

Defining and Describing Benefit Appropriately in Clinical Trials

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Institutional review boards (IRBs) and investigators are used to talking about risks of harm. Both low risks of great harm and high risks of small harm must be disclosed to prospective subjects and should be explained and categorized in ways that help potential subjects to understand and weigh them appropriately. Everyone on an IRB has probably spent time at meetings arguing over whether a three-page bulleted list of risk description is helpful or overkill for prospective subjects. Yet only a small fraction of all the time and attention lavished on risk disclosure has been devoted to discussing whether and when potential benefit to subjects can reasonably be claimed and, if so, how it should be described in the consent form and process.

Traditionally, IRBs and regulators have worked to ensure that clear lines can be drawn between research that, by definition, carries no potential for direct benefit — because it uses healthy volunteers or because it is not foreseeably focused on the development of treatments — and research that does have the development of effective treatments as its goal.¹ Because of this, we have allowed ourselves to assume that all clinical research using patients as subjects and directed toward developing treatments offers a reasonable potential for direct benefit to subjects. This assumption is incorrect in many cases, resulting in what has been called the “therapeutic misconception.”²

When the consent form and process go into great detail about the risks of harm and little is said about the potential for benefit, it is understandable that all those involved in clinical research — prospective subjects, investigators and other study personnel, referring physicians, regulators and policy makers, and the general public — generally assume that the intervention being studied is the best

treatment option and that it would not be offered to prospective subjects if it was not going to work.

The therapeutic misconception has become more widespread because of recent technological optimism and public relations blitzes that preview even the most preliminary preclinical research results in the popular press.³ This trend is far from new, but increasingly common. Indeed, the press conference has become a standard method of promoting research. For example, a recent cartoon depicts several white-coated researchers in front of a bank of microphones: “And while the drug hasn’t been tested on humans, it works on mice and the stock market.”

Unfortunately, this kind of discussion and promotion can result in confusion and betrayal of trust when patient-subjects realize that the optimistic assessment of their chances of benefit was really a misconception. Articles with headlines like “Patient or Guinea Pig? Dilemma of Clinical Trials”⁴ and “When the Dying Enroll in Studies: A Debate Over False Hopes”⁵ have become commonplace in the popular press over the last several years.

The Common Rule⁶ actually doesn’t say much about benefit. In order for research to be approved, it requires 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” (that is, the benefit to society from the results of the research).⁷ And benefits to subjects or others “which may reasonably be expected from the research” should be described in the consent form and process.⁸

Thus, for all research using patients as subjects, IRBs and investigators must do more than distinguish between research that is and is not focused on the development of treatments. In addition, for all research focused on the development of treatments, it is essential, first, to determine whether participation in the research holds out a reason-

able prospect of direct benefit for subjects and, second, to describe and discuss the prospect of direct benefit sufficiently to permit informed decision-making by prospective patient-subjects. That is, there must be a *reasonable chance* of benefit in order for a prospective subject to make a *reasonable choice* about participation based on anticipated benefit.⁹ Note that “reasonable” is not synonymous with “rational.” Reasonableness requirements take into account circumstances and values, not just statistics, but can nonetheless be subjected to deliberation and discussion.

It is especially important to try to determine whether there is a reasonable chance of benefit to subjects because, under the current regulatory scheme, so much hinges on distinguishing between research that does offer subjects the potential for direct benefit and research that does not. Being able to claim that there is potential benefit for subjects is linked to:

- research bearing more than minimal risk and involving children,¹⁰ pregnant women and fetuses,¹¹ persons with questionable decisional capacity,¹² and prisoners;¹³
- waiver of consent in emergency research;¹⁴
- emergency use of a “test article” without IRB approval, including without consent;¹⁵
- use of so-called “treatment ‘investigational new drugs’” (INDs);¹⁶ and
- insurance reimbursement for research costs.¹⁷

Thus, there is a natural tendency for investigators and IRBs to indulge in “benefit creep.” That is, to ensure that research considered beneficial to *society* can go forward, investigators and IRBs may exaggerate or even invent benefit to subjects.

WHAT IRBs CAN DO

Even outside of these particular research categories and populations, it is important to correct what has become the pervasive and routine underdescription and overestimation of benefit in clinical research. There are four things IRBs should do, discussed below.

Keep the types of benefit separate

There are three distinguishable types of benefit possible from research:

- *direct* benefit to subjects, which is properly defined as benefit arising from receiving the intervention being studied;
- *collateral* benefit to subjects (the National Bioethics Advisory Commission calls this “indirect” benefit¹⁸), which is benefit arising from being a

subject, even if one does not receive the experimental intervention (for example, a free physical exam and testing, free medical care and other extras, or the personal gratification of altruism);

- *aspirational* benefit,¹⁹ or benefit to society and to future patients, which arises from the results of the study.

Payment to subjects, though technically a collateral benefit, is classified and treated separately in research ethics and policy.²⁰

In clinical research designed to develop future treatments, it is direct benefit that is of greatest interest to patient-subjects. And it is, unfortunately, quite common to combine and confuse direct benefit with aspirational benefit. One of the ways this happens is through the background and purpose sections of consent forms. These sections at the beginning of the consent form often contain extensive descriptions of what the research hopes to prove — that is, of the generalizable knowledge and societal benefit sought — in terms that are easy to confuse with what patient-subjects hope for themselves. This problem is compounded when the purpose section in an early-phase trial describes the aspirational benefit expected from the entire line of research, not just from the particular trial. This fosters confusion between what the investigators hope to show by the end of the clinical trials process and what individual subjects can anticipate in that trial.²¹

It is also common to combine and confuse direct and collateral benefit, as investigators do when they express their firm belief that “patients get the best treatment on-study” because they are at the best academic medical centers and getting more attention than they would off-study. Indeed, direct and collateral benefit are confused any time the discussion of benefit is limited to “benefit from participating in this research” rather than focusing on both “benefit from receiving the intervention being studied” *and* “other benefits from participating.”²²

To give a recent example, the 1998 study of IRBs by the National Institutes of Health’s Office of Extramural Research, “Evaluation of NIH Implementation of Section 491 of the PHS Act, Mandating a Program of Protection for Research Subjects,” contains only one paragraph about benefit:

Investigators were also asked to identify the types, level, and likelihood of benefits to subjects that were anticipated when their protocols were submitted. Analysis revealed the majority of investigators expected for each type of benefit both a medium or high level of beneficial effect and a 50 percent or greater chance of the benefit occurring.²³

This is pretty optimistic, but the optimism is made more understandable when you realize that the report's types of benefit — medical, social, psychological, educational — do not distinguish between direct and collateral benefit at all.

