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Decision-Making Process Related to Participation in Phase I Clinical Trials: A Nonsystematic Review of the Existing Evidence

Alessandra Gorini Ketti Mazzocco Gabriella Pravettoni

Department of Health Science, University of Milan, and European Institute of Oncology, Milan, Italy

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Phase I clinical trials · Cancer · Decision-making · Optimistic bias · Ethical concerns · Decision tool

Abstract
Due to the lack of other treatment options, patient candidates for participation in phase I clinical trials are considered the most vulnerable, and many ethical concerns have emerged regarding the informed consent process used in the experimental design of such trials. Starting with these considerations, this nonsystematic review is aimed at analyzing the decision-making processes underlying patients' decision about whether to participate (or not) in phase I trials in order to clarify the cognitive and emotional aspects most strongly implicated in this decision. Considering that there is no uniform decision calculus and that many different variables other than the patient-physician relationship (including demographic, clinical, and personal characteristics) may influence patients' preferences for and processing of information, we conclude that patients' informed decision-making can be facilitated by creating a rigorously developed, calibrated, and validated computer tool modeled on each single patient's knowledge, values, and emotional and cognitive decisional skills. Such a tool will also help oncologists to provide tailored medical information that is useful to improve the shared decision-making process, thereby possibly increasing patient participation in clinical trials.

Introduction

Phase I trials serve to investigate the safety profile of novel drugs or treatment modalities. They are usually performed on small samples (20–80 individuals) of healthy volunteers to assess drug or treatment safety, a safe dosage range, and potential side effects. Oncology is one of the rare fields where terminal patients are included in phase I clinical trials (human trials at that), since treatments in this field are too toxic for healthy subjects. Due to the actual limited availability of effective standard treatment options for these patients, their participation in early-phase clinical trials is of great importance for developing new drugs and ultimately improving clinical outcome. Nevertheless, it is estimated that less than 5% of all adult cancer patients agree to participate [1–3]. In the past years, such low rates of participation have represented a significant concern with regard to the necessary development of new drugs. This issue is even more crucial

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E-Mail karger@karger.com
www.karger.com/phg

Alessandra Gorini
European Institute of Oncology
Via Ripamonti 435
IT–20141 Milan (Italy)
E-Mail alessandra.gorini@unimi.it

today, in the era of personalized medicine, in which targeted agents need to be developed that have a therapeutic benefit in molecularly defined patient subsets.

Moreover, considering that patients who are proposed for participation are facing their own death, that there is an uncertain and low potential for individual benefit, and that there is an uncertain and significant potential for side effects [4], many ethical concerns have been raised about the informed consent process used in phase I studies. In fact, in these conditions, the psychological distress experienced by patients and families may further increase patients' vulnerability and create challenges to comprehension and decision-making which alter the free informed consent process.

Role of Optimism Bias with Regard to Participating in Phase I Studies

Many studies have analyzed cancer patients' understanding of and motivation for participating in phase I trials and showed that many of them are subject to so-called therapeutic optimism. This means they consider their own chance of obtaining medical benefit high or even higher than participants in general, expressing and trusting their hope rather than considering facts [5]. Despite this hope, less than 5% of patients enrolled in phase I trials actually benefit from participation [6, 7]. From a rational point of view, such therapeutic optimism appears to be completely unfounded, since more than two thirds of the interviewed patients offered participation in phase I trials feel they would live 2 or more years receiving an experimental treatment, and nearly half feel they would live 2 or more years with standard therapy, even if they are fully informed about having a life expectancy of months due to their refractory malignancies [8]. Apart from therapeutic optimism, other reasons why patients agree to participate include the fact that they know that they have no other chances [9–11] as well as the presence of altruistic feelings [10, 11].

