

# **The Ethical and Epistemic Issues in Inferior Treatment in Clinical Research**

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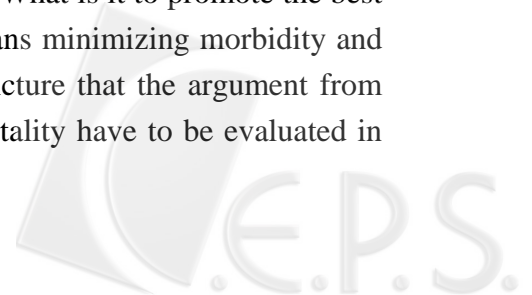
Current opinion, both internationally and in the United States, seems to be converging on the view that clinical trials are never justified when they provide inferior treatment—treatment that is less effective than the available standard of care. The most recent revisions to the Helsinki Declaration, for example, adopted more explicit and uncompromising wording in this direction. I want to argue that this emerging consensus is misguided. There are serious ethical issues about how we conduct clinical research and serious changes called for. But they are independent of the morality of placebos and the like and are I shall argue much more serious to boot.

I shall proceed as follows. I will first briefly argue that inferior treatment in a clinical trial may be unobjectionable under certain conditions. But even if you reject that conclusion, you are unlikely to deny that inferior treatment without consent is even more morally objectionable. Yet inferior treatment without consent is endemic in unrecognized ways I shall argue. I finish by considering responses—both that deny the problem exists and that make recommendations for how to eliminate the problem.

There are of course various different ways patients may receive inferior treatment in a clinical trial. The most obvious is when the control group receives a placebo when there is an agreed upon standard of care. Inferior care can also arise when the treatment group gets a new experimental regimen that is not as good as standard of care or when the control group gets standard of care when the experimental treatment is superior (Freedman 1987).

The emerging consensus view is that all such inferior treatment is unjustified. Patients should receive the best available standard of care in all circumstances. Added to this view is usually the claim that only when there is genuine uncertainty in the medical community which treatment is better—standard of care vs. placebo, etc.—can a clinical trial go forward.

The standard argument for this conclusion invokes the physician's duty to beneficence. My objections to this reasoning are twofold: inferior treatment may still be in the patient's best interest and patient autonomy can reasonably override the physician's duty to beneficence. Does a physician who enrolls a patient in a clinical trial that provides inferior treatment inevitably go against the patient's best interest? I don't think so. What is it to promote the best interests of the patient? A standard answer would be that it means minimizing morbidity and mortality-- minimizing sickness and extending life. It is this picture that the argument from beneficence assumes. Yet it is implausible. Morbidity and mortality have to be evaluated in



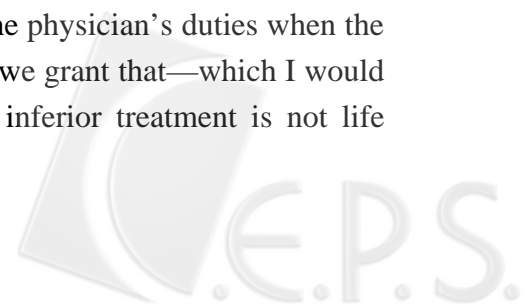
terms of the patient's goals and values. For example, an open-heart surgery that has the chance of extending life may not be in a patient's best interests. Open-heart surgeries typically result in loss of cognitive function, perhaps an IQ drop as great as ten points. If an individual takes intellectual activity to be an essential part of a life worth living, then the cost of surgery may be too much. In short, there is no deciding when it is beneficial to alleviate or remove a condition without considering what is important to the patient. (Of course, we do not want any or all patient goals to be defining. Some notion of "rational goals" is called for, but defining that notion is not necessary to my argument.)

Why does this fact about the best interests of the patient matter? It matters because we might further patients' goals by allowing them to participate in clinical trials where they may get inferior treatment. One obvious example involves clinical trials for minor conditions where the control group foregoes the standard treatment. Individuals may participate in such trials despite the potential inferior treatment either because they are paid or because they want to contribute to knowledge. In either case subjects may judge they are better off by participating; that judgment does not seem automatically irrational. So the physician who promotes the patient's best interest in this case allows the inferior treatment that clinical trials may bring. The duty to promote the patient's best interests does not automatically condemn inferior treatment in trials.

