

Bench to Bedside

Mapping the Moral Terrain of Clinical Research

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Medical research is widely thought to have a fundamentally therapeutic orientation, in spite of the fact that clinical research is thought to be ethically distinct from medical care. We need an entirely new conception of clinical research ethics—one that looks to science instead of the doctor-patient relationship.

Gastrointestinal stromal tumor is a rare cancer that, when inoperable or metastatic, was historically always fatal. Several years ago, imatinib, the first drug in a new class of anticancer agents, was shown to be highly effective for patients with this kind of cancer (known by the acronym GIST).¹ Unfortunately, many patients become resistant to imatinib, and until recently, no effective therapies were available for them. To address this problem, a multicenter randomized controlled trial compared sunitinib (a novel drug in the same class as imatinib) against placebo for people with imatinib-refractory GIST. The trial demonstrated that, compared with placebo, sunitinib markedly reduced the risks of both tumor progression and death.²

Because patients eligible for the trial have a very poor prognosis, the use of placebo controls was quite

controversial.³ According to an official at the University of Michigan Cancer Center, which had refused to join the trial, “When patients have an advanced cancer and the cancer is growing, there isn’t any way the placebo can be helpful. . . . To argue that a placebo trial is in society’s interests has nothing to do with helping these patients.” The legal scholar and bioethicist George Annas endorsed this position, asserting, “You have to give people in that situation something that might help them. . . . I don’t see any justification for withholding that drug.”⁴

What’s at stake in these differing views are fundamental questions about how clinical trials should be designed and conducted and the very nature of investigators’ moral obligations to research participants. Such questions have become ever more pressing. Consider two more examples.

A recent open-label randomized controlled trial compared surgical to nonsurgical management of lumbar disk herniation. The trial showed differences in symptoms and outcomes that favored surgical

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management, but these differences were statistically insignificant. In discussing the limitations of their trial, the authors acknowledged that “practical and ethical constraints” had prevented them from using sham surgery as a placebo control. “Therefore, any improvements seen with surgery may include some degree of ‘placebo effect.’”⁵ An accompanying editorial challenged the decision not to use a sham surgical control: “Because of limitations in design and study operation, the proper role and benefits of these competing interventions are still unclear. Given the large number of patients potentially exposed to the risks of these strategies, a sham surgical trial may be the only effective and ethical next step.”⁶

Placebos are not the only topic that raises questions about the nature of investigators’ moral obligations to subjects. A few years ago, a multicenter randomized trial compared the drug letrozole to placebo for postmenopausal women who had completed five years of standard therapy for localized breast cancer. Consistent with rules specified in the study protocol and with the recommendation of the data and safety monitoring committee, the trial was stopped early because women in the letrozole arm were experiencing markedly fewer recurrences of cancer.⁷ An accompanying editorial acknowledged the obligation to adhere to the protocol requirements, but nevertheless bemoaned the loss of information that resulted from stopping the trial.⁸ The National Breast Cancer Coalition, a respected patient advocacy group, also criticized the decision: “We don’t know the long term side effects, which could outweigh the benefit of fewer recurrences. More importantly, recurrence is an interim outcome measure, and is not the correct end point for this trial. The study should not have been stopped unless a marked mortality benefit was shown for one of the two interventions.”⁹ A *New York Times* editorial called the decision to stop the trial “ethical overkill.”¹⁰

The core issue in all these cases is the proper relationship between clinical research and medical care.¹¹ Despite widespread endorsement of the distinction between medical care and clinical research articulated in the *Belmont Report*, leading ethical guidance and the bioethics literature have nevertheless adopted a *therapeutic* orientation to clinical research.¹² Accordingly, research ethics is characterized by a basic incoherence: on the one hand, clinical research is seen as

health of my patient will be my first consideration,” and Article 28 maintains that “The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value.” These articles define the logical structure of the Declaration: (1) the researcher is first and foremost a physician; (2) clinical research is a special case of medical care; (3) therefore, physicians’ duties to their pa-

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ethically distinct from medical care; on the other hand, the obligations of investigators, especially in clinical trials, are thought to be grounded in the ethics of the doctor-patient relationship. The cases outlined above highlight this tension. Physicians’ obligations to their patients are invoked to justify the criticism of placebo controls in the first case, the refusal to use sham surgical controls in the second, and termination of the letrozole trial for efficacy in the third. To date, however, a coherent and sound alternative to this therapeutic orientation has been missing from the literature on clinical research ethics.

The Declaration of Helsinki is perhaps the clearest and most influential statement of the therapeutic orientation to clinical research.¹³ The Declaration begins—withstanding its status as a treatise on *research*—by articulating *physicians’* duties to *patients*. Article 2 asserts that “It is the duty of the physician to promote and safeguard the health of the people.” Article 3 states that “The Declaration of Geneva. . . binds the physician with the words, ‘The

tients govern clinical research, along with additional, research-specific duties. And in particular, since physicians ought to promote the medical best interests of patients, researchers should promote the medical best interests of subjects.