Examine any claim of potential benefit carefully

Some clinical trials with patients as subjects clearly do not offer the prospect of direct benefit. Some IRBs recognize this and require investigators to be candid in the consent form. For example, one of the first gene transfer research protocols for cystic fibrosis took place at the University of North Carolina. Corrected genetic material was combined with a modified virus “vector” designed to transport the material into the subject's cells, and was instilled into subjects' nasal passages. Since cystic fibrosis profoundly affects patients' lungs and other organs, this experiment could not make a difference in their disease even if it were completely successful in “transfecting” cells in the subjects' noses. The consent form appropriately said: “You will not benefit.”²⁴

Such clear statements are rare. Nonetheless, in many early-phase clinical trials, the prospect of direct benefit may be too small, too attenuated, too unlikely, too uncertain to hold out as reasonable to expect. Phase I trials like the nasal gene transfer study, which test the safety and toxicity of drugs, biologicals, or other interventions not yet tried in humans, generally fall into this category; yet consent forms for many Phase I oncology trials, for example, contain a great deal of optimistic, treatment-oriented language addressing potential benefit. When benefit cannot reasonably be expected, the consent form should say, “You will not benefit.”

For early-stage research, investigators should be required to demonstrate to the IRB that “You will not benefit” is *not* what should be in the consent form. Currently, it is often presumed that benefit can be shown. The presumption should be reversed in order to elicit better and more complete evidence about the potential for benefit.

What is a reasonable chance of direct benefit? That is a critical and difficult question. IRBs and investigators haven't often looked at this question, and in my view, many guidance documents like *The Belmont Report*,²⁵ the IRB Guidebook²⁶ issued by the Office for Human Research Protections (formerly the Office for Protection from Research Risks), and the Food and Drug Administration's Information Sheets²⁷ are better at illustrating the problem than offering a solution. Yet other scholarly and guidance documents are clearer and require more. For example, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research states that to be considered direct, the possibility of benefit must be “fairly immediate” and the expectation of success should be well-founded scientifically.

This definition provides a little more specificity, even

though it still leaves some terms to be defined.²⁸ Significantly, it makes clear that any “reasonable chance” threshold requirement is *evidentiary* in nature — that is, within the province of the IRB and scientific knowledge. Only the reasonable *choice* requirement is personal because what counts as a reasonable choice, after appropriate disclosure and discussion, is left to the prospective subject.

Investigators and IRBs need better guidance in making and evaluating claims of potential benefit to subjects. But even without setting a reasonable chance threshold, IRBs can do much to improve disclosure and discussion and to enable reasonable choice about benefit.

Discuss the dimensions of benefit

There are three dimensions of potential benefit that should be described and discussed in the consent form and process, just as they are discussed with respect to risks of harm:

- the nature of the potential benefit;
- the magnitude (size and duration) of the potential benefit; and
- the likelihood of the potential benefit.

It is immediately evident that these dimensions overlap in some respects, as they do for risks. It is also clear that it is somewhat difficult to be specific about these dimensions as applied to the type of benefit of greatest interest — direct benefit — since this is exactly what is being studied. But this “uncertainty factor” is equally true for risks of harm, and we talk about risks in the same kind of detail all the time — indeed, it is strongly encouraged.²⁹

Most importantly, though, as thoughtful IRB members will recognize, detailed statements about anticipated benefit must be very carefully articulated in order to avoid precisely the conflation that must be avoided: confusing societal benefit — that is, future effects of the research results — with direct benefit from receiving the experimental intervention.³⁰ Will more description inevitably produce more overselling? I don't think so, provided that the description is accurate in its depiction of the uncertainties and limitations of the evidence.

Nature

What kind of benefit is expected? In some early-phase research, the kind of benefit may be difficult to specify, as the research design will be focused on measuring toxicity and evaluating safety. Some protocols may measure surrogate endpoints — laboratory measures thought to serve as markers for long-term, harder-to-measure improvements in morbidity and mortality. Sometimes, it is not clear to IRBs or to potential subjects what clinical effects are anticipated to correspond with the measured endpoints. But a general

description of the nature of the benefit, accompanied by a clear statement of the uncertainties, unknowns, and unproven status of the intervention being studied, is possible and necessary.

Magnitude

How great is the potential benefit expected to be, and how long is it expected to last? These two components of magnitude are rarely discussed in consent forms, leading to the natural assumption that the intervention being studied promises a complete and permanent cure, when often the most that could ever be expected is partial: a reduction in symptoms or an improvement in a condition. In research on most surgical procedures and some drugs and biologicals, the beneficial effects that could be realized are permanent; but more often, they are temporary, in ways that are obvious (e.g., effects of the study drug last only as long as you are taking it) or not so obvious (e.g., effects of the intervention are expected to wear off or fade over time). “We do not know how long any beneficial effects might last” is always a true statement about an unproven intervention being studied.

Likelihood

How likely is it that any given subject will experience a direct benefit? This is, of course, quite difficult to predict, but several things are surely true. First, the likelihood can at least be partially signaled by the results of preclinical (laboratory and animal) research. Although 100 percent effectiveness in a test tube does not portend the same success rate in human trials, a low incidence of effectiveness in preclinical trials does generally suggest a low likelihood in human trials.

Second, the likelihood of effectiveness will probably be quite low in the earliest phases of clinical trials and may change (along with specificity about the other dimensions of potential benefit) in later phases, as more information is gathered about effectiveness — either about how to maximize it or about its failure to materialize.

Third, the likelihood of effectiveness is affected by design elements, such as placebo or standard treatment arms, dose escalation designs, and the assignment of subjects to different dosing cohorts or regimens. Even when the likelihood of beneficial effect from the intervention is relatively high, it is lowered for individual subjects by the probability that they could be assigned to a placebo arm or to a cohort receiving a low dose. Likelihood need not be characterized by percentages, but all necessary information must be used in any characterization. Thus, if animal studies showed that two of twelve rabbits had a change in a surrogate measure at the highest dose level, but only one of those two rabbits had a change great enough to show clinical effect in hu-

mans and only the third dosing cohort (3–6 subjects) in a Phase I study is going to receive a dose comparable to that given to the twelve rabbits, the likelihood that any of the subjects in this Phase I trial is going to benefit directly from participation is, at best, very low — and should be so described.

