

Therapeutic Obligation in Medical Research

February 2003

Kenneth D. Pimple, Ph.D. and Julia A. Pedroni, Ph.D.

“A physician should not recommend for a patient therapy such that, given present medical knowledge, the hypothesis that the particular therapy is inferior to some other therapy is more probable than the opposite hypothesis.” (Marquis)

“Physicians are typically thought to have an obligation to treat a patient in a way which yields the best chance of recovery.” (Gifford)

Contents

1. Introduction.....	2
2. The Dilemma	2
3. Attempts to Resolve the Dilemma	4
4. Alternatives to Randomized Clinical Trials.....	6
5. Some Limits to the Therapeutic Obligation.....	7
5.1 Standard of Care	8
5.2 Continued Treatment After a Trial	9
5.3 New Findings.....	10
5.4 Inadvertent Findings	10
6. The Therapeutic Obligation in Non-Therapeutic Settings.....	10
7. Conclusion	13
Appendix: Therapy, Research, and Quality Assurance/Improvement Studies.....	15
References.....	19

Copyright 2001-2003, The Trustees of Indiana University. All rights reserved.

For information about this work, please contact the Poynter Center for the Study of Ethics and American Institutions, Indiana University, 618 East Third Street, Bloomington IN 47405-3602; 812-855-0261; FAX 855-3315; poynter@indiana.edu; <http://poynter.indiana.edu/>.

Permission is hereby granted to reproduce and distribute copies of this work for nonprofit educational purposes, provided that copies are distributed at or below cost, and that the authors, source, and copyright notice are included on each copy. This permission is in addition to rights of reproduction granted under Sections 107, 108, and other provisions of the U.S. Copyright Act. Before making any distribution of this work, please ascertain whether you have the current version by checking <http://poynter.indiana.edu/sas/res/> or contacting the Poynter Center.

The authors discussed an earlier draft of this paper with Jeffery L. Geller, University of North Carolina-Pembroke; Mark A. Graber, University of Iowa; and Charles J. Kowalski, University of Michigan. We are grateful for the insightful comments they made, many of which have been addressed in this draft.

Development of this essay was supported by the National Institutes of Health (Grant Number 1 T15 AI07601) and the Poynter Center.

1. Introduction

Anyone seeking a physician's care expects that the physician will provide the best care possible under the circumstances. Anyone learning that her physician was using a treatment discarded fifty years earlier by the medical community would rightly be outraged. This is the therapeutic obligation.

Is there any difference when the treatment is not generally used because it is too new?

Most old, discarded treatments are cast aside in favor of newer, better treatments; whereas new treatments are not widely used precisely because no one knows (yet) how effective they are. Using an old treatment is wrong when the physician knows that there is a newer, better alternative. Using a new treatment is wrong when the physician has no strong reason to believe that it is better than the current standard.

For the rest of this essay, we will assume that the physician who wants to use a new, experimental treatment is also a researcher taking part in a randomized clinical trial designed to demonstrate whether or not the experimental treatment is an improvement over available options. We use the word "physician" as a shorthand reference to all health care providers with whom a patient's primary relationship is therapeutic in nature; thus nurses and pharmacologists are included, but hospital or research administrators are not.

2. The Dilemma

Given the physician's therapeutic obligation, experimental treatments cannot replace current ones until the former are proven to be better. But the best (only?) way to identify better treatments is to try them on patients. We find ourselves on the horns of a dilemma, faced with two unattractive options:

- Give some patients treatments that are not known to be the best available.
- Abandon virtually all hope of medical progress.

The idea of the physician's therapeutic obligation is ancient – it is central to the Hippocratic tradition in medicine – and as long as we think of the person administering the experimental treatment as a physician, it is difficult to see any way out of the dilemma. But once we shift emphasis to the other role and think of her as a researcher, the dilemma can be thought to resolve itself, for the Hippocratic tradition governs the relationship between the physician and her patient, not between the researcher and her subject.

Although this is a handy way out, it is also unacceptable, but to show why, it will be necessary to consider her two roles separately.¹ For simplicity of presentation, we will call our researcher-physician Dr. Shelley and her subject-patient Mr. Victor.²

Dr. Shelley's actions are constrained by two sets of moral obligations:

- (1) Those arising from the relationship between Dr. Shelley and Mr. Victor in his role as her patient.
- (2) Those arising from the relationship between Dr. Shelley and Mr. Victor in his role as the subject of her research.³

In the abstract, there are relevant differences between the moral obligations inherent in each of these relationships, and they can be analyzed separately. For example, relationship (1) requires Dr. Shelley to provide the best care available to Mr. Victor; relationship (2) requires Dr. Shelley to treat Mr. Victor in accordance with the established research protocol. These two obligations may well be at odds. We think of Sinclair Lewis's 1925 novel Arrowsmith, in which the researcher-physician, determined to conduct a controlled experiment in the natural laboratory of a tropical island stricken with plague, withholds treatment from a control group as the only way to prove that his treatment actually works. He reasons that solid, scientific proof will save many more lives in the future.

One could separate these relationships and arrange them in a hierarchy, deciding, for example, that the norms governing relationship (1) supercede those governing relationship (2), meaning that when there is a conflict, the physician-patient relationship wins.

Although this is possible (though by no means easy) in the abstract, in actual practice it is impossible, and any strong attempt to make this separation in practice is seriously misguided. As Fried puts it, "the relationship of assisting a person in need is an action and a relationship which have a special integrity of their own. They form a unit, a unit of value, and thus one may assert a coherent interest in personal care" (69). In Fried's terms, these relationships cannot be "disaggregated" (74). They do not form a hierarchy; they form a whole.