It is not only in cases of minor health conditions that inferior treatment may be in a patient's best interest. Consider any Phase I or II trial where the patients in question have a terminal prognosis. Many Phase I or II trials have no prospect of benefiting the participants; the point of the trials is to determine safe doses alone. Moreover, participating in the trial may expose patients to risks that will shorten their lives. Patients, however, may participate fully understanding those risks and the lack of therapeutic benefit for themselves. They generally do so because their participation and potential contribution to future patients gives their remaining life a kind of meaning it would not otherwise have. A patient who finds that kind of meaning may be better off even if standard palliative care is better care in the normal sense of the word.

My second objection to the prohibition on inferior treatment is simply that patient autonomy can override the physician's duty. Consider a parallel case from outside medicine. A financial advisor has a fiduciary obligation to his or her client—an obligation to promote their best interest. But it would be ridiculous to claim that the client cannot or cannot be allowed to go against the advisor's advice, assuming that advice is fully understood. The client's right to autonomy prevails, regardless of whether they want to use their money in ways that does not maximize their total wealth. The financial advisor's duty is trumped. The advice of a physician would seem to have the same status.

Is there some relevant difference between the financial and medical case? The most obvious is that one's life may be at risk rather than one's money and so different standards are called for. Maybe the principle of autonomy does not override the physician's duties when the choice is to end one's life or significantly shorten it. But even if we grant that—which I would not—it still leaves us with the many clinical trials where the inferior treatment is not life



threatening. Those clinical trials provide inferior treatment, but beneficence is overridden by autonomy just as in the financial case.

So the arguments against inferior treatment are not compelling. However, inferior treatment without consent seems a much different case—we cannot justify it on the grounds of patient autonomy. Nor can we justify it on the grounds that patients find participation meaningful. This much seems noncontroversial. What is less obvious is that inferior treatment without consent is widespread. I turn next to that claim and its implications.

What kind of information are patients not getting? Obviously the important information are the facts crucial to the decision to participate in clinical research. One kind of such information concerns risks—the potential side effects and adverse events associated with treatment. Equally important however is information about treatment alternatives—in particular, what is known about the relative efficacy of the treatment in the study compared to other possibilities.

Relevant risks are those any rational person would want to know. I take it that they include known side effects and possibly related adverse events in human use as well as the same information from animal studies.

Information about alternatives and efficacy is more complex. It seems to me that there are numerous sources of evidence that a rational person would want to consult in making a decision to participate. This information will be about the relative efficacy of an experimental treatment compared to the standard of care and the standard of care to placebo. Such information would include previous results such as:

Efficacy in animal studies

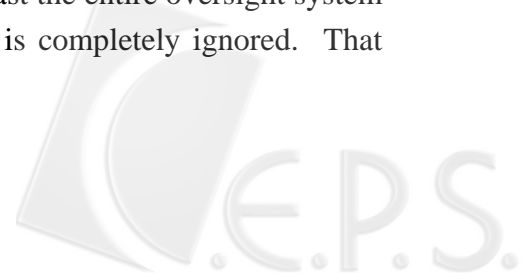
Efficacy in Phase II studies

Previously conducted Phase III studies for studies that are repeated

Data collected so far in for someone entering an ongoing study

Without such data I would argue that an informed decision is not possible. Consider, for example, previous Phase III studies. In the US the FDA requires efficacy in two Phase III trials for a drug to reach market. If a previous study indicates that the experimental treatment is better than the standard of care, I would want to know that—especially if the experimental treatment is available outside of the trial. If a previous Phase III indicated that the standard of care was probably better, I would want to know that too. Without that information I cannot make an intelligent choice and thus cannot consent.