Such evidence seems to weaken the ethical concerns that patients who agree to participate in phase I studies do not really understand a trial's purpose and/or do not have enough information to take an informed decision [12–15]. Even if not completely denied, these concerns seem to be at least exaggerated, as discussed in the study by Agrawal et al. [16], which assessed the decision-making process of oncologic patients enrolled in phase I trials, showing that those who agree to participate are usually aware of existing alternatives to phase I studies (i.e. palliative care) but do not seriously consider them. When asked why they choose to participate, they say that this is the only way for them to maintain their hope of fighting their cancer, and that almost no adverse effect, including death, would dissuade them from enrolling [17]. Again, rather than having therapeutic misconceptions, the interviewed patients demonstrate that they are guided by therapeutic optimism [18, 19], with only 3% reporting personally to be very or somewhat unlikely to benefit from participating in phase I studies. Meropol et al. [4] confirmed these findings by showing that when asked whether they would benefit from treatment that offers a 20% chance of a cure, 44% of patients reported they would be among those who benefited. Thus, according to the authors, patients make the decision based on their confidence in their individual treatment outcomes rather than on the relative frequency of a response in a population.

An interesting model that predicts patients' choices regarding their future treatment options is the Health Stock Risk Adjustment model [20]. According to this model, 'as one's perception of future health, relative to baseline health, declines, a patient will tend to overvalue potential benefits and undervalue potential risks in deciding whether to choose an experimental treatment' [21]. In particular, patients for whom standard therapy failed show an optimistic mindset regarding the benefits of experimental therapy. These findings explain why these patients agree to participate in phase I studies, choosing to receive treatment with a great perceived potential benefit and a low perceived risk [20, 22, 23].

While a diffuse hope for a direct benefit of phase I trials has been found even in adolescent patients [15, 24], the only patients who represent an exception regarding the therapeutic optimism bias are the elderly (patients over 65 years). Only few studies [25–30] are available on these patients, because the frequent comorbid conditions in these individuals are often incompatible with protocol eligibility requirements; however, they are numerous enough to allow us to note that elderly are similar to younger patients regarding cancer screening and cancer care, while they are clearly less willing to accept toxic treatment that could eventually prolong their survival but may affect their quality of life [31]. Differently from younger patients, older patients do not seem to exhibit the therapeutic optimistic bias and to place less importance on the chance of living longer to be a good reason for participating in clinical trials [32, 33]. Focusing more on quality of life than on a longer life, they are less willing to participate in phase I trials than other patients.

Patients are not the only ones that experience an optimism bias. It has been observed that even family members tend to filter dialogues with physicians by means of an optimism bias when hearing bad news [34], often forcing patients to make a treatment decision contrary to what the patients themselves want. Even physicians are not immune to this kind of bias. Comparing their predictions about the survival of terminally ill patients to the actual outcomes, physicians show a systematic and substantial optimism bias, especially with regard to the patients they know better, see more often, and have known longer. In these cases, a physician's overestimation of patient survival results not only from a belief in self-fulfilling prophecies, a desire to influence patients and their disease, and the expectations patients have regarding what they are being told, but also from a professional desire to maintain control over a patient's clinical course, both by encouraging him/her to follow the doctor's recommendations and by bolstering the physician's perception of his/her own effectiveness [35]. The optimism bias is one of the most consistent, prevalent, and robust biases documented in psychology, and it is often one of the main reasons why patients participate in phase I trials and why physicians propose them.

Is It Possible to Help Patients in Making a Responsible and Satisfactory Decision?

The optimism bias is an important component of any decision to participate in a phase I study, but it is not the only one. In particular, it does not explain why participation in these trials is so scarce. Understanding why this occurs and helping patients with no remaining treatment options in making a responsible and satisfactory decision is a laudable goal that should be pursued by the entire health care staff.

As stated by Collins et al. [36], 'decision quality' refers to the extent to which the patient's choice is (a) informed, (b) consistent with his/her personal attitudes (i.e., his/her 'values') about the therapeutic options' pros and cons, and (c) acted on [37].

Providing Information and Understanding

Data collected in previous studies on phase I participants showed a correct understanding among subjects between 33 and 43% [38–40]. These data suggest an alternative and/or complementary explanation for the high expectations regarding treatment outcome in patients, which are usually significantly different from those expressed by physicians [41–43]. It is possible that, in many contexts, and in particular in those involving life-threatening illnesses, the differences between patients and physicians result from suboptimal patient-physician communication [16, 44–49]. Poor patient-physician interaction and understanding may produce unexpressed misconceptions and fears regarding participation in clinical trials (especially in phase I), preventing cancer patients from agreeing to be enrolled. Catania et al. [50] showed the importance of recognizing and discussing these topics to make patients feel free and aware of their choice as to whether or not to participate in a phase I clinical trial. This is particularly important considering bioethical concerns, given the common preference of cancer patients for a shared decision-making model [51].

