RESEARCH ARTICLE

THERAPEUTIC OPTIMISM AND INFORMED CONSENT IN PHASE I ONCOLOGY TRIALS

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ABSTRACT

Therapeutic optimism can be defined as the belief on the part of research subjects that they are more likely to receive a benefit and less likely to experience risk than others who are similarly situated. It can be distinguished from other forms of therapeutic misunderstanding including therapeutic misconception and therapeutic misestimation. Empirical evidence from subjects who participated in phase 1 oncology trials indicates that therapeutic optimism is high in a significant percentage of these subjects. The phenomenon of the optimistic bias (overestimation of benefit and underestimation of risk) underlies the therapeutic optimism. Among the risk factors that may dispose a subject to optimistic bias is the factor of perceived controllability in which the very act of consent may inform the optimism. Two theories in social psychology may be useful in explaining the optimistic bias. These are Gollwitzer's mindset theory and Kahneman's fast and slow thought system theory. According to these theories the implementation mindset and the fast thought system may in part explain the optimistic bias. Application of these theories to the informed consent process and using the empirical evidence derived from subjects in phase 1 oncology trials, a hypothesis is offered that the decision to participate in such trials is accompanied by an active rejection of the risk content of informed consent and occurs early in the informed consent process. Exploitation of the optimistic bias and steps that may be taken to curb this exploitation are discussed.

In order to approach the definition of therapeutic optimism (Jansen 2006, Jansen 2011) it is first necessary to exclude the contributions of therapeutic misconception (Lidz et.al 2004; Applebaum et al 2004; KImmelman 2007; Wood et.al 2014) and therapeutic misestimation (Scott 2013; Pentz et al 2012) of participants in clinical trials. This has been done in exemplary fashion by Horng and Grady (2003) and a brief summary of the key features of each form of therapeutic misunderstanding are given below.

Therapeutic misconception

1. The subject believes that every aspect of the research project is designed to benefit the subject directly.

2. There is failure on the part of the subject to understand that the research design and methodology is a distinct form of clinical

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care. Subject conflates research with clinical care. (Henderson et.al 2007)

3. There is expectation that in the research, personal care will be maximized and individualized as it is in routine clinical care.

4. There is failure to understand research methodology and its implications – for example failure to understand the implications of randomization and placebo controls; failure to understand the risks of research based procedures in the clinical trial.

5. The subject believes that the researcher physician has the subject's best health interests rather the best interest of the research enterprise in mind.

Therapeutic misestimation:

1. This is different from therapeutic misconception in that the subject understands that the research procedures are distinct form clinical care and that research procedures may pose special risks and benefits unique to the research. The subject does not conflate research with clinical care.

2. Despite this, there is an overestimation of the benefit that is likely to accrue from the clinical trial even when presented with objective estimates of benefits. There is underestimation of risk where this is stated.

Therapeutic optimism:

The subject understands the research procedures, identifies them as separate from clinical care, and understands the probability of benefit may be low but hopes that he/ she will fall into the group that would receive the benefit. The subject believes that they are more likely to experience a positive outcome than others who are similarly situated. For example, the subject may understand the possibility of a therapeutic benefit is less than 5% but strongly believes that he will be in the "5% that benefits". This phenomenon is referred to as the "optimistic bias".

The optimistic bias in phase 1 oncology trials – the empirical evidence

Weinfurt et al 2012 (also Weinfurt et.al 2008) have pointed out that participants in early phase clinical trials express high expectations of benefit.

Possible reasons for this include

a) The subjects did not receive information during the consent process

b) Subjects received information but did not understand what it meant

c) Subjects elected not to incorporate information in their expression of expectations of benefit.

The authors point out that the subject's lack refusal to incorporate information in the informed consent is the most likely possibility and the one underlying the optimistic bias. In support of this they point out that in a study of informed consent documents by Horng et al. (2002) the authors have observed that descriptors in consent forms for early phase oncology trials make it clear that that there was little or no benefit, and none offered the possibility of a cure. In addition, the consent forms expressed serious harm and the probability of death. Considered together these findings suggest that the "expression of optimism", presumably a manifestation of optimistic bias, occurs very early in the consideration of participation in early phase oncology trials and not only precedes the informed consent process but remains immune to the risks mentioned in the consent form.

