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Phase 3 Oncology Clinical Trials in South Africa: Experimentation or Therapeutic Misconception?

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Abstract

Although clinical research in oncology is vital to improve current understanding of cancer and to validate new treatment options, voluntary informed consent is a critical component. Oncology research participants are a particularly vulnerable population; hence, therapeutic misconception often leads to ethical and legal challenges. We conducted a qualitative study administering semi-structured questionnaires on 29 adult, Phase 3, oncology clinical trial participants at three different private oncology clinical trial sites in South Africa. A descriptive content analysis was performed to identify perceptions of these participants regarding Phase 3 clinical trials. We found that most participants provided consent to be included in the trial for self-benefit. More than half of the participants had a poor understanding of Phase 3 clinical trials, and almost half the participants believed the clinical trial did not pose any significant risk to them. The word "hope" was used frequently by participants, displaying clear optimism with regard to the clinical trial and its outcome. This indicated that therapeutic misconception does occur in the South African oncology research setting and has the potential to lead to underestimation of the risks of a Phase 3 clinical trial. Emphasizing the experimental nature of a clinical trial during the consent process is critical to address therapeutic misconception in oncology research.

Keywords

oncology, research ethics, oncology clinical trials, therapeutic misconception, informed consent

Cancer is the leading cause of death in resource-rich countries and the second leading cause of death in developing countries. According to the World Health Organization's most recent Globocan Project, there were nearly 12.7 million new cancer cases and 7.6 million cancer deaths worldwide in 2008. This number is expected to increase to 21 million by 2030 (Ferlay et al., 2010; World Health Organization, 2008). Clinical research in oncology is therefore vital to improve our current understanding of cancer and to validate new treatment options. According to a recent report prepared by Battelle Technology Partnership Practice (2015) for the Pharmaceutical Research and Manufacturers of America (PhRMA), Phase 3 oncology clinical trials are currently amongst the most common and largest pharmaceutically-sponsored clinical trials; often using 1000 to 5000 patients per trial. This represents a global trend.

Good Clinical Practice (GCP) in clinical research requires that voluntary informed consent and documentation of the process forms one of the cornerstones of ethical research. This is especially important in vulnerable populations such as oncology research participants (Del Carmen & Joffe, 2005; Verastequi, 2006). These participants meet the criteria for vulnerability outlined in key research ethics guidelines, including the Belmont Report (the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, 1979), the Declaration of Helsinki (World Medical Association, 1997), the Council for International Organisations of Medical Sciences (CIOMS; 1993), the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines on Good Clinical Practice (ICH GCP; 2003), and the South African Good Clinical Practice Guidelines (SA GCP; 2006). As a result of this vulnerability, there are a number of factors specifically related to oncology research, which could affect the quality of informed consent, including therapeutic misconception.

Three main concepts from these guidelines apply to vulnerability in all cancer research participants: first, limited decisional capacity due to multiple factors unique to cancer

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patients; second, psychological dependence, as cancer research participants are often dependent on their attending oncologist's opinion (Penman et al., 1984) as well as financial dependence on a clinical trial for further oncological treatment; and third, susceptibility to research harms, by virtue of their exposure to experimental, unregistered treatment with the potential for severe side effects.

A common factor limiting decisional capacity in oncology research participants is impaired cognitive function, which can often be quite subtle (Appelbaum, 2007; Vardy, Wefel, Ahles, Tannock, & Schagen, 2008). Sixty percent of new patients seen in oncology are elderly persons, above 65 years (Berger, Savvides, Koroukian, Kahan, Deimling, Rose, Bowman, & Miller, 2006), a population with a high prevalence of impaired cognitive function (Chouliara, Kearney, Worth, & Stott, 2004). Opioids are frequently used for pain relief in oncology and can cause cognitive impairment in the first few weeks of treatment (Ersek, Cherrier, Overman, & Irving, 2004; Kurita, Lundorff, de Mattos Pimenta, & Sjøgren, 2009). Fatigue, malignant brain lesions, other comorbidities, treatment side effects, concomitant medication, and depression are additional common factors with the potential to affect cognitive functioning in cancer patients (Casarett, Karlawish, & Hirschman, 2003; Marson, Martin, Triebel, & Nabors, 2010).