If Fried is right about the integrity of the clinical researcher's role, and if, at the same time, the medical profession has an obligation to advance clinical knowledge, some way to resolve the dilemma must be found.

The simplest way to resolve the dilemma would be to exclude physicians from research; after all, non-physician researchers have no therapeutic obligation to individual patients. This is clearly an absurd notion because of the impossibility of medical research without the assistance of

¹ The following discussion expands on Fried's analysis of "the obligation of personal care," which we are calling the "therapeutic obligation." The obligation of personal care is the patient's "claim to the unreserved ministrations of the physician" (50).

² Some readers will recognize that Dr. Shelley is named for Mary Wollstonecraft Shelley and Mr. Victor for her famous protagonist, Victor Frankenstein.

³ An analogous table of obligations and corresponding analysis could be produced with Mr. Victor at the center of consideration. We leave this as an exercise for the reader.

physicians. Also, of course, non-physicians are obliged by law (and morality) not to practice medicine. We will consider at greater length several non-absurd, though (we argue) mistaken, approaches to resolving the dilemma.

3. Attempts to Resolve the Dilemma

Perhaps the most influential way to resolve the dilemma is to hold that randomized clinical trials (RCTs) may (and may only) be conducted under conditions of “equipoise,”⁴ a state in which it is unknown whether the experimental treatment is better or worse than the standard treatment.⁵ There are three logical possibilities:

1. If the experimental treatment is known to be worse than the standard treatment, it simply cannot (morally) be tested.
2. If it is known to be better, there is no reason to test it – it should simply be adopted as the standard.
3. If it is unknown which treatment is better, then providing either the standard or experimental treatment will be consistent with the therapeutic obligation, and so using a method of randomization to determine treatment assignment will also be acceptable.

This has been called the **knowledge argument**, one of three key strategies⁶ we will examine for dealing with the therapeutic obligation in the randomized clinical trial.

The logic and conclusions appear to be unassailable, and insofar as this argument is applied to initiating a clinical trial, we agree with it. But a clinical trial is not instantaneous; it occurs over time, and the state of “knowledge” of treatment superiority will almost always change during the course of a clinical trial.

The force of the argument depends on the highly problematic words “known” and “unknown.” A detailed discussion of epistemology is obviously beyond the scope of this essay, but in order to make our point we will distinguish between the “everyday” and “scientific” uses of the word “to know.”

⁴ Equipoise comes in at least two flavors: individual and clinical. In individual equipoise, the judgment that there is no reason to believe that the experimental treatment is worse than standard treatment falls to Dr. Shelley; in clinical equipoise, the judgment falls to the clinical community. (Although Fried [1974] first coined the word “equipoise,” it was Freedman [1987] who clarified the distinction between individual and clinical varieties.) It is also possible to parse this in a different way, balancing the judgment that the experimental treatment is acceptable for Mr. Victor against the parallel judgment regarding patients in general.

⁵ It is worth noting here that “better” and “worse” are simple terms for complex concepts, covering not only comparative efficacy of regimens, but also side effects and burdensomeness of treatments, their cost, and so forth.

⁶ These strategies and their faults are identified in a superb paper by Gifford (1986). We treat the other two key strategies, the “division of labor” and “informed consent” arguments, below. In addition, Gifford identifies a fourth strategy, which he calls the “special designs” strategy. We take up this approach in Section 4. Alternatives to Randomized Clinical Trials.

In the everyday sense, saying, “I know that drug D is effective against disease Δ ,” is the equivalent of saying, “I have good reason to believe that drug D is effective against disease Δ .” In this sense, having personal or second-hand evidence of the truth of a proposition is adequate to say the proposition is “known” to be true. If Dr. Shelley learned that D is effective against Δ in medical school, her clinical experience supports the claim, and there is no stronger evidence to the contrary, she can claim that she “knows” it to be true (in the everyday sense) and is justified in using D against Δ in her clinical practice because doing so is in accord with her best clinical judgment.

In the scientific sense, by contrast, the standard of proof is much more demanding. In order to say anything scientifically about the effects of D against Δ , rigorous empirical research and, by convention, a p-value of 0.05 or lower is necessary. Saying that one knows something in the scientific sense is equivalent to saying one has “conclusive evidence” that it is so. Furthermore, as far as medical treatments are concerned, scientific knowledge is statistical and probabilistic, meaning that what is actually known is something more like “drug D, when used in manner M (dose, frequency of administration, etc.), is effective against disease Δ in 90% of patients with characteristics C (presence or lack of other diseases and complicating factors, etc.).”

Equipose can thus be construed as having one of two possible thresholds: the “good reason to believe” threshold and the “conclusive evidence” threshold. Insofar as equipose is construed at the “conclusive evidence” level of uncertainty, we suggest it will invariably lead to a mistaken conclusion about the ethics of randomized clinical trials.

The problem with accepting the “conclusive evidence” threshold for equipose in clinical trials is that in everyday medical practice the “good reason to believe” threshold actually prevails. There is no conclusive evidence that most commonly used treatments are best, though there is good reason to believe that they are. And since research takes time, in the course of almost any well-designed clinical trial there will be “good reason to believe” that one treatment is superior before “conclusive evidence” has been attained.

To make it concrete: When Dr. Shelley enrolls Mr. Victor (with his informed consent) into a clinical trial which, in her best clinical judgment, will provide treatment equivalent to or better than the treatment he would receive outside the study, no matter which treatment he receives (experimental, standard, placebo, etc.), and all of the possible study treatments are equally appropriate for him, she has made a morally justified decision. But when interim data indicates that there is “good reason to believe” that one particular treatment under study would be better for Mr. Victor, she is faced with the possibility that she is violating her therapeutic obligation to him because he may not be receiving the treatment which, in light of the new findings and according to her best clinical judgment, is best for him.

