An exploration of the experiences, motivations and expectations of patients with advanced cancer, without any standard options, during phase-I trials.

Patients' **E**xperiences, **M**otivations and **E**xpectations during **Phase-I** trials

Acronym: PemePh-I

A generic qualitative study

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Samenvatting

Titel: Patiënten ervaringen, motivaties en verwachtingen tijdens oncologische fase-I studies

Achtergrond Patiënten die deelnemen aan oncologische fase-I studies kunnen misconceptie en therapeutisch optimisme ervaren en zijn gemotiveerd door anderen, zoals familie en behandelaar. Ondanks ervaren bijwerkingen continueren patiënten de deelname. Vooralsnog is er weinig bekend over de ervaringen, motivaties en verwachtingen van deze patiënten wanneer zij mee blijven doen aan deze studies.

Doel Het onderzoeken van de ervaringen, motivaties en verwachtingen van patiënten met vergevorderde kanker, zonder behandelopties, die mee doen aan een fase-I studie.

Methode Generiek kwalitatief onderzoek waarin tien semigestructureerde interviews thematisch zijn geanalyseerd volgens de methodiek van Braun en Clarke.

Resultaten Participanten zijn blij dat zij hun dagelijkse bezigheden weer kunnen doen, terwijl zij ook bijwerkingen en belasting van de studie ervaren. Belasting zoals de confrontatie met het feit dat reguliere behandeling niet meer mogelijk is en het ervaren van mentale- en psychische vermoeidheid. Alle participanten krijgen motivatie door de uitkomst te proberen te controleren, goed doen voor de ander en leven in harmonie. De participanten die net mee doen aan een studie durven, in tegenstelling tot de participanten die al langer mee doen, niet ver in de toekomst te kijken.

Conclusie Deelname aan een fase-I studie is een grote onzekerheid. Deelname geeft het gevoel dat er alles aan gedaan wordt gepast te behandelen. Dit geeft niet alleen motivatie tot deelname, maar zorgt ook voor altruïsme. Familie, vrienden, hoop, realisme, optimisme en het helpen bij de productie het medicijn zorgen ook voor motivatie. Ondanks verschillende lasten, bijwerkingen en zich een test persoon te voelen, zullen de participanten niet stoppen met deelname, ter voorkoming dat zij zullen zeggen: ‘Had ik maar’.

Aanbevelingen Het is aanbevolen om de levenseinde zorg, de lasten en de motivaties te bespreken tijdens de fase-I studie.

Sleutelwoorden: fase-I studie, vergevorderde kanker, verwachtingen, ervaringen, motivaties

Abstract

Title: Patients' experiences, motivations and expectations during oncological phase-I trials

Background Patients who enroll in a phase-I clinical trial, may have therapeutic misconception, therapeutic optimism and are often motivated by other people, like their family and doctor. Despite side effects these patients continue to participate. Little is known about the experiences, motivations and expectations when they continue participation in these trials.
Aim To explore the experiences, motivations and expectations of patients with advanced cancer, without treatment options, during phase-I trial participation.
Methods A generic qualitative study in which ten semi-structured interviews were thematically analyzed according to Braun and Clarke methodology.
Results While most participants were pleased they could perform their daily activities again, they also experienced side-effects and burden. Burden such as being confronted with the fact that they have no regular treatment options and experiencing mental and physical fatigue. All participants got their motivation from controlling the outcome, to do good for one another and living in harmony. Participants who just enrolled only tended to look into the future in the short term, while participants who had several tumor evaluations dared to look further into the future.
Conclusion Participating in phase-I trial is a great uncertainty. Participating creates the feeling that they tried everything and they are treated to the limit. This not only gives the motivation to continue participating but also a sense of altruism. Family and friends, hope, realism, optimism and helping to develop a new drug also provide motivation. Despite different burdens, side-effects and the feeling of being a test-subject, the participants will not easily choose to stop participation, in order to prevent to say afterwards: "If only I had".
Recommendation It is recommended to discuss end-of-life care, burdens and motivations during phase-I trial.

MESH terms: 'Phase-I clinical trial', 'Advanced cancer', 'expectations', 'experiences', 'motivations'

Introduction

Research shows that as of January 1st, 2019, approximately 578.000 people in the Netherlands had cancer (1). This group can be divided into patients who are treated with a curative intent, and patients who no longer have treatment options and can only receive palliative care (2-3). This last group may be eligible to participate in a phase-I clinical trial (phase-I trial) where a new systematic therapy or new combinations of drugs is given to people for the first time (4-6) Only a small portion, two to seven percent, of patients with cancer in the palliative stage participate in clinical trials (7).

