

quality of the evidence for differences in use of resources should be graded by using the approach outlined above for other important outcomes.

How it works in practice

Table 2 shows an example of the system applied to evidence from a systematic review comparing selective serotonin reuptake inhibitors with tricyclic antidepressants conducted in 1997.² After discussion, we agreed that there was moderate quality evidence for the relative effects of both types of drugs on severity of depression and poisoning fatalities and high quality evidence for transient side effects. We then reached agreement that the overall quality of evidence was moderate and that there were net benefits in favour of serotonin reuptake inhibitors (no difference in severity of depression, fewer transient side effects, and fewer poisoning fatalities). Although we agreed that there seemed to be net benefits, we concluded with a recommendation to “probably” use serotonin reuptake inhibitors because of uncertainty about the quality of the evidence. We had no evidence on relative costs in

this exercise. Had we considered costs, this recommendation might have changed.

Conclusions

We have attempted to find a balance between simplicity and clarity in our system for grading the quality of evidence and strength of recommendations. Regardless of how simple or complex a system is, judgments are always required. Our system provides a framework for structured reflection and can help to ensure that appropriate judgments are made, but it does not remove the need for judgment.

Contributors and sources: see bmj.com

Competing interests: Most of the members of the GRADE Working Group have a vested interest in another system of grading the quality of evidence and the strength of recommendations.

- 1 Thompson DC, Rivara FP, Thompson R. Helmets for preventing head and facial injuries in bicyclists. *Cochrane Database Syst Rev* 2000;(2):CD001855.
- 2 North of England Evidence Based Guideline Development Project. *Evidence based clinical practice guideline: the choice of antidepressants for depression in primary care*. Newcastle upon Tyne: Centre for Health Services Research, 1997. (Accepted 5 March 2004)

Medical researchers' ancillary clinical care responsibilities

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Investigation of participants in clinical trials may identify conditions unrelated to the study. Researchers need guidance on whether they have a duty to treat such conditions

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BMJ 2004;328:1494-6

Researchers testing a new treatment for tuberculosis in a developing country discover some patients have HIV infection. Do they have a responsibility to provide antiretroviral drugs? In general, when do researchers have a responsibility to provide clinical care to participants that is not stipulated in the trial's protocol? This question arises regularly, especially in developing countries, yet (with rare exceptions¹) existing literature and guidelines on research ethics do not consider ancillary clinical care. We propose an ethical framework that will help delineate researchers' responsibilities.

What is ancillary care?

Ancillary care is that which is not required to make a study scientifically valid, to ensure a trial's safety, or to redress research injuries. Thus, stabilising patients to enrol them in a research protocol, monitoring drug interactions, or treating adverse reactions to experimental drugs are not ancillary care. By contrast, following up on diagnoses found by protocol tests or treating ailments that are unrelated to the study's aims would be ancillary care.

Two extreme views

When asked how much ancillary care they should provide to participants, the first reaction of many clinical researchers, especially those working in developing

countries, is that they must provide whatever ancillary care their participants need. From an ethical perspective, this response makes sense. Research participants in trials in the developing world are typically desperately poor and ill, and everyone arguably has a duty to rescue those in need, at least when they can do so at minimal cost to themselves.^{2,3} Yet this response fails to acknowledge that the goal of research is to generate knowledge not care for patients.^{4,5} When researchers consider that offering ancillary care this broadly may drain limited human and financial resources and confound study results, they tend to retreat from this position.

Some researchers veer to the opposite extreme. “We may be doctors,” they note, “but these are our research participants, not our patients, so we owe them nothing beyond what is needed to complete the study safely and successfully—that is, we owe them no ancillary care.” But this extreme position is ethically questionable. Consider the case of researchers studying a rare disease. It is ethically unacceptable to say to a participant, “We are going to monitor the toxicity and effectiveness of this experimental drug, and we will make sure it does not kill you, but we are not going to provide any palliative care for your condition.” Closely monitoring a participant's disease without being willing to treat it in any way amounts to treating him or her as a mere means to the end of research.

Hypothetical case: trial of antimicrobials for sexually transmitted diseases in a developing country

While performing clinical examinations on female patients to check for sexually transmitted diseases or side effects of the antimicrobial drug, researchers are likely to discover many women with vaginal candidiasis.⁸ More than half are likely to be suffering from the results of poor dental care and hygiene. What care should be provided for these problems?