This is the crux of the matter. Use of the “conclusive evidence” threshold means that when interim results show that there is “good reason to believe” that one treatment is superior, that “knowledge” is ignored in treating some of the subjects. They are therefore not treated the same way as ordinary patients, which is an unacceptable disaggregation of these two roles.

As a researcher, Dr. Shelley naturally wants to use the “conclusive evidence” threshold. As a physician, she is often barred from doing so.⁷

One way to maintain the higher threshold of conclusive evidence and still reach a scientifically conclusive end of the trial is to adopt the **division of labor argument**. The line of reasoning here suggests that as long as Dr. Shelley does not have any interim information indicating treatment superiority, she does not violate her therapeutic obligation because she is still in equipoise – she is unaware of the availability of a treatment that there is “good reason to believe” is superior. The data monitors, who do have the interim results, are not physicians for individual patients, and therefore have no therapeutic obligation to violate.

This is a breathtaking feat of sophistic legerdemain. However, reflection shows that Dr. Shelley violates her therapeutic obligation when she agrees to remain ignorant. We do not allow professionals to escape their obligations on the basis of ignorance – one moral obligation of all professionals is that they keep their skills and knowledge up-to-date – and remaining ignorant willfully is worse than doing so out of incompetence or lack of time.

Finally, the **informed consent** argument acknowledges that equipoise will dissolve before a trial produces conclusive evidence of treatment superiority/inferiority, and simply suggests that subjects may voluntarily elect to forgo optimal treatment. In other words, patients may waive, in advance, their “right” to treatment in accordance with the therapeutic obligation should equipoise be disturbed by interim findings.

Certainly we believe that, all things being equal, patients have the moral right to refuse treatment and to select between treatments. But the informed consent argument shifts the moral burden far too easily from Dr. Shelley, a physically fit researcher who stands to gain materially and professionally from the research, to Mr. Victor, a dying man who has enrolled in the study as a last desperate attempt to save his own life. It hardly seems sporting.

4. Alternatives to Randomized Clinical Trials

If each of these three strategies fails to avoid the conflict between the therapeutic obligation and randomized treatment assignment in RCTs, another approach is to use non-randomized clinical trial designs. (Gifford calls this the “special designs” strategy).

As implied in the foregoing, the paradigmatic conflict is between the physician’s therapeutic obligation and the researcher’s obligation to optimize scientific design. However, it is not clear that randomized treatment assignment is a necessary feature of good clinical trial design.⁸ Today there are more research options than Martin Arrowsmith’s blunt use of a control group receiving

⁷ Other core aspects of randomized clinical trials, such as the use of placebos, masking, and withholding of interim findings, can also conflict with the physician’s therapeutic obligation. These practices are most troublesome because most clinical researchers wrongly believe they are critical for making valid inferences and hence are essential aspects of good clinical research design.

⁸ For a recent debate of this issue, see Concato J, Shah N and Horwitz RI (2000), Benson and Hartz (2000), and associated commentaries/letters.

no treatment. Consider two frequently mentioned alternative designs which increase the likelihood that a patient-subject receives an optimal therapy:

- Cross-over designs (sometimes called self-paired or self-controlled designs), in which each subject receives sequentially both the experimental and the control regimens (a design obviously suited only to the subset of clinical trials in which the experimental and control treatments are not mutually inimical).⁹
- Adaptive designs, such as a so-called “play-the-winner” design,¹⁰ in which each site begins with one of the two treatments (experimental or control). If the first patient-subject does well under the treatment, the second patient-subject receives the same treatment; if not, the second patient-subject receives the alternate treatment. In this design, if one of the treatment options always succeeds, the second may never be tested.

But while these techniques obscure the conflict through a kind of shell-game sleight-of-hand, they both involve giving some patients, some of the time, a treatment that can reasonably be construed as being less than optimal; therefore neither resolves the fundamental dilemma.

Gifford argues that when any of these designs are used, we must accept and acknowledge the existence of the conflict between design and therapeutic obligation. We should not pretend that we are honoring the obligation through a special design if we are not, in fact, doing so,¹¹ and we are left to decide on an *ad hoc* basis whether we are justified in overriding the therapeutic obligation on the basis of expected benefits to society.

We believe that there is one special design for clinical trials that does resolve the dilemma of the therapeutic obligation in research: Kadane’s (1996) controversial Bayesian treatment allocation scheme. In this design, subjects are assigned to experimental arms on the basis of a computer model that uses known variables to predict which treatment is likely to be best for each individual patient; the model is constantly updated to reflect the best information available at the moment, including information generated by the current study. Thus, at every step of the research, every patient-subject is receiving the best treatment known. A Bayesian treatment protocol is more complex than the standard randomized clinical trial (which is, in itself, highly complex) and there can be reasonable objections to such a design on practical grounds. On moral grounds, however, we think it is clearly superior to the current alternatives.

5. Some Limits to the Therapeutic Obligation

The therapeutic obligation is serious and far-reaching, but it is not all-encompassing for researchers any more than it is for physicians. For example, although Dr. Shelley must give Mr.

⁹ For a complete review of cross-over design trials, see Jones and Kenward, 1989; Jones and Lewis (1995) advocate the use of cross-over designs in Phase III cancer trials.

¹⁰ See Zelen, 1969. For a widely discussed use of a modified play-the winner design, see Bartlett, *et al.*, 1985 and the accompanying commentary by Paneth and Wallenstein. For a more recent review and trial using such a design, see Rosenberger, 1999, and Thall *et al.*, 2000, respectively.