Another important example of the therapeutic orientation is the widely accepted doctrine of clinical equipoise in randomized controlled trials. Benjamin Freedman, Charles Weijer, and others have argued that investigators designing randomized controlled trials must ensure that no subject receives an intervention that is known in advance to be inferior either to other treatments in the trial or to contemporary standards of care.¹⁴ In his seminal paper on clinical equipoise, Freedman wrote that randomized controlled trials satisfy this standard when there is “no consensus within the expert clinical community about the comparative merits of the alternatives to be tested.”¹⁵ Freedman further asserted that clinical equipoise is “grounded in the normative nature of clinical practice, the view that a patient is ethically enti-

pled to expect treatment from his or her physician—an entitlement that cannot be sacrificed to scientific curiosity.¹⁶ Thus, according to the argument for clinical equipoise, an RCT that exposes some subjects to a predictably inferior intervention is unethical because the physicians participating in such a trial fail to satisfy their professional duties to care for their patients.¹⁷

The therapeutic orientation to clinical research has various theoretical and practical problems,¹⁸ but the goal in this paper is constructive: we will try to go beyond the criticisms and offer an entirely new conception of clinical research ethics based on a scientific orientation. The challenge is to articulate ethical objectives and constraints appropriate to scientific investigation with human subjects, without making any appeal to the therapeutic norms governing the physician-patient relationship. In doing so, we are inspired by Jay Katz's insight that "Physician-investigators must see themselves as scientists only and not as doctors."¹⁹ We anticipate resistance to this conception. Some will fear that it grounds at best an ethically impoverished, narrowly contractual view of the investigator-subject relationship. Yet such fears are misplaced. A scientific orientation to clinical research can give investigators robust obligations to respect, protect, and promote the interests of research subjects within the context of pursuing methodologically rigorous experimental design.

Rather than beginning by presuming that physicians' familiar ethical obligations to patients also define investigators' obligations to research participants, we take the ethical obligations of the scientist in the laboratory as our starting point. Briefly, we contend that a full description of the normative structure of clinical research ethics—or of any legitimate institutional activity—must recognize three dimensions of the activity. First, because clinical research is goal-directed, we must clearly define its proper *objectives*.²⁰ Second, as a scien-

tific activity dedicated to the pursuit and communication of empirically verifiable knowledge, clinical research is governed by a series of *internal norms*. Research that violates these norms is defective science or, at the extreme, not science at all. Clinical research shares these two normative dimensions with basic and preclinical biomedical research. Finally, by virtue of involving human subjects—particularly sick patient-subjects—clinical research is governed by a rich set of *ethical constraints*, which, though more numerous and complex than those governing basic and preclinical research, are fundamentally continuous with them. Thus, by starting at the bench and reasoning stepwise toward the bedside, it is possible to map the moral terrain of clinical research as a form of experimentation that can nevertheless do justice to participants' special status as sick patient-subjects.

Research Ethics: From Bench to Bedside

According to the scientific orientation, biomedical research constitutes a spectrum of activities anchored at one end by the laboratory scientist who conducts *in vitro* experiments and at the other by the clinical investigator who tests potential interventions (whether prophylactic, diagnostic, or therapeutic) on sick patient-subjects. The nature of biomedical research at any point along this spectrum can be characterized by reference to three dimensions: the ethically appropriate goals of the activity, its internal ethical norms, and the ethical constraints that regulate it. Two of these dimensions—goals and internal norms—are stable across all forms of biomedical research, no matter where they fall along the continuum. Indeed, these two dimensions are precisely what define an activity as biomedical science.²¹ Although research ethics is often identified with the protection of human subjects, the goal of biomedical research—promoting socially valuable knowledge about health, disease, and treat-

ment—is ethically central. Furthermore, the integrity of scientific research, defined by its internal norms, underpins its ability to achieve its major goal.

Ethical constraints on biomedical research are necessary because the activity has morally significant consequences for the subjects of the research (whether animal or human), as well as for others directly affected by it. Hence, the goal of generating socially valuable scientific knowledge does not necessarily justify the means of scientific experimentation. The ethical constraints on the activity vary depending, for example, on whether one is a laboratory researcher working *in vitro* or a clinical trialist studying new interventions in sick patient-subjects. These constraints, which derive mainly from differences in moral status of the experimental materials with which investigators work, distinguish the several forms of biomedical research from one another. At the same time, different forms of research also share important, though little-recognized, constraints. In fact, the ethical constraints governing the various forms of research are cumulative: the constraints that apply to *in vitro* experiments still apply as one moves toward clinical science, even as additional constraints accrue. Moreover, the ethical constraints relating to the use of human subjects are in important respects continuous with those pertaining to the use of sentient animals. In sum, bench scientists and clinical researchers occupy points along a spectrum because the professional activities in which they engage have common goals, share internal norms, and raise a related set of basic ethical concerns. As a result, investigators should see themselves primarily as scientists developing generalizable knowledge, regardless of where on this spectrum their own work falls.

