Limits to research risks

F G Miller,1 S Joffé2

ABSTRACT
Risk–benefit assessment is a routine requirement for research ethics committees that review and oversee biomedical research with human subjects. Nevertheless, it remains unclear how to weigh and balance risks to research participants against the social benefits that flow from generating biomedical knowledge. In this article, we address the question of whether there are any reasonable criteria for defining the limit of permissible risks to individuals who provide informed consent for research participation. We argue against any a priori limit to permissible research risks. However, attention to the uncertainty of potential social benefit that can be derived from any particular study warrants caution in exposing prospective research participants to a substantial likelihood of serious harm.

Risk–benefit assessment is an essential component of the planning and oversight of medical and public-health research. The (metaphorical) terminology for this assessment is the same as in clinical medicine: the task is to determine whether a research intervention or study protocol has a “favourable risk–benefit ratio”.1 Risk–benefit assessment in research, however, differs importantly from risk–benefit assessment in clinical medicine. In standard clinical practice, risks and benefits are assessed with respect to the individual patient: risks to patients from diagnostic or treatment interventions are justified by the prospect of medical benefit to those patients. Clinical uncertainty, coupled with treatment alternatives, can complicate these patient care assessments; however, the weighing and balancing of risks and potential medical benefits to individual patients or classes of patients generally does not pose difficult conceptual or normative problems. In contrast to clinical medicine, risk–benefit assessment in clinical research involves weighing the net risks to individual subjects—risks that are not compensated for by the prospect of direct benefits to them from research participation—against the potential social benefits that flow from generating biomedical knowledge. Research ethics committees are charged with the task of risk–benefit assessment as a routine responsibility. Yet it remains far from clear how to do this in an ethically sound way.

Various theoretical rationales can be given for risk–benefit assessment in research. It may be understood as an application of the basic ethical principles of beneficence and nonmaleficence or as a form of justified paternalism, on the assumption that research subjects are not positioned to adequately protect their interests by means of consent.2 Here we presume the salience of risk–benefit assessment. It may be clear how to do this in an ethically sound way. Yet it remains far from clear how to do this in an ethically sound way. The key question for this inquiry is this: is there a maximum level of net risks to consenting research subjects that can be justified by the potential social benefits from a particular scientific investigation?

Regulatory standards and canonical codes of research ethics provide minimal guidance to answer this question. The US federal regulations for the protection of human subjects, known as “The Common Rule,” simply state that risks to subjects must be minimised “by using procedures …which do not unnecessarily expose subjects to risks,” and that “risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result”.3 Provided that risks to subjects are necessary to answer the research question, the Common Rule stipulates no determinate limit on permissible net risks to competent adult subjects.

The Nuremberg Code, promulgated in the wake of the Nazi concentration-camp experiments, stipulates a limit on permissible research risks: “No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects”.4 Although this rule appropriately directs attention to concern about risks of mortality and morbidity produced by research interventions, it does not make clear what antecedent estimate of the chance of death or disability, not compensated by the prospect of medical benefit to subjects, makes a study impermissible. Furthermore, the Code does not clarify whether the value of the knowledge that the study may yield should influence determinations of the ceiling on permissible risk. The ambiguous exception for higher-risk research, involving self-experimentation, was included with an eye to the famous yellow fever experiments conducted by Walter Reed at the turn of the 20th century. Consideration of Reed’s research is instructive, both as a historical example and as a prompt to considering whether we would be prepared today to justify such “heroic” research, with grave risks of harm to subjects but the prospect of great public-health benefit?

Lederer, in a recent essay on Reed’s research, notes that “It would not be an exaggeration to describe yellow fever as the scourge of the American South”.5 At the time of Reed’s experiments in Cuba, no treatment other than supportive care was available for this dreaded disease, the mortality of which was estimated at 10–60%. Victims suffered severe and frightening symptoms, although without lasting harm for those who survived. In the effort to determine experimentally the mode of transmission of yellow fever, Reed
conducted a series of studies, which involved exposing research participants to the mosquitoes hypothesised to be the vector for the disease, as well as to injections of blood drawn from infected patients. Accordingly, Reed and his colleagues could anticipate that some research subjects would contract yellow fever as a result of research participation, and that one or more might die from the disease. In fact, several of the 53 volunteers, including members of the research team, became sick with yellow fever and one self-experimenting investigator died. Were the risks of severe short-term illness and death justified in view of the potential public-health importance of the knowledge to be gained from the research? To be sure, those volunteers residing in Cuba were naturally exposed to the risk of contracting yellow fever, which was endemic on the island, but deliberate experimental interventions anticipated to transmit infection to research subjects certainly increased risks of mortality and morbidity beyond the background risks faced by inhabitants of Cuba.