¹¹ There may be benefits from using a special design other than meeting the therapeutic obligation, but a discussion of those other benefits is beyond the scope of this essay.

Victor the best care possible under the circumstances, she also has to maintain a certain degree of objectivity and avoid becoming overly emotionally involved with him and his plight. Getting too close to a patient would undermine Dr. Shelley's effectiveness as a physician, and it would serve no good end.¹²

The other issues we raise in this section are presented as questions for which we can offer no conclusive answer.

5.1 Standard of Care

One useful maxim in ethics is "ought implies can." No one can be rightly said to have a moral obligation to do something that she simply cannot do. Thus Dr. Shelley is not obliged to provide Mr. Victor better care than possible under the circumstances, including her own personal circumstances. Like all researchers and all physicians, she has limits to her personal resources and skills. She might be unable, due to lack of time or money, to provide Mr. Victor with a treatment that would help him. This is deeply regrettable, but it is a fact of life.¹³

This said, it is important to note that research projects lacking the resources to provide adequate care should not be undertaken. This may seem self-evident; if Dr. Shelley wants to study an experimental treatment for AIDS but she cannot afford to provide the standard treatment to all of her subjects, she should find adequate funding before she begins.

But what if Dr. Shelley's research takes place in an indigent community in sub-Saharan Africa? In this case, the seemingly simple idea that the physician is obliged to provide the best care possible under the circumstances becomes complex. What circumstances count? Or, to put it in more commonly used terms, which standard of care should prevail – the standard of Dr. Shelley's research hospital in Indianapolis, or the standard of the impoverished medical clinic in Kampala¹⁴ where the research is taking place? In one sense, the best care possible under the circumstances would meet the standard of care of Dr. Shelley's home hospital; but Dr. Shelley might well argue that this standard is too high and that holding her to it will only make it impossible for her to do important research. Under her actual circumstances, Dr. Shelley can only secure funding for a placebo-controlled trial, but participating in the trial may be beneficial to individual participants (even those receiving the placebo may benefit) and the findings of her research might be extremely valuable for Ugandans and others.

Certainly such research may be tinged with racism; certainly it may be undertaken in a cynical dodge to skirt stringent regulations and cash in on treatments that will not, in the end, be available in Uganda; but it is also possible that this research truly is intended to discover a treatment that Ugandans and other very poor people can afford. It is also possible that the

¹² There are limitations to the therapeutic obligation even setting aside the complication of research; for example, a physician may be morally (and legally) required to confine a patient to quarantine not for his own good (and perhaps to his detriment), but for the good of society. A discussion of other such exceptions to the therapeutic obligation outside the context of research is beyond the scope of this essay.

¹³ Of course, Dr. Shelley has a professional obligation to recognize when she is unable to give adequate care and to take appropriate action, which may include referring a patient to another physician, securing additional training, or, if it is a chronic problem, perhaps retiring from practice.

¹⁴ The capital of Uganda in equatorial Africa.

research will provide great benefit without introducing new harms. For example, if subjects would not have received any treatment outside of the study, giving some subjects a placebo will not deprive them of any substantial good and will not expose them to any substantial new harm. As is so often the case, the intention of the researchers is central here, but the shadow of colonial racism and unspeakable past exploitation make reading intentions accurately very difficult.¹⁵

The question then becomes: Should this research wait until the circumstances improve – until Dr. Shelley can raise the funds to treat her subjects in Kampala at the Indianapolis standard?¹⁶

5.2 Continued Treatment After a Trial

Suppose that Shelley secures sufficient funding to provide all of her Ugandan subjects with the Indianapolis standard of care, but her trial will only last three years. None of her surviving subjects will be cured, and they will no longer have access to the treatments and other benefits they enjoyed during the trial.

¹⁵ Principle 29 of the 2000 revision of the World Medical Association’s Declaration of Helsinki states:

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
[http://www.wma.net/e/policy/17-c_e.html]

Guideline 7 of the 2001 revised draft of the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects quotes Principle 29, adding “Any departure from this principle requires a sound scientific and ethical reason to use a control other than the best current method.” The commentary on this guideline says, in part:

There are two sound scientific and ethical reasons for departing from the principle regarding placebo controlled studies stated in the Declaration of Helsinki and repeated in this Guideline: (1) withholding the best current treatment will result in only temporary discomfort and no serious adverse consequences; and (2) a comparative study of two treatments will yield no reliable scientific results.

* * *

There are circumstances in which sponsors and researchers in technologically developed countries may propose to collaborate with counterparts in other countries to develop inexpensive alternatives to expensive therapies that are recognized as the “best current therapeutic method.” In some such cases it may be appropriate to compare the new inexpensive alternative with a locally available product rather than with the locally unavailable ‘best proven therapeutic method.’ Although there is no general agreement on this point, there are commentators who have concluded that in such circumstances use of a control other than the best current method is justified if: 1) the scientific and ethical review committees in both the country of the sponsoring institution and the host country determine that use of the best current method as a control would be likely to invalidate the results of the research or make the results inapplicable in the host country; 2) plans to make the therapeutic product reasonably available in the host country or community are securely established; and 3) a process of planning and negotiation, including justification of a study in regard to local health-care needs, has taken place with the health authorities in the host country before the research begins.
[http://www.cioms.ch/draftguidelines_may_2001.htm]

¹⁶ Relevant publications on this subject include Angell 1997; Lurie and Wolfe 1997; Msamanga and Fwazi 1997; Varmus and Satcher 1997; Whalen *et al.* 1997.