For example, in mid-October 1999, the first human trials of endostatin for tumor suppression were started. Dr. Judah Folkman emphasized in an interview with the *Chicago Tribune* that despite the enormous optimism and publicity surrounding his research — three subjects were picked by lottery from thousands of “hopeful applicants” — success in mice does not necessarily portend even partial success in humans. After all, he noted, “Most drugs fail.”³¹

Acknowledge uncertainty without ambiguity

Instead of detailed discussion designed to promote careful assessment and reasonable decision-making, prospective subjects are more likely to read “boilerplate” statements, such as the following, in the benefit section of the consent form:

- “It is not known whether your participation in this research study will have a beneficial effect.”
- “You may not benefit from this research study.”
- “Personal benefit cannot be guaranteed.”
- Or the standard version used in much oncology research, “A potential benefit is control of your disease, if you should respond to these treatments. However, it is possible that your condition could worsen despite treatment.”

Often, this is the only description of potential benefit in the entire document, aside from the aspirational benefit description in the purpose section. The vagueness of these statements is particularly troubling because they are so general that they could be applied to any standard treatment of proven effectiveness and, therefore, do nothing to distinguish research from treatment or to signal the uncertainty appropriate to most research settings. Surely we can do better than this.

Several examples of improved benefit boilerplate statements follow:

- “This medical research project is not expected to benefit you” (scholars from the University of Pennsylvania’s Bioethics Center have recommended that this statement be prominently placed near the beginning of all consent forms for Phase I studies).³²
- “What you need to know before entering a clinical trial: You are not a patient” (the headline on a sidebar in a *U.S. News Online* story about

the brief suspension of Duke University's federal authorization to perform human subjects research in April 1999).³³

Are these better? Yes. Are they good enough? No. The problem is that detail and evidence are required when direct benefit is being discussed. Boilerplate is simply inadequate; it is essential to particularize.

The following statement, compiled from three consent forms for early-stage research that had unusually detailed benefit sections, may serve as one example of particularization:

This research project is primarily testing the safety of an experimental intervention with which we have little experience. It is not likely that participation will benefit you. Results of earlier research have shown that a few subjects experienced reduction in symptoms, but most did not benefit in any way. We hope that the tumor may become smaller for a period of time, but we do not know if this will occur or for how long any benefit will last.

It is obvious how much more this attention to detail requires of both investigators and IRBs — namely, to craft and review descriptions of potential benefit whenever it can be reasonably claimed and to be sure that claims of potential benefit are adequately supported and not overstated. But because so little attention has been given to describing and discussing benefit in research, improvements here could greatly improve decision-making.

A REASONABLE CHANCE OF DIRECT BENEFIT

Better disclosure of and discussion about the potential for direct benefit could also provide needed insight into whether a “reasonable chance of benefit” threshold can be established for clinical research. What should count as a reasonable chance of benefit? How should it be measured and by whom? Can a threshold be set?

A definition?

The easiest way to talk about direct benefit is by using lawyerly language, familiar from informed consent case law, using as a reference point the famed “reasonable person.” One possible definition follows: *A reasonable chance of direct benefit exists when a reasonable person under all the circumstances would consider the nature, magnitude, and likelihood of direct benefit sufficient to reasonably choose to participate in research in anticipation of the benefit.*

“A reasonable person” really means *all* reasonable people. This is implicit, but not discussed, in the applica-

tion of the reasonable-person standard to informed decision-making. It makes obvious sense because otherwise only one reasonable person would be needed to establish a standard for everyone. Yet all that is required is that the potential for direct benefit be generally considered sufficient to choose on that basis. It does *not* mean that all reasonable people would so choose, because, as we also know from the law, reasonable minds may differ.

The important thing about the reasonableness of the chance lies in the definition's implicit demand that *evidence* be presented with respect to all three dimensions of direct benefit and that, in combination, they be judged sufficient to support a decision to become a subject in order to gain the chance to benefit. It is essential that supporting evidence appropriate to the stage of research be presented to potential subjects³⁴ — including laboratory and animal evidence, and human data if available. A plausible, logical theory is not enough.

Remember that a reasonable chance of direct benefit and a reasonable choice about participation are not the same. The proposed definition of reasonable chance does not mean that all reasonable people would choose to participate. That would wrongly equate the evidentiary reasonable-chance standard with the only reasonable choice. Instead, a reasonable chance means that all reasonable people would consider the information sufficient to attempt to secure the benefit. The emphasis is on the presentation of evidence sufficient to support a benefit-seeking choice.

Skepticism about claims of direct benefit in clinical research is essential. Nonetheless, the evidence required to claim direct benefit from an investigational intervention should not be expected to be the same as what is required to prove that an intervention is beneficial as treatment. It stands to reason that, because of uncertainty and the need to gather evidence, benefit claims about an intervention that is unproven and being studied should necessarily require less evidence than benefit claims about standard treatment.

Finally, reasonable minds may differ. Saying no to research participation is always a reasonable choice, even when there is a reasonable chance of direct benefit. Deciding about research participation depends upon a variety of potential reasons, including, but certainly not limited to, differences in values and preferences as applied to the evidence about benefit and different valuations of the burdens of research participation.

Thus, (1) there must be a reasonable chance of direct benefit from an intervention being studied before the possibility of direct benefit may be offered to potential subjects; and (2) the possibility of direct benefit must be well-described to potential subjects in terms of all the dimensions of benefit.

Because the chance of direct benefit supports a decision to enroll in research in anticipation of that benefit, this is a *disclosure* issue, not a matter of *risk-benefit assessment*

in the first instance. The absence of a reasonable chance of direct benefit in early-phase research will not normally affect the ability of the research to satisfy conditions of value and validity³⁵ or the balance between risks of harm and aspirational benefit.³⁶ Nor will the absence of a reasonable chance of direct benefit preclude well-informed potential subjects from choosing to participate in research on other grounds, ranging from altruism to collateral benefit to the belief that trying for a very long shot at direct benefit is worth it under all the circumstances.

The last possibility is especially likely to be true in circumstances where available treatments are so imperfect and the burden of disease is so great that long-shot treatments would be considered worth trying by some reasonable patients. It would be paternalistic to consider this reason for research participation invalid, yet it is extremely difficult, in practice, to minimize the potential for the therapeutic misconception. One essential way of doing so is to explain that no direct benefit is expected for subjects and why. Only Jay Katz's formulation — "Remember, you will be a subject; you will not be my patient"³⁷ — can adequately frame the necessary disclosure and discussion here.