Furthermore, poor communication between investigator and participant, and poor understanding of the clinical trial by the participant can limit decisional capacity (Albrecht et al., 2008; Gattelari, Voigt, Butow, & Tattersall, 2002). The study population participating in early- and late-phase oncology research usually includes patients with a good performance status, that is, patients who are able to perform all self-care and are up and about for more than half of their waking hours. This unfortunately does not always guarantee a good understanding of the informed consent process (Bergenmar, Molin, Wilking, & Brandberg, 2011; Wray, Stryker, Winer, Demetri, & Emmons, 2007). In addition, readability of informed consent forms will also determine how well a participant understands the clinical trial (Grossman, Piantadosi, & Covahey, 1994). It is well established that when facing a life-threatening illness, patients are desperate for any glimmer of hope. The culture of faith, hope, and optimism plays an important role in patients' decisions and reasons for participating in clinical trials (L. Jansen, 2011; Sulmasy et al., 2010).

An important factor affecting decisional capacity in oncology research is the phenomenon of therapeutic misconception. The false belief, unrealistic expectation, or poor understanding that the purpose of a clinical trial is mainly to benefit and to address the needs of the participant as an individual may involve the underestimation of possible risks involved, despite an adequate informed consent process (Appelbaum & Lidz, 2008; Emmanuel et al., 2008; Joffe, Cook, Cleary, Clark, & Weeks, 2001a).

Oncology patients are often offered participation in a clinical trial as the "last hope," because there are no further registered treatment options available. Most patients rely completely on the attending oncologist's expert opinion regarding which interventional option will be best for them in a specific situation. Patients often do not want to disappoint their oncologists by declining the option of participating in a clinical trial and also fear worsening of the disease, should they not enroll (Penman et al., 1984).

Limited financial resources could be another possible reason for dependency in oncology research participants. The Board for Healthcare Funders (BHF) of Southern Africa reported in 2011 that medical schemes in South Africa did not cover all cancer treatment under Prescribed Minimum Benefits (PMB), particularly the more expensive new biological therapies (Board of Healthcare Funders of Southern Africa, 2011). According to the South African Council of Medical Schemes, PMB is a set of defined benefits to ensure that all medical scheme members have access to certain minimum health services regardless of the option they have selected.

The third concept of risk relevant to vulnerability of cancer research participants facing a life-threatening illness is an important issue to address in oncology research. There is more information available on study drug safety and efficacy profiles in Phase 3 trials compared with early-phase oncology clinical trials. This could, however, lead to a bigger risk of therapeutic misconception by creating the false impression that safety and efficacy have been well established. Phase 3 drugs still pose serious risks to participants, which could be an ethical and legal challenge, especially if participants have misconceptions about the clinical trial.

Although the ethics of Phase 1 oncology clinical trials have been studied extensively (Agrawal & Emmanuel, 2003; Cheng et al., 2000; Miller & Joffe, 2008), therapeutic misconception in later-phase trials has received less attention. Because the risk of therapeutic misconception may indeed be higher in Phase 3 oncology trials, and as later-phase clinical trials are performed on a much larger scale than Phase 1 trials, there are potentially a greater number of participants at risk. Many previous studies on therapeutic misconception in oncology clinical trials have been conducted in other countries, as mentioned and in other non-oncology fields of medicine in South Africa (Moodley, Pather, & Myer, 2005), but these are not necessarily generalizable to the South African oncology research setting.

In the investigator's experience, research participants and carers often become greatly disillusioned, angry, and distressed when their cancer progresses while on trial treatment and the trial has to be discontinued, despite discussions around the likelihood of this possibility before commencing the trial. The investigator therefore has a personal concern about therapeutic misconception in desperate and vulnerable oncology patients. To date, there has been

no published literature on therapeutic misconception in oncology clinical trials in South Africa. This study therefore provides the first empirical evidence of this important aspect of oncology research in South Africa.

Method

Research Design

A qualitative research design was chosen to explore individual perceptions and understanding of oncology clinical trial participants in a sub-study after the informed consent process of pharmaceutical-sponsored clinical trials.

Sample Selection and Recruitment

Purposive sampling was used to recruit current Phase 3 clinical trial participants from a large multi-centered private oncology group practice at three different research sites over South Africa over a 4-month period from August 2012 to November 2012. All the clinical trials conducted in these three units were international industry-sponsored clinical trials. This group practice collectively represents 25% to 60% of the South African private oncology research sites and 20% to 35% of South Africa's total oncology research units depending on the specific clinical trial. The three research sites of this group practice are all part of the main practice but are situated in separate geographical areas.