Valdespino-Gomez et al. (2000) describe a parallel case. They briefly describe the short-term impact of the completion of a TB-prevention study of HIV-infected individuals in Mexico, and ask what “ethical responsibilities remain after clinical trials end?”

Is there a mechanism that ensures that patients (who may have received their diagnosis as a result of their participation) continue receiving the benefits that they received during the trial? What happens when these benefits are not economically feasible and are not included in the local “standard of care?” Should changes in host country health policies emerge from the results of clinical trials?

It seems evident that under normal conditions, a physician’s therapeutic obligation to her patient ends when their professional relationship ends. There can be many reasons for such a termination, but it may be an open question whether the end of a clinical trial is morally equivalent to a typical termination or whether it more closely resembles patient abandonment.

5.3 New Findings

Now consider a situation in which the physician-researcher fulfills her therapeutic obligation throughout the study and the termination of the relationship with the subject is nonproblematic. Do researchers have any obligation to get back in touch with former subjects when new information comes to light that may be therapeutically useful to those subjects?

For example, when Mr. Victor took part in Dr. Shelley’s study of treatments for Chlamydia, she typed the virus. Two years after the termination of the study, researchers learned that the strain Mr. Victor contracted is highly correlated with the development of a certain type of cancer, meaning that Mr. Victor should be screened more frequently than persons who have not contracted that strain. Is Dr. Shelley morally obliged to inform Mr. Victor of this finding and its implications for his own health care?

5.4 Inadvertent Findings

The last question we will raise about the limits of the therapeutic obligation concerns a conceptual, rather than a temporal, limit. Is there an obligation to report to subjects health findings not related to the study?

In this instance, Dr. Shelley is conducting a study of potential treatments for sleep apnea. At the moment, this is the only condition for which she is treating Mr. Victor.¹⁷ On one of the two dozen EEGs she performs on Mr. Victor, Dr. Shelley finds a spike and wave suggestive of a minor seizure. Is she obliged to share this information with him? If so, is she obliged to treat him or help him seek treatment?

6. The Therapeutic Obligation in Non-Therapeutic Settings

Up to this point, we have been considering the therapeutic obligation in the narrow context of the

¹⁷ By now we are struck by Dr. Shelley’s versatility and Mr. Victor’s extreme misfortune in terms of health.

relationship between a physician-researcher and her patient-subject. Clearly a great deal of research involving human subjects falls outside of this context. In this last section, we argue that researchers outside the therapeutic context often have an analogous obligation to their subjects.

We will argue that this analogous obligation is stronger than either the moral obligation of non-maleficence (not doing harm) owed by all to all or the moral obligation of “ordinary” specific beneficence.¹⁸ The latter obligation is a context-specific obligation to do good when (a) the good is substantial and (b) the cost to the actor is negligible – for example, if Mr. Victor can save Dr. Shelley from grave bodily harm without any real risk to himself (as by shouting “Watch out!” as she is about to step in front of a speeding bus), he is morally obliged to do so.

Professional ethics, which we take to cover lawyers, physicians, teachers, and researchers (among others), demands at a minimum that professionals treat their clients, patients, students, or subjects fairly and honestly within the narrow context of the professional relationship.¹⁹ The argument we are about to develop would apply to other kinds of professionals, but we will limit our discussion to researchers.

We argue that researchers in non-therapeutic settings, including behavioral and social science research, have an obligation to do good for their subjects in (admittedly limited) ways that go beyond their narrowly construed professional relationship. For lack of a better term, we will refer to this obligation as role beneficence.

For example, let us suppose that Dr. Shelley is interviewing public housing residents for an oral history of the community and that in the course of an interview, she learns that Mr. Victor is unaware that he is entitled to Social Security benefits.

Several questions arise.

1. Would it be unprofessional of Dr. Shelley to inform Mr. Victor of his entitlement and help him secure those benefits?
2. Would it be morally acceptable for Dr. Shelley to take no action whatsoever?
3. Is Dr. Shelley under some moral obligation to inform Mr. Victor of his entitlement?

The wording of these questions is deliberate. Dr. Shelley may feel that it is unprofessional to interfere in Mr. Victor’s personal life, rightly understanding that acting in a professional manner means acting with impartiality, without favoritism, and within the limits circumscribed by the professional relationship. This is the standard of professionalism that forbids Dr. Shelley from seeking or consummating a sexual relationship with Mr. Victor. We suggest, however, that if Dr. Shelley determines that telling him about his entitlement to Social Security benefits is “too personal” and therefore “unprofessional,” she has over-generalized.

¹⁸ For a discussion of the concepts of general and specific beneficence, see Beauchamp and Childress, pp. 263-269.

¹⁹ What counts as “fairly and honestly” in these contexts is substantially similar, but there are clearly some differences. An exploration of those differences is beyond the scope of this essay.

In short, our answer to the first question is that it would not be unprofessional of Dr. Shelley to inform Mr. Victor of his entitlement and help him secure those benefits.

In regard to the second and third questions, we argue that it would not be morally acceptable for Dr. Shelley to look the other way, taking an attitude that it is none of her business, or that rendering this kind of assistance would be patronizing or a violation of Mr. Victor's privacy, which obviously implies that we think that Dr. Shelley does have a positive duty to help Mr. Victor secure the Social Security benefits to which he is entitled.

Some might argue that if Dr. Shelley had learned this from any stranger she would be obliged to act out of common decency, and that her professional relationship with him is irrelevant. We do not agree. Certainly it would be morally praiseworthy for anyone learning of Mr. Victor's ignorance to inform him of his entitlement and help him secure it, but not all praiseworthy acts are obligatory.