Partly due to this low percentage, a large amount of research has been conducted into motivation of patients to enroll in phase-I trials (7-8). Three main concepts emerge from this research: therapeutic optimism, therapeutic misconception and 'to do good for another'. These three concepts are also reflected in the self-determination theory (4). This theory consists of three personal needs that influences the motivation behind choices: competence, relatedness and autonomy (9).

Competence is interpreted as the way to influence personal outcomes and can be linked with therapeutic optimism and therapeutic misconception. Therapeutic optimism is seen in more than 80% of patients, they are hopeful, optimistic and motivated by the potential of a clinical benefit (7,10-13). Although trials follow strict scientific standards, such as informed consent, research shows that 68% of phase-I patients had therapeutic misconception (11). They did not understand the nature and purpose of the study, where they could not distinguish between the aim of the trial and the actual treatment (8,10,12,14-15). Relatedness can be understood as the interactions, relations, and experiences with others, which may affect decision making. The concept 'to do good for another' can be linked to relatedness: patients genuinely want to help researchers obtain scientific knowledge that might benefit future patients with the same disease (10-11). Autonomy is the third need and is defined as the desire to be in charge of one's own decision, to live and act in harmony with one's integrated self. This personal need can be linked with all three concepts (9).

After the enrollment into a phase-I trial, side effects are closely monitored, usually on a weekly basis (Figure 1). Six to eight weeks after enrollment, a tumor evaluation takes place which results in two scenarios; one scenario is that the patient may continue trial participation, another scenario is that the patient has to withdraw due to adverse health effects.

Insert Figure 1 here

While a considerable amount is known about the motivations of patients in the enrollment phase as this has been widely studied, little is known about the motivations of patients if they continue to participate beyond this phase. It is known that during phase-I trial participation their performance status worsens and symptoms increase (8,16). Van der Biessen et al. (2018) detected a significant decrease in Health-Related Quality of Life outcomes and a decrease in hope during trial participation in all patients. Nevertheless, this decrease did not cause patients to withdraw consent (17). Patients participating in phase-I trials undergo many changes in physical and mental functioning (8,16-18). Up to now little qualitative research is done exploring patients' experiences, motivations and expectations during phase-I trials.

Aim

Therefore, the aim of this study is to explore the experiences, motivations and expectations of patients with advanced cancer, without treatment options or options with low expected benefit, during phase-I clinical trial participation. It is hoped that with this research, patients' perspectives can be understood, and the best evidence-based support and care can be offered during future oncologic phase-I clinical trials.

Methods

Study design

This study has a generic qualitative design using semi-structured interviews as this is the most appropriate method to explore experiences, motivations and expectations (19). COREQ guidelines were followed (20).

Population & domain

The target population consisted of patients who participated in an oncology phase-I trial at an academic hospital in the Netherlands. Participants were eligible for inclusion if they were: 1) older than 18 years, 2) participating in oncology phase-I trials at the Centre of Drug Development of the Erasmus MC 3) able to speak and understand the Dutch language in conversation and in writing. No exclusion criteria were used. A purposive sampling strategy was used to ensure a maximum variation based on cancer diagnosis and moment of participation. Patient participation occurs in four stages: 1) Evaluation of first cycle took place but no tumor evaluation; 2) First tumor evaluation has taken place; 3) Several tumor evaluations have taken place and 4) The participant has to withdraw. Interviews were conducted between February 2020 and March 2020.

Procedures

The nurse practitioners from the phase-I clinical staff identified eligible patients and invited them by phone to participate. If interested, they received verbal information and an information letter was sent by email. In the following outpatient visit, or hospital admission the nurse practitioner asked if the patient agreed to participate. After agreement, an interview was conducted by the executive researcher in an enclosed room. All participants were asked for a member check (21-23). All participants received a narrative summary of the interview and answered that no additional comments were necessary. Baseline characteristics were obtained from the electronic patient files.

Data collection

An interview guide was composed to give direction to the semi-structured interviews. The topics were experiences, motivations and expectations. Questions were based on relevant literature about the enrollment phase (9-17,24-26). The interview guide was pilot tested during the first interview and evaluated with two senior nurse investigators (DB and WO) (21,27). After the first interview evaluation, the question about other treatment options such as palliative care and alternative medicine was introduced more extensively and additional questions about future expectations and quality of life were specified. Notes about remarkable statements or actions and non-verbal communication were written down during and after the interview (25). Data saturation took place when no new codes and themes emerged in the two final interviews during analysis.