Research unit staff members were personally trained on the study by the principal investigator at the three different sites. Possible eligible participants were identified by each research unit's staff members and names given to an independent study administrator. These patients were then approached and informed about the research ethics substudy by the independent study administrator at their next routine clinic visit. Those willing to participate provided written informed consent.

Eligible participants were all patients with active cancer of different types who had an Eastern Cooperative Oncology Group (ECOG) performance status of zero to two, meaning that they were able to perform all self-care and were up and about for more than half of their waking hours. Participants were required to have normal cognitive function, as per the discretion of the clinical trial investigator involved, and were able to read and write independently. All participants signed a voluntary informed consent form for this sub-study separate from the main Phase 3 trial consent form, prior to completing this questionnaire.

The participants had different types of metastatic solid tumors and were already enrolled in different industry-sponsored multi-center Phase 3 clinical trials. Almost all trials were randomized and double blind (see Table 1 below containing the different types of studies).

Research Instrument

A semi-structured, self-developed questionnaire was administered to 29 eligible adult, Phase 3 oncology clinical trial participants to complete 1 week to 3 months after they had signed consent to participate in an independent, separate Phase 3 oncology trial. Participants were asked to complete the questionnaires by themselves in their own handwriting while in the waiting room. A selection of open- and close-ended questions was chosen to explore the perceptions of current Phase 3 trial participants. The questionnaires were available in both Afrikaans and English as these are the languages spoken by patients at these three sites.

The following five open-ended questions were asked:

1. In your own words, briefly mention the reason(s) why you decided to participate in the clinical trial.
2. What are your personal expectations from participating in this clinical trial?
3. In your own words, what does a "phase 3 clinical trial" mean?
4. What are the benefits of the clinical trial for you?
5. What are the potential risks you are facing by participating in this clinical trial?

For the full questionnaire, please see the online appendix (http://jre.sagepub.com/supplemental).

Data Management and Analysis

A separate Participant Information Management Form was kept with the unique participant identifier, name, surname, and contact details of each participant for confidentiality and feedback purposes. The questionnaires were transcribed into an encrypted Microsoft Office Excel (MS Excel) spreadsheet designed for the study by the principal investigator.

A qualitative descriptive content analysis was used to identify particular perceptions among current oncology trial participants, which could contribute to therapeutic misconception. The data were coded manually by the principal investigator, and themes were identified. The data were independently reviewed by the co-investigator who interpreted the data in the same way. MS Excel was used to capture demographic data, and summary statistics were used to describe the participants' demographic variables.

Research Approval

This study was approved by the University of Stellenbosch Health Research Ethics Committee, and permission to conduct the study was obtained from the group practice manager as well as each study's principal investigator prior to recruitment of participants.

Table 1. Different Phase 3 Clinical Trials Participants Were Enrolled In.

Study design	Study treatment	Study population
1. Randomized, double-blind, placebo-controlled	Study drug as adjuvant treatment	Women with early-stage breast cancer at high risk of recurrence
2. Randomized, double-blind	Study drug versus standard treatment versus placebo	Advanced non-small cell lung cancer following progression after one prior chemotherapy regime
3. Randomized, double-blind	Standard treatment plus a study drug or placebo	Recurrent partially platinum sensitive or resistant epithelial ovarian, peritoneal, or fallopian tube cancers
4. Randomized, open-label study	Two doses of a study drug in combination with standard treatment	Metastatic resistant prostate cancer previously treated with standard first-line treatment
5. Randomized, double-blind	Study drug and standard treatment with study drug and placebo	Newly diagnosed extensive-stage disease small cell lung cancer
6. Randomized, double-blind	Study drug plus best supportive care versus placebo plus best supportive care	Patients with advanced neuro-endocrine tumor
7. Randomized, double-blind, placebo-controlled	Study drug versus placebo	Patients with carcinoid syndrome
8. Randomized, double-blind	Study drug with standard treatment with placebo and standard treatment	Metastatic castration-resistant prostate cancer that has progressed during or after standard first-line treatment
9. Randomized, double-blind	Study drug with standard treatment with placebo	Metastatic castration-resistant prostate cancer prior to standard first-line treatment
10. Randomized controlled	Study drug versus standard treatment	Patients with acute venous thromboembolism and advanced cancer

Ethical Considerations

Participants were encouraged to contact the unit should they feel distressed or have new questions or concerns regarding the main oncology study after completing the questionnaire. After data analysis, the participating research units were contacted to inform them of participants who presented with a degree of therapeutic misconception. Debriefing and counseling of these participants was offered. A separate review of consent form information relating to the main trials was also conducted.