Goals of biomedical research. The unifying characteristics of biomedical research start with the fact that, whether conducted in the laboratory or in the clinic, the activities that fall within its scope share certain basic

Table 1. The structure of experiments across the continuum of biomedical research

| | Laboratory science using basic biological materials and lower organisms | Research on laboratory animals | Research on healthy volunteers | Research on sick patient-subjects |
|--|---|--|--|---|
| Research question or hypothesis | To test the hypothesis that linezolid inhibits initiation of protein synthesis in bacteria | To test the hypothesis that linezolid is active in experimental models of bacterial infections in mice | To assess the bioavailability of oral linezolid, and to assess the impact of a fatty meal on absorption of oral linezolid | To test the hypothesis that linezolid and vancomycin have equivalent efficacy and safety in treating methicillin-resistant <i>S. aureus</i> (MRSA) infections |
| Experimental materials | Ribosomes isolated from experimental strains of <i>E. coli</i> and <i>S. aureus</i> | Specified strains of mice | Healthy men and women, twenty-five to thirty-five years old, within 15 percent of their desirable weight | Hospitalized individuals thirteen years of age or older, weighing 40 kilograms or more, with presumed MRSA infections |
| Experimental conditions | Application of study drug to suspensions of ribosomes and reagents in vitro, under specified conditions | Inoculation of mice with various bacterial strains, followed by administration of linezolid | Oral or intravenous administration of specified doses of study drug after an overnight fast or immediately after a high-fat meal | Randomization, open-label administration of study drug, adherence to other protocol requirements |
| Intervention(s) under study | linezolid | linezolid | linezolid | linezolid, vancomycin |
| Measurement devices | Binding of radiolabelled transfer RNA to ribosomal subunits in vitro | Assessment of survival of study mice | Measurement of linezolid concentrations in plasma and urine using high-performance liquid chromatography | Clinical, laboratory, and radiologic assessment of cure (resolution of baseline clinical signs and symptoms), microbiological success, and toxicity |

goals. Primary among these is the pursuit of generalizable knowledge that has the potential to contribute, sooner or later, to improvements in human health. Particular projects, such as clinical trials, may have substantial potential for immediate therapeutic application; others, such as studies of cellular physiology, form the foundation for subsequent applied work. Nevertheless, this quest for generalizable knowledge in the service of improved health is what unites biomedical research, no matter where along the continuum it lies.

The substantial societal investment in biomedical research makes clear the ethical significance of pro-

moting human health. In a seminal article on the ethics of human experimentation, Hans Jonas declared, “Let us not forget that progress is an optional goal, not an unconditional commitment.”²² Certainly the pursuit of biomedical research is not an unconditional commitment—this is precisely why we recognize ethical constraints on scientific investigation. However, it does not follow that progress in biomedical research is an optional goal. The moral concern with promoting health and relieving suffering gives rise to an ethical imperative to commit resources to socially valuable research. Accordingly, research ethics calls for giving due at-

ention simultaneously to promoting science and to protecting subjects. Furthermore, the potential of a proposed experiment to realize its goal of developing socially valuable knowledge is a necessary ethical consideration in justifying any risks to animal or human subjects.

Internal norms. Defining the goal of an activity as the pursuit of generalizable knowledge in the service of improved health is necessary but not sufficient to establish that activity as an instance of legitimate biomedical science. The second dimension necessarily shared by all forms of this genre is respect for the internal norms of science.²³ These norms are more diffi-

cult to articulate and are somewhat more contested than the goals of science, but there is general agreement that certain norms are intrinsic to the scientific process, so that any activity that failed to respect them would constitute a more or less defective instance of the class.²⁴

The first category of internal norms relates to the methods of scientific investigation. As Claude Bernard recognized almost one hundred and fifty years ago, the structure of scientific experiments is fundamentally stable all across the basic-clinical spectrum.²⁵ The essential dimensions of all scientific experiments include: (1) articulation of the research question or hypothesis; (2) specification of the experimental materials; (3) identification of the intervention under study; (4) stipulation of the experimental conditions, including the use of appropriate controls; and (5) description of the methods for measuring study outcomes and other study data. This structure of scientific experimentation permits the development of knowledge that can withstand replication and critical scrutiny, thereby meriting designation as generalizable.²⁶ (Table 1 illustrates the continuity of this basic structure across four experiments from bench to bedside that contributed to the development of linezolid, a novel antibiotic currently used to treat infections caused by certain drug-resistant bacteria.²⁷)

The second category of internal norms includes obligations related to scientific integrity: “intellectual honesty in proposing, performing, and reporting research.”²⁸ Failure to uphold scientific integrity constitutes research misconduct, which the United States Office of Research Integrity defines as “fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.”²⁹ Additional norms stem from recognition that science takes place within—and validated knowledge emerges from—a community of investigators working in col-

laboration and in competition.³⁰ Such norms include “accuracy in representing contributions to research proposals and reports”; “fairness in peer review”; “collegiality in scientific interactions”; “adherence to the mutual responsibilities between investigators and their research teams”; and sufficient description of research methods to permit confirmation of experimental results.³¹ These and other internal norms govern research as the pursuit, communication, and collective validation of scientific knowledge. Adherence to these norms, along with the ethical constraints discussed below, ensures the trustworthiness of the biomedical research enterprise.³²

Ethical constraints. Finally, all investigators are governed by ethical constraints on their activities.³³ Unlike the investigator who violates the goals or internal norms of science, a researcher who fails to respect the ethical constraints governing his or her research would still be engaged in genuine science; it would just be unethical science. Constraints governing research involving human subjects have received the most attention, those governing research involving animals (especially higher animals) have received less attention, and those governing research involving depersonalized and nonsentient experimental materials such as molecules, lower organisms, and intact cells (with rare exceptions such as human embryonic stem cells and tissue samples) have received virtually none. As we will show, however, even the laboratory investigator conducting *in vitro* research is governed by an exacting if circumscribed set of ethical constraints on his or her scientific activities.