The circumstances and the alternatives

Assessment of whether there is a reasonable chance of benefit is, of course, always "under all the circumstances." That modifier covers a lot of ground. Indeed, the circumstances are likely to be so complex and variable that no single threshold standard can be set. It seems more plausible to consider context-specific threshold requirements — specific to the disease or condition, the subject population and the degree of disease burden, available treatments and their benefits and burdens, and other relevant contextual features. Reasonableness judgments are likely to be contingent and time-consuming for IRBs and may benefit from input from scientific and disease constituencies at a national level.

It is therefore tempting to take a shortcut — to assume that every investigational intervention offered to a patient-subject carries a reasonable chance of benefit, since every time an offer is accepted, it signals the reasonableness of the choice. This shortcut is wrong, though, because offers made in a last-chance mode might easily be supported by insufficient evidence and be grounded more in desperation than in expectation. This shortcut would simply routinize the therapeutic misconception.

A reasonable chance and clinical equipoise

Another tempting but wrong-headed shortcut would be to equate the existence of equipoise with a reasonable chance of benefit. It is tempting to do this because clinical equipoise³⁸ requires a difference of opinion among reasonable minds about whether the investigational intervention is likely

to be better than standard treatment or better than nothing. But ensuring that equipoise exists is not the same as establishing a reasonable chance of benefit.

Equipoise takes into consideration a range of factors, not solely nor primarily the potential for direct benefit. The ultimate focus of equipoise is the entire risk-of-harm/chance-of-benefit calculus, encompassing aspirational benefit in particular. That is, equipoise is a reasonable difference of opinion about what *will be* the better *treatment* for future patients — not about what *is* better for current subjects.³⁹ Importantly, the precise nature and focus of clinical equipoise may shift according to different stages in the clinical trials process, and in early-phase trials, the focus of equipoise may be limited. For example, in Phase I safety studies, equipoise is primarily or exclusively about safety. The question, "Is the investigational intervention at least as safe as standard treatment?" expresses the equipoise that must be disturbed, one way or another, by a completed Phase I trial; yet, the successful completion of that first trial is not yet determinative of safety. It is not until the successful end of the entire clinical trials process that equipoise can definitively be disturbed in favor of the investigational intervention, which thereby earns the title "new treatment."

The oncology example

Oncology research takes place in a very complex and particular context: Available treatments are unproven, unsatisfactory, and often toxic; potential subjects and investigators alike feel a sense of urgency and even desperation; and there exists a publicly acknowledged commitment to increasing cancer patients' participation in research. Most of the time, patients are expected to have exhausted all standard and otherwise available treatment options before enrolling in research, so that they will not be tempted to forgo imperfect but accepted treatments off-study in hopes of a very long shot on-study. As a result, early-phase clinical trials in oncology have been said to enroll not only the most desperate patients as subjects, but also those least likely to benefit from a new intervention — at least from a new variant of the same classes of interventions to which they have not responded previously. However, many physicians, investigators, and patients believe that the academic medical setting and close monitoring offered as collateral benefits in trials make research the best treatment option. And increasingly, patients who have not exhausted all conventional treatment options are choosing — and being encouraged to choose — research participation earlier.⁴⁰

One consequence of these trends is increased blurring between research and treatment. The ideal of genetic tumor typing is the development of a regimen specifically tailored to the disease and the genetic makeup of each individual.⁴¹ Since "tailored treatments" cannot be studied like conventional agents, this ideal views each patient as an ex-

periment with an n of 1, seeking the development of generalizable knowledge before and during individual interventions rather than through the traditional “gold standard” clinical trial process.

Is it possible, then, to consider early-phase oncology research as offering a reasonable chance of direct benefit to subjects? In traditional oncology research — from which the best data about whether Phase I trials show any tumor effects are derived — the answer is clearly no. Even so, however, little information is provided that would inform potential subjects better. Well-known and often-quoted data show very low likelihoods of tumor response, generally placed at less than 5 percent for subjects in Phase I trials.⁴² A higher percentage of tumor responses is seen in Phase II trials, as most doses in this phase are clustered near the maximum tolerated dose identified in Phase I.⁴³ But most of these data do not quantify tumor response beyond its standard definition of greater than 50 percent shrinkage, and none appear to provide any indication of response duration.

More importantly, tumor response is not usually defined in either the consent form or the consent process. Since patient-subjects generally hope for remission or cure, tumor response is at least somewhat likely to fall below the level of clinical benefit that potential subjects may consider “worth it” as part of a “reasonable chance” determination.

It seems clear that conventional oncology research suffers from very poor disclosure and that assessing the reasonableness of the chance of benefit in a given trial is not possible without better disclosure of existing data and better discussion of what is known and not known. At present, it appears that no Phase I trial can offer a reasonable chance of direct benefit — and that more information about the burdens of research participation and the alternatives of palliative and supportive care is imperative. Yet it is certainly also possible that a few classes of interventions may have a sufficiently different evidentiary basis to support the claim of a reasonable chance of benefit sooner in the trial process — still not in Phase I, because of uncertainties and unknowns, but perhaps in Phase II if stronger evidence of efficacy has been gathered in Phase I than usually appears.⁴⁴

The gene transfer example

Whether gene transfer research holds out a reasonable chance of direct benefit is an especially complicated question to address. Gene transfer’s direct benefit claims have received perhaps even less attention than most because of its presumed safety — “it can’t hurt, so why not just try it?” — until the death of Jesse Gelsinger in a Phase I study in the fall of 1999.⁴⁵

Most gene transfer research has turned out to be oncology research, raising similar or identical concerns about the low likelihood of direct benefit and the enrollment only

of subjects with no remaining viable treatment options. But some gene transfer research is directed toward chronic but not life-threatening diseases and to circumstances in which patients with relatively stable disease are asked to serve as subjects.

The oncology model, applied to the very different intervention of gene transfer, can promote a “biggest bang for your buck” mentality, much as in oncology. When investigators look first to patients for whom all else has failed, it is easy to think that because these patients are the sickest and the most in need of a successful intervention, they are also the most likely to benefit from the intervention being studied. However, subjects’ desperate circumstances cannot increase the likelihood of benefit. When there is only preclinical evidence to support efficacy in humans, that is enough evidence to maintain equipoise, but not enough to disturb it.

