

Therapeutic misconception in early phase gene transfer trials

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Abstract

Many subjects in early phase clinical trials expect to benefit in some way from the research intervention. It is understandable that people hope for improvement in their condition, no matter what the evidence. Yet unreasonable expectation of medical benefit may reflect problems with informed consent: Investigators may not disclose clearly that direct medical benefit from an early phase experimental intervention is unlikely or impossible, or subjects may not appreciate the differences between treatment and research. This paper presents findings from recent interviews with researchers and subjects and analysis of consent forms in early phase gene transfer research, a cutting-edge technology often called ‘gene therapy’. We use three variables to construct a composite measure of therapeutic misconception TM, tapping misconceptions about the purposes of early phase research and the potential for direct medical benefit in these trials. Our multivariate model demonstrates the importance of both subject- and study-level factors as predictors of this TM index: education, disease type, and communication by study personnel about the likelihood of benefit. We hope that this work will deepen the discussion of how to define and measure TM, and refine the specification of factors that are related to subjects’ TM.

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Introduction

Many subjects in early phase clinical trials are motivated by the expectation that they will benefit in some way from the research intervention (e.g., Ackerman, 1995). This may be especially true when there is a diagnosis of terminal illnesses for which standard treatments have been exhausted (Dresser, 2002), or when scientific and lay publications promote an exciting new technology (Churchill, Collins, King, Pemberton, & Wailoo, 1998). It is understandable that people hope for improvement in their condition, no matter what the

evidence. Yet unreasonable expectation of medical benefit from early phase trials may be the result of problems with informed consent. Investigators may not disclose clearly that direct medical benefit from an early phase experimental intervention is unlikely or impossible, or subjects may not appreciate the differences between treatment and research.

The term ‘early phase’ refers to small studies (phase I) of an experimental intervention that assess safety and side effects with increasing doses, and to slightly larger studies (phase II) designed to begin an evaluation of effectiveness at a dose level found to be safe, as well as to continue to test for safety and side effects. Effectiveness in phase II trials is often measured by changes in laboratory values that may be surrogates for clinically

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meaningful measures of how a patient feels, functions or survives (Temple, 1995). Empirical evidence demonstrates that early phase studies hold far less potential for improved clinical outcomes for participants than phase III studies, which are designed to test the experimental intervention against standard treatment or placebo on a sample large enough to demonstrate whether the intervention is effective (Horstmann et al., 2005).

Subjects' misunderstandings of the nature of early phase trials have been an object of scholarly investigation, both conceptual and empirical. Appelbaum, Roth, and Lidz (1982) first defined 'therapeutic misconception' (TM) in subjects¹ as the mistaken belief "that the research, like the therapy [subjects] have received previously, is designed and will be executed in a manner of direct benefit to them". While the original definition was primarily applied to phase III trials, empirical studies have subsequently confirmed that subjects in early phase trials misunderstand both their purpose and their potential to provide direct medical benefit (e.g., Daugherty et al., 1995). Many of these studies have been conducted with subjects in phase I cancer trials, the majority of whom think they will "get medical benefit from the treatment in this study" (Daugherty, Banik, Janish, & Ratain, 2000) and are unaware of "the unproven nature of treatment and the uncertainty of benefits to self" (Joffe, Cook, Cleary, Clark, & Weeks, 2001). More recently, Horng and Grady (2003) argue that it is misunderstanding the nature and intent of research that is most ethically problematic, while misestimating the probability of direct benefit may be less worrisome.

Empirical studies have clearly documented the presence of TM but, reflecting lack of agreement in the conceptual literature, they have not defined or measured it in the same way, nor have they differentiated studies of subjects in early phase from later phase trials. Most studies have used simple "yes-no" or forced-choice questions about whether subjects expect medical benefit, how likely they think it is, or what motivates them to join a trial. Two studies have employed measures that attempt to tap more than one dimension of TM, thus acknowledging that it is a complex phenomenon. Joffe et al. (2001) developed a knowledge score for subjects that combines questions about the basic elements of informed consent and trial-specific questions about the purpose of clinical research and the difference between research and medical treatment. Most recently, Appelbaum, Lidz, and Grisso (2004) created a qualitative measure of TM that gives equal weight to two components: inaccurate beliefs about individualized

treatment and unrealistic appraisals of the likelihood of medical benefit.

Studies also differ in the choice of variables theorized to predict TM. Most have focused on individual characteristics such as older age, lower education, illness severity, and being recruited by one's physician (e.g., ACHRE, 1995). Others have examined trial characteristics (e.g., Schaeffer et al., 1996) and various aspects of consent forms and the consent process, including who is present (e.g., Cheng et al., 2000). There is no consistency across these studies regarding which variables are studied or how they are defined; moreover, there are few attempts to include both subject- and study-level variables, and only one published study attempts to jointly assess their contribution through multivariate analysis. In that study, Joffe et al. (2001) found that "improved knowledge" among cancer trial subjects was significantly related to subjects' age and education, and to four factors that measured aspects of the consent process and the quality of consent forms.

In this paper, we use a unique set of semi-structured interviews from early phase gene transfer trials to examine predictors of TM, broadly defined as misunderstanding the meaning of research. Gene transfer research (GTR) has been applied to a wide range of disorders. The majority are cancer trials, thus providing a natural comparison to the literature on TM in phase I oncology trials, although inherited disease, infectious disease, and peripheral and coronary artery disease are also represented. Since the first trial in 1989, GTR—often known as "gene therapy"—has inspired scientists and the public alike with the possibility of a genetic treatment for medical conditions (Churchill et al., 1998; Friedmann, 1996; King, 1999). As a "cutting edge" technology, GTR is an appropriate place to investigate the presence of TM among study subjects.

We employ three variables from our interview questions as measures of the concept of TM. While each has strengths and weaknesses, in combination they tap fundamental misconceptions about the purposes of early phase research and the potential for direct medical benefit in these trials. Our multivariate model demonstrates the importance of both subject- and study-level factors as predictors of this TM index. While our approach is exploratory, we hope that this work will deepen the discussion of how to define and measure TM, and refine the specification of factors that are related to subjects' TM.

Methods

Sample

As part of a broad study of benefit in early phase gene transfer research (GTR), we contacted principal inves-

¹We also recognize the potential for therapeutic misconception in investigators, as do Appelbaum and colleagues, but do not address it in this paper (see Henderson et al., 2004).

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