The Scientific Orientation to Research

The remaining task is to outline the ethical constraints governing research. In what follows, we consider four archetypes of biomedical research. (An overview is found in Table

2.) Our objectives are twofold. First, we seek to trace the unbroken ethical thread that binds investigators doing disparate kinds of work. Second, we aim to demonstrate that it is possible to view researchers who work with sick patient-subjects as scientists first, while simultaneously offering a morally satisfactory account of the duties that such investigators owe participants in their clinical research projects.

Research involving inanimate or nonsentient experimental materials.

The researcher who studies inanimate or nonsentient experimental materials must respect a limited but exacting set of ethical constraints on her work. Because her experimental materials lack moral status—they have no interests or rights—the constraints governing her research derive not from her obligations to that material itself, but rather from the potential adverse effects of her research on others. (We set aside controversial cases such as embryonic stem cell research, as well as research involving human tissues that involves derivative obligations, such as confidentiality, to the individuals who gave the tissues).

The effects on others can arise in two ways. First, harms could result directly from the conduct of the experiment. For example, if confinement methods are inadequate, an infectious agent under study could escape and cause disease among laboratory staff or among members of the surrounding community. Thus, the first ethical constraint governing the activities of bench scientists is to minimize the external risks from their experiments. Second, harms could occur as a consequence of the knowledge generated from the experiment. Some have worried, for example, that the recent publication of the genome sequence of the virus responsible for the 1918 influenza pandemic was unethical, on grounds that the information could be used for biological warfare.³⁴ Research could also produce information that, if publicly released, might be used for chemical warfare. Re-

Table 2. Ethical constraints across the continuum of biomedical research

| Domain of Research | Ethical Constraints |
|--|--|
| Laboratory science using basic biological materials and lower organisms | <ol style="list-style-type: none"> 1. Minimization of external risks <ul style="list-style-type: none"> • containing infectious or toxic agents used in research 2. Pursuit of beneficent purposes <ul style="list-style-type: none"> • attending to national security concerns, such as access to agents or knowledge that could be used in biological or chemical warfare • avoiding studies that can generate knowledge useful only for destructive purposes |
| Research on laboratory animals | <p>All of the above, plus constraints that stem from higher animals' capacity to experience pain and other burdens:</p> <ol style="list-style-type: none"> 1. Minimization of risks and burdens for animals in the experiments <ul style="list-style-type: none"> • reducing the number of animals used to the minimum necessary for meaningful results • refining procedures to minimize pain and other burdens • whenever possible, replacing animal subjects with in vitro models or less sentient organisms 2. Independent review of the research to ensure that requirements are met |
| Research on healthy volunteers | <p>All of the above, plus constraints that stem from participants' status as human subjects:</p> <ol style="list-style-type: none"> 1. Avoidance of unacceptable levels of risk (of commission) for subjects 2. Respect for persons <ul style="list-style-type: none"> • providing information to subjects before, during, and after the study • assuring voluntary informed consent • attending to privacy and confidentiality • assuring freedom to withdraw from the study 3. Fairness in subject selection 4. Satisfaction of ancillary care obligations, such as responding to clinically significant information uncovered during, or caused by, the subject's participation 5. Fair compensation, commensurate with the burdens of participation |
| Research on sick patient-subjects | <p>All of the above, plus constraints that stem from participants' status as sick patient-subjects:</p> <ol style="list-style-type: none"> 1. Minimizing risks of omission, consistent with achieving the scientific aims of the study <ul style="list-style-type: none"> • avoiding unacceptable levels of risk of omission 2. Honesty regarding the nature of participation in clinical research <ul style="list-style-type: none"> • clarifying how the clinician-investigator/patient-subject relationship differs from the traditional clinician-patient relationship • attending to transitions to and from the status of patient alone 3. Adoption of a caring attitude that acknowledges subjects' status as sick individuals 4. Maximizing direct benefits, consistent with achieving the scientific aims of the study <ul style="list-style-type: none"> • maximizing benefits that flow from design choices regarding delivery of the intervention under study • maximizing benefits from other research procedures incorporated within the study |

searchers working with basic biological materials operate under two primary ethical constraints: to minimize external risks from the conduct of their research, and to proceed under the good-faith assumption that the

societal benefits of the knowledge derived from their research are likely to outweigh any potential societal harms.

Research involving laboratory animals. Investigators who conduct ex-

periments involving laboratory animals must respect the same ethical constraints—minimizing external risks and ensuring beneficent (or at least nonmaleficent) purpose—that govern researchers who work in vitro.