In contrast, currently stable patients with chronic disease are much more like so-called healthy volunteers. They may be less likely to think of themselves — or to be thought of by investigators — as likely to benefit, because they are less in need of something that works. People with genetic diseases like cystic fibrosis, hemophilia, and various enzyme deficiency disorders have all been enrolled in research with no reasonable chance of direct benefit, and fairly often they are told exactly that. The tricky part here is to address the argument that gene transfer is so unprecedented a field, with such irresistible therapeutic logic, that disclaiming direct benefit will understate reality and mislead potential subjects in a different way.

Claims of direct and substantial benefit to subjects enrolled in some Phase I gene transfer trials have been in the news lately.⁴⁶ If a Phase I trial does not collect efficacy data sufficient to make a claim about direct benefit meaningful, no such claim can be plausible: A claimed reasonable chance of benefit that is not adequately supported by evidence is not a reasonable chance. But the increasingly common combination of Phase I and Phase II trials, the unique way that gene transfer is thought to work, and the high disease burden of most genetic disorders may combine to make early claims of direct benefit plausible in some studies, if they are well-supported.

COLLATERAL BENEFIT, TREATMENT, AND JUSTICE

When investigators argue that “patients do better on-study,” so that enrolling in research is their best treatment option, they are making a collateral benefit claim.⁴⁷ The provision of collateral benefit in a research project raises issues of justice in two ways. First, providing a potentially higher standard of care to those enrolled in research than those receiving standard treatment potentially discourages the improvement of standard treatment. Second, because collateral benefits are entirely under the control of research

investigators and sponsors, their provision poses the risk of manipulating or possibly even coercing participation from subjects who are disadvantaged or otherwise vulnerable. At the very least, questions are raised about the standard of care and about the best ways to provide and finance health care for those in need.

Yet the problem of collateral benefit may be more complicated still. Remember that what distinguishes collateral benefit from direct benefit is that direct benefit is linked to the intervention under study and collateral benefit is available to all subjects simply by virtue of being in the study. There are several new research design trends that seek to make it difficult to distinguish between these two types of benefit. Conflation of direct and collateral benefit serves the argument that research is the best treatment, which in turn makes it difficult to remember that patients may also be subjects.

Some thoughtful investigators and policy makers have begun to broaden their definitions of the intervention being studied as well as to design studies that include several stages in order to maximize the potential for direct benefit to subjects.⁴⁸ This is most readily seen in psychiatric research, especially drug trials and comparisons of drug and non-drug interventions, and is largely a response to public concern about placebo designs, challenge studies, and wash-out periods. Proponents of this viewpoint do not consider the potential benefit from the study drug in isolation from the rest of the study. They do not regard study design features that minimize risk or provide collateral benefit (e.g., monitoring and testing, rescue medications, non-study physician available to monitor subjects — all means of minimizing risks to subjects; crossover designs and post-study open label extensions — two means of ensuring that all subjects gain at least limited access to the drug being studied) in isolation, either. Instead, they take it all together, rolling risk-minimization features and collateral benefit features into one package, and view the whole study as providing direct benefit. According to this view, the whole study has been designed to maximize the potential for direct benefit to all subjects.⁴⁹

Robert Levine has called this view, which takes all the components of the study as a whole, “the fallacy of the package deal.”⁵⁰ He has condemned it when it is used to label an entire study “nontherapeutic,” as has been done in the past, because it contains some unproven and/or purely research components. But its use as described here turns the “fallacy of the package deal” to the opposite effect — to label an entire study “therapeutic” despite the clearly experimental character and unproven benefit of its central component, i.e., the drug being studied.

This view rightly recognizes that a treatment program has many interconnected features and components and that maximizing potential benefit for patients requires a grasp of this dynamic complexity. Analogizing from the treatment

setting, this view considers a research protocol to be a plan for cutting-edge treatment — but the analogy goes too far. A research protocol is not treatment, no matter how much all parties wish it so. Treatment requires genuine attention to the best interests of the patient as an individual, including individual attention and individual tailoring or complete changing of any regimen for maximal efficacy.⁵¹ Even if the organization, scope, and duration of a clinical trial were compatible with these goals, the uncertainties and unknowns attendant upon use of an unproven intervention make individual tailoring almost meaningless, especially in early-phase trials. Moreover, the trialists’ mandate to collect data systematically makes individual tailoring largely incompatible with the development of generalizable knowledge.⁵²

Nonetheless, this view of trials as cutting-edge treatment supports the research systematization trend now gaining momentum in oncology and HIV/AIDS research in particular. Patients with some conditions have little access to interventions of any sort outside research. Pediatric oncology is the best example; most children with cancer are enrolled in research because the community of practice agreed to develop an all-encompassing research agenda in order to make progress against the disease.⁵³ Most patients with HIV disease are enrolled in research, but for a different reason: They cannot afford to pay for highly active antiretroviral therapy regimens themselves. A great many HIV patients have lost their health insurance, have exceeded their lifetime policy limits, or have never been insured; thus, enrolling in research may be their only access to any drug treatment.⁵⁴

In contrast, in some very unsettled areas of disease and treatment, investigators have found it difficult to enroll subjects in studies of unproven interventions because those interventions are available off-study; are believed by patients, physicians, and the general public to be better than standard treatments; and are often paid for by health insurance. The classic example is high-dose chemotherapy followed by bone marrow transplantation (or, more recently, stem cell transplantation) for solid tumors, especially for breast cancer. Despite a paucity of evidence showing that this type of highly risky, burdensome, and indeed dangerous regimen is effective, dying women initiated a flood of lawsuits during the 1980s and 1990s against their health insurers and managed care organizations to get this expensive intervention paid for.⁵⁵ Many patients lost these suits; more won. Many insurers paid up; more changed their policies to improve coverage for enrollment in research “likely to be beneficial,” though the likelihood of benefit was rarely discussed since death was otherwise inevitable. Blue Cross announced early on in this long battle that it would subsidize clinical trials in order to gather some meaningful evidence about the efficacy of this extremely risky and burdensome intervention. At length, in late 1999, stud-

ies that had taken many more years to complete than had been originally hoped, because of slow enrollment, all showed that overall survival and quality of life were not meaningfully improved by this type of regimen.⁵⁶ But in the meantime, every community hospital was doing it.⁵⁷ And as a result, the cancer research community has announced its intention to ensure that every cancer patient will also be a research subject. The reasoning? It makes better data available faster and patient-subjects will be treated with a uniformly high, academic-medicine-based standard of care.