APPROACHES TO LIMITING RISKS
The fundamental question, highlighted by Reed’s experiment, which has yet to be answered convincingly by theorists of research ethics, is: are there any clear and cogent principles that define allowable net risks of research? If not, what considerations are relevant to making judgments about the reasonableness of research risks in light of potential knowledge benefits?

Equipoise
One prominent approach to risk–benefit assessment of clinical research invokes the principle of equipoise. Clinical trials administering treatment interventions to patients diagnosed with a medical condition are ethical, under the principle of equipoise, only when there is uncertainty about the risk–benefit profile of these interventions when compared with each other and with the established standard of medical care outside the trial. When equipoise is satisfied, no research participant is given a treatment intervention known in advance to be inferior to other available therapies. It follows from the principle of equipoise that participants in clinical trials should not be exposed to known net risks, compared with the standard of care, from receipt of the treatments under investigation.

The equipoise principle essentially applies standard medical risk–benefit assessment to potentially beneficial interventions evaluated in clinical trials. According to this principle, because patients seek treatment by enrolling in clinical trials, their welfare should not be compromised for the sake of generating scientific knowledge. Although equipoise seems intuitively plausible, it is not clear why in the context of research, as distinct from medical care, it is unethical for well-informed consenting patient-subjects to be exposed to modest net risks from treatment interventions (or from omissions of treatment interventions, as is typical with placebo controls) for the sake of generating valid and important research results. Furthermore, regardless of the merits of equipoise as a principle for risk–benefit assessment of treatment interventions in research, it fails to provide comprehensive guidance for allowable risks across the spectrum of human subject research. Clinical trials enrolling patient-subjects often require research interventions such as blood sampling, biopsies or imaging procedures using radiation, which are designed solely to evaluate study outcomes. Such evaluative procedures typically lack any compensating prospect of medical benefit for participants. The principle of equipoise is silent on risk–benefit assessment for these interventions. Moreover, equipoise as a principle of risk–benefit assessment provides no guidance on the entire spectrum of pathophysiology research with patient-subjects that does not involve evaluation of treatment interventions, nor about research that recruits healthy volunteers, who can receive no medical benefit from participation.

Comparison with non-research activities
Noting the limitations in scope of equipoise as a guide to risk–benefit assessment, London proposes a general principle concerning the limitations of allowable net risk in research that deserves examination: “In all cases, the cumulative incremental risks to the basic interests of individuals that derive from research activities that are not offset by the prospect of direct benefit to the individual must not be greater than the risks to the basic interests of individuals that are permitted in the context of other socially sanctioned activities that are similar in structure to the research enterprise.” The similar structure, according to London, has three basic features. First, the comparator activity must be devoted to the purpose of helping others; thus we recognise the risks to participants being justified by benefits to others. In this respect, London mentions public service activities such as firefighting and emergency paramedical services. Second, to provide an accurate guide to allowable risks in research, the comparator activity should be one that involves a “principal-agent relationship” characteristic of research. (Notably, few activities devoted to helping others involve principal-agent relationships.) Third, there should be some form of public oversight of the comparator activity.

Although the nature of the relationship between investigators and research subjects may be relevant to the search for an appropriate comparator activity, it is questionable whether the “principal-agent” characteristic applies to clinical research. Typically, in the context of professional activities, such as medicine, law and investment management, the agent is authorised by the principal to act on his or her behalf, with the understanding that the agent is charged with promoting the best interests of the principal within a particular domain. Clinical research, however, is not a helping profession aimed at promoting the best interests of research subjects. Nevertheless, research participants voluntarily subject themselves to risks of procedures administered by investigators and entrust them to perform those procedures in as safe a manner as possible so that they are protected from avoidable harm. Because clinical research involves participants’ voluntary but passive submission to the direction of a professional, charged with subject-protective responsibility, an ideal comparator activity would involve a similar relationship.