How is that patients may not get this information? One route reflects a failure on the receiving end—a failure of patients to comprehend such information even though it is present in the consent form or the consent process. We don't know specifically how prevalent this route is, but there are some troubling indications. In the US at least the entire oversight system focuses on the informed consent form and the consent process is completely ignored. That



alone is sufficient reason to be worried. Moreover, the empirical research on the issues is discouraging (Casselith et al 1980; Appelbaum et al 1987)

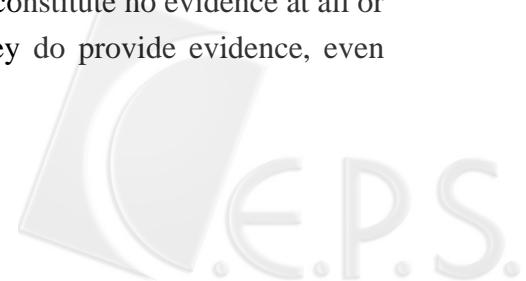
Patients may also not understand because they are just never given the information—it is not in the consent form nor in discussions surrounding its signing if there are such. My anecdotal but extensive experience suggests that this problem is widespread. Previous Phase III studies are not mentioned. The standard of care is not described. And data from an ongoing trial is not made available to patients.

Here is a typical recent example. A major drug company is currently doing a multicenter study on a treatment for asthma in children and adults. Current standard of treatment supported by extensive past clinical trials is use of both a bronchodilator and a steroid inhaler. Currently these are taken as two separate inhalers. The drug company is testing a new product that basically puts the two compounds together in the same inhaler device so that both drugs are received at once. This new combination is being tested against a control group that receives only the steroid and no bronchodilator. The consent form does not mention that steroid alone is not standard of care nor does it mention the extensive evidence showing that bronchodilator plus steroid is superior to steroid alone. A newly diagnosed patient being entered in this trial will very likely not already know this information. They will thus get inferior treatment without understanding that and thus without consenting to it. Studies like this with similar deficits in what subjects are told are commonplace, at least in US drug trials.

What might possibly be said in response to justify such practices? The response I have heard most often goes like this: Patients are not generally being denied the relevant information because we do not really know that one treatment is better than another in these cases. This reflects a major tenet of contemporary clinical medicine: only replicated randomized clinical trials suffice for knowledge. Passing on more preliminary information to patients is both misleading and will lead patients to refuse to participate in trials, resulting in a serious decline in our ability to discern what treatments really work and what do not.

Thus the ethical issue turns on an epistemic one: what are the appropriate standards of knowledge for clinical medicine? Obviously this epistemic question is complex and not something I can adequately address here. But I do want to sketch the issues involved and make a preliminary case that the clinical trials gold standard is misplaced, with serious ethical consequences following.

We should first note that this response has a very foundationalist ring about it. It is foundationalist in that it sets out a single criterion and then proclaims it necessary and sufficient for knowledge. This is a rather traditional epistemic outlook and it is one that misses the fact that evidence and rational belief come in degrees and are unlikely to be captured solely by one universal criterion. For our purposes this is important, because it makes sense to deny patients information about preliminary clinical trials only if they constitute no evidence at all or are irrelevant to what a rational person would consider. If they do provide evidence, even



limited evidence, then they provide information patients will want to know and information without which they cannot provide informed consent.

No doubt providing such information routinely would cut down on the willingness to participate in clinical trials. There are two reasonable responses to this difficulty, one ethical and the other epistemic. The ethical point is that we should not trade patients' informed consent for knowledge, if indeed that trade is inevitable. I take it this is uncontroversial in principle even if it is violated in practice. The other reply is that the divide between RCTs and other forms of evidence about treatment effectiveness is exaggerated. Passing a RCT is not the universal criterion for knowledge.