Jansen, et al (2011) have observed the impact of unrealistic optimism in early phase clinical trials that the unrealistic optimism of the study subjects was strongly associated with distortions regarding how subjects

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applied general risk and benefit information to themselves and their situations.

In an important study, Agrawal and colleagues (Agrawal et.al 2008) have observed most participants in early phase oncology trials

a) Expressed pressure to participate in the clinical trial because their cancer was growing

b) That the most important factor in their decision making was that the drug killed cancer cells

c) That adverse risk related effects of the drug was not rated among the most useful information available.

The authors conclude that

a) Subjects were aware of alternatives to the clinical trial but did not consider these to be serious alternatives

b) The main goal was to fight the cancer and almost no adverse effect including death would dissuade them from enrolling in the study.

These observations are also supported by the study of Schutta and Burnett (2000).

Sulmasy et al (2010) echo the findings of Weinfurt et al (2012) and observe that expression of high therapeutic benefit "had little to do with knowledge and more to with expressing optimism". Justification universally invoked themes of hope and optimism which included positive thoughts and expression improve chances of benefit, fighting cancer as a battle, faith in God, science or both.

Pentz et al. (201112) have reported that the estimates of therapeutic misconception are uniformly high in participants in oncology phase 1 clinical trials, and that most participants misestimated risk and benefits and these misestimations were related to an overestimation of benefit. A significant portion of the subjects rated their personal risk to be lower than the population risk and their benefit to be higher than the population benefit suggested that, in a significant portion of the participants, therapeutic optimism was manifest.

The impact of the health status on optimistic bias in system and mindset theories.

An important aspect that has not been discussed in the literature concerns the impact of the subject's health status on the decision making process. Most subjects considering phase 1 oncology trials have failed conventional chemotherapy and radiation and probably present with a depleted physical and mental strength.

A study by Schaeffer and colleagues (Schaeffer et.al 1996) points out that severely ill phase I subjects retained the least information about risks and side effects relative to healthy volunteers and that phase I subjects entered phase I studies primarily for treatment purposes and the consent document was rated less useful by subjects with more advanced disease.

Perreira et al. (1997) have observed that that a significant percentage of terminally ill cancer patients in their study sample had cognitive impairment and had low scores on the Mini-Mental State Examination (MMSE). They concluded that cognitive impairment is "highly prevalent" in this population and advise cognitive screening of advanced cancer patients prior to enrollment. The impact of cognitive impairment on informed consent in severely ill patients, and on the optimistic bias in informed consent remains largely unexplored.

Menikoff (2009) approaches the problem of ignoring thought capacity problems in patients with medical illnesses and points out the while IRBs remain sensitive to diminished or altered thought capacity in subjects with psychiatric diagnoses, they remain largely oblivious to such deficits in

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patients with medical illnesses. He poses the questions "how are subjects who have capacity but are subject to conditions which strain that capacity and thus at least make its exercise somewhat questionable, to be dealt with?" The author suggests that specific steps be taken to ensure that the benefits of the "treatment" offered in clinical trials to severely ill patients should provide special protections to prevent their misconstruing the benefits of the offered treatment. "Might not the circumstances (of medical illness) sometimes be considered as creating the type of "undue influence" that IRBs are warned to watch out for". The author notes that pressure for enrollment into clinical trials may in fact preclude such special precautions.

Response rates in oncology trials:

Horstman et al. (2005) report that in terms of "classic" phase I trials of single investigational agents the response rate was 4.4%.

Von Hoff and Turner (1991) report a response rate of 6% in phase 1 trials and conclude that although the response rate is low, responses can occur.

Lidz et al (2004) report that a significant proportion of study participants in clinical trials reported "no risks or disadvantages in spite of being explicitly asked about them; only a small percentage reported any risks or disadvantages from the research design itself including randomization, placebos double-blind designs and restrictive protocols.

Miller and Joffe (2008) have examined the possibility of a direct medical benefit in phase 1 oncology trials and have concluded that data related to tumor shrinkage or stabilization of disease do not allow for an inference of a definitive estimate of a clinical benefit. They suggest that that there can be "no objective third party judgment about the reasonableness of the prospect of a direct medical benefit" and that the reasonableness of a direct benefit is "entirely a subjective judgment on the part of the potential participant."