Results

Participant Demographics

As indicated in Table 2, participants in this study were on average 65 years old (ranging from 32 to 84 years). The sample comprised predominantly Christian (72%), male (62%) participants with a high level of education. Most of the participants (79%) had either a Grade 12 or a tertiary education.

Participant perceptions of Phase 3 oncology clinical trials

Reasons for participating in the clinical trial. Many participants gave more than one reason for participating in the trial. The most common reasons were self-benefit (16/29) and altruism (13/29). Self-benefit was reflected as follows:

- "I think after my initial chemo sessions it should benefit me to participate in the clinical trial."
- "I want to be cured."

And altruism was reflected as follows:

- "It will be of benefit to many other fellow cancer patients and I'd like to help. It is an honour to have been asked to participate."

Other less common reasons given by nine of the participants were as follows:

- The only option available:
  - "As the chemo was unsuccessful, I had no other option but to sign for a trial."
- Financial reasons:
  - "Finances, as cancer treatment is expensive and medical aids cannot always cover the cost. Trial is free."
- On recommendation of their attending clinician:
  - "My Oncologist recommended it."
- To please the attending doctor:
  - "To help the doctor."

Table 2. Summary of Participant Demographics.

Age (years)	*M*	Range
	65	(32-84)
Age category	Number	%
30-39	2	7
40-49	2	7
50-59	2	7
60-69	11	38
70-79	10	34
80-89	2	7
Total	29	100
Gender	Number	%
Male	18	62
Female	11	38
Total	29	100
Education level	Number	%
Grade 7	0	0
Grade 10	3	10
Grade 11	2	7
Grade 12	7	24
Post school training	16	55
Missing data	1	3
Total	29	100
Religion	Number	%
Agnostic	1	3
Atheist	2	7
Christian	21	72
Muslim	2	7
Other	3	10
Total	29	100

- To avoid chemotherapy and radiotherapy:
    - "Chemotherapy and radiation seems to be very ineffective and the side-effects are far worse than the trial side-effects, I believe."

Expectations of the clinical trial. Most participants expected self-benefit from the trial:

- "I expect that the medicine should work for my disease."
- "To stop the cancer."
- "A reduction and elimination of the tumour."
- "Excellent check-ups which I would not be having."

Meaning of a Phase 3 clinical trial. Most participants (18/29) had a poor understanding of a Phase 3 study, five participants had a reasonable understanding, and five had a good understanding. One participant did not give an answer.

Understanding was assessed by the investigator's personal impression of the answer given to the question of explaining a Phase 3 clinical trial in the participant's own words.

Examples of participants' own words that seemed to reflect a good understanding of a Phase 3 clinical trial are as follows:

- "It is the last stage of research for a drug before it can be approved."
- "Tests done to see how well the medication works and how safe it is."

Participants who had a reasonable understanding mentioned the following:

- "It is the drug just before it goes on the market."
- "I'm not exactly certain, but I know it means that it is not an initial study of the drug's effectiveness. It is a study to fine tune the optimal dose of the drug."
- "Testing of the drug on humans in a controlled environment."

Examples of participants' responses that seemed to have a poor understanding are as follows:

- "I have no idea."
- "The fact that I'm now in phase 3 means that I am progressing well. The treatment is working."
- "In phase 3 there are more tests to check if the cancer has stopped or not."

Benefits from the clinical trial. In general, participants mentioned more than one expected benefit. Most participants (24/29) believed that the benefit from the clinical trial was mostly for them personally. The most commonly perceived personal benefit was to receive more effective treatment from the clinical trial than what is currently available, despite having been informed that the treatment is still experimental:

- "As the treatment is more targeted to my cancer type, there should be a better response."
- "Hope for a more effective treatment."

Another less common personal benefit was that participants will have access to high-quality medical care, which is probably the case in most oncology clinical trials in South Africa.

As participants mentioned,

- "I will be very closely monitored throughout."
- "The numerous medical check-ups which I would not normally have."