We argue, however, that by virtue of her professional contact with Mr. Victor, Dr. Shelley has a positive duty to intervene. Whence springs this additional degree of moral responsibility? Like the therapeutic obligation, role beneficence is rooted in the special relationship between a researcher and her subject. It is not, typically, as vital or intimate as the physician-patient relationship, but it can, at times, be characterized by an imbalanced relationship between a researcher who has expertise, knowledge, and other resources and a subject who is vulnerable in any of a number of ways.

Researchers typically have expertise that enables them to identify what will be beneficial to the people they study, and they often have access to sources of assistance, at least in the form of relevant contact information or relatively easy ways to find such information. Furthermore, in at least some cases, subjects are likely to expect researchers to know how to help them and to believe that researchers are obliged to help them. In such cases, it is likely that subjects agree to enroll in a study, at least in part, because they expect a benefit. To some people, the distinction between a researcher and a social worker can be hazy at best. This is similar to the "therapeutic misconception" identified by Appelbaum – the misconception held by many subjects that research-related medical interventions have therapeutic value. These misconceptions are difficult to dispel even through a vigorous effort in the informed consent process.

Role beneficence is also motivated by reciprocity. Without human subjects, Dr. Shelley's research is impossible. Mr. Victor is voluntarily assisting her in her work. It is only fair that she help him if he needs help and she is able to provide it.

Naturally, role beneficence demands a degree of tact, circumspection, and sound judgment. If a researcher believes that a subject should be under a psychiatrist's care, but the researcher herself has no training in diagnosing or treating mental illness, she must not overstep her expertise and make matters worse, or state her opinion to the subject in a way that might cause him undue stress or worry – or anger.

We hope that the above discussion does not convey a patronizing attitude toward human subjects. We know that many – perhaps most – human subjects are not in need of any particular

assistance from researchers; they are capable of taking care of themselves. But suppose a mere 1% of Dr. Shelley’s subjects could use some kind of extra assistance that she is uniquely positioned to recognize and meet. She may be conditioned by her experiences with the other 99% not to notice, or to take it for granted that her job is narrow and well-defined. An awareness of role beneficence ideally would not lead researchers to become busybodies, but would motivate them to render assistance when it is actually needed.

Finally, these same considerations – the researcher’s expertise and access to resources, the subjects’ expectation of benefit, and reciprocity – suggest that in some instances role beneficence can extend to communities (as might the therapeutic obligation). Dr. Shelley’s oral history project may lead to an obligation to help improve living conditions for everyone living in the housing project, not just the people she interviews.²⁰ Again, “ought implies can;” Dr. Shelley is not morally obliged to do the impossible, nor to sacrifice her career. But she may have expertise and resources that she can reasonably put to work for the people she studies and their community.

7. Conclusion

In this essay, we try to make a strong argument that randomized clinical trials (RCTs) involve an unavoidable conflict with the therapeutic obligation of physician-researchers. This is to say that even under conditions of equipoise (individual or clinical), constraints on the information and options available to Dr. Shelley and Mr. Victor interfere in principle with the Dr. Shelley’s ability to provide individually optimized care to Mr. Victor.

The solution to this conflict is far from obvious. Dealing with the therapeutic obligation in the context of medical research will likely require creativity in research design, careful delineation of the conditions under which an informed waiver of the therapeutic obligation may appropriately be requested, and careful assessment of whether the expected benefits for society justify a violation of a *prima facie* right to the therapeutic obligation.

This last approach to the problem – that of justifying an out-and-out violation of the therapeutic obligation – is perhaps the most controversial. Research that carries a real risk to subjects with no conceivable benefit to anyone is clearly impermissible. The therapeutic obligation in research is problematic precisely because it pits potential harm to patient-subjects against potential benefits for society. There may be ways to calculate this expected harm-benefit ratio,²¹ but they are neither easy nor obvious, particularly in a society in which individual rights are typically protected in preference to the “rights” of groups, communities, or society as a whole. This calculation might be easier in societies in which power is not viewed, at base, as coercive, dangerous, and suspect, as it is in the United States. We suggest, however, that most Americans would regard such calculations with unease, at best.

²⁰ An additional consideration in this case (and others like it) is that the research is about the community – in a sense the community itself is a research subject that might enjoy benefits, or suffer harms, from the research.

²¹ The standard term, “risk-benefit ratio,” is misleading. “Risk” implies potential harm; “benefit” implies certain benefit. An ideal phrase would imply both potential harm and potential benefit, but we know of no word analogous to “risk” in this sense. We therefore prefer to use the more balanced term “expected harm-benefit ratio.”

Of course, not all human subjects research is medical research, and so in this essay we also sketch arguments for an obligation of role beneficence, an analogue of the therapeutic obligation in the non-therapeutic context. This obligation, unlike the therapeutic obligation, does not have roots in a therapeutic relationship, but rather in morally important characteristics of the researcher and the investigator-subject relationship that are common with the therapeutic relationship. These include, for example, the researcher's expertise about and access to forms of assistance for the subject, subjects' expectations about the researcher's role, and the duty of the researcher to reciprocate the subject's willingness to do something of benefit to the investigator. We suggest that these features of the researcher's role and relationship with subjects require a special degree of beneficence beyond that of casual or business acquaintances, for example. Moreover, the unique ways in which research can affect whole communities may well impose an obligation of role beneficence in that context, as well.

The cornerstone of all these arguments is the presumption that the therapeutic obligation and its analog in non-biomedical research are foundational principles of ethical research, and that the burden of justification lies squarely with those who would violate them for the sake of research progress. Only in the rarest of cases will medical or social research be necessary for society in the same way therapeutic treatment or other assistance is necessary for individuals (see Jonas 1969, with respect to medical experimentation). It is for this reason that the therapeutic obligation in research must be given a special priority over other worthy goals, and violations of the therapeutic obligation regarded very seriously.