Types of optimistic bias.

The optimistic bias is thought to underlie the phenomenon of therapeutic optimism.

Two types of optimistic bias have been commented on. These are dispositional optimism and unrealistic situational optimism. (Jansen et al., 2016; Jansen, 2016; Jansen, 2011)

Dispositional optimism relates to those individuals who have a "naturally" optimistic view of life events, whereas situational optimism relates to optimism expressed with respect to a particular event or activity.

These two forms of optimism are not strongly correlated. Persons, who do not have a positive view of all life events, may have a very positive outlook with respect to specific situations.

While dispositional optimism relates to all situations involving life events, situational optimism may be further sub classified into either realistic or unrealistic optimism.

Realistic optimism is manifest then the person subscribes to a view of success when the probability of success for all group members is rated to be high.

Unrealistic optimism (Shepard et al 2013; Shepard et al. 2015; Davidson and Prkachin 1997; Weinstein 1980, 1984) is manifest when a person subscribes to a view of success when the probability of success for the group as a whole is rated to be low. For example, Jansen (2011, 2016) cites the following example of a smoker who is asked to compare his chances of getting cancer relative to others with a similar background, and rates his chances of getting lung cancer as being significantly lower than the rest of the group. In the context of clinical trial, if

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the probability of benefit in phase I oncology trial is rated to be 5%, the subject expresses confidence that he is exceedingly likely to be a member of that 5% group.

This is to be distinguished from therapeutic misestimation where the subject believes the probability of benefit to be significantly greater than 5%. In unrealistic situational optimism, the subject is fully aware of the risk to the group of which he is member but chooses to overrate personal benefit or underrate personal risk.

A key difference between dispositional and situational unrealistic optimism is seen in the consequences for behavior in the two groups. In situational unrealistic optimism, there is marked tendency to enhanced risk taking with respect to individual situations; underestimation of personal risk was associated with engagement in riskier behavior, lesser attentiveness to risk related information, and reduced worry about the consequences of the risky behavior. Situational unrealistic optimism may interfere with the voluntariness and autonomous decision making that is important in the informed consent process. In this view, situational unrealistic optimism is regarded as an internal coercive factor distorting the informed consent process.

Measures of dispositional and situational unrealistic optimism. (Jansen 2011)

Dispositional optimism is measured using the Revised Life orientation test. This questionnaire asks respondents to state their agreement with positive statements such as "I expect good things to happen to me" or "In uncertain times I expect the best."

Situational unrealistic optimism can be rated using the Comparative Risk/Benefit Assessment questionnaire (CRBA), which asks respondents to assess risk with respect to themselves and their group for specific situational health related events.

Risk attribute factors underlie the optimistic bias (Radcliffe and Klein 2001; Jansen 2016; Weinstein 1989)

The following factors have been identified as contributors to the optimistic bias:

a) Past experience with an event (not relevant for initial informed consent in phase 1 oncology trials)

b) a salient thought image of the type of person likely to experience the event (more applicable to general health risk factors such as smoking and alcoholism than to early phase oncology clinical trials)

c) Egocentrism (weak link to early phase oncology clinical trials)

d) Perceived controllability (strong link to consent in early phase oncology clinical trials).

Perceived controllability: (Klein and Hedwig-Larson 2001; Harris 1996; Harris et al. 2008)

Perceived controllability in the context of early phase oncology trials may relate to the possibility of the act of participation in the clinical l trials is therefore a manifestation of perceived control of having the drug cure, control, or improve the health of the subject. The act of informed consent may inform the optimism. Perceived controllability ignores the contribution of external factors to the outcome – these include factors such as the individual health condition, the genetic makeup, and the contribution of factors not understood in the drug's efficacy ("luck").

Support for this view comes from the study of Agrawal (2008) who found that a significant percentage of participants in a clinical trial reported that the act of participation gave them a sense of control over their disease. They concluded that "desire to actively do something to fight their cancer appears to motivate these participants to enroll in phase 1 oncology

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trials" and that the participants expected personal benefit while believing the majority of participants would not benefit thus confirming optimistic bias.