Other personal benefits mentioned were as follows:

- An improvement of the disease:
  - "Slowdown of melanoma."
  - "Healing."
  - "Better quality of life."
- Prolonging life:
  - "To give me a prolonged life expectancy," which is usually the primary objective of the clinical trial treatment, although not guaranteed.
- To be the first to receive a new effective treatment:
  - "If this treatment works I will be one of the first people to benefit from it."

A few participants felt it was already effective by the time the questionnaire was completed and that therefore they were already experiencing personal benefits:

- "Currently the treatment is working. I see progress. The swelling has subsided and I am pain free."

Eight participants believed that being part of the clinical trial has financial benefits:

- "That I may get free treatment."
- "The sponsor will be paying for all the expensive scans and exams and bloods needed to monitor response to the treatment."

Only three participants mentioned altruistic benefits. One patient wrote,

- "Future generations suffering from the same illness will bear the fruit."

Potential risks of the clinical trial. More than half of the participants (15/29) believed the clinical trial did not pose any or very little risk to them. Some patients (3/29) mentioned they were not informed or not sure of any risks, despite a few pages dedicated to possible risks in all the informed consent forms and an in-depth protocol discussion prior to signing consent. These are responses of some participants to the question of what the potential risks of the clinical trial are:

- "Aware of none."
- "The risks were not explained to me."
- "Very little risks as it is at phase 3."

The rest of the participants (10/29) mentioned the following as being risks to them:

- "Side-effects."
- "To make me feel bad."
- "Dangerous side-effects."
- "The side-effects may be debilitating to the point where I can't work, even from home."
- "Poor response to treatment."
- "That treatment may fail."
- "Ending up with the placebo instead of the real thing."

Although not the aim and focus of this study, the informed consent forms of these Phase 3 clinical trials have been found to contain extensive listing and explanations of the possible risks of participation. However, the concept of a Phase 3 clinical trial was generally not explained in detail.

Therapeutic Misconception

Clear evidence of therapeutic misconception was found in the participants' responses. Many decided to participate in the trial for personal benefit, almost all participants expected to benefit personally from the clinical trial, and most participants believed the benefit from a clinical trial is personal. Furthermore, half of the participants believed there is no or little risk involved and about five participants clearly expressed therapeutic misconception in their answers, for example, "I want to be cured," "a reduction and elimination of the tumour in my epigastric area," and "the trial drug will contain the spread of the cancer."

Hope and Optimism

The word "hope" was often used by participants (8/29) in their answers, displaying obvious optimism with regard to the clinical trial and its outcome. Examples of this expressed optimism are as follows: "*hoping* to be one of the patients the treatment can help," "I *hope* to be cured," "I *hope* for the lesions currently in the liver, lungs and bone to shrink or disappear," "to assist in the search for an alternative for my cancer in the *hope* of a permanent cure," "*hope* for a more effective treatment," "*I hope* for an improvement," and "*I hope* to get well so that I can enjoy life."

Discussion

Therapeutic misconception clearly exists in this specific sample of research participants. The main features of therapeutic misconception displayed were the misunderstanding that the clinical trial's purpose is mainly for personal benefit, the underestimation of risks when participating in a Phase 3 oncology clinical trial, and obvious optimism about the outcome of the clinical trial. Interestingly, the elderly (>65 years) participant group displayed more therapeutic

misconception and more altruism in comparison with the group below 65 years.

Although there is no approved method to measure comprehension and understanding of informed consent accurately, the majority of participants in this study expected to benefit personally and believed the main benefit of the clinical trial was personal despite an in-depth discussion of the clinical trial prior to signing of consent. These findings are similar to previous larger studies conducted. In a study by Joffe et al. (2001a) on 207 Phase 1, 2, and 3 oncology research participants, only 46% recognized that the main purpose of a clinical trial is to benefit future patients and not themselves. In another study by Penman et al. (1984) of 144 oncology patients, 78% expected large benefit from the clinical trial. In a very similar, small study of eight participants by Barret (2005) who also used the questionnaire developed by Joffe et al. (Joffe, Cook, Cleary, Clark, & Weeks, 2001b), 50% of the participants did not understand that clinical trial treatment was not standard treatment and that it might involve additional risks.

Most new oncology clinical trials are conducted on biological targeted therapy and not cytotoxic chemotherapy, and, contrary to popular belief, severe side effects are still encountered, even in the later phase trials.

