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The presumption of benefit in clinical research with children and adolescents

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> "Researchers and IRBs need a clear definition and conceptual understanding of research benefits, and how prospective research participants may be inclined to perceive them and be influenced by them."

The concept of benefit is integral to the conduct of child and adolescent clinical research. When evaluating the ethical acceptability of research protocols, Institutional Review Boards (IRBs) must determine if benefits of the proposed study outweigh the risks and whether the research offers the prospect for direct benefit. This latter consideration is a particularly crucial determinant in situations where the child or adolescent wishes to dissent to research participation, since parents may legally overrule a dissenting child and compel their participation in research only when the IRB has concluded that the study offers the prospect for direct benefit [1].

Direct benefit refers to research where the purpose is to establish efficacy for an actual treatment for a disease, disorder or problem behavior [2]. King distinguishes other types of benefits that are ancillary to the primary purpose of the research, such as medical procedures or diagnostic tests, medical care, relationships with healthcare providers, positive feelings associated with altruistic behavior and financial compensation as 'collateral benefits' [2]. Future benefits to society are further classified as 'aspirational'. However, a survey of IRB chairs responsible for reviewing research involving children revealed that direct and collateral benefits are often conflated. For example, the availability of psychological counseling unrelated to the research purpose was considered a direct benefit by 60% of the IRB Chair respondents and medical evaluations unrelated to the research purpose were thought to offer the prospect of direct benefit by 51% of the IRB Chairpersons sampled [3].

IRB Chair responses raise the concern that research involving children may be inappropriately perceived as offering direct benefit that, in turn, can curtail the autonomy of children and adolescents to dissent. Researchers and IRBs need a clear definition and conceptual understanding of research benefits, and how prospective research participants may be inclined to perceive them and be influenced by them.

Keywords: adolescent • child • informed consent • research benefit • research participation decision-making

Participant perceptions of benefit

Numerous studies have determined that adult research participants often perceive or presume potential therapeutic benefit to research where none exists [4]. This concept, called the therapeutic misconception, has been a consistent and persistent finding for over 25 years [5,6]. The primary focus in counteracting the therapeutic misconception has been to improve the quality of informed consent

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documents. While these efforts are important, there are also substantial, yet little discussed and largely unrecognized, cognitive and social/contextual factors associated with research participation decisions that would explain and, in fact, predict a normative 'presumption of benefit' for most participants in most clinical research. These factors are well described in the psychological literature and involve complex interrelated systems, such as remote and long-term memory, automatic thought processes, emotional reactions and the use of heuristics in decision-making [7].

Our social and physical environments have a powerful influence on emotional and behavioral responses. When parents and children enter a church, school or a healthcare facility, they behave in accordance with the norms associated with that setting. Furthermore, they seek and receive cues from the social and physical environment to guide thoughts, feelings and behavior, particularly in novel or ambiguous situations. This phenomenon begins in early childhood where children engage in 'social referencing' or watching adult care providers for information on how to understand and respond with appropriate emotions to ambiguous social situations. When parents and children encounter novel, unique or ambiguous social situations, they attempt to match them with previous experiences and then react and initiate behaviors similarly to those earlier remembered situations. People also detect 'normative power differentials', recognizing their own authority or lack of it in different situations. In this way, settings create 'role constraints'. Children in schools, prisoners in jails and patients in hospitals assume a subservient role because of their dependent status and the assumed authority of the people in charge of caring for them [8,9].

When parents and children assess benefit and make decisions about participating in clinical research, they process information and establish decision-making heuristics using only a subset of available information [10]. For example, 'attentional bias', is the tendency to attend solely to emotionally stimulating information to the neglect of other potentially relevant data and 'confirmation bias' reflects the tendency to attend to information that supports one's preconceived ideas. People consciously and unconsciously employ these and other biases to simplify complex and emotionally difficult decisions, although they may lead to irrational and sometimes maladaptive decisions and behaviors. A number of environmental cues called 'demand characteristics' can affect how individuals behave in specific situations and may have profound effects on research participation decisions. For example, people reference their earlier experiences with physicians and healthcare providers for guidance about how to behave and react when placed in a biomedical research setting. They make assumptions that they continue to be 'patients' rather than research participants and that the physician continues to be just a 'healer' with only their best interests and personal healthcare in mind, rather than a clinical investigator with dual roles as researcher and clinician. Parents and children may ignore disconfirming information and attend to the more salient (for them) emotions they are experiencing and form their heuristics based on this information. In short, parents and children are likely to presume they will receive a health benefit, because past experience and the information they are attending to tells them so.

Studies of research participation decision-making

In our own studies examining contextual issues related to research participation decisions for children and adolescents with asthma, we find remarkable consistency, regardless of study, in the presumption of research benefit and the powerful influence perceived benefit plays in participation decisions [11]. In a recently conducted study of school-aged children with asthma, we described a hypothetical minimal-risk research clinical trial involving allergy medication that did not offer a direct benefit to participants. Approximately 85% of the parents agreed to enroll their school-aged child in the study and 50% of these parents indicated that the medical benefits they thought their child would receive was their primary reason for participating. Most of these parents also presumed their child's individual data, along with a meaningful interpretation of the individual results, would be available to them, much like test results from a medical appointment. In response to the question: "What is the main reason for your participation decision?" parents told us, for example: "I am interested in knowing if allergy medications are affecting my child's learning;" "To help my son feel better at school;" and "To see how any medications might be affecting my daughter with learning" [12]. Using structural equations modeling, we also recently examined factors that predicted research participation decisions in a hypothetical clinical trial for adolescents with asthma and their parents. Our analyses demonstrated that the adolescents' perceptions of benefits were dependent upon the protocol procedures (i.e., study-related medical evaluations), the relationship with the physician-investigator and study compensation. The structural model we developed highlighted the extent to which factors associated with research participation decisions were inter-related. Perceptions of, and the development of heuristics related to, research benefit (and risk) are actually quite complicated, operate automatically and to some extent outside the level of conscious awareness [13].

Implications for research

Situational contexts and cognitive processes can influence decision-making for investigators, IRB administrators and potential research participants alike. When direct benefits are presumed that do not exist, child and adolescent dissent may be inappropriately overridden. When any type of benefit is overstated, research is conducted on less-solid ethical grounds. Therefore, it is important to recognize and address biases that lead to the presumption of benefit in most research situations.

Some research experts may view aspirational benefits as sufficient for conceptually exciting research to proceed. Investigators may overestimate the benefit potential of their own research [2], which leads to vague descriptions of research benefit on consent forms that may confuse, mislead or encourage participants to overestimate the prospect for benefit. Experts can begin to address biases in their own assessments of research protocols by providing more thorough and empirically grounded disclosure of the nature, magnitude and likelihood of research benefits on consent forms [2]. In many cases, researchers and IRBs might consider making explicit instructions to research participants that they should not expect to receive any benefit from their research participation.

Investigators can take steps to minimize the biasing effects of social/contextual factors and automatic cognitive processing for potential participants. One method for reducing or eliminating these biases is to call attention to them specifically, exploring the prospective participant’s past research experiences and attitudes. Together, investigators and potential participants can create and review a list of common thinking errors associated with research participation. Potential participants may be asked to indicate the benefits they expect to receive through research participation in order to allow investigators the opportunity to discuss how realistic each one is for participants. Calling attention to role differentials and environmental demand characteristics that may influence decision-making, may also help lessen their automatic and biasing effects. In essence, requiring individuals to engage in slower, more effortful processing of consent-form information is likely to result in research participation decisions that reflect rational and realistic estimates for all relevant potential benefits.

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