CONCLUSION

If increasing the enrollment of patients as subjects in research is a good thing, it is good for the following reasons: Medical research will expand, knowledge will increase, and perhaps future patients will benefit if the new knowledge produces better treatments.⁵⁸ Even if all these benefits materialize, it is still not necessarily true that patients will get better treatment if they enroll in research — nor that they will benefit from receiving the intervention being studied. If data are needed, if more needs to be learned, investigators can surely tell patients several important things:

- their help is needed to look for better treatments for future patients;
- in exchange for their help, they will receive either the best current treatment or something unproven in a study setting;
- investigators, study sponsors, and IRBs will do their utmost to protect them from harm;
- disclosure and discussion will be thorough and honest, telling them what benefit they can and cannot expect from receiving an unproven intervention and from being a research subject, as compared with receiving standard treatment.

Why does this disclosure and discussion seem so insufficient to many investigators and even to some IRBs? Some have argued that it is not enough because people do not want to be guinea pigs; instead, they want to be taken care of. It is possible to take good care of subjects in clinical trials; indeed, it is the investigator's duty to do so. Yet when no standard treatment works very well, no physician can fulfill a duty to take care of the patient if care means only cure — although, of course, it should mean more than that.

If patients who are subjects are properly cared for, only those who prefer to be deceived will want to be enrolled in research and told it will help them. Others may choose to enroll to advance science or to help future patients; still others will choose not to take part in research. And certainly there are investigators who may simply be unwilling or unable to have honest and respectful conversations with

patients. Perhaps they fear that other investigators will continue to be deceptive and will thus enroll more subjects; or perhaps they fear that too few patients would enroll in research if they knew how unlikely direct benefit is for subjects.

If the only way to address these fears is to make sure that every patient is a research subject, then we have strayed very far from any morally reasonable goal in health care or in research. Improving disclosure about all dimensions of potential benefit to subjects has the capacity to promote more reasoned discussion about what can and cannot be expected in research. From there, improving public discourse about the goals of clinical research seems possible, necessary, and long overdue.

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1. This is the outdated but persistent distinction between “nontherapeutic” and “therapeutic” research. See, for example, World Medical Association Declaration of Helsinki, “Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects,” revised 1996, reprinted in *JAMA*, 277 (1997): 925–26; see also A.M. Capron, “Ethical and Human-Rights Issues in Research on Mental Disorders That May Affect Decision-Making Capacity,” *N. Engl. J. Med.*, 340 (1999): 1430–34; F. Rolleston and J.R. Miller, “Therapy or Research: A Need for Precision,” *IRB*, 3, no. 7 (1981): 1–3; R. Levine, “The Need to Revise the Declaration of Helsinki,” *N. Engl. J. Med.*, 341 (1999): 531–34.
2. P.S. Appelbaum, L.R. Roth, and C. Lidz, “The Therapeutic Misconception: Informed Consent in Psychiatric Research,” *International Journal of Law & Psychiatry*, 5 (1982): 319–329; P.S. Appelbaum et al., “False Hopes and Best Data: Consent to Research and the Therapeutic Misconception,” *Hastings Center Report*, 17, no. 2 (1987): 20–24; P.S. Appelbaum, “Commentary: Examining the Ethics of Human Subjects Research,” *Kennedy Institute of Ethics Journal*, 6 (1996): 283–287. It has also been called the “therapeutic illusion.” J. Katz, “Statement by Individual Committee Member,” in Advisory Committee on Human Radiation Experiments, *Final Report* (Oxford University Press, 1996): 545.
3. L.R. Churchill et al., “Genetic Research as Therapy: Implications of ‘Gene Therapy’ for Informed Consent,” *Journal of Law, Medicine & Ethics*, 26 (1998): 38–47. See also G. Kolata, “Separating Research From News,” *New York Times*, July 18, 2000.
4. D. Grady, “Patient or Guinea Pig? Dilemma of Clinical Trials,” *New York Times*, Jan. 5, 1999.
5. G. Kolata, “When the Dying Enroll in Studies: A Debate Over False Hopes,” *New York Times*, Jan. 29, 1994.
6. The Common Rule is the shorthand name for the set of federal regulations that govern federally funded research with human subjects. The regulations, which implement Pub. L. 93–348 (the National Research Act of 1974), were harmonized into

the Common Rule in 1991 for 17 federal departments and agencies, and are codified separately for each. The Common Rule itself was published in the Federal Register, 56 Fed. Reg. 28,012 (June 18, 1991). The codifications most familiar to those involved in research oversight are the U.S. Department of Health and Human Services regulations, 45 C.F.R. pt. 46, and the Food and Drug Administration regulations, 21 C.F.R. pts. 50 and 56. The FDA has not adopted the Common Rule; its regulations are somewhat modified, though overall quite similar.

7. § __.111(a)(2).

8. § __.116(a)(3).

9. I am indebted to Alex Capron for the “reasonable chance/reasonable choice” formulation.

10. 45 C.F.R. pt. 46, subpt. D, “an intervention or procedure that holds out the prospect of direct benefit for the individual subject.”

11. 45 C.F.R. pt. 46, subpt. B, “the purpose of the activity is to meet the health needs of the mother” or “the particular fetus”; a revised subpart B, which has for some time been awaiting final signoff, would change this.

12. National Bioethics Advisory Commission, *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity, Report and Recommendations of the National Bioethics Advisory Commission* (December 1998) [hereinafter cited as NBAC Report] (“protocol that ... offers the prospect of direct medical benefit to the subject”).

13. 45 C.F.R. pt. 46, subpt. C, research on innovative practices “which have the intent and reasonable probability of improving the health and well-being of the subject.”

14. FDA, 21 C.F.R. § 50.24; DHHS, 61 Fed. Reg. 51,531 (preclinical studies and other evidence “support the potential for the intervention to provide a direct benefit to the individual subjects”).

15. FDA, 21 C.F.R. § 56.102(d) (“life-threatening situation in which no standard acceptable treatment is available” — potential benefit implicit); 21 C.F.R. § 50.23(b) (informed consent also waived if “immediate use of the test article is, in the investigator’s opinion, required to preserve the life of the subject”).

16. FDA, 21 C.F.R. § 312.34–35 (data show that drug “may be effective”). A “treatment IND” is the use of an investigational new drug (IND) for treatment. The FDA issues “IND numbers” to unapproved drugs to authorize their testing for eventual approval.