Appendix: Therapy, Research, and Quality Assurance/Improvement Studies

The discussion of the therapeutic obligation in research presumes that research activities are distinguishable from other types of related activities, in particular from therapeutic practice (or more simply, therapy), on the one hand, and from quality assurance or quality improvement studies, on the other. Differences among these types of activities have important implications for the moral obligations that professionals engaging in them have toward the well being of other individuals involved.

Defining therapy, research, and QA/QI.

Therapy. In delineating research from therapy, the Belmont Report describes therapeutic practice as comprising “interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success.” (Belmont Report, Part A, Section A) These may include diagnostic procedures as well as preventive, symptomatic or curative treatments that are provided to specific individuals. What is distinctive about therapy, as opposed to therapeutic research, is neither the types of procedures performed in each nor even necessarily their novelty. Rather, the hallmark of therapy is the singular intent to benefit the patient.

Research. Research, on the other hand, denotes “a systematic investigation . . . designed to develop or contribute to generalizable knowledge.” [45 CFR46.102(d)] More specifically, the Belmont Report suggests that the term

. . . designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective. [Belmont Report, Part A, Section A]

While one may make a distinction between therapeutic research and non-therapeutic research, depending on whether or not the activity is designed to test the therapeutic value of a given regimen, the pivotal feature of research is the intent to contribute to general understanding rather than to provide benefits to specific individuals. If the only thing a therapeutic research project accomplishes is improving the welfare of the subjects enrolled, it has failed as research.

QA/QI. Finally, quality assurance or quality improvement studies may be described as “internal exercises to assess the quality of the operations of the specific organization with no intention of producing generalizable knowledge.” [Institute of Medicine, p. 2] Like research, the primary purpose of QA/QI is to learn something rather than to produce specific outcomes. It may, for example, involve carefully designed protocols to test specific hypotheses. Unlike research, however, the results of QA/QI studies are not meant to be disseminated publicly.

	Therapy	Research	QA/QI
Generalizable Knowledge	No	Yes	No
Benefit to Identifiable Individual	Yes	?	No
Benefit to Others	No	Yes	Yes

Moral Implications of the Differences between Therapy, Research, and QA/QI

The differences noted above between therapy, research, and QA/QI shape the ways in which important moral principles should be understood and implemented in the course of conducting these activities. The following is a brief sketch of how the familiar principles of respect for persons/informed consent, beneficence, and justice may be interpreted differently in each type of intervention.

Informed consent. The moral obligation to respect persons and their capacity for making autonomous decisions requires that people not be used or acted upon without their willing cooperation. Generally, this means that medical and behavioral professionals need to have the informed consent of the individuals who are the subjects of their interventions. The most familiar paradigm of informed consent is an explicit (usually written), prospective expression of one’s willingness to be involved in a particular activity. However, the obligation of informed consent may also be satisfied if, for example, the informed consent of that individual is clearly implied in other actions or statements of that person (implicit consent), or if the person does not object to the intervention when given adequate information and opportunity to do so (tacit consent).

Therapy and research typically require the explicit and prospective informed consent of the individuals involved, although the rationale is somewhat different for each. In the therapeutic context, informed consent is needed to ensure that all interventions really are in accordance with the patient or client’s autonomous wishes. Since the goal of therapy is solely to benefit the patient or client, the worry isn’t so much about using that individual to further the interests of others, as it is in research. Instead, the point of obtaining informed consent to therapy is to ensure that the patient or client is the one who defines what is in her interest. As complex as many therapeutic decisions are, nothing short of explicit and prospective informed consent will satisfy this obligation. Research, on the other hand, is undertaken to contribute to generalizable knowledge, and thus primarily to benefit others. In this context, explicit and prospective informed consent is the only way to obtain the willing cooperation of the individual that allows the investigator to avoid merely using that person as a means to further the interests of others.

QA/QI studies, however, often involve a different standard of informed consent. While the interventions used in QA/QI studies are not intended for individual benefit, as they are in therapy, neither are the participants in QA/QI studies used for the benefit of some nebulous “general public,” as in research. Rather, QA/QI activities are intended to benefit well defined groups with whose interests the studies’ participants have already chosen to identify. For example, a QA/QI study of staff-patient contact time in a physician’s office is intended to benefit the practice with which the staff member has chosen to work as well as that practice’s patients. In addition, the likelihood of such QA/QI studies is often disclosed as a part of the employment

agreement, and so accepting employment may reasonably be construed as either tacit or implicit informed consent to participation in QA/QI activities. To the extent that these statements are not true, e.g., when QA/QI studies involve patients or clients, or when employees are unaware that they may be the subjects of QA/QI activities, the moral obligation shifts toward obtaining explicit informed consent.

Justice. If a key distinguishing feature of therapy, research and QA/QI is the matter of who is the intended beneficiary of each activity, the principle of justice will be relevant insofar as it indicates the appropriate distribution of these benefits and the burdens of obtaining them. Setting aside issues of macroallocation of health resources and health care access, in the context of individual therapy, the patient or client is the sole bearer of both the burdens and the potential benefits of intervention, and so it seems to raise few concerns from the standpoint of justice. In QA/QI studies, specific individuals may bear the risks while the institution as a whole receives the benefits, and so issues of distributive justice may arise in this context. The close identification of the individual with the institution, however, may mitigate this apparent dissociation of risk and benefit. Because research is intended primarily to benefit others through increased understanding and knowledge, careful attention is required to ensure fairness in the selection of subjects who bear the risks and burdens of the research, as well as in the research agenda which determines who will benefit from the research.