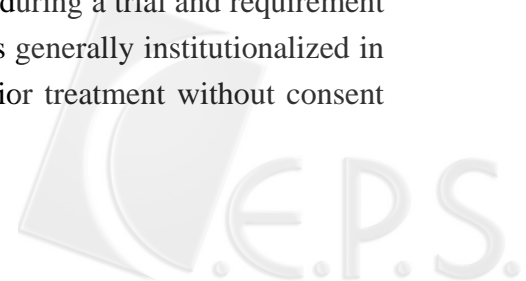
RCTs are no guarantee of reliable results and evidence from nonrandomized trials—say trials using historical controls—can be much more compelling than is generally granted. RCTs are overrated in that:

- 1.) The inclusion and exclusion criteria are often so restrictive that it is not clear what trial results tell us about treatment for the general population.
- 2.) RCTs are almost always convenience samples and thus it is an open question whether they are representative. Randomization after selection of course does nothing to help.
- 3.) Randomization does nothing to control for unknown factors associated with the treatment itself, since the treatment comes after randomization.
- 4.) Randomization only assures that control and treatment groups are balanced in a great many repetition of the same trial—we have no basis to infer that about a single repetition.

Furthermore, evidence from nonrandomized studies has been given an unnecessary bad name. Historical controls can be carefully chosen for known and suspected confounders and in that way control achieved in a conscious way. Recent empirical studies, moreover, show that historical controls can be just as accurate as RCTS (Benson and Hartz 2000; Concato et al. 2000).

Thus I am arguing that changes are called for in the way we conduct clinical research—both for ethical and epistemic reasons. If you think that inferior treatment is never justified, then these epistemic issues about RCTs of course take on great weight, for they suggest that we do not have to trade off knowledge for doing the right thing. If you think inferior treatment must be explicitly acknowledge and that this will diminish our ability to conduct RCTs, then these epistemic points suggest that once again doing the right thing is not so at odds with gaining knowledge.

I claimed earlier that information acquired during a trial was information patients would want and information we do not give them. The issues here are even more complicated than those discussed concerning historical controls and the like. In the US there is a requirement that patients be told any new information that becomes available during a trial and requirement for ongoing data monitoring. In large Phase III trials the latter is generally institutionalized in the form of a Data Safety Monitoring Board. How much inferior treatment without consent



shows up in these contexts is a matter of controversy. When there are not DSMBs then patients may fairly often not get new relevant information, especially about efficacy. But whether DSMBs ensure the relevant information is passed on is controversial as well, again on epistemic grounds.

The issue concerns the implications of repeated significance tests and is at heart the debate between the classical frequentists and subjectivist Bayesians about the foundations of statistics. The dominant approach today focuses on supposed errors introduced by repeated significance tests. So interim analyses are done infrequently and when they are done, a very high significance level is set as a penalty for repeated testing. This is the frequentist approach. But there is a strong argument from the Bayesians that statistical significance is misinterpreted and overrated and that constant data monitoring during a trial is perfectly reasonable (Berry 1985; Bernardo and Smith 1994). Obviously if we follow this route, then DSMBs are not providing patients with relevant ongoing information about efficacy gained during a trial, and large changes are called for.

I know of course that this quick story about the reliability of RCTs and significance tests vis-à-vis historical controls and frequent interim analysis is not going to be convincing on its own. But what is convincing, I hope, is my claim that inferior treatment without consent is widespread and that therefore debating how RCTs might be modified and supplemented is a pressing concern.

## References

- Appelbaum PS, Roth LH, Lidz CW, Benson P, Winslade W. (1987) False hopes and best data: consent to research and the therapeutic misconception. *Hastings Cent Rep* 17:20–4.
- Benson, K and Hartz, A. (2000). “A Comparison of Observational Studies and Randomized, Controlled Trials.” *New England Journal of Medicine* 342: 1878-1887.
- Bernardo, Jose and Smith, Adrian (1994). *Bayesian Theory*. New York: Wiley.
- Berry, Donald (1985). “Interim Analysis in Clinical Trials: Classical vs. Bayesian Approaches.” *Statistics in Medicine* 4: 521-526.
- Cassileth BR, Zupkis RV, Sutton-Smith K, March V. (1980). Informed consent—why are its goals imperfectly realized? *N Engl J Med* ;302:896–900.



Concato, J., Shah, N., and Horwitz, R. (2000). "Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Designs." New England Journal of Medicine 342: 1887-1893.

Freedman, B. (1987). "Equipoise and the Ethics of Clinical Research." New England Journal of Medicine 317: 141-145.