Vaginal candidiasis

This is clearly within the scope of entrustment because the diagnosis results from examinations essential to the research. The underlying duty of care also seems strong because untreated candidiasis will greatly affect their wellbeing and treating it is relatively cheap and easy

Decision: Researchers ought to treat vaginal candidiasis

Dental problems

These are not within the scope of entrustment. If we assume that the poor dental hygiene is apparent on casual observation, its diagnosis would not result from exercising the permission participants granted on entering the study. The question of strength thus does not arise.

Decision: Dental care falls outside the scope of ancillary care responsibilities



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How much responsibility do researchers have for conditions not included in the trial?

single magnetic resonance image from each participant yields a limited scope of entrustment, pertaining mainly to the researchers' collection and use of the image. A study involving an extended inpatient stay, by contrast, will yield a far broader scope of entrustment.

Although the scope of this partial entrustment will vary, it is possible to generalise. Since a participant typically gives permission for a disease under study to be monitored, the scope of entrustment typically includes caring, as needed, for that disease. Since participants' permission is needed for doing tests or collecting confidential medical information, the scope of entrustment typically includes following up on any clinically relevant information or diagnoses generated.

How strong is the entrustment responsibility?

Researchers do not automatically have a responsibility to provide complete care for all aspects of health that fall within the scope of entrustment. Rather, the responsibility to provide ancillary care depends on the strength of the underlying, relationship based duty of care. This is influenced by at least four factors:

- Participants' vulnerability
- Participants' uncompensated risks or burdens
- Depth (intensity and duration) of the researcher-participant relationship⁷
- Participants' dependence on the researchers.

These four factors can vary independently.

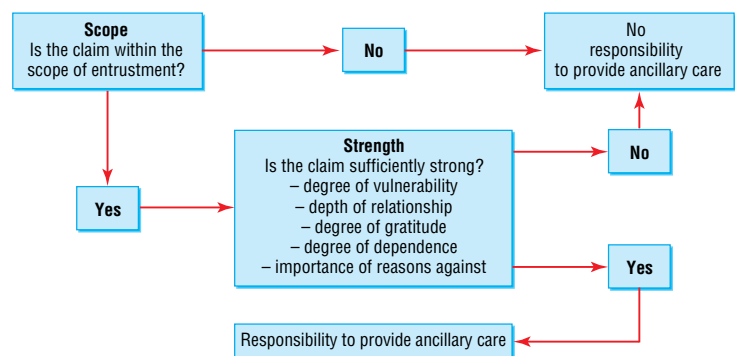


Diagram for assessing researchers' responsibility for ancillary care

A better model

We propose a model of the researcher-participant relationship that lies between these two views. It rests the special responsibilities of researchers on the idea that the relationship involves a partial and limited entrustment of participants' health to researchers.⁶

When participants join research trials, they implicitly or explicitly give researchers permission to access confidential medical information, to perform procedures and treatments, or to take samples. With this permission, researchers have discretionary power over how to respond to any collected medical information and potential diagnostic insights. Because researchers' responses to these needs will greatly affect participants' health and wellbeing, participants are vulnerable to the researchers. Participants thus tacitly entrust aspects of their health to researchers through the permission they give when joining a study.

The participants' entrustment is limited and partial. The permission entrusts only specific aspects of their health to researchers, not their health in general. Furthermore, how far researchers must go in caring for entrusted aspects of health will differ from case to case. In order to identify the depth and breadth of researchers' ancillary care responsibilities, we distinguish between the scope of entrustment (what is entrusted) and the strength of the duty of care.

What do participants entrust to researchers?

In the partial entrustment model, the scope of entrustment depends on the study. The research protocol, which specifies the information, interventions, tests, and sample required, will determine what permission needs to be obtained. A protocol that collects only a

The vulnerability of participants is assessed by looking at how much their wellbeing would be affected by researchers exercising their discretion—this is the vulnerability resulting from the participants' consent to participate. Participants' pre-existing vulnerabilities, such as those caused by illness, oppression, or poverty must also be taken into account. The researchers' debt of gratitude to participants depends on whether participants have accepted uncompensated risks and burdens or offered researchers a hard to come by scientific opportunity. The depth of the relationship between a researcher and participant will vary from study to study because different protocols demand interactions of varying intensity, duration, and longevity. Researchers have a stronger moral responsibility to engage with the full range of participants' needs when the relationship is deeper. Finally, dependence matters because it may indicate that the research team is in a unique position to help participants. Participants may become dependent on researchers because they are impoverished, lack insurance, or have an otherwise untreatable disease and join a trial because it is their last hope. In each case, these strength factors need to be judged against the competition for limited financial and human resources and the danger of confounding study results. These considerations generate a decision tree, which can be used to determine when researchers have a responsibility to provide ancillary care (figure). The boxes give hypothetical examples.