Beneficence. The principle of beneficence can be understood in a number of ways. At its core, however, it includes obligations concerning the welfare of others – obligations toward specific individuals and toward society in general; obligations to avoid causing harm and to take action to promote or improve the well being of others, etc. In therapy, the nature of the therapeutic relationship specifies that the professional's duty is to actively promote the well being of the patient or client with only very few and limited concessions to considerations of the welfare of other parties. By contrast, in QA/QI studies, which are intended to benefit neither specific participants nor society in general, the principle of beneficence is generally interpreted as requiring little more than avoiding harm to participants. Participants in QA/QI activities do not have the kind of therapeutic relationship with QA/QI personnel that imposes specific obligations on professionals engaging in therapy; moreover, QA/QI participants are closely identified with the institution whose welfare is of primary concern. In research, however, and most particularly in therapeutic research, the principle of beneficence will require investigators to promote the well being both of individual participants and of society in general.

Table 2: Interpretation of <u>Belmont</u> principles in different kinds of interventions			
	Therapy	Research	QA/QI
Respect for Persons / Informed Consent	Explicit, prospective informed consent generally required to ensure treatment in accordance with patient or client's autonomous wishes	Explicit, prospective informed consent generally required to avoid instrumentalizing subjects by using them solely for the benefit of others	Tacit or Implicit informed consent generally regarded as sufficient
Beneficence	Obligation to actively promote the well being of specific patient or client (TO), owing to therapeutic relationship	Obligation to actively promote the well being of individual subjects AND to promote overall social benefit	Generally limited to a duty to avoid harming participants (i.e., duty of non-maleficence) since no 'therapeutic' relationship exists and activity is not undertaken to produce social benefit
Justice	Not a significant concern, since patient or client bears burdens and enjoys benefits of therapy	Obligation to seek fairness in the distribution of burdens and benefits, both in terms of subjects selection and research agenda	Limited concern, since individual participants bear burdens and institution as a whole, with which individual identifies, receives benefits

References

- Angell, Marcia. 1997. "The Ethics of Clinical Research in the Third World." The New England Journal of Medicine, 337(12).
- Appelbaum PS, Roth LH, Lidz CW, Benson P, and Winslade W. 1987. "False Hopes and Best Data: Consent to Research and the Therapeutic Misconception." *Hastings Center Report* 17(2): 20-24.
- Bartlett RH, Roloff DW, Cornell RG, Andrews AF, Dillon PW and Zwischenberger JB. 1985. "Extracorporeal Circulation in Neonatal Respiratory Failure: A Prospective Randomized Study." *Pediatrics* 76: 479-487.
- Beauchamp TL and Childress JF. *Principles of Biomedical Ethics*, 4th ed. New York: Oxford University Press, 1994.
- Benson K and Hartz AJ. 2000. "A Comparison of Observational Studies and Randomized, Controlled Trials." *New England Journal of Medicine*. 342(25):1878-86.
- Concato J, Shah N and Horwitz RI. 2000. "Randomized, Controlled Trials, Observational Studies, and the Hierarchy Of Research Designs." *New England Journal of Medicine*. 342(25):1887-92.
- Freedman, Benjamin. 1987. "Equipoise and the Ethics of Clinical Research." *New England Journal of Medicine*. 317(3): 141-145.
- Fried, Charles. *Medical Experimentation: Personal Integrity and Social Policy*. New York: American Elsevier, 1974.
- Gifford, Fred. 1986. "The Conflict Between Randomized Clinical Trials and the Therapeutic Obligation." *Journal of Medicine & Philosophy*. 11(4): 347-366.
- Institute of Medicine. 2000. *Protecting data privacy in health services research. Executive Summary*. Washington, DC: National Academy Press. Available online at http://books.nap.edu/html/data_privacy/
- Kadane JB, ed. 1996. *Bayesian Methods and Ethics in a Clinical Trial Design*. New York: John Wiley & Sons.
- Lurie, Peter, and Sidney M. Wolfe. 1997. "Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries." The New England Journal of Medicine, 337(12).
- Msamanaga, Gernard I., and Wafaie W. Fawzi. 1997. "The Double Burden of HIV Infection and Tuberculosis in Sub-Saharan Africa." The New England Journal of Medicine, 337(14).

Paneth N and Wallenstein S. 1985. “Extracorporeal Membrane Oxygenation and the Play the Winner Rule.” *Pediatrics* **76**: 622-623.

Rosenberger, WF. 1999. “Randomized Play-the-Winner Clinical Trials: Review and Recommendations.” *Controlled Clinical Trials*. 20(4): 328-42.

Thall PF, Millikan RE and Sung HG. 2000. “Evaluating Multiple Treatment Courses in Clinical Trials.” *Statistics in Medicine* **19**(8):1011-28.

Valdespino-Gomez JL, de Lourdes Garcia-Garcia M, and Palacios-Martinez M. 2000. “Long-term Obligations to Human Subjects in Clinical Trials.” [Letter] *JAMA* 284(8): 960-961.

Varmus, Harold, and David Satcher. 1997. “Ethical Complexities of Conducting Research in Developing Countries.” *The New England Journal of Medicine*, 337(14).

Whalen, Christopher C., et al. 1997. “A Trial of Three Regimens to Prevent Tuberculosis in Ugandan Adults Infected with the Human Immunodeficiency Virus.” *The New England Journal of Medicine*, 337(14).

Zelen M. 1969. “Play the Winner Rule and the Controlled Clinical Trial.” *Journal of the American Statistical Association* **64**:131-146.