Data analysis

All data was audio recorded, transcribed verbatim and analyzed by the executive researcher. Data was analyzed in Nvivo 12 using the thematic analysis approach of Braun and Clarke (28). Analysis took place within two weeks to prevent information loss (25). The total process of analyzing was an iterative process where constant comparison took place (22,28). To enhance the trustworthiness and accuracy of the data all steps were reviewed by DB and to ensure completeness of the analysis, cases that do not fit the pattern were not ignored (22,28).

Analysis started after the first four interviews were conducted. First, the transcripts were read several times to become familiar with the data, after which the first codes were generated. These codes were discussed with DB and adjusted by consensus. Hereafter, initial themes were generated. The codes that matched together made a theme. The analysis was repeated after four more interviews were conducted. This resulted in some codes being moved to other themes, merged or adjusted. Themes were slightly adjusted to those changes. DB reviewed those changes and consensus was reached. The analysis was repeated after the last two

interviews. The penultimate interview provided a number of new codes and the themes were not adjusted following this. The last interview resulted in no adjustments in codes and themes. Lastly, all steps were reviewed by a novice researcher (AP) and no adjustments were made. The themes were linked to the research question, after which the report was drawn up.

Ethical Considerations

The Medical Research Ethics Committee of the Erasmus MC approved the study protocol (MEC-2020-0006) and concluded that the study did not meet the requirements of the Medical Research Involving Human Subjects Act. All participants were ensured complete confidentiality and anonymity. This study was conducted according to the ethical principles of the Declaration of Helsinki, the quality standard of the Good Clinical Practice Guidelines and the Dutch Data Protection Act (30-32). Participation in this study did not affect patient participation in their ongoing phase-I trial. All participants provided written informed consent before participation.

Results

Participants & demographic data

Ten of the eleven invited participants were willing to participate (6 men and 4 women) with a median age of 63 [range = 43-76 years]. One patient did not consent due to expected psychological impact. Additional demographic characteristics and information about diagnoses are shown in Table 1.

[Insert Table 1 here]

Findings

Seven themes and multiple subthemes were found as a result of the analysis. These are all classified under the three interview guide topics, e.g. ‘experiences’, ‘motivations’ and ‘expectations’. Experiences are divided into positive and negative study experiences, motivations are divided into control of the outcome, to do good for another and harmony and expectations are divided into future expectations and study expectations (Figure 2).

[Insert Figure 2 here]

Experiences

Negative study experiences

Almost all participants experience side-effects, matching with side-effects that are expected according to the study protocol. The participants expressed their concerns surrounding certain aspects of the trial such as sampling of their blood, hospital admissions, the precise intake time of medication, the amount of medication and the feeling of being a test-subject.

P109:"Expectations. They just aren't there. You're kind of. Experiment. It is an experiment… and the protocol, that is very fixed.."

Participants feel burdened in several ways during the phase-I trial. The first mentioned burden is that the trial confronts them with the fact that there is no regular treatment possible and the fear that they have to stop trial participation. Secondly, they feel mental and physical fatigue. Having enough concentration to carry out hobbies, for example, is sometimes absent. Finally, they feel burdened by the fact that they have to travel to the hospital and sometimes spend their precious days on a hospital visit.

P101:"Uhh confrontational. Uhmm because for me phase-I, this study of mine, is the last possible resort. .. It consumes a lot of energy. This creates fatigue again. At least with me. Constantly working on it. Uh.. I get tired because of that, the days after that I have to give up. Physically. And therefore not getting enough quality from your life.".

P106:"Sometimes you just don't get around to reading. If you are reading a book then, say, two days later you pick up that book again, then you have to think.. oh how was it. Then you have to go back a few pages to start recording the story again.".

Positive study experiences

A few participants mentioned that not experiencing any side-effects is an advantage. If they have experienced side-effects, some compared it with past regular treatment, which they experience as heavier.

P107:"At some point I could no longer tolerate the chemo. Then we switched to other things that did not work. .. It was too intense for me. We were halfway through that and he said I don't want your death on my conscience.".

Being able to continue to do daily activities is experienced as positive. Alongside this, they experience stabilization or decrease of cancer progression, or are just 'happy' that they can participate. Some even experience the feeling that they are treated to the limit. Besides this, some participants have the feeling that they 'are not finished yet'.

