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Patients in Clinical Cancer Trials

Understanding, Motivation and Hope

TOVE GODSKESEN



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Abstract

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The overall aim of this thesis was to study participants' understanding of clinical cancer trials, and their motivation for participation. Of particular interest was the question of whether the patients hoped for a cure resulting from the trial. The thesis was based on four studies and used three methods: interviews, a questionnaire, and empirical bioethics. The results of Study I indicated that the participants in phase 1 trials understood most of the information provided, but were unaware of both the very small potential for treatment benefit, and the risk of harm. Patients in phase 3 trials had a good understanding of the trial, except regarding side effects and their right to withdraw. Some found it hard to ask questions and felt they needed more information (Study III). The participants in phase 1 trials were strongly motivated by the generally unrealistic hope for therapeutic benefit (Study I). When the chances of a cure are minuscule, as for participants with end-stage cancer in phase 1 trials, hope can play an important, positive role and offer meaning to one's remaining life. However, hope for an unrealistic outcome could also deprive patients of an opportunity to spend their remaining lives, as they would otherwise choose (Study II). The participants in phase 3 trials indicated that their motivation for participation was multifaceted; the most common motivations included hope of therapeutic benefit, altruism, access to extra clinical examinations or better care, and a wish to repay society for the help they had received (Study III). After stratifying and analysing the motivation data by gender, age, education and previous experience of trial participation, males and those aged ≥ 65 years were significantly more motivated to participate out of a desire to reciprocate the help they had received, either because of a sense of duty or because their families or friends considered that they should attend (Study IV). In conclusion, the informed consent process seems to work relatively well, with good results within most subgroups. However, patients with end-stage cancer who are participating in phase 1 trials are a vulnerable group as they have very little potential for treatment benefit coupled with a tangible risk of harm.

Keywords: cancer, adults, clinical trials, phase 1 trials, phase 3 trials, patient information, patient education, informed consent, hope

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To Samuel and Simon

Mitt i livet händer det att döden kommer
och tar mått på människan. Det besöket
glöms och livet fortsätter. Men kostymen
sys i det tysta.

Tomas Tranströmer

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I. Godskesen, T., Nygren, P., Nordin, K., Hansson, M. & Kihlbom, U. (2013). Phase 1 clinical trials in end-stage cancer: patient understanding of trial premises and motives for participation. *Support Care Cancer*, **21**, 3137-42.
- II. Godskesen, T., Hansson, M.G. & Kihlbom, U. (2014). ‘I have a lot of pills in my bag, you know’. Institutional norms in the provision of hope in phase 1 clinical cancer trials. (*In manuscript*).
- III. Godskesen, T., Nygren, P., Nordin, K. & Kihlbom, U. (2014). Hope for a cure and altruism are the main motives behind participation in phase 3 clinical cancer trials. *Eur J Cancer Care*, **24**, 133-141.
- IV. Godskesen, T., Nordin, K., Silén, M., Kihlbom, U. & Nygren, P. (2015). Differences in trial knowledge and motives for participation among cancer patients in phase 3 clinical trials. *Eur J Cancer Care*, doi: 10.1111/ecc.12319.

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Background

Without clinical trials there would be no new anticancer drugs, no improvement of existing medicines, and no evidence-based development of treatments. Clinical cancer trials depend on the participation of patient volunteers who usually do not gain any therapeutic health benefit from their participation. The medical need to undertake clinical cancer trials and the ethical requirement to do so in a morally justified way make it vital to understand how research participants relate to participation. Much international research has investigated cancer patients' decisions to participate. However, there is further need for extensive research into cancer patients' reasons for participating in clinical trials, their understanding of the trial process and their experiences when participating, in order to increase their influence on the process of clinical-trial participation. The overall aim of this thesis was to describe and analyse the understanding, motivation and hopes of patients in the decision-making process in clinical cancer trials.

Clinical Cancer Trials

The evaluation and development of a new drug involves a long process that historically has taken about 10-15 years and costs up to USD 1.7 billion (1).