Research involving laboratory animals is further constrained, however, by ethical obligations deriving from animals' capacity to experience pain and other harms or burdens.³⁵ The basic tenets of ethical animal research include the three Rs: *reduce* the number of animals used to the minimum necessary for meaningful results, *refine* procedures to minimize pain and other burdens, and *replace* whole-animal experiments with in vitro models or experiments with less sentient organisms whenever possible.³⁶ Finally, to ensure researchers' accountability for meeting these obligations, studies involving higher animals must undergo independent review by an Institutional Animal Care and Use Committee or equivalent body.³⁷

Research involving human subjects that evaluates normal biology or pathophysiology. We are getting closer to the bedside, but first we must confront the ethical issues raised by human subjects research when considering studies of normal biology or pathophysiology involving human volunteers. Several authors have described a basic duty of nonexploitation in human subjects research.³⁸ Although avoiding exploitation encompasses many of the most important ethical constraints in human investigation, this negative obligation lacks sufficient specification and is too thin to capture adequately the affirmative sense of responsibility that clinical investigators hold toward human subjects. We need a positive conception of investigators' duties to human subjects in order to flesh out this negative frame.³⁹

First, investigators who conduct studies of human biology or pathophysiology must respect the ethical constraints that govern more basic research. They share with scientists who conduct in vitro experiments the obligation to minimize external risks and pursue beneficent purposes. And—though rarely acknowledged in these terms—they share with researchers working with animals the obligation to reduce the number of subjects to the minimum necessary

for meaningful results, refine procedures to minimize risks and burdens, and replace human experiments with in vitro or animal models whenever possible. Like researchers who work with higher animals, they must also subject their research to independent review to ensure that it meets high scientific and ethical standards.

Investigators who use human volunteers to study normal biology or pathophysiology are also subject to ethical constraints that derive from the special moral status of human beings. The history of research abuses—most egregiously the Nazi medical experiments—shows what can happen when research on humans disregards ethical constraints.⁴⁰ The basic obligations, though contested at the margins, are largely though not completely captured by widely accepted principles of nonmaleficence, respect for persons, and justice in research.⁴¹

The obligation of nonmaleficence requires that researchers who work with human subjects strive to minimize, consistent with the scientific aims of their research, the risks and burdens that their experimental procedures impose. (Mostly the concerns here stem from acts of commission—about what is *done to* the subject. With rare exceptions, such as drug withdrawal studies, there are no concerns about acts of omission in research on normal biology or pathophysiology.) The obligation to minimize risks and burdens is an extension of the constraints that bear on research with animals; what is novel when we arrive at research involving human subjects, however, is the determination to keep the levels of experimental risk and burden within allowable limits, regardless of the scientific benefits that might accrue from exceeding them. For example, research aimed at determining the lethal toxicity of investigational agents, although common (if controversial) in animal experimentation, would be ethically unthinkable in research with human subjects. This constraint underlies the Nuremberg Code's near-absolute injunction that

“no experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur.”⁴² Although the status of a requirement to limit allowable risks remains controversial, and there are no widely accepted standards and principles to specify and justify maximum allowable risk, few commentators would endorse scientifically valuable research that exposes subjects to a high probability of grave harm.

It is important to recognize that the obligation of nonmaleficence in clinical research differs from that in clinical medicine. The physician's obligation “to do no harm” means that, in the practice of medicine, risks to patients are justified only when outweighed by potential benefits to patients. (A notable exception is the practice of living organ donation, in which risks to the donor are justified by benefits to the recipient.) In research on healthy volunteers who have no prospect of medical benefit from research participation, nonmaleficence plainly does not require proportionality of risks and benefits for the subjects themselves. This lack of a requirement for proportionality is less obvious for sick patient-subjects, but it is still true. In both cases, it is both ethically justifiable and permissible, within appropriate limits, to expose research subjects to risks that are justified by the value of the knowledge to be gained from the research.⁴³ Accordingly, risk-benefit assessment differs fundamentally between medical care and clinical research.

A second obligation that emerges when researchers begin working with human subjects is that of respect for persons. Specific duties necessary to meet this obligation include the requirements to share important information with subjects before, during, and after the study; to obtain voluntary informed consent; to respect subjects' privacy and protect any information that they share in confidence; and to ensure subjects' freedom to withdraw from the study at any time.⁴⁴

Experiments involving human subjects must also satisfy the requirements of justice. For example, researchers must select subjects in an equitable manner, so that the risks and burdens of the research do not fall disproportionately on vulnerable individuals or groups.⁴⁵

Finally, researchers who work with human subjects in studies of normal biology or pathophysiology have several additional, if more controversial, obligations to subjects that do not fit easily within the categories above. First, within reasonable limits, they have duties of ancillary care for any incidental conditions that come to attention during the course of the research.⁴⁶ For example, if a researcher is conducting eligibility testing for a study of the effects of salt loading on blood pressure, and the researcher discovers that a prospective subject likely has previously undetected kidney disease, the researcher has an obligation at least to notify the individual of this finding and to recommend that she seek medical care. In addition, researchers must ensure appropriate treatment for, as well as compensation to, subjects who experience harms as a result of participating in their research.⁴⁷

One obligation commonly associated with clinical research—to maximize or at least enhance direct medical benefit to participants from the study intervention—does not arise at all in studies of normal biology or pathophysiology. This obligation first appears in studies designed to evaluate the safety or efficacy of a potential diagnostic, prophylactic, or therapeutic intervention among patient-subjects. We discuss such studies below.