Illusion of control (Langer1975)

One error in perceived controllability is to view the event as controllable when it is not. This error is also referred to as the Gamblers' fallacy. (Sekowski and Birnbaum 2013)

The belief that participating in phase 1 oncology trial may confer health benefits even when the probability of group success is low is an example of this illusion of control.

There are two possible components to the gamblers' fallacy.

The first is the belief that something with fixed probability will increase or decrease in odds based on recent occurrences – in the roulette game the recent occurrence of four reds increases the odds that the fifth spin will yield black. This is referred to as a negative recency effect.

Sekowski (2013) explains that the misestimation of a direct benefit in phase 1 oncology trials – mistaking the odds of benefit because of a mistaken underlying belief about the clinical trial represents this type of gambler's fallacy. All previous attempts at a cure have failed so perhaps this one will succeed, is a manifestation of the recency effect.

The second type of gambler's fallacy arises from the desire to find order in a random process by giving in to the human predilection to avoid base rate probabilities while giving into "intuition". In this view the gambler knows the statistical basis for a sound decision but believes that this will not apply to him.

Thus a participant in the phase 1 oncology clinical trial may well know the that the odds of a benefit are low but is convinced that he will be in the group that may benefit from it.

Theories of perceived controllability:

Two theories have been discussed in the literature to explain the basis of perceived controllability. The first of these is Gollwitzer's mindset theory and the second is Kahneman's thought system theory. These are discussed below.

Mindset theory:

Gollwitizer and colleagues (Taylor and Gollwitzer, 1995; Gollwitzer 2003; Gollwitzer and Kinney 1989) have defined two phases of action which they have termed as mindsets.

These are deliberative and implementation mindsets (Jansen 2014).

The deliberative mindset has the following features:

a) The deliberative mindset predominates in the process of making decisions.

b) People can easily open the window to the deliberative mindset – trying to achieve clarity on an unresolved problem can trigger the deliberative mindset.

c) The deliberative mindset allows them to accurately assess whether a desired outcome can be controlled by their actions whereas those in the implementation mindset favor illusionary optimism with respect to controlling their outcome.

The features of the implementation mindset include the following:

a) Implementation mindsets are not predisposed to finding clarity, are associated with susceptibility to irrelevant thoughts, are less likely to reflect on pros and cons, are more focused on how to achieve goals rather than an evaluation of them. Distorted probability estimates of success are a feature of the implementation mindset.

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b) Post decisional individuals in the implementation mindset seem "protected" from an accurate analysis of feasibility related formation. The illusionary optimism makes them strive harder to achieve their goals especially in the face of hindrances and barriers. Thus the implementation mindset can be strongly self-reinforcing.

c) In the implementation mindset having settled on a plan the individual focuses on how to achieve the goals and less on its intrinsic value or desirability and is less likely to pay attention to information that bears on how likely the individual is to be successful while perceptions of control are strongly prevalent as does the illusion of invulnerability.

d) Perceived desirability and perceived feasibility and a closed mind focus are exaggerated in the implementation mindset. This leads to prolonged persistence of the implementation mindset. Persistence in failing causes of action is a feature of the implementation mindset.

The authors have shown that the implementation mindset strongly correlates with illusion of control, feelings of invulnerability and a thought state in which information negative to their implementation goals is strongly rejected. Thus, the implementation mindset is a strong contributor to perceived controllability, illusions of control and the optimistic bias.

In Kahneman's theory of fast and slow thought systems (Kahneman 2011) the following features are noted:

1) The fast thought system operates automatically and quickly with little effort, is impulsive and intuitive and forms impressions and jumps to conclusions, quick estimates and assumptions and is influenced by mood and turns impressions into belief and is the origin of many of the errors of intuition. It is prone to predict wild outcomes on weak evidence.

2) Specific descriptions trigger the associative mechanism of the fast thought system as is the emotional evaluation of gain and loss.

3) Conscious and subconscious exposure to images and ideas primes the fast thought system to anticipate similar ideas.

4) The fast thought system constructs representation of a typical member of the population and uses it to make judgments about other members.

5) In the fast thought system, if an individual is given identical choices but one is framed in terms of gains and the other as losses he will choose the one framed as gains.