P101:"Personal attention, you are treated as a patient everywhere, but I feel that I am still treated personal. Uhhh all possible knowledge, all possible things that are sorted out, that are investigated, uhhhh. Are applied to me.".

P107:"It gives me the feeling that I am not finished yet. It is as simple as that..".

All participants would like to take part in the trial again if they were asked for a second time. They actually indicated that there is no option to not think about not trying to treat the cancer in a phase-I trial. All participants thought about their quality of life and have varied descriptions.

P105:"The way I live right now, it can be sustained. Every time I am here for a week and I get all the side-effects. So be it. Is still doable for me. If my health deteriorate and I have to come in here with a wheelchair, um, things like that. I have an euthanasia statement and then it is over.".

Motivations

Control of the outcome

Control of the outcome is shown by all participants out of hope. The participants are hopeful for a phase-I trial where the side-effects are less or none compared to the previous treatments and which can extend anticipated life expectation. In addition to hope, more than half of the participants seek some motivation in optimism or realism. Optimism can be found in the probability of success that the phase-I trial has. They want that the probability of success is greater than zero and are optimistic that this probability, may apply to them. This group of participants remains as positive as possible, they all share the opinion that without this positive approach you cannot sustain participation. Some participants know that the probability of the phase-I trial working out well is small and are therefore realistic about the outcome. Finally, one participant indicates that he gets motivation from his religion.

P107:"I have more optimism than hope. There I have to get it out, I shouldn't get it out of hope. I can see that for myself. It is beautiful when it is included. I want to stop that cancer. And that I can live in a normal way for a few more years. That is reason, that is not hope. I just want that.". .. "Yes. There is still hope. There is still a chance. And I grab it with both

hands. And I'll see where it ends. And this makes sure that I don't feel down, that I'm not down. That I am not depressed. I still feel motivated. ".

P104:"I take courage from different things. And, yes, you have to have positivity, otherwise you will not be able to sustain this.".

To do good for another

Participants want to stay alive as long as possible with their family, partners and friends. They get motivated by opinions, actions and words of their friends or family and the research team.

P106:"I do it for others, and for myself. Seeing your grandchildren grow up. I have been married for almost 58 years. But I would still like to reach 60 years of marriage.".

Furthermore, some want to do good for the research team and future patients. In addition, the role of developing new medicine or new treatments also plays a role. Ultimately, this will help future cancer patients.

P103:"It is also important for the people who come after me. That the researchers are happy, that people are going to participate and that is also necessary.".

Harmony

Harmony is found in the fact that normal life, such as their hobbies and work can continue. Motivation is also found in good results and that they may continue trial participation. Participants find harmony and peace in the fact that they have gone through all possible treatment options.

P110:"I go along with it and we see how far we get. If I don't do this, I can say. If I only had... Now I don't have to say. If only I had. Now I have done it. I have tried everything. .. The motivation why you do it, I do this to make sure you have excluded everything. Without question.".

Expectations

Future expectations

The future expectations of the participants vary from short term future expectations, such as from a couple of days or weeks, to long term future expectations, such as a few weeks or even years. Participants who had just recently enrolled and were in the early stages of the trial only

look into the future in short terms, while many participants who had several tumour evaluations and were further along the trial look further into the future.

P110:"Now I live by the day. Now I live to arrange everything in such a way that when I die everything can continue. I was working on that before, but not very intensively. To a lesser extent. And that has completely changed. I completely reversed that.".

P103:"My expectations is that I can continue trial participation for a while. That I can continue this trial for a few more years.."

Switching between having short term future expectations and having long term expectations occurs with some participants. There is no congruent reaction when they talk about their future expectations.

Treatment expectations

All participants can give a clear description of the definition of the trial and they can all describe in detail how their treatment will go according to the trial protocol.

P108:"I know that, uh, late March they will make a scan again and then I will hear the results of this in early April. Anyway, I have three options. Or the treatment has started and the tumor has become smaller. That is the most favorable situation. Or the situation has remained stable. Or they say.. nothing happened..".

Almost all participants think about the period after trial participation. They think about end-of-life care, such as hospice-care and euthanasia. This comes to the thought of their death and the moment when they must leave their loved ones behind. Some said it is a difficult subject and that they sometimes need guidance.

