have been addressing ancillary-care issues already. Asking these committees—especially those in host countries—to examine ancillary-care issues may impose a further burden on them. Their capacity will need to be enhanced, an effort that international sponsors of research should support. Local RECs are well placed to consider specific local factors, which matter more to ancillary-care issues than to some other issues of research ethics; but in considering these factors they will need to draw on the advice and support of the international medical research community.

In reviewing each proposed research study involving developing-country participants, RECs should consider the three questions set out in Box 1, which address the contextually variable features that bear on ancillary-care needs and obligations in an important way [15].

Guidelines and Policies Needed

Just as individual research teams should not have to shoulder, unaided, the moral burden of determining the boundaries of their ancillary-care obligations, so too do RECs deserve some general ethical guidance on ancillary-care issues. Because of the contextual variability just noted, this guidance should take the form not of specific rules but of general guidelines. These guidelines should be developed in tandem with policies and guidance addressed to research sponsors, and they should be international, so as to minimize the danger that a country's stringent ancillary-care standards would cause research studies to locate elsewhere. While fully establishing the content of any ancillary-care guidance obviously must await further debate, discussion, and experience, we suggest that any adequate guidance must contain, in addition to the framework of the three questions set out in Box 1, the four points ("the four P's") described in Box 2.

Unintended Consequences

We propose these three questions and "four Ps" of minimal ancillary-care guidance as a necessary start. We recognize that any guidance that can be seen as adding requirements may have unintended consequences, some of which can be foreseen. One concern is the additional paperwork demanded of researchers and the additional attention demanded of REC members in what is already a difficult process. This we view as an unavoidable downside of allocating the moral burden of ancillary-care determinations more fairly and efficiently. A second concern is that the financial and logistical burden on researchers of providing ancillary care may further inhibit research in developing countries, in particular, research on such relatively neglected conditions as Chagas disease and leishmaniasis. Any guidelines should be sensitive to this danger, and should also consider how international ancillary-care standards may burden researchers based in developing countries. A third concern is the possible disruption of local efforts to improve health care conditions. Such disruption can happen for very different reasons: because researchers' provision of care takes the pressure off of local governments to provide it, for example, or because researchers divert scarce local medical talent. RECs should do their best to address this kind of concern.

Conclusion

We have offered some guidelines, but more debate and analysis of the grounds for and extent of researchers' ancillary-care obligations is needed at the conceptual level. Many difficult issues, such as how to characterize the standard of care appropriate in providing ancillary care, remain to be addressed. Empirical research about researchers and research participants' attitudes, perceptions, and expectations, as well as about current ancillary-care practices, should be

undertaken to inform the debate and the development of appropriate guidelines. ■

Acknowledgments

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Author contributions. This paper began as a synthesis of the contributions of each of the 15 named authors to the Workshop on the Ancillary-Care Obligations of Medical Researchers Working in Developing Countries, held at Georgetown University, Washington, D. C., October 20–22, 2006. Working from the authors' PowerPoint slides and/or from notes on their contributions and in consultation with C. Grady and R. Lie, H. Richardson produced the drafts of this article. Each of the 15 coauthors participated in the rounds of revision, of which there were several.

Competing Interests: MDC declares that he is a retired employee of the pharmaceutical company Eli Lilly and Company, and also owns Lilly stock. PBC declares that he is a general partner of a private equity fund that buys potential medicines in development and develops them further, usually to regulatory approval. He is the retired head of Science and Technology for Pfizer and has stock options as well as stock in the company. He also receives retirement benefits and deferred compensation. He is a board member of Cbio, a biotech company based in Australia, for which he receives remuneration. He is advisor to the president for an information technology firm called Global Edit in New York City, for which he will receive future equity if the company is successful. Payments are donated to charities of his choice. He is a chair or a member of the following Boards: Joyce Theater (New York City), Georgetown University Board of Regents (Washington, D. C.), New York Academy of Sciences (New York City), C-Path Institute (Tuscon, Arizona), Institute of Medicine Drug Forum (Washington, D. C.), and International Partnership for Microbicides (Washington, D. C.). He receives no compensation, directly or indirectly, for any of these positions. SD is Chief Innovation Officer at Quintiles, which has contracts with all of the major pharmaceutical firms. The remaining authors declare that they have no competing interests.

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