In appraising this comparative risk assessment strategy, it is important to recognise its intrinsic limitations. Appeal to a comparator activity in guiding risk–benefit assessment in research is vulnerable to begging the question of allowable risks. Given that we are puzzled about the acceptable level of net risks in research, it helps to appeal to a non-research activity for guidance only if we are confident that the net risks that are accepted in the comparator activity are ethically justified. London notes that the comparator activity should be “socially sanctioned,” but the gap between “is” and “ought” looms here. What ethically grounds the acceptability of the risk–benefit profile of the comparator activity? Just because a society is disposed, as a matter of fact, to sanction an activity that exposes some people to a certain level of net risks in order to produce benefits to others, it doesn’t follow that this risk
exposure is justified. Moreover, even when we are justifiably confident about risk–benefit assessment in the comparator activity, we face the question of whether the research situation is similar in all morally relevant respects to the comparator—that is, relevant with respect to the ethics of risk–benefit assessment.

Accordingly, the comparative strategy to risk–benefit assessment invokes analogical reasoning. It adopts the following logic: we are disposed to accept a certain level of net risks to some for the benefit of others in a putatively relevant comparator activity, hence we should accept comparable net risks in health research. Because it may be difficult to be confident about the acceptable risk level in the comparator, and because its similarity to research in all morally relevant respects will be open to question, appeal to the comparator is, at best, suggestive.

Notwithstanding these limitations, the comparative strategy may help in thinking about acceptable limits to research risks, for at least two reasons. First, identifying the relevant similarities and differences between two activities, along with the effect that those similarities and differences should have on determinations of permissible net risk, helps to clarify the factors that properly influence risk–benefit assessment. Second, identification of a relevantly similar activity for which relative clarity exists about the ceiling of permissible net risk, subject to the limitations discussed above, may provide substantive guidance as to the appropriate risk ceiling in clinical research.

Live-organ donation as a comparator activity

In considering analogies that may help guide risk–benefit assessment in research, we suggest that the activity of live-organ donation by unrelated donors within clinical medicine merits consideration as a potentially relevant comparator. (Live-organ donation by related donors is a less apt analogy, because beneficiaries of knowledge gained in research are typically unrelated to research participants.) Living donation of solid organs and tissue resembles clinical research in that risks to the donor are justified by benefits to another—namely, to the recipient of the transplanted organ. Living donors must rely on expert clinicians to inform them about the risks of donation and must trust clinicians’ competence in extracting organs or tissue safely. Similarly, research participants must rely on investigators to inform them about risks and to ensure research interventions are administered safely. In other words, asymmetry of knowledge and trust in professional competence characterise both activities.

Furthermore, in both the practices of live-organ donation and of clinical research, the relationships between clinicians and donors and between investigators and subjects differ from the fiduciary professional relationship characteristic of clinical medicine. Clinicians involved in extracting donor organs and tissue clearly do not function, strictly speaking, as fiduciaries, as donation from a medical perspective is not in the best interests of the donor; the extraction of organs or tissue is for the sake of the recipient. Likewise, in clinical research, investigators are dedicated primarily to follow a prescribed scientific protocol for the benefit of others in the future, not to doing what is best medically for research participants. At the same time, both transplant surgeons and clinical investigators assist donors and research participants, respectively, with the pursuit of their altruistic aims. In addition, both are obligated to minimise risks to donors and participants, consistent with achieving their respective goals of transplantation and of generating scientific knowledge.

Living donation clearly carries substantial risks and burdens. In donations of kidneys and portions of lungs and livers, healthy donors are exposed to a relatively low risk of operative mortality (approximately 0.03–0.5%), somewhat higher-risks of complications, and a certain burden and discomfort from invasive procedures. Long-term risks to living organ donors have not been rigorously assessed. The analogy between live-organ donation and research participation raises the question: should we permit net risks in potentially valuable clinical research that are comparable to those permitted in live-organ donation?