6) The optimistic bias leads people to neglect probabilities of success and overestimate the degree of control and there is a tendency to downplay the influence of the external factors. These are all features of the fast thought system.

7) When the fast thought system runs into trouble, it calls on the slow thought system to help out – this applies to questions which the fast thought system cannot understand.

Features of slow thought system include the following:

1) The slow thought system carefully evaluates pros and cons, and carries out statistical estimates of probabilities of events. The slow thought system requires attention and effort to fulfill complex thought activities including statistical evaluations and is much more cautious and analyzes impressions and moods.

2) Conscious doubt is not a feature of the fast thought system while unbelieving is a feature of the slow thought system.

3) When the slow thought system is depleted, self-control diminishes and the fast thought system predominates.

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The fast thought system is a key contributor to the illusion of control, perceived controllability, and the formation and consolidation of the optimistic bias.

Comparison to the Gollwitizer mindset theories.

There has been no attempt in the literature to compare or reconcile the Gollwitizer mindset theories and the Kahneman thought system theory. The Kahneman fast thought system would seem to be linked to the implementation mindset described by Gollwitizer. The illusion of control, a favorable perceived desirability and feasibility, and exaggerated estimation of success are common features of the implementation mindset and the fast thought system.

Application of mindset and Kahneman theories to the informed consent process.

How do the mindset and Kahneman system theories apply to the informed consent process? Specifically, where in the overall consenting process does the optimistic bias play a role and what is the relationship of this optimistic bias to the mindset and Kahneman theories in the informed consent process?

To consider this application we put forward a likely sequence of events invoked in the informed consent process.

a) Early impression of risk benefits of the clinical trial (recruitment phase).

b) Information absorption about the clinical trial.

c) Assessment of pros and cons.

d) Decision to participate.

e) Informed consent process initiation and completion, including re-evaluation of pros and cons and the decision to participate.

f) Longer term evaluation of whether to stay in the phase 1 oncology clinical trial.

Scenario 1.

In the first scenario we consider the possibility that the optimistic bias follows the initial evaluation of pro and cons of the clinical trial and therefore appear late in the informed consent process. (Jansen 2014; Jansen 2016a)

According to mindset theory, the subject starts in the deliberative phase (steps a-d) and moves into the implementation mindset while actually reading the informed consent (step e). According to this view, the onset of the implementation mindset coincides with the evaluation of the informed consent itself.

According to the Kahneman view, the slow thought system is at work in the initial steps (a-d) and the fast thought system takes over late in the informed consent process (step e).

Scenario 2.

An alternative scenario is that the optimistic bias, the implied perceived controllability and the implementation mindset are prevalent at the very beginning of the process (step a) and persist throughout the subsequent steps and the deliberative mindset is not significantly operational in the decision making process.

In the Kahneman view, the fast thought system which ignores risks and overrates benefits is operational at step a and persists throughout the informed consent process.

We favor the hypothesis in scenario 2 that the implementation mindset and the Kahneman fast thought system are prevalent at the very outset of the thinking about the participation in the phase 1 oncology trials.

The long term decision to stay in the phase I clinical trial may be attributed to the persistence in goal directed behavior which is a characteristic of the implementation mindset. (Brandstatter and Frank 2002)

Evidence which favors scenario 2 are the following:

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A) The Agrawal study (2008) which points out that the expectation of benefit and the imperviousness to risk are present early in the decision making process and that no adverse effect including death would prevent them from enrolling.

B) The Weinfurt study (2012) points out that high expectations of benefit and the reluctance to incorporate information in the informed consent into the expectations of benefit and that this occurs despite the fact that most informed consents are explicit about serious harm in the clinical trial including the possibility of death.

C) These findings are supported but the study of Summary et al. (1996) and Pentz et al. (2012) (discussed above) who have reported similar conclusions.

D) A seminal observation is that of Schaeffer et al., which showed that severely ill patients retained the least amount of information about the informed consent and that the consent document was rated less useful by subjects with more advanced disease.

