

If Research is Therapeutic, Where's the Misconception?

By Jim Gearhart

Introduction

In clinical research, consent forms must state that the study's purpose is to expand general knowledge, not to provide clinical care to the participant. This requirement addresses the therapeutic misconception, the concept¹ that potential research participants might confuse joining a clinical trial with receiving medical benefits. Regulations that govern the ethics of clinical research require that the informed consent process make clear this distinction between research and treatment, but current trends and recent events suggest that society no longer accepts this dichotomy. Instead, current social values might be leaning toward expecting that clinical research should provide some direct benefit to study participants.

At the very least, the traditional division between pure research and routine medical care might be blurring. Industry publications increasingly call for considering clinical research as part of treatment: "clinical research as a care option (CRAACO)." The possibility of returning research results, once dismissed out of hand, is becoming a basic expectation. If these developments represent a shift in societal norms toward expecting benefits from clinical research, does it follow that we should alter our ethical approach to the therapeutic misconception?

Preventing Therapeutic Misconception

For decades, medical ethicists have insisted on a clear distinction between clinical care and clinical research. The purpose of clinical treatment is to cure a patient or to alleviate suffering: "First, do no harm." The primary aim of clinical research, on the other hand, is to scientifically explore new treatments, not to provide personal medical care to study participants. Our ethical guidelines about therapeutic misconception require that we hold those two pursuits as distinct, with potentially conflicting goals. Psychiatrist Paul Appelbaum and others have shown that people are predisposed to seeing clinical research as a kind of treatment, even in a placebo-controlled study of an experimental treatment with no proven benefit.² A potential consequence of this misconception is that people might act against their own best interest, such as enrolling in a study with very unlikely benefit and real health risks. The ethical requirement, therefore, has been to ensure that the informed consent process explains that participating in a trial will not provide any medical benefit, even when such possible benefit might actually exist.³ In addition, any stipends for participation also cannot be portrayed as a benefit.

A countercurrent, however, is also present: What if participating in a clinical trial *does* provide some benefit to its participants? An experimental treatment might provide some relief or cure of a condition even before it is approved. In fact, the whole point of clinical research is to assess a potential health benefit. Should we, therefore, not be surprised when study participants ignore our disclaimers and assume there is, in fact, a good chance they will obtain a health benefit? Studies of why participants agree to join (or decline to join) clinical trials suggest this is the case. In 2002, the ECCRI Health Technology Assessment Information Service conducted a review of past studies on this topic and found that, on average, 45% of study participants cited a potential health benefit as a reason for volunteering.⁴ Another study, in 2016, found that just over half of participants in oncology trials volunteered because they believed the trial offered the best available treatment.⁵

In addition, participating in a trial could provide someone with knowledge about his or her condition, provide better care and monitoring than he or she would have received otherwise, or just offer hope during a very trying time. Our ethical standards usually prevent us from presenting these possibilities as benefits. As one paper on therapeutic misconception puts it, "The presence of concomitant clinical care and the potential for benefit associated with trial participation should not be confused with the fundamentally scientific goals of clinical trials."⁶ But what if general society feels differently?

In 2007, a workshop about therapeutic misconception asked attendees to consider the true purpose of research.⁷ A survey question posed the following choices about a typical research study's purpose:

The purpose of the study is to help:

1. Only patients enrolled in the study, or
2. Only patients in the future, or
3. Both patients enrolled in the study and patients in the future.

While many said that only (2) can be true, others — including some attendees at that workshop — argued that (3) is also a valid choice. Not only does research benefit the patients of the future, but it also can provide some benefit, or the chance of benefit, for those who enroll in a study today.

The same workshop ended by presenting a common definition of therapeutic misconception:

Therapeutic misconception exists when individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial.⁸

This definition might hold, but only if everyone agrees that it is fundamentally misleading to suggest that a clinical study could provide any benefit whatsoever to its participants. Going further, what if our societal norms are shifting and society expects clinical studies to provide benefits to participants? If such is the case, an updated definition of therapeutic misconception might be as follows:

Depending on the situation, therapeutic misconception exists when individuals do not understand that (a) the *sole* purpose of a clinical study is to produce generalizable knowledge, with *no* possible benefit to the subjects, or (b) the *sole* purpose of a clinical study is to produce generalizable knowledge, *regardless* of any possible benefit to the subjects, or (c) the *primary* purpose of a clinical study is to produce generalizable knowledge, with only the *possibility* of benefit to the subjects.

This definition prompts a corollary, and potentially contentious, question: Is it ever possible for therapeutic misconception to not exist? To say "yes" suggests that the risks and benefits of joining a clinical trial could be indistinguishable from the medical care a person receives otherwise. But even in a research study that compares two approved treatments, the choice of treatment depends on the protocol, not on what a physician might decide is best for the individual patient. This, combined with the risks that can come with participation in any research, suggests that the potential to confuse research for treatment will always exist. At the same time, for diseases without a cure or effective treatment — such as terminal cancer — the risks of research and the unknown chance of benefit might seem equivalent to the limited effectiveness of an existing treatment. In such extreme cases, some argue, the therapeutic misconception should not be a concern.

Shifting Societal Norms?