Before clinical research can be carried out, experimental drugs are tested in pre-clinical studies in cells, tissues and animals. Clinical trials of drugs are commonly divided into four phases (Figure 1), each designed to respond to different types of clinical question.

**Clinical trials are conducted in stages, called phases.
Each phase is designed to answer separate research questions**

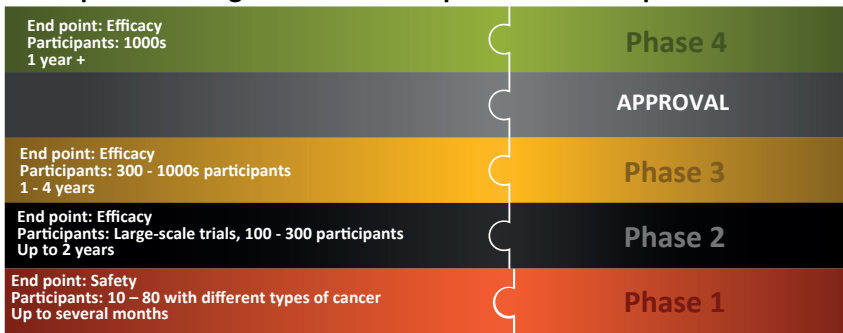


Fig. 1 The four phases for clinical cancer trials

Phase 1 trials

A phase 1 trial is the earliest step in the clinical development of new anti-cancer drugs. The primary aim of phase 1 trials is to define the safety profile and recommend an appropriate drug dosage range for phase 2 trials, rather than to demonstrate efficacy (2, 3). In these experimental studies, a new drug or treatment is initially given to a very small (commonly up to 20) group of patients. The trials are often open to patients with any type of cancer that can no longer be controlled by established treatments (4, 5).

It has been widely established that the results of pre-clinical testing in animals (mice, rats, dogs) cannot routinely be extrapolated to humans. Thus, a very low dose is used in classical phase 1 trials. These trials generally take place in oncology clinics and are often performed in stages. The first cohort of three participants is given an extremely low dose of the drug, often 1/10 of the lethal dose in preclinical testing, which is not expected to provide patient benefit, but is used to gain information on the pharmacodynamics and pharmacokinetics of the drug in humans. The dose is then escalated in three to six patients until dose-limiting toxicity is seen in at least two patients. The recommended dose for subsequent phase 2 trials is conventionally just below the level of dose-limiting toxicity (6, 7).

Phase 2 trials

The aim of phase 2 trials is to find the best dosage range and investigate the safety of the drug, in addition to finding preliminary evidence of its efficacy. Phase 2 trials usually include a greater number of patients than phase 1 trials (often up to 50 participants), most of whom have the same diagnosis. Cancer patients participating in phase 2 clinical trials are generally more similar to

those participating in phase 3 trials than to those in phase 1 trials in terms of treatment options and survival (8).

Phase 3 trials

Phase 3 trials compare promising new drugs with the current standard of care for a particular type of cancer. They also provide further information on potential possibly has fewer side effects. Phase 3 clinical trials are frequently multicentre, multinational studies that can take years to complete; these are the most expensive studies. Because the differences between treatment effects are usually small, hundreds or even thousands of patients are required to take part (9).

Phase 3 trials are usually randomized controlled trials (RCTs). Randomization is the procedure by which each participant is randomly allocated to the control group (standard treatment or placebo) or the intervention group (the new treatment being tested). In single-blinded trials, the researcher knows the group to which the patient is randomized but the patient does not. In double-blinded trials, neither the patient nor the researcher knows which of the two study groups the patient belongs to until the study is finished (10).

There is a consensus that randomized, double-blinded, placebo-controlled trials are the “gold standard” for assessing the efficacy and safety of a new treatment, because the randomization minimizes both known and unknown confounders. Double blinding minimizes the risk of influence from the researcher (11, 12). However, because of the toxicity of most cancer drugs, blinding and placebo controls are less effective than in other therapeutic areas (12, 13).

Phase 4 trials

Phase 4 clinical trials investigate drug efficacy and safety in a routine clinical healthcare setting, following drug approval. These trials may also include endpoints reflecting health economy and drug