How is this depletion of physical and thought strength to be incorporated into the two theories? Kahneman's system theory provides a valuable insight into this process. It notes that the depletion of the slow thought system encourages the switch to fast thought system decision making. One possible hypothesis is that the physical and mental depletion that characterizes subjects in phase 1 oncology trials facilitates the formation of the optimistic bias and leads to an erosion of the slow thought system. In terms of the Gollwitzer's mindset theory the deliberative mindset is considerably weakened in subjects considering phase 1 oncology trials

Considered together, these observations favor the hypothesis that the implementation mindset of the Kahneman fast thought system of decision making are prevalent in the very earliest phases of decision making in the informed consent process and may precede the signing of the consent document itself.

A required section in the informed consent form relates to alternative procedures. For the most part the alternatives listed to clinical trials are a) no alternatives b) standard of care. It is our hypothesis that the decision making process in phase 1 oncology trials is greatly distorted by the fact that there no viable alternatives available in the consent form for such clinical trials. The application of the gambler's fallacy to the subject in clinical trials may not be entirely appropriate. A gambler believing in the recency effect of a favorable run at a roulette wheel still has a choice between two options both of which are feasible. By contrast, subjects in a phase 1 oncology clinical trial may not feel that they have a viable option and may lean toward participation because of the belief that this is their only choice. The relationship of such a narrowed option menu to the optimistic bias needs to be explored further. The absence of viable alternatives may predispose subjects to the optimistic bias concerning the clinical trial (best last hope), facilitate the formation of the Kahneman fast thought system and the Gollwitizer implantation mindset. Jansen and colleagues (Jansen et al 2014) have observed that participants in early phase clinical trials expressed an appreciation of the treatment that they were about to receive, that some participants may have believed that no treatment was available to them outside the clinical trial and that the treatment could be no worse than the standard of care. Others have observed that the patients with advanced cancer and the terminally ill are particularly vulnerable to being manipulated into making treatment decisions and into believing that no good options exist except to enroll in the offered study which has low or no expected benefits. (Menikoff 2009). These features may

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contribute to the early formulation of the optimistic bias in the informed consent process with the prevalence of the implementation mindset or fast thought system (scenario 2).

Exploitation of the optimistic bias and informed consent

Martin (2008) observes that "hope for an unlikely cure can reduce research participants' autonomy even if they do not suffer from the therapeutic misconception". They may "understand very well that early phase research aims for generalizable knowledge about toxicity and not a medical benefit; but hope for an unlikely cure may impair deliberation about whether to participate by discounting information which she knows to be relevant such as the side effects of a drug". If researchers take advantage of this impairment they are no less exploitative than those who take advantage of the therapeutic misconception". In this context, the researcher's doctrine "temper honesty with hope" may be exploitative. Verbal presentations that accompany the informed consent process may in part include subconscious strategies to play along with the optimistic bias, a phenomenon that is rendered even more likely if there are significant pressures to enroll a given number of subjects in a clinical trial.

Steps to counteract the optimistic bias.

Verbal scripts for recruitment and the informed consent presentation introduction.

The need to improve communication in the informed consent process has been commented on in the literature (Meropol et al. 2003; Cox et al. 2006; Daugherty et al. 1995)

Conscious or subconscious upbeat presentation of the possibilities in phase one oncology trials may be fed by compelling circumstances governing enrollment. Compensation to the investigator or to the institution by the trial's sponsor is dependent on meeting enrollment targets. The promise of publication related "publicity" may also feed into enthusiastic presentation of such studies. These can be significantly curbed by having a written script for verbal recruitment and informed consent introductions which are reviewed by the IRB. Such scripts are optional in most institutions but making them mandatory for phase 1 oncology trials would allow the IRB to review what will be said and whether the optimistic bias is being "fed" or exploited in the early recruitment and informed consent process.

Subject advocate

The appointment of a subject advocate, who can provide additional information on the clinical trial in an unbiased fashion and particularly advise participants on the alternatives to participation, including treatment combinations other than the trial in which they are currently being enrolled, would reduce the pressure on subjects to view the clinical trial as the only and last option. Resistance to the appointment of such a subject advocate by the principal investigator is likely. However, the IRB can require a witness to informed consent processes in high risk trials. Doing the same for phase 1 oncology trials would be a small step forward in ensuring that the optimistic bias is not being exploited by the researcher.

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