Research testing potential diagnostic, prophylactic, or therapeutic interventions among sick patient-subjects. Investigators who test the safety or efficacy of interventions among sick persons historically have faced the greatest difficulty in defining coherently their obligations to subjects. Participants in such studies typically are in need of care, and they bring with them a set of deep-seated expecta-

tations for optimum treatment. They want both access to interventions and personalized attention and recommendations from their physicians.⁴⁸ When they agree to participate as research subjects, they are owed respect not only because they are human beings, but also because of their special role as sick individuals participating in biomedical research. In other words, respect for people in clinical research involves more than recognizing ethical constraints relating to the fact that the experimental subjects are human beings. It also requires re-

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specting the needs and reasonable expectations of patient-subjects for medical attention within the context of conducting scientific research.

According to the dominant view of human subjects research ethics, the only way researchers can satisfy the rights and expectations of sick people in need of care is to impose constraints on study design—such as the requirement for equipoise in randomized controlled trials—that allow investigators simultaneously to fulfill their therapeutic duties as physicians. This therapeutic orientation fails both logically and pragmatically to ground the ethics of clinical research, for reasons we will not review here.⁴⁹ Following Katz, we advocate a different view: the investigator who tests potential diagnostic, prophylactic, or therapeutic interventions is a scientist conducting experiments among sick patient-subjects, not a physician who grafts the pursuit of research objectives onto his or her primary therapeutic commitments.⁵⁰ John Ziman, the social theorist of science, recognized this continuity between the laboratory scientist and the clinical in-

vestigator in defining the concept of an experiment:

[T]he most effective way of projecting an experiment on to a particular theoretical dimension is to undertake it in carefully contrived circumstances where all other potential disturbing factors are eliminated. Every branch of science has its strategies for doing this—studying the behaviour of bacteria on clean petri dishes rather than in mucky soil, scattering electrons from homogeneous beams of particles rather than in hot plasmas,

testing a therapeutic drug against a placebo by a double-blind trial rather than just administering it to all needy patients.⁵¹

To date, we have lacked a comprehensive and coherent conception of the ethical obligations governing the activities of scientists who conduct clinical trials with sick patient-subjects. Indeed, because the therapeutic orientation to clinical trials has been widely accepted, we have not even recognized that such a conception is needed. But a rich account is now at hand.

Like scientists in other contexts, the clinical investigator who tests potential diagnostic, prophylactic, or therapeutic interventions among sick individuals is bound by the goals of biomedical research and must adhere to its internal norms. In addition, she must respect the ethical constraints that govern the work of her more basic colleagues. Indeed, virtually all of the obligations that she must fulfill are already in place once we have identified the ethical constraints for studies of normal biology or pathophysiology involving human volun-

teers. These duties include those of respect for persons, such as the obligation to obtain voluntary informed consent; minimization of risks and harms associated with acts of commission, consistent with achieving scientific objectives; respect for reasonable ceilings of absolute risk; independent review; appropriate ancillary care responsibilities; and compensation for research-related harms. All that remains to complete our model for clinical trials involving sick patient-subjects is to further specify several previous constraints and to articulate one new obligation.

One constraint that must be further specified is the duty to minimize risks and burdens on subjects. In addition to risks of commission, research testing potential new interventions among sick patient-subjects may also involve risks of *omission*, such as the use of placebo controls in randomized controlled trials despite the availability of a known effective therapy. Risks of omission arise because patient-subjects may be asked to volunteer for research procedures that depart from the standard medical care that would be offered in clinical practice. In light of the duty to minimize risks, exposing patient-subjects to interventions known to be inferior to the standard of care requires a careful justification. However, because randomized controlled trials are scientific experiments, the key question for ethical assessment is not whether medically indicated treatment is “denied” or physicians’ clinical obligations are fulfilled; rather, the central issue is whether the risks that derive from omitting treatment are justified in light of the scientific rationale for omitting treatment. Contrary to the doctrine of clinical equipoise, such studies are not necessarily unethical.

The point here is that considerations of scientific validity may warrant placebo controls despite the existence of a proven effective treatment, provided that the controls do not pose undue risks of harm.⁵² In other words, according to the scientific orientation to research, placebo controls

are in principle the same as *any* research intervention that poses risks to subjects (in this case, risks of omission) without a prospect of benefit. Researchers considering such studies must choose the design that minimizes risks of omission while still permitting valid answers to their study questions.⁵³ This constraint would dictate, for example, that researchers actively monitor study participants for evidence of clinically significant signs or symptoms, and that they be prepared to break the blind or withdraw them from the study in the event of unreasonable risks. In addition, researchers must remain below the ceiling of acceptable absolute risk that results from withholding the treatment that is otherwise available. Thus, it would be unethical to withhold treatment from subjects in a control group of a study for a life-threatening condition for which effective therapy exists, even if there were strong scientific reasons for doing so.