More than half of participants in this study believed the main clinical trial did not pose any or very few risks. This concurs with findings of a cross-sectional survey by Joffe, Cook, Cleary, Clark, and Weeks (2001a) conducted on 207 participants; 63% did not understand the increased risk involved with participation and 70% that treatment was not proven. In another study of 155 participants with a range of different illnesses by Lidz, Appelbaum, Grisso, and Renaud (2004), 24% of the participants reported no risks, and more than 85% of the participants did not mention any risk relating to the specific methodologies of clinical trials such as randomization and placebos. Only one participant mentioned falling into the placebo group as a risk in the discussed study. Less than half of the participants mentioned risks that were associated with treatment side effects.

Oncology research participants tend to ignore serious risks, focusing all hope on possible benefits,as seen in this and other studies. This phenomenon is sometimes called "*risk intolerance*" which ties in with the well known concept of therapeutic misconception. The terms *planning fallacy* (Smith & Longo, 2012) and *therapeutic misestimation* (Sulmasy et al., 2010) have also been used in the literature to explain the tendency to incorrectly overestimate benefits and underestimate risks.

Hope, optimism, and faith in God and science have been shown to play a role in Phase 1 oncology clinical trial participants as "justification of high expected personal medical benefit" in a study done by Sulmasy et al. (2010). In this study, the word "hope" was used quite frequently and, interestingly, the demographic data analysis shows that 90% of the participants belonged to a specific religion. As shown in Sulmasy's study, expressing high expected therapeutic benefit does not necessarily mean participants do not understand that the probability thereof is low, *therapeutic optimism*, nor that it will impair quality of informed consent. In the study by Agrawal and Emmanuel (2003) on Phase 1 oncology research participants, 70% of the participants understood that they would not benefit directly from the study but still hoped to benefit personally.

Is this phenomenon of therapeutic misconception then not just being hopeful when facing a life-threatening disease? There is a fine distinction between therapeutic optimism and mis-estimation. According to Smith and Longo (2012), "self-deception is a valuable personal coping tool" and "people have an optimistic bias which helps us cope with the inevitability of death."

Furthermore, Miller and Joffe (2008) found that direct personal medical benefit is actually received by participants of Phase 1 oncology clinical trials, and that accurately informed participants have reason to expect direct personal benefit from these trials, which does not compromise the validity and quality of informed consent. Agrawal and Emanuel also found the risk–benefit ratio of Phase 1 oncology clinical trials to be favorable. Although not researched in the Phase 3 oncology clinical trials, the situation might be similar or more favorable in terms of direct medical benefits and favorable risk–benefit ratios offered by Phase 3 oncology clinical trials.

This study focused mainly on the informed consent process as one way of minimizing therapeutic misconception. There are, however, a few other important factors that could have contributed to therapeutic misconception, and these will be mentioned briefly. One such factor is the ethical dilemma that exists within a physician-investigator. Responsibilities as investigator may be in direct tension with the role of clinician as discussed by Miller and Brody (2003) 10 years ago in the Hastings Centre Report (Miller & Brody, 2003). To protect these vulnerable participants from exploitation prospective, research participants should therefore be informed explicitly on how research differs from clinical management outside a clinical trial. Language used when discussing the clinical trial protocol with participants, for example, "therapeutic research," "therapeutic intent," and "patient" instead of "participant" may also contribute to therapeutic misconception.

In a non-academic private practice environment, as was the case in this study, the distinction between clinical research and clinical care could be quite blurred. Although separate from the main clinic areas, the context of these three research units could have also contributed to how participants understood the informed consent process and the goal of research treatment as discussed by Fisher (2006). The research units share the same warm décor and friendly receptionists, which could result in the assumption that

research and clinical care are the same. *Procedural misconception* as defined by Fisher (2006) page 3 is "the tendency for individuals to make false assumptions about research by responding to what is similar to other non-research contexts and overlooking what is different. Individuals respond to certain cues in their social contexts that indicatehow they should behave or how they should interacrt with others in those contexts" and could be one of the main causes of therapeutic misconception, especially in a non-academic set-up.

According to a discussion in June 2013 by Cook and Hoas (2014), the belief exists that by participating in clinical trials, participants have access to the best medical care, but it is not clear how this can be ensured with "the uncertainty that accompanies research and the need to follow a strict research protocol." Cook and Hoas (2014) also mention that this belief often forms part of the protocol discussion between researcher and potential participant prior to enrolment and could contribute to therapeutic misconception to a large extent. Although the informed consent form can be regulated by the Research Ethics Committee, the conversation between researcher and potential participant is not.