17. See, for example, R. Pear, “Managed-Care Plans Agree to Help Pay the Costs of Their Members in Clinical Trials,” *New York Times*, Feb. 9, 1999; “NIH, HMO Group Pact Will Enable Increased Member Access To Clinical Trials,” *The Blue Sheet*, Feb. 17, 1999; G. Kolata and K. Eichenwald, “Group of Insurers Will Pay for Experimental Cancer Therapy,” *New York Times*, Dec. 16, 1999; R. Pear, “Clinton to Order Medicare to Pay New Costs,” *New York Times*, June 7, 2000. Both individual states and the federal government are moving toward mandating insurer coverage of late-phase clinical trials on a case-by-case basis according to their potential for direct benefit as well as coverage of routine medical expenditures in research if they would be covered outside the research setting.

18. NBAC Report, *supra* note 12, at 45, citing National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Research Involving Those Institutionalized as Mentally Infirm* (1978): at 31, and E.W. Keyserlingk et al., “Proposed Guidelines for the Participation of Persons with Dementia as Research Subjects,” *Perspectives in Biology and Medicine*, 38 (1995): 319–62, at 327–28.

19. L.R. Churchill, “Toward a More Robust Autonomy: Re-

vising the *Belmont Report*,” paper prepared for NBAC (presented April 17, 1999).

20. N. Dickert and C. Grady, “What’s the Price of a Research Subject? Approaches to Payment for Research Participation,” *N. Engl. J. Med.*, 341 (1999): at 198.

21. For example, a purpose statement that declares, “The purpose of this research is to develop a new kind of cancer treatment, which works by helping the body’s immune system to attack cancer cells,” could be misleading in a consent form for a Phase I study when the intervention has not yet been tried in humans. Potential subjects could easily take this to mean that in this Phase I study they will receive a “new treatment” that “works.”

22. See NBAC Report, *supra* note 12; Keyserlingk et al., *supra* note 18.

23. *Final Report* (June 15, 1998): at 21 (visited Dec. 11, 2000) <http://ohrp.osophs.dhhs.gov/hsp_report/hsp_final_rpt.pdf>.

24. R.C. Boucher and M.R. Knowles, “Clinical Protocol: Gene Therapy for Cystic Fibrosis Using E1-Deleted Adenovirus: A Phase I Trial in the Nasal Cavity, The University of North Carolina at Chapel Hill,” *Human Gene Therapy*, 5 (1994): 615–639. In the Purpose section, the consent form states: “I understand that this study is not designed for treatment, and that I will not get any medical benefit from this nose study of adenoviral gene transfer” (at 636). In the Benefits section, the form states: “I will not benefit directly from the nose study of adenoviral gene transfer” (at 638).

25. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, DHEW Pub. No. (OS) 78–0012, (Washington, D.C.: U.S. Gov’t Printing Office, 1978). The *Belmont Report* was reprinted in the Federal Register in 1979 and is now available online at <<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm>>.

26. The *IRB Guidebook* was published in hard copy in 1993, and is currently available at <http://ohrp.osophs.dhhs.gov/irb/irb_guidebook.htm>.

27. The *FDA Information Sheets* were last updated in 1998. They are available at <<http://www.fda.gov/oc/oha/irb/toc.html>> as well as in hard copy.

28. NBAC Report, *supra* note 12, at 44, citing National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Research Involving Those Institutionalized as Mentally Infirm* (1978): at 31. See also J.W. Berg, “Legal and Ethical Complexities of Consent with Cognitively Impaired Research Subjects: Proposed Guidelines,” *Journal of Law, Medicine & Ethics*, 24 (1996): 18–35, at 24–25.

29. For example, the guidance document provided for investigators preparing gene transfer research protocols (Appendix M of the NIH Guidelines, “Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subjects”) requires “clear itemization” in the consent form of “types of adverse experiences, their relative severity, and their expected frequencies.” It suggests that risks of harm be categorized as mild, moderate, and severe, and that any verbal descriptions of frequency, such as rare, uncommon, or frequent, be explained. It also mandates mention of the possibility of unforeseen harms (Appendix M-III-B-1-e). See N.M.P. King, “Rewriting the ‘Points to Consider’: The Ethical Impact of Guidance Document Language,” *Human Gene Therapy*, 10 (1999): 133–39.

30. I am indebted to Dr. Jon Gordon for first calling my

attention to this concern.

31. J. Crewsdon, "Human Trials of Cancer Treatment Set to Begin," *Chicago Tribune*, reprinted in *Herald-Sun*, Durham, N.C., Oct. 18, 1999; see also F. Russo, "The Clinical-Trials Bottleneck," *Atlantic Monthly*, May 1999, at 30–36 ("no more than 20 percent" of experimental interventions succeed in Phase III trials, where success is defined as extending median survival by 25 percent); Kolata, *supra* note 3.

32. J. Moreno et al., "Updating Protections for Human Subjects Involved in Research," *JAMA*, 280 (1998):1954.

33. "Human Guinea Pigs," *U.S. News Online*, May 24, 1999 (visited Dec. 12, 2000) <<http://www.usnews.com/usnews/issue/990524/nycu/trials.b.htm>>.

34. See N.M.P. King, "Experimental Treatment: Oxymoron or Aspiration?" *Hastings Center Report*, 25, no. 4 (1995): 6–15; L.R. Churchill et al., *supra* note 3; J. Goldner, "An Overview of Legal Controls on Human Experimentation and the Regulatory Implications of Taking Professor Katz Seriously," *Saint Louis University Law Journal*, 38 (1993): 63–134, at 125.

35. The essential goal of clinical research is to "develop or contribute to generalizable knowledge." Common Rule, § 102(d). In order to achieve this goal, proposed research must demonstrate both *value* and *validity* — that is, the research must ask a question that is of scientific and societal importance (value) and the research design must have the capacity to answer that question, in either the affirmative or the negative (validity). E. Emanuel et al., "What Makes Clinical Research Ethical?" *JAMA*, 283 (2000): 2701–2711.

36. Of course, a continuing failure to produce data supporting direct benefit in later phases of research will affect the promise of the line of research and its aspirational benefit.

37. J. Katz, personal communication (November 1997).

38. B. Freedman, "Equipose and the Ethics of Clinical Research," *N. Engl. J. Med.*, 317 (1987): 141–45.

39. The extensive debate about the ethics of randomization in Phase III clinical trials is largely about when enough evidence exists to assert that one treatment is superior. This complex literature is beyond the scope of the present discussion of early-phase trials.