Consider the following thought experiment. Suppose that a study has been designed to develop important knowledge aimed at improving the success of organ transplantation—for example, to evaluate methods for prolonging the viability of the organ after removal from the donor. The experimental procedures in our hypothetical study require laboratory investigation (and subsequent disposal) of donated organs—eg, kidneys or parts of lungs or livers from healthy donors. Could we justify the risks of such donation for the sake of science and future patients, rather than for transplantation to recipients? An obvious concern would be the loss of organs that could be used to save the life or enhance the quality of life of patients in need of transplantation. For the purpose of the thought experiment, we set this concern aside, focusing solely on the risk–benefit assessment of the research in question, without regard to any external consequences.

Studies involving donation of bone marrow, which pose discomfort but low risk of harm, might well be justifiable, depending on the importance of the research question. Solid-organ donation solely for the purpose of research, however, would certainly give research ethics committees pause. Why, then, do we think that these risks are justifiable in the case of living-donor organ transplantation? We submit that this hesitation stems from the recognition that it is doubtful whether the potential value of any particular laboratory experiment on solid organs from research volunteers would ever seem sufficiently compelling to justify the risks of operative complications, the certain burdens of the procedure and the uncertain long-term health risks to the subject. Relevant contrasts between organ donation and clinical research come into view in facing this question. First, in organ donation there is an identifiable recipient in need of help who is very likely to benefit dramatically from the transplantation. Second, typically, there will be a pre-existing relationship between donor and recipient, although the incidence and ethical acceptance of donation by altruistic people with no prior relationship to the recipient is increasing. These differences are psychologically salient, but their moral relevance with respect to risk–benefit assessment is open to question. Rescuing identifiable beneficiaries via transplantation is not necessarily of greater ethical importance than generating knowledge with great promise of saving the lives of many. Furthermore, although relationships may be morally relevant, as noted above, there is increasing acceptance of organ donation by those lacking any relationship to recipients—a practice that closely parallels clinical research.

The most important ethically relevant distinction between organ extraction for transplantation and organ extraction for research is the substantially greater likelihood of or confidence in preventing grave harm and producing benefit in the transplantation case, compared with clinical research. In transplantation, known probabilities of substantial benefit to the recipient are balanced against the risks to the donor of organ extraction. In contrast, in research there is an inherent and unquantifiable uncertainty that any given study will produce...
reasonable to suppose that the public is not prepared to tolerate warrants risking life or severely compromising health. It is clinical research is generally not seen as an activity that be high risk. Yet the negative public reactions suggest that was not anticipated by investigators and review committees to

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demonstrating that a vaccine is effective in preventing a lethal infectious condition, for example, may have immense public-health significance. Much less value accrues, however, if a candidate vaccine fails to prove protective. In addition to the differential value of failure and success in testing experimental interventions, clinical research is more or less remote from direct application to improvement in the prevention or treatment of disease. At best, most experiments will contribute incrementally to the development of knowledge that has the potential for being used to improve medical care or promote public-health.

Thus, we face substantial uncertainty regarding benefit in clinical research. We are necessarily uncertain about the answer to research questions—otherwise there would be no point in doing the research—and we are uncertain about the social value that findings from a given study will generate. This makes the benefit side of the risk–benefit assessment much more speculative for clinical research protocols than for the practice of live-organ donation. Transplantation from living donors in each case can be expected to save or improve lives. We can be much less confident about the value of any particular research project. Finally, despite the substantial aggregate benefit of many clinical research studies, the incremental contribution of each individual research participant to that benefit is typically modest, in contrast to the substantial benefit that is expected to accrue from the gift of each individual organ donor.

Returning to the thought experiment of organ extraction for research, the factor of uncertainty helps explain why it is doubtful that any specific research study aimed at improving transplantation could be thought to have sufficient potential social value to justify the known risks and burdens of having a kidney or part of a lung or a liver removed. Instead of a high probability of contributing to important medical benefits for identifiable recipients, we have an unquantifiable possibility that a promising experiment may produce knowledge that might improve the practice of transplantation in the future. The upshot is that it is difficult to justify clinical research that imposes high net risks, in view of the uncertainty of translating research results from a specific study into health benefits. Typically, the severity and likelihood of risks will be much better defined than the magnitude and probability of benefits, raising doubts about the reasonableness of exposing subjects to serious risks of harm.