Furthermore, lack of alternative treatment options as discussed by McKay and Timmermans (2009) and lack of financial resources and medical aid funding, as mentioned earlier, are causing oncology patients to be more dependent on clinical trials, as shown in this study, which renders them more vulnerable to therapeutic misconception.

Limitations of the Study

The findings in this population might not be directly transferable to the broader public health sector in South Africa, as socio-economic factors differ from patients seen in the private health sector. These factors have been shown to possibly influence the quality and validity of the informed consent process negatively in a prospective analysis conducted in Mexico (Verastequi, 2006) on 35 participants of whom the majority were poor with low levels of education. Most of the participants in this study had post high school education (55%), and although not assessed in this study, most patients attending private practice health care have medical aids or funding to pay private rates. One can probably assume that the degree of therapeutic misconception may be worse in the South African public sector, but further research will be necessary to confirm this.

Although sample sizes are generally smaller in qualitative studies, 29 participants is a small population from which to draw conclusions. Oncology management is becoming more individualized, and the majority of current industry-sponsored oncology clinical trials on new biological targeted therapies are conducted on small, specific genetic populations. Current oncology trials therefore do not recruit on a large scale as in the past.

Recall bias is a possibility in this study; participants were therefore allowed to complete the questionnaire only in the period of a week to 3 months after signing consent to the main Phase 3 oncology trial. Although limited, previous studies on surgical patients showed that participants' recall of important information given to them in the informed consent discussion starts deteriorating at 2 weeks after the discussion (Pesudovs, Luscombe, & Coster, 2006). Recall seems to have been at its best immediately after the discussion. According to old but existing data (Lavelle-Jones, Byrne, Rice, & Cuschieri, 1993), 60% of the participants were poorly informed and 40% well informed when assessed 4 to 6 weeks after informed consent was discussed. At 6 months, 84% were poorly informed, and only 16% well informed. There is no exact duration for normal recall memory. It is complex and may be influenced by many different factors such as age, cognitive function, stress, and emotional status (Arnsten, 1998; J. Jansen et al., 2008; Lavelle-Jones et al., 1993).

Due to time and resource constraints, the investigator chose to use a simple, self-developed questionnaire to assess perceptions of this population although a standardized, validated tool was already developed and published by Joffe et al. (2001b). Self-completion of the questionnaires may have contributed to considerable overlap of the answers, which could have been minimized by involving an interviewer to clarify questions.

The following strategies were implemented to minimize bias: Only the independent study administrator explained the study and collected signed informed consent forms and completed questionnaires from participants; each participant had a number, which was listed by the independent study administrator on a separate participant information sheet, and the co-investigator independently reviewed and interpreted the data.

Conclusion

Therapeutic misconception does exist in this sample of research participants in the Phase 3 oncology clinical research setting. The main features seem to be the expectation of personal benefit from the trial, underestimating the risks of participating in a Phase 3 clinical trial, and obvious optimism about the outcome of the clinical trial in this vulnerable population.

Best Practices

More attention to the informed consent process, among other possible contributing factors, can be helpful in addressing therapeutic misconception. Explaining the difference between treatment and research prior to enrolment is particularly critical. A recommendation to minimize therapeutic misconception is to assess participants' appreciation of risks and benefits within the first few weeks after signing consent by performing a quick assessment of the participant's understanding

and re-explanation if indicated. The questionnaire (online appendix) used for this study can be used as a quick, screening tool for therapeutic misconception.

Research Agenda

More research is, however, necessary in developing a short, quick, and efficient screening tool for therapeutic misconception in busy oncology research units.

Although the findings of this study were found to be comparable with findings of other similar studies, more research will be needed to verify and quantify findings of this study in the broader South Africa public health setting. It would also be interesting to research the influence of medical aid status and participant recruitment in private research units.

Educational Implications

This study again shows the importance of training research staff, as well as Health Research Ethics Committee members in Good Clinical Practice, particularly in the correct informed consent process as well as in the important ethical principles involved in clinical research, particularly in vulnerable population groups.

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Declaration of Conflicting Interests

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Supplementary Material

The online data supplements are available at http://JRE.sagepub.com/supplemental

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