Discussion

This study explored the experiences, motivations and expectations of patients with advanced cancer, without treatment options or options with low expected benefit, during phase-I clinical trial participation. The first main finding of the study is that most participants were glad that they could perform their daily activities again, while these participants also experienced the side-effects and the burden of participating. Burden such as being confronted with the fact that they have no regular treatment options and experiencing mental and physical fatigue If patients

had to reconsider consent, they would do it all again, they want to be treated to the limit. The second main finding is that all participants got their motivation from controlling the outcome, to do good for one another and living in harmony. There is a fine line between hope, optimism, and realism. This fine line caused shifts between optimism and realism, while they all remained hopeful. It seems that the benefits outweigh the disadvantages for these patients because there is a chance of extending life. In addition, they do not want to have regrets and say afterwards: 'If only I had..'. The last main finding is that participants who have just enrolled only tended to look into the future in the short term, while participants who have had several tumor evaluations dared to look further into the future.

These study results correspond to therapeutic optimism and to do good for another, and therefore correlate with the self-determination theory (4,9). Therapeutic optimism is seen in this study by the fact that the participants are hopeful for a phase-I trial where the side-effects are less or none compared to the previous treatments and which can extend anticipated life expectancy. It is therefore not surprising that literature shows that 48,7% of 300 patients answered no when they were being asked if the phase-I trial could cure their cancer (33). In addition, a complex relationship between knowing the reality of their situation and hoping that there still might be a treatment that would have a positive effect. `Trying everything' appeared to be a way of maintaining hope (34). In this study, all participants are hopeful. It is precisely this hope that is important when participating in a phase-I trial. Hope ensures a lower score on psychological distress and a positive relationship was found between hope and perceived health (35). It is therefore suggested that phase-I trials allow some patients to construct their lives meaningfully by enabling hope (34). The participants of this study genuinely want to help researchers obtain scientific knowledge that might benefit future patients with the same disease. The observation of altruism, matches findings in other studies (10-12). This approach is not surprising, as literature shows that the closer patients are to death, the greater the desire to help others (34). This phenomenon takes place due to a greater emphasis on the role of altruism in their decision-making in an attempt to give meaning to their suffering (34). Unexpectedly, therapeutic misconception does not seem to play a role in this study. All participants talked about their treatment expectation in accurate detail. It seems that they are well informed about the nature and purpose of the trial. This may be due to the fact that the participants already have experienced participation.

A major strength of this study is the generic qualitative design, which allows an in-depth analysis of the outcomes. Besides this, the constant comparative method was used to improve data collection by adapting the topic list to findings from previous interviews. In addition, independently coding of the transcripts and discussing findings until consensus improved the

internal validity. Last, recall bias was reduced by interviewing participants as they experienced their feelings and by analyzing the interviews within two weeks. A limitation of this study is that it was only performed at one academic hospital. Saturation could not be achieved. No new findings emerged in the last interview, but because of the study restrictions during the COVID-19 pandemic, the two final interviews could not be held and no participant at stage four could be included. Hereby, the generalizability of the study might be reduced. Nevertheless, this study included participants from different studies, with different types of cancer, variation in age and moment of participation. In addition, the richness of the data shows that the analysis has captured the most typical aspects of participants participating in phase-I trials.

A recommendation based on these study findings is that it is meaningful to clarify the importance of altruism for patients on phase-I trials; almost all participants got motivation from doing good for one another. Besides this, a study can be conducted into guidance into end-of-life care and the experiences of the participants when they need to withdraw. In order to give patients better support during phase-I trials, it is recommended to discuss the end-of-life care, the burdens and the motivations during the outpatient visit or the hospital stay.

It can be concluded that participating in phase-I trial is a great uncertainty. Participating creates the feeling among patients that they tried everything and are treated to the limit. This not only gives the motivation to continue participating but also a sense of altruism. Family and friends, hope, realism, optimism and helping to develop a new drug also provide motivation. Despite different burdens, side-effects and the feeling of being a test-subject, the participants will not easily choose to stop participation in order to prevent to say afterwards: "If only I had".

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Appendix A: Figures and tables

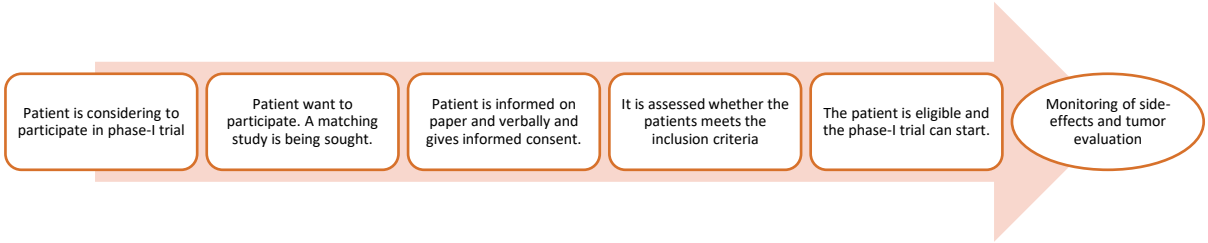

Figure 1: From enrollment till monitoring

Table 1 Demographic characteristics of the phase-I participants (n=10)