An additional reason for caution in exposing research subjects to substantial risks of serious harm relates to public confidence in the research enterprise. Deaths and severe adverse events to research subjects in studies lacking a prospect of medical benefit evoke strongly negative public responses; examples include the deaths of Jesse Gelsinger in a phase 1 gene transfer trial 19 and of Ellen Roche in an experiment relating to the pathophysiology of asthma. 20 and the drastic immune responses in several healthy volunteers enrolled in a phase 1 trial of a novel biological agent in the UK. 21 To be sure, in at least the last two cases the research was not anticipated by investigators and review committees to be high risk. Yet the negative public reactions suggest that clinical research is generally not seen as an activity that warrants risking life or severely compromising health. It is reasonable to suppose that the public is not prepared to tolerate the level of risks posed by live-organ donation in the setting of clinical research, especially because the visibility and immediacy of offsetting benefits is much greater in the clinical practice of transplantation. Concern for maintaining the public’s support and trust, on which the enterprise of clinical research depends, argues for caution concerning the level of net risks that are judged permissible. Attention to the potential effect of research-related harm on public trust does not, of course, mean that the public’s threshold of acceptable risk is substantively correct. However, from a pragmatic point of view, it would be foolish to ignore the possible consequences of serious harm to public support of research.

JUSTIFYING HIGHER-RISK RESEARCH

We have argued that the uncertainty of potential social benefit from any particular study calls for prudence in exposing research subjects to substantial net risks. Nevertheless, the fruits of research can have a marked effect on the lives and welfare of many people, suggesting that higher-risk studies might be justified when judged to have a high likelihood of producing great social value. This makes it doubtful that we can definitively specify the limits on permissible net risks for research participants who are prepared to assume such risks voluntarily.

Research aimed at addressing dire public-health emergencies may warrant exposure of consenting subjects to considerably higher-risk than does routine clinical research. The urgent importance of knowledge relating to the ability to prevent or minimise the public-health threat, with the potential for rapid translation into substantial health benefits for large populations, must be weighed in the balance. Furthermore, as in the case of Walter Reed’s experiments, volunteers for high-risk public-health research may be subject to substantial background risks from public-health threats, such as potentially lethal infectious diseases for which effective treatment is lacking. It is thus the incremental net risk from the research that must be assessed against the prospect of public-health benefits from the study results. For example, in the face of an epidemic of avian influenza, what level of incremental net risk to volunteers challenged with the infectious agent might be justifiable in the effort to develop an effective vaccine that could save millions of lives? Relevant comparator activities might be risks to firefighters or rescue workers facing a large-scale disaster or those to battlefield medical personnel. To be sure, the risk-takers in these latter activities are not passively submitting to risks administered by professionals; however, in the case of research responsive to a public-health emergency, it is not clear that this relational factor bears on the level of acceptable risks to research subjects. The foremost heroes of Walter Reed’s experiments were those volunteer subjects who placed themselves at risk of serious illness and death. Placed in this context, the risks posed by the yellow-fever experiments might not be out of line with what could be judged acceptable today to address a public-health emergency.

CONCLUSION

We have suggested four considerations that are relevant to assessing the limits of allowable research risks for consenting subjects: (1) appealing to an appropriate comparator activity outside the context of research; (2) recognising the inherent uncertainties surrounding ex ante judgments about benefit in human investigation; (3) judging the proportional contribution to risks of offsetting public-health benefits for the research subjects and the anticipated benefits of the research in

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light of the first two considerations; and (4) appreciating the need to maintain public confidence in human research. None of these, separately or together, defines an absolute limit on the level of allowable risks in research. It is difficult to see how any non-arbitrary principles could be formulated that specify a priori a reasonable limit to the probability of death or the probability and magnitude of health burden from research interventions, regardless of the anticipated value of the knowledge that may result from a particular study. Careful attention to eliminating unnecessary risks is critical to risk–benefit assessment, but there is no substitute for fallible judgments of proportionality and reasonableness of risks to subjects in relation to potential benefits to society. As in many areas of regulation, two types of errors must be faced: being underprotective of research subjects, thus exposing them to undue risks of harm, and foregoing social benefits from valuable research through overprotection.

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