Societal norms can change over time, and so can the actions we consider ethical. For example, one ethical standard that stood for millennia was that it was preferred or required to conduct medical research on prisoners. Since ancient Greece, societies often concluded that the public benefit of scientific results outweighed the physical injury (or death) of convicted criminals in human experiments, and that the suffering of prisoners was an acceptable part of their punishment. In the second half of the 20th century, however, the Nuremberg trials revealed the horrors of coerced research and accounts such as Allen M. Hornblum's *Acres of Skin* shifted our ethical standards away from allowing unfettered medical research on prisoners. Instead, we now require a careful ethical review process with *additional* precautions for the incarcerated.⁹

Some trends suggest that we as a society are shifting to the expectation that people should enjoy some benefit, including possible improvements in their health, as a result of participating in research. The idea that clinical research should not be held so distant from clinical care seems to be evolving into the new societal norm. Some examples are as follows:

Research Industry Viewpoints. In the summer of 2018, the industry publication *Applied Clinical Trials* produced a special issue entitled, "Research as Treatment." An article in the issue lauded the benefits of unifying research and treatment: It could attract more participants into research, increase the speed of approvals, and increase the pace of adoption of newly approved treatments.¹⁰ Therapeutic misconception was not mentioned. Similarly, a conference in the spring of 2018, "Bridging Clinical Research & Clinical Healthcare," considered strategies for bringing research and treatment together.¹¹

Return of Results. Until recently, research subjects were told that they would not learn results from tests they underwent, nor would they receive any information about the study's outcome. Expectations in both cases are shifting. In Europe and Canada, mandates to publish lay reports of results are gaining ground; so too are calls for individualized test results to come back to participants. In the United States, when the Secretary's Advisory Committee on Human Research Protections (SACHRP) reviewed the question of returning individual results, it recommended a "general but rebuttable presumption towards disclosure" as an ethical approach.¹² Previously, the complexity involved in returning individual results or preparing public reports sufficed as justification for not making the effort. That argument, increasingly, does not hold, and pressure is increasing on researchers to find ways to provide both individual and generalized results.¹³ Europe and Canada lead the United States in this trend; in 2014 Canada revised its human research subject protection regulations to endorse the return of results whenever possible,¹⁴ and the European Union plans to require the release of lay-person summaries of trial results.¹⁵ The return of results was not an ethical requirement before, but it seems to be evolving into one now.

Patients as Partners. There is a current trend in the direction of regarding study subjects as "partners" in clinical studies, thus the emergence of "participant" as the preferred term for study "subject." Study participants are no longer largely passive recipients of assessments and laboratory tests. Increasingly, clinical studies rely on study participants for "patient-reported outcome" data (including subjective quality-of-life measures) through eDiaries, mobile phone apps, and wearable devices.¹⁶

Right to Try. Right-to-try laws blur the divide between experimental and approved treatments, in theory giving patients and their personal physicians access to experimental medications as an almost normal part of the medical armamentarium.

The line between treatment and research might already be blurred more than current regulations acknowledge. Ethicists and researchers might argue whether a comparison of two accepted treatments is research, a method of evidence-based medicine, or quality improvement. Pragmatic trials¹⁷ appear on this spectrum as a comparison that is part accepted treatment and part protocol-based research. So too does the “learning healthcare system,” in which clinical research and clinical care are part of a constant cycle of examination, analysis and improvement.¹⁸ Another idea, which the 21st Century Cures Act¹⁹ endorses, is that real-world evidence can support approvals for some treatments.²⁰ These evolving methods of gathering knowledge and understanding what might work better than something else appear to weaken the divide between pure research and pure medical care still further.

Conclusion

Ethics can shift as a society changes, as we learn from experience, or as technology advances. Dr. Stephen Rosenfeld, Quorum IRB Chair, has argued that ethical reviewers, such as an IRB, have a responsibility not to define society’s ethics, but to apply them in light of the ethical norms a society holds. If society is now challenging the boundaries of what we call “therapeutic misconception,” we cannot just ignore that trend.

Even if we do expect benefits from participating in research, some categories of studies remain solely for the advancement of knowledge, without any offer of health benefits. For example, most Phase I, first-in-human studies are designed to establish baseline safety and dosage with no possibility of a health benefit. In the many cases where therapeutic misconception remains an ethical concern, such as comparing an experimental treatment with placebo, any discussion of clinical research and its relationship to clinical care must occur within the confines of the principles established by the Belmont Report²¹ and the regulatory framework that governs medical research. In such cases, researchers have clear steps to follow (see the checklist below).

In those cases where treatment is envisaged as part of a trial, such as comparing methods of care, the informed consent process still must present treatment as a secondary, not a primary, purpose. A thinning boundary between research and treatment might work to the good, so long as people can understand the salient differences between them. Nevertheless, we must continue to appreciate that any benefit from participation in research is an additional gain and not the main intention of the work.

When treatment and research converge, the nature of the work becomes less clear, so dispelling therapeutic misconception might become even *more* important. In most cases, we must make it clear to participants that clinical studies can always pose meaningful risks.

Therapeutic Misconception Checklist

When therapeutic misconception is a risk — that is, when participants or potential participants in human subjects research must understand the differences between research and treatment — IRBs should ensure that the following steps are taken:

- Unless informed consent (or an aspect of it) is waived by the IRB, all research participants (or their legally authorized representative) must give informed consent.
- Informed consent and recruitment materials should not promise therapeutic benefit.
- An IRB must review and approve the informed consent document and protocol, along with any announcements or recruitment materials.
- The informed consent process should provide enough information for a potential participant to make an informed decision about participation.

- An IRB must review protocols when research will be conducted without informed consent, such as emergency research, or when a waiver of all or part of the informed consent process is anticipated.

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