40. See the NCI booklet "Taking Part in Clinical Trials: What Cancer Patients Need to Know," available online at <<http://cancertrials.nci.nih.gov/understanding/bookshelf/treatment/index.html>>. This change is based not only on the reasons stated but also on the growing use of diagnostic technologies to give information on tumor cell types and their probable responses to conventional treatments, as well as on the development of new classes of investigational interventions that may have effects on treatment-refractory disease.

41. See, for example, J. Groopman, "Dr. Fair's Tumor," *The New Yorker*, Oct. 26/Nov. 2, 1998, at 78–102.

42. See, for example, C. Daugherty, "Impact of Therapeutic Research on Informed Consent and the Ethics of Clinical Trials: A Medical Oncology Perspective," *Journal of Clinical Oncology*, 17 (1999): 1601–17.

43. C. Daugherty et al., "Perceptions of Cancer Patients and Their Physicians Involved in Phase I Trials," *Journal of Clinical Oncology*, 13 (1995): 1062–72.

44. Some have argued for redesigning Phase I trials, especially in oncology and other serious diseases, to cluster intervention dosing around the probable maximum tolerated dose (MTD) as predicted by lab and animal studies. See, for example, B. Brody, Chapter 8, in *The Ethics of Biomedical Research: An International Perspective* (Oxford: Oxford University Press, 1998); K. Kipnis, "Vulnerability in Research Subjects: An Ethical Taxonomy," pa-

per prepared for NBAC (July 2000). However, it is not clear that this would substantially increase the likelihood of direct benefit in Phase I trials. That would be true only if the drug is actually effective, if the duration of the trial is sufficient to produce meaningful clinical effects, and if the projections about the MTD turn out to be reasonably accurate. With no previous human experience and probably rather sketchy preclinical data, that is a lot of ifs. See also M. Miller, "Phase I Cancer Trials: A Collusion of Misunderstanding," *Hastings Center Report*, 30, no. 4 (2000): 34–43, at 39–40.

45. See, for example, "The Biotech Death of Jesse Gelsinger," *New York Times Magazine*, Nov. 28, 1999. Gelsinger, who had just turned eighteen, was enrolled in a Phase I safety and toxicity study in which corrected genetic material, combined with a modified adenovirus vector, was injected into subjects with a genetic deficiency of an essential enzyme called ornithine transcarbamylase, which affects liver function. The injection apparently caused an overwhelming inflammatory response. At the time, safety concerns in the field of gene transfer research were directed primarily toward the risk of inadvertently altering subjects' germlines (a safety issue for the subjects' future offspring) and long-term risks of causing mutations in subjects (an issue similar to the possibility that successful cancer treatment could cause new malignancies decades from now). Little attention was directed toward risks of immediate and direct harm since the worst that had been publicly discussed was "flu-like symptoms" after an injection of genetic material in a modified viral carrier "vector," like adenovirus. The consent form for the study in which Gelsinger died promised no direct benefit to subjects, but Gelsinger's father testified before the U.S. Congress last February that he and his son were given somewhat different and misleading information during the consent process. Jesse Gelsinger's death has spurred significant new oversight activity in all human subjects research. See, for example, D. Shalala, "Protecting Research Subjects — What Must Be Done," *N. Engl. J. Med.*, 343 (2000): at 800.

46. See, for example, J. Stephenson, "Gene Therapy Trials Show Clinical Efficacy," *JAMA*, 283 (2000): 589–90.

47. All claims of benefit, including collateral benefit, should address all three dimensions of benefit. In some respects, collateral benefit claims may be questioned, but that discussion is beyond the scope of this paper.

48. See Daugherty, *supra* note 43.

49. See, for example, W.T. Carpenter and R.R. Conley, "Sense and Nonsense: An Essay on Schizophrenia Research Ethics," *Schizophrenia Research*, 35 (1999): 219–225, at 223. See also *supra* note 44.

50. R. Levine, "Uncertainty in Clinical Research," *Law, Medicine & Health Care*, 16 (1988): 174–82.

51. See *The Belmont Report*, *supra* note 25. The *Belmont Report* defines treatment (or "practice") as "interventions that are designed solely to enhance the well being of an individual patient ... and that have a reasonable expectation of success."

52. J. Katz, "Human Experimentation and Human Rights," *Saint Louis University Law Journal*, 38 (1993): 7–54, at 25–26. But see G. Norquist et al., "Expanding the Frontier of Treatment Research," *Prevention & Treatment*, 2 (1999):1–5.

53. G. Kolata and K. Eichenwald, "In Pediatrics, A Lesson in Making Use of Experimental Procedures," *New York Times*, Oct. 3, 1999.

54. Patients who are uninsured, underinsured, or otherwise economically vulnerable are, in general, at some risk of exploitation when researchers, even with the best of intentions, offer them research participation as a treatment substitute. R. Levine, *Ethics and Regulation of Clinical Research*, 2d ed., (New Haven: Yale

University Press, 1988): 82–84; G. Kolata and K. Eichenwald, “For the Uninsured, Experiments May Provide the Only Treatment,” *New York Times*, June 22, 1999.

55. See, for example, D. Light, “Life, Death, and the Insurance Companies,” *N. Engl. J. Med.*, 330 (1994): 498–500; S. Boren, “I Had a Tough Day Today, Hillary,” *N. Engl. J. Med.*, 330 (1994): 500–502.

56. P.A. Rowlings et al., “Factors Correlated With Progression-Free Survival After High-Dose Chemotherapy and Hematopoietic Stem Cell Transplantation for Metastatic Breast Cancer,” *JAMA*, 282 (1999): 1335–43; W.J. Gradishar, “High-Dose Che-

motherapy and Breast Cancer,” *JAMA*, 282 (1999): 1378–80.

57. G. Kolata and K. Eichenwald, “Health Business Thrives on Unproven Treatment, Leaving Science Behind,” *New York Times*, Oct. 2, 1999.

58. Unfortunately, the ability to disseminate and apply the best current knowledge gleaned from clinical trials is compromised by publication bias in the reporting of study data. See, for example, D. Rennie, “Fair Conduct and Fair Reporting of Clinical Trials,” *JAMA*, 282 (1999): 1766–68. This raises the problem of how the results of clinical research can and should influence practicing physicians.

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