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EDITORIAL

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Optimism and oncology trials: help or hindrance?

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"...at what point does the presence of cognitive bias (in the form of unrealistic optimism) undermine the decision-making capacity of a potential trial participant, such that it becomes ethically problematic to enroll that participant into a study?"

A fundamental tenant in the ethical conduct of human subject research is that participants enrolling in a clinical trial be properly informed and consented [1]. Any contribution towards the improvement of the consent process in clinical research is to be lauded, and the work presented by Jansen *et al.* in the January–February 2011 issue of *IRB* is an important contribution to the field [2]. Their research focused on determining how well cancer patients, considering enrollment into early-phase oncology trials, assess their probability of benefitting or being harmed by participating in a clinical trial.

In their article, Jansen *et al.* published the results of a small, prospective, observational study involving 72 patients being enrolled in various early-phase (Phase I, I/II and II) oncology studies. The study confirmed the authors underlying hypothesis: that 'unrealistic optimism' is present in a population of patients enrolled in early-phase oncology trials, and that this phenomena was unrelated to the existence (or not) of therapeutic misconception [2]. However, an important and as yet unanswered question remains from Jansen *et al.*'s work: at what point does the presence of cognitive bias (in the form of unrealistic optimism) undermine the decision-making capacity of a potential trial participant, such that it becomes ethically problematic to enroll that participant into a study?

In most countries, the legal requirements underpinning the doctrine of informed consent requires that investigators who are responsible for enrolling research subjects into their study must ensure that participants are capable of making an informed decision. The accepted standard in the determination of decisional capacity requires that the participant is able to understand the information relevant to making a decision and appreciate the reasonably foreseeable consequences of a decision to enter or not enter into the trial [3]. The requisite ability to understand and appreciate is determined during the informed consent process, when the protocol is discussed with the prospective research subject. In addition, the investigator must also ensure that the consent is voluntary and not initiated through misrepresentation. Informed consent for incapable research subjects is still possible through a proxy or substitute decision maker when allowed for in the research protocol.

Full disclosure is essential to a valid informed consent process – but it is not sufficient. Emphasis must also be placed on ensuring the information is understood and assimilated by the research subject. The criteria for establishing the degree of understanding and appreciating would seem to be at the heart of the issue we are most concerned with. Understanding information is a very different process compared with transmitting or conveying information. Ethicists and trialists have spent considerable effort studying the methods intrinsic to the transmission of information to potential participants. Practices that reduce the likelihood of being coercive for research subjects are encouraged, such as, suggesting physician/investigators employ

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research coordinators to consent their patients into their research when possible. The readability, length and language used in consent forms has also been improved as has the appropriate amount of time required for research subjects to properly consent. However, what have not been sufficiently studied are the patient-centered aspects, such as, age, illness, altruism, or optimism (as a natural characteristic of the individual involved, or as a performative expression of hope) [4].

Studies that have investigated the degree of a potential participant's subjective 'understanding' of the information in the context of obtaining informed consent, has identified three potential sources of bias. First, therapeutic misconception involves the mistaken notion that a trial is designed to benefit them as an individual patient. Second, therapeutic misestimation is based on an incorrect understanding of the probability of benefit. Finally, unrealistic optimism involves the expectation of high personal benefit despite the correct understanding that the aggregate probability of benefit is low [5]. Appreciating that systems approaches, such as GCP, well-developed consent forms and improved communications may help to mitigate for therapeutic misconception and misestimation, the question centers on what to do with the third category– in therapeutic optimism?

To determine the prospective research subjects' understanding of a research protocol, the investigators of clinical trials will need to determine the degree of bias existing for the research subject (see Perilous Calculus) as part of the consent process.

Bias (β) = Factual data (expressed as probability of both severity and frequency of harms and benefits) - belief [subjective] that the individual is more likely to experience positive outcomes (or less likely to experience negative outcomes) than others similarly situated.

Perilous Calculus

In addition, an assessment of the subjects' appreciation will also be required. These assessments are complicated in light of a cancer patient's alternative to registering into an early-phase oncology trial, which may be tantamount to admitting 'defeat' in the face of certain death.

In their original research, Jansen *et al.* adapted a validated social psychology tool, previously used by Neil Weinstein at Rutgers University, to determine if participants in oncology trials exhibit unrealistic optimism [2]. Weinstein was interested in determining whether college students exhibited unrealistic optimism; he asked college students to rate their likelihood of developing a list of 45 health problems, ranging in seriousness from warts to cancer [6]. Interestingly, he found significant optimistic bias in 34 of the conditions. Weinstein concluded that healthy individuals tend to overestimate the probability of good things happening to them, and that they also tend to underestimate the probability of bad things (including health problems) happening [6].

Jansen *et al.* attempted to quantify if unrealistic optimism existed in patients enrolling in early-phase oncology trials. As part of their methodology, Jansen *et al.* asked five questions relating to the comparative risk and benefit of trial participation; individuals were asked to rate their likelihood of benefit or risk of harm in comparison with other trial participants and to quantify this on a seven-point scale. On average, trial participants indicated that they had a slightly above average chance (a +1 out of a possible +3) of having their cancer controlled or experiencing a health benefit from participation in the trial compared with other research subjects. For comparison sake, a score of '0' meant that the respondent believed they were at the same risk of harm or benefit compared with other trial participant, while a +3 or -3 rating indicated that the participant was significantly more likely to benefit or experience risk, respectively. A shortcoming of their study was that the authors failed to explain or justify why a definitive response value of +1 was chosen as a marker for unrealistic optimism. In addition, we believe that Jansen *et al.* findings could have been significantly strengthened had they been able to compare unrealistic optimism between healthy and unhealthy research subjects. Such a comparison could determine the relative magnitude of unrealistic optimism as it relates specifically to the cancer patients with refractory disease enrolling in early-phase trials.

"...the informed consent process should address the unique cognitive and emotional distortions that can exist from sick patients looking at early-phase trials."

In this editorial we were challenged to determine whether optimism in early-phase oncology trials were a help or hindrance. Unfortunately, the level of evidence presented to date makes it difficult to render a verdict and as such we recommend that further research is conducted. We offer the following comments to guide future efforts. First, it is very important to understand that the contextualization of the data are critical in determining its actual impact on the informed consent process. Qualitative research methodology should be employed to better understand the 'why' that motivates potential participants to believe that they are more likely to benefit compared with others participating in

the trial. For example, perhaps research participants were not able to rate their chances of benefit as being '0' (i.e., the same as others enrolled in the trial) out of fear that their response would become a self-fulfilling prophesy, suggesting the existence of a strong performative bias underscoring the reason for their response. Alternately, research participants may be biased in their interpretation of the information presented to them. Either of these contexts, if true, would better inform us in knowing how to interpret unrealistic optimism in relation to informed consent. In the former scenario research subjects seem to understand and appreciate, while in the later they may not. Second, as Weinstein's research noted, a majority of people are generally likely to underestimate risks of harm and overestimate the probability of benefit. To better understand this reality, we would recommend further research focus on the determination of how sensitive the ranking system (+ and -3) is for this tool. Does a score of + or -1 really indicate a concern for investigators? Or does this represent a general 'pre-existing' bias that is not of special concern for this context?

In conclusion, meaningful informed consent requires that a potential research subject has the information and capacity to carefully weigh the risks and benefits of an experimental intervention and to then voluntarily consent to either enter into a study or to choose not to participate. Appreciating that historically the standard threshold level for determination of a potential research subject's decision making capacity has been low, we recommend that when better understood, the informed consent process should address the unique cognitive and emotional distortions that can exist from sick patients looking at early-phase trials.

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