In the context of research on potential new treatments among sick individuals, the duty of respect for persons takes on additional dimensions because of the need to acknowledge participants’ status as *patient-subjects*, rather than as subjects only. First, obtaining informed consent for such research requires honesty about the nature of participation, such as the need to clarify how the relationship between clinician-investigator and patient-subject differs from the traditional clinician-patient relationship.⁵⁴ Efforts to dispel the therapeutic misconception should be incorporated into the routine informed consent process for clinical trials.⁵⁵

Second, respect for persons demands attention to the trajectory that patients follow in considering research participation, enrolling in a study, and returning to medical care. Investigators must attend not only to the transition from being a patient seeking medical care to being a patient-subject treated in the context of research that occurs when a patient joins a trial, but also to the need to adopt a caring attitude in the course

of research, and finally to the transition back to patient alone that occurs at the end of a trial. Investigators have a range of obligations relating to this trajectory. Typically, prior to the decision to enroll, investigators should encourage prospective patient-subjects to consult with their regular physicians regarding research participation.⁵⁶ During the course of the research, the duty of respect for persons requires that the investigator adopt a caring attitude towards subjects. This attitude is not equivalent to physicians’ stance of clinical fidelity to their patients because the investigator-subject relationship is not a fiduciary one,⁵⁷ but neither is it insincere or intended to mislead subjects into false assumptions about the nature of their interactions with the investigator. Rather, such an attitude, which must remain consistent with duties of fidelity to the scientific objectives of the clinical trial, is owed to subjects in recognition of their distinct moral status as sick individuals, possessing rights and interests, who have volunteered to assist in the pursuit of biomedical knowledge. While there may be tensions between caring and conducting science, researchers must view participants as human beings rather than as experimental material or data points. Thus, at the conclusion of research, investigators must debrief subjects, provide medically relevant information about them that has emerged during the course of research, and make appropriate referrals for or provide ongoing treatment.

In short, respect for persons in clinical research is more than a general requirement to avoid treating subjects as a mere means to scientific investigation. It also requires that investigators relate to patient-subjects as ill persons, while recognizing that the purpose of the research activity is not personalized medical care. Maintaining professional integrity within this relationship is a complex ethical challenge.

One new constraint is particular to research that tests the safety or efficacy of interventions on sick patient-

subjects. This is an obligation to maximize direct benefit to the participants. This duty is not synonymous with the therapeutic obligation inherent in the traditional view of clinical research ethics, which holds that the duty to benefit is central to the very purpose of the activity. Rather, it acts as an ethical constraint on the pursuit of a valid and reliable answer to the clinical or scientific question that motivates the research.⁵⁸ The distinction between the therapeutic obligation to optimize personal medical outcomes and the researcher's obligation to maximize direct benefits to patient-subjects derives from the differences in purpose and focus between medical care and research. The physician providing personalized care is obligated to maximize medical benefits for each individual patient. The investigator, seeking generalizable knowledge, should aim to maximize benefits for participants so long as this is consistent with answering the relevant scientific questions.

In this respect, the duty to maximize benefits is parallel to the duty to minimize risks: both are relative to the purpose of pursuing scientifically valid research. Thus, the researcher choosing between two ways of designing a trial, either of which is likely to address his study question, is under at least a presumptive obligation to select the design with the greater prospect for benefiting subjects in the trial. In contrast, the researcher who wishes to test the efficacy of a promising new drug for a life-threatening condition with no established treatment is justified in selecting a placebo-controlled design, rather than administering the drug to all eligible individuals in a single-arm trial, if despite its greater potential for direct benefit, the latter approach would preclude his ability to determine whether the drug is effective.

One important clarification is needed before concluding our discussion of intervention research among sick patient-subjects. In criticizing the therapeutic orientation, we acknowledge that patient-subjects participat-

ing in clinical trials often simultaneously receive a substantial amount of standard medical care, which may be specified by or delivered alongside the study protocol. This standard medical care is appropriately governed by therapeutic norms. The therapeutic and scientific orientations differ, however, in the choice of norms that should govern those interventions or procedures that are properly considered integral to the clinical experiment. Proponents of the former view hold that therapeutic norms govern some or all of the interventions in this category, whereas we view extension

foremost as experiments designed to obtain valid answers to important clinical questions. The scientific orientation creates a presumption that trials will be designed with the greatest possible methodological rigor, subject to compliance with a robust set of ethical requirements. Accepting this conception of clinical trials acknowledges that participation may entail risks or burdens for at least some individuals who join. At the same time, the model provides appropriate substantive and procedural guidance regarding the constraints that define whether and when such

The scientific orientation can also clarify the acceptability of research procedures, such as biopsies, that are important for answering study questions but that offer no prospect of benefit to patient-subjects.

of these therapeutic norms to cover research activities as a conceptual mistake. Such research interventions should instead be judged according to norms specific to clinical research.