Conclusion

Researchers and ethics committees should attempt to anticipate the ancillary care responsibilities that will

Hypothetical case: HIV treatment in tuberculosis treatment trial

The trial calls for screening out patients who are HIV positive and dropping participants who seroconvert during the trial. The local standard of care for HIV and AIDS includes only palliative care. Do the researchers have a responsibility to help provide antiretroviral drugs to people they find to be HIV positive?

People screened out because they are HIV positive
Such people are within the scope of entrustment because the study calls for checking HIV status; but the strength of the duty of care is questionable. Although vulnerability and dependence are high (since HIV infection is deadly and other sources of antiretroviral drugs do not exist), engagement and gratitude are weak because these are not yet research participants.

Decision: Researchers probably do not have a responsibility to provide drugs

Participants dropped mid-trial because they seroconvert

Treatment is within the scope of entrustment because the study design calls for monitoring HIV status, and the strength of the duty of care is high. Vulnerability and dependence remain high and with enrolled participants engagement and gratitude are greater.

Decision: Researchers probably have a responsibility to provide antiretroviral drugs

Summary points

Researchers need ethical guidance regarding their responsibilities for providing ancillary care to participants

An ethically acceptable approach would recognise a partial entrustment of participants' health to researchers

The scope of this entrustment is determined by the permission researchers need to do the study safely and validly

Whether ancillary care should be provided then depends on the strength of the duty of care

The strength of the duty of care depends on participants' vulnerability, dependence, and uncompensated risks or burdens and the depth of the researcher-participant relationship

arise in a given protocol. Funding to cover researchers' ancillary care responsibilities must be included in research budgets. Many major research sponsors have been hesitant to fund medical care that is not necessary for the scientific success of a trial. Our hope is that the partial entrustment framework will encourage ethics committees, researchers, and sponsors to regard fulfilling ancillary care responsibilities as an essential part of ethical research.

We thank Ezekiel Emanuel, Christine Grady, Frank Miller, Leif Wenar, and David Wendler, and audiences at the Parasitology and International Programs Branch at NIAID, led by Lee Hall; the Department of Clinical Bioethics; the 3rd Africa Conference on Ethical Aspects of Clinical Research in Developing Countries, Kampala, Uganda; the Kennedy Institute of Ethics, Georgetown University; and the Latin American Conference on Ethical Aspects of International Collaborative Research. Kawango Agot, Kirana Bhatt, Stephen Chanock, Steven Holland, Samia Hurst, Matti Parri, Beyene Petros, Donald Rosenstein, Catherine Slack, and Douglas Wassenaar provided useful written comments and criticisms.

Contributors and sources: LB and HSR attended the rounds of clinical researchers at the National Institutes of Health and interviewed them about ancillary care issues. In addition, they observed and met clinical researchers in Argentina and Uganda. LB has training in political theory, biology, and international health policy, and HSR is a professor of philosophy at Georgetown University with additional graduate degrees in law and public policy.

Competing interests: HSR owns shares in various publicly traded pharmaceutical companies.

- 1 Nuffield Council on Bioethics. *The ethics of research related to healthcare in developing countries*. London, 2002: 97.
- 2 McIntyre A. Guilty bystanders? On the legitimacy of duty to rescue statutes. *Philos Public Aff* 1994;23:157-91.
- 3 Scanlon TM. *What we owe to each other*. Cambridge: Harvard University Press, 1998:224-8.
- 4 Miller FG, Rosenstein DL, DeRenzo EG. Professional integrity in clinical research. *JAMA* 1998;280:1449-54.
- 5 Katz J. Human experimentation and human rights. *St Louis Univ Law J* 1993;38:7-54.
- 6 Richardson HS, Belsky L. The ancillary-care responsibilities of medical researchers. *Hastings Cent Rep* 2004;34:25-33.
- 7 Pellegrino ED. Nonabandonment: an old obligation revisited. *Ann Intern Med* 1995;122:337-78.
- 8 Fitzgerald DW, Behets F M-T. Women's health and human rights in HIV prevention research. *Lancet* 2003;361:68-9. (Accepted 24 March 2004)