Participant Number	Gender	Age	Marital Status	Cancer diagnoses	Moment of interview[1]	WHO[2]	Education[3]	Interview duration[4]
p101	Male	43	Single	Melanoma	1	1	5	23:55
p102	Female	53	Married	Glioblastoma	3	0	4	13:02
p103	Male	68	Married	Leukemia	3	0	4	18:55
p104	Male	73	Married	Prostate cancer	1	1	4	22:21
p105	Female	57	Married	Endometrial cancer	1	0	3	24:05
p106	Female	76	Married	Leukemia	3	1	4	29:25
p107	Male	73	Married	Prostate cancer	1	1	4	30:49
p108	Male	61	Married	Lung cancer	2	1	3	43:36
p109	Female	43	Single	Ovarian cancer	3	1	8	22:14
p110	Male	64	Married	Lung cancer	1	1	5	31:24

[1] 1) Evaluation of first cycle took place but no tumor evaluation; 2) First tumor evaluation has taken place; 3) Several tumor evaluations have taken place; 4) The participant has to withdraw; / [2] WHO = WHO Performance Status / [3] Education = ISCED 2011 levels of education; 0: early childhood education, 1: primary education, 2: lower secondary education, 3: upper secondary education, 4: post-secondary non-tertiary educations, 5: short-cycle tertiary education, 6: bachelor or equivalent, 7: master or equivalent, 8: doctoral or equivalent / [4] Interview duration = minutes and seconds.

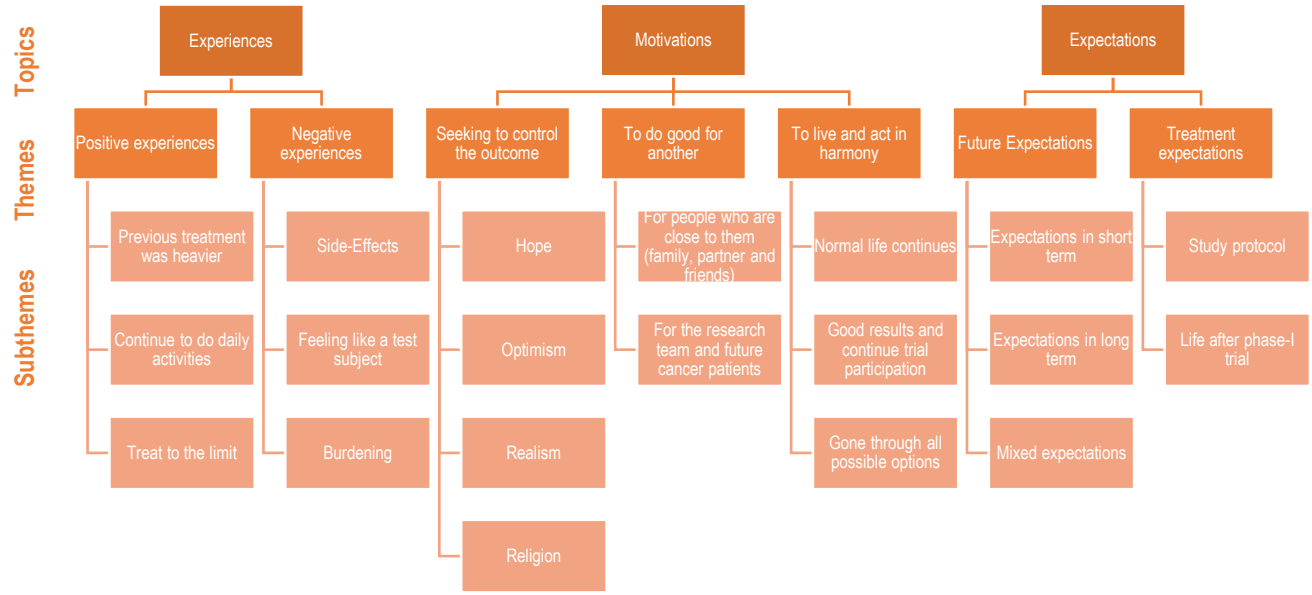

Figure 2: topics, themes and subthemes