Implications of the Scientific Orientation

Adopting a scientific orientation to clinical research ethics leaves many familiar ethical norms intact. Indeed, the scientific orientation cannot by itself solve many of the fundamental ethical questions that arise in biomedical research, such as what ceiling should be placed on the risk that a fully informed, consenting subject can accept in the course of a study, or what burdens may be imposed on an animal subject. Nevertheless, adopting a scientific orientation allows us to confront the hard questions in research ethics unencumbered by misguided therapeutic presumptions.

The fundamental advantage of the scientific orientation is its insistence that we view clinical trials first and

risks or burdens may be imposed. In the cases we began with, for example, the scientific orientation would be more likely than the therapeutic orientation to endorse the use of placebo controls in the first case, the use of sham surgical controls in the second, and the continuation of the trial until primary objectives were achieved in the third. In sum, it would promote the social value of clinical research while observing those protections of the rights and well-being of research participants that are appropriate to the enterprise of clinical research as distinct from medical care.

Several specific virtues of the scientific orientation bear mention. First, it avoids erroneous ethical guidance with respect to the design and conduct of randomized controlled trials. The therapeutic orientation in the guise of the principle of clinical equipoise categorically rules out the use of placebo controls when proven effective treatments exist for the disorder under investigation.⁵⁹ This limitation unjustifiably constrains scientific investigation and promotes use

of methodologically inferior study designs.⁶⁰ Instead of focusing on the “denial” of medically indicated treatment in placebo arms, we should emphasize the methodological rationale for the use of placebo and the level of risks to subjects receiving placebo in the context of time-limited trials with careful monitoring.⁶¹

The principle of clinical equipoise also encourages researchers to stop clinical trials prematurely. In the therapeutic approach, a trial must be stopped when equipoise is “disturbed” by emerging data about efficacy. But sound ethical thinking should focus not on physician-investigators’ “therapeutic obligations,” but rather on the level of risks to which subjects are exposed and on the importance of additional scientific data.⁶²

Second, the scientific orientation can clarify the acceptability of research procedures, such as biopsies, that are important for answering study questions but that offer no prospect of benefit to patient-subjects. Owing to the pervasive therapeutic orientation, there is substantial discomfort among investigators and IRB members with requiring such biopsies as a condition of entry into a clinical trial.⁶³ The scientific orientation, in contrast, would endorse the requirement for such biopsies provided that basic criteria of scientific value, acceptable risk, and informed consent were satisfied.

Third, the scientific orientation helps in appropriately specifying the principles of biomedical ethics for the context of clinical research as distinct from medical care. The principles of respect for autonomy, nonmaleficence, beneficence, and justice apply to both clinical research and medical care; however, their meaning cannot be the same in these different domains without incoherently distorting the ethics of clinical research. For example, in the context of medical care, beneficence and nonmaleficence are understood as having a distinctly therapeutic meaning. Beneficence entails the obligation of the health care

provider to do what is best medically for particular patients, and nonmaleficence entails the obligation to avoid exposing patients to harms or risks of harm that are not compensated by the prospect of direct medical benefits. In clinical research, in contrast, beneficence directs investigators to promote social value by generating scientific knowledge, in addition to promoting medical benefit for subjects when consistent with the design of the research; nonmaleficence requires that risks are minimized and justified by the potential value of the knowledge to be gained by the research.

It is important to note that adopting a scientific orientation to clinical research helps to clarify the positive as well as the negative obligations that investigators hold toward subjects. The positive obligations include truthfulness when describing and making disclosures about proposed research projects, maximizing benefits for participants (consistent with obtaining a valid answer to the study question), and returning summary results to subjects at the conclusion of a study in order to acknowledge their role as partners in the research enterprise. This rich set of positive duties belies the fear that viewing clinical investigators as scientists necessarily implies an impoverished conception of the researcher-subject relationship.

Finally, the scientific orientation promotes ethical honesty and research-appropriate professional integrity. In contrast, the therapeutic orientation suggests that it is possible to engage in clinical research while maintaining obligations to patients that are characteristic of medical care. Given that research is not devoted to doing what is best medically for research subjects and that it justifiably exposes subjects to risks that are not compensated by medical benefits to them, the therapeutic orientation diverts attention from the ethical challenges of human investigation. Also, by viewing clinical research through a therapeutic lens, this orientation arguably contributes to promoting therapeutic misconceptions among pa-

tient-subjects, thereby compromising informed consent.

A scientific approach to the ethics of clinical research starts not with the ethics of the doctor-patient relationship but with the normative obligations that govern the work of the laboratory researcher at the bench. From there, it proceeds in stepwise fashion toward the obligations of the clinical researcher at the bedside. This orientation illuminates the ethical similarities and distinctions between clinical trials involving sick patient-subjects and studies of normal biology or pathophysiology involving sick or healthy human volunteers, and clarifies the relationships between different kinds of biomedical research. Despite omitting any reference to physicians’ therapeutic obligations, it grounds a rich and morally justifiable relationship between investigators and sick patient-subjects.

Disclaimer

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