From a cognitive point of view there is another important reason for providing patients with exhaustive and clear information apart from understanding: to help them, as much as possible, to avoid regretting their decision. In medicine, regret is experienced when patients feel they made an error in their choice related to their illness or the therapeutic path they took, and they wish they had made an alternative choice. Regret is frequent in situations of poor information and is often associated with a poor quality of life and/or a bad perceived health status, even when the patient does not experience any evident side effects of treatment.

Analysis of Patient Values

The available data show scant attention to patients' values given by physicians when making a treatment plan or proposing participation in clinical trials. Starting with this evidence, Hendershot et al. [52] developed a 'values tool' to be used in phase I clinical settings in order to collect patients' priorities and preferences for the next step in care. This first feasibility study showed that most of the patients checked at least one value and that 63% of the physicians who received the tool discussed it. The idea of a values tool is a promising step toward facilitating patients' expression of their needs, which is of primary importance to avoid coercion and the violation of patients' rights.

Strictly related to patients' values are quality-of-life outcomes, which are becoming important endpoints in clinical trials [53, 54]. It has been observed that a good quality of life is strongly correlated with the expectation of survival and also with the expectation of a benefit from experimental interventions [21]. This implies that quality of life may affect patient expectations of benefits from experimental therapy and, ultimately, their agreement to participate in clinical trials.

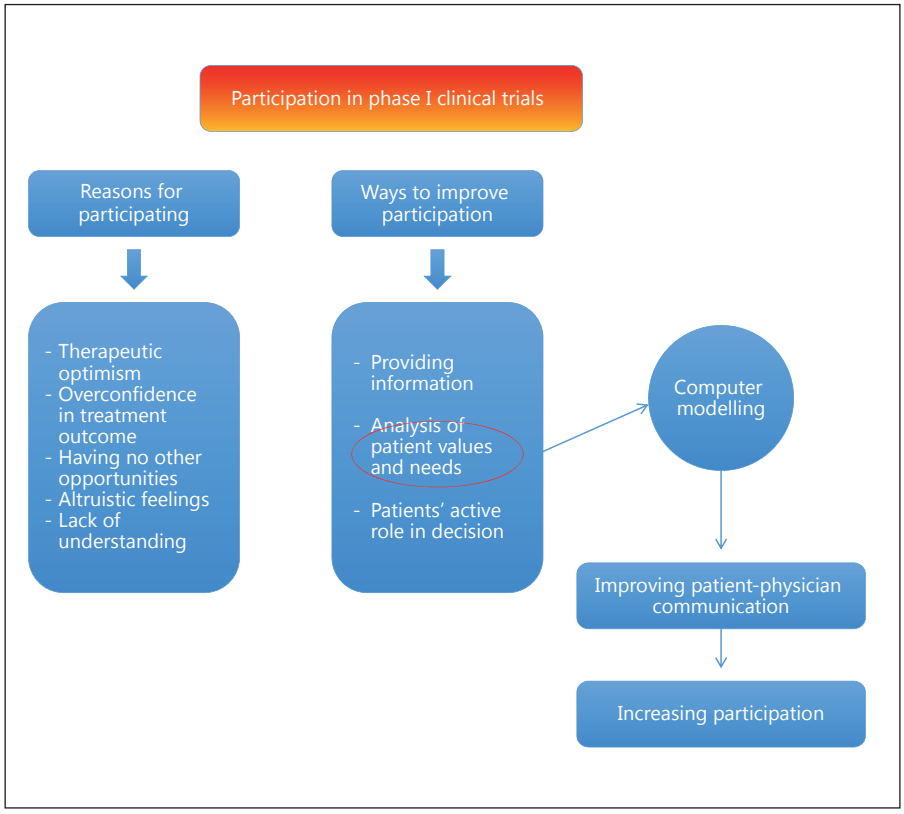

Fig. 1. A schematic representation of the proposed computer model for increasing participation in phase I clinical trials.

Acting on Patients' Decisions

Regarding the role taken by patients in the difficult decision about whether to participate or not in early-stage clinical trials, Meropol et al. [4] observed that approximately 47% of the patients in their sample took a passive decision-making role, 38% took an active role, and 15% took a shared role. The decision-making style does not appear to be predictable by age, education, ethnic group, or marital status and to change over time; in particular, after having experienced treatment failure or adverse effects, patients who had a passive decisional role at the beginning of the treatment tended to become more active in the following decisions. This is probably an indirect consequence of the fact that patients who perceive to have little control of the situation experience more regret in case of a negative outcome than those patients with high control. Having information about a patient's preferred decision-making style is important for oncologists to plan the consultation in a way that is most likely to be considered satisfactory by their patients [55]. Moreover, allowing patients to choose their preferred decision-making style will probably prevent them from regret and its related negative effects.

Looking for an Optimal Strategy for Improving Participation in Phase I Clinical Trials

The data discussed above highlight the major practical and ethical concerns and controversies related to the participation of cancer patients in early-stage clinical trials. In order to address ethical issues and to obtain a real 'informed consent' to participate, it would be necessary to understand when the high expectations regarding treatment benefits observed in patient responses reflect optimism and confidence and when they, alternatively, display an incomplete understanding of outcome probabilities. On the other hand, in order to increase the number of participants, it would be important to establish independent predictors of cancer patients' decision to enter a phase I clinical trial.

This is a very ambitious aim considering that even among patients who consent to participate there is no uniform decision calculus. Moreover, many demographic (sex, age, and educational level), clinical (cancer type, stage of disease, and proposed treatment plan), and personal (anxiety, optimism and trust in treatment options, cognitive abilities, emotional status, and personal needs

and values) factors may influence patients' preferences for and processing of information [56, 57]. Last but not least, the relationship with their physicians can make patients dissatisfied with, deny, or misunderstand the information presented to them. On the other hand, physicians interviewed about what helps in and hinders patients' decision-making [58] answered that they consider the main barriers to be (1) lack of time, (2) patient misunderstanding, and (3) patient anxiety.

We argue that a rigorously developed, calibrated, and validated computer model [59] including all patient variables could be a valid method for maximizing the information gained from patient evaluations in order to bridge the current knowledge gaps and to advance clinical cancer care and research by increasing the number of participants in phase I trials. Such a model should be different from a traditional decision aid mainly in terms of personalization. Traditional decision aids (to our knowledge there is only one devoted to decisions in clinical trials [60]) are usually based on providing information to increase knowledge and reduce decisional regret without taking into account the individual differences and needs of users. In contrast, we consider individual differences and personal characteristics of patients fundamental for providing patients with personalized information and predicting their choices regarding future treatment options [61, 62]. When discussing the possibility of being enrolled in a clinical trial, physicians will encounter many different patient profiles: some of the patients will be affected by optimism bias and will not need much information before agreeing to participate, since they will probably have already made their decision; others will be absolutely averse to taking risks and will never agree to participate. Again, it is fundamental to identify patients whose treatment decision-making is adversely influenced by misunderstandings in order to give them special attention when communicating information about the risks and benefits of the proposed treatment [63]. All this information, apart from the demographic and clinical characteristics of each individual patient suitable to participate in an early-stage clinical trial, should be collected and included in the model in order to provide clinicians with a summary report including information about their patient's knowledge, values, and emotional and cognitive decisional skills, as well as overall treatment preferences for use during the consultation. Receiving such a report before meeting their patients allows physicians to address knowledge gaps, discuss values, and reduce uncertainty about involvement in clinical trials. This serves to tailor care to individual patients' values and treatment preferences [36], improving patient-physician understanding, promoting shared decision-making, and assessing ethical concerns related to excessive optimism and/or poor understanding (fig. 1). Moreover, fostering an effective collaborative decision-making process reduces the consultation time and renders subsequent consultations more succinct [64–66].

In conclusion, now that treatment options are increasing in number, and patients are becoming more responsible for their decisions in medical contexts, the creation of a smart support tool that helps oncologists convey messages aimed at building a sense of an alliance, giving personalized support, and providing tailored medical information in an understandable language is strongly encouraged. We hope that the considerations emerging from the present nonsystematic review about participation in phase I trials provide the insight necessary to optimally devise a strategy for improving cancer patient recruitment to early-stage clinical trials.

Disclosure Statement

The authors report no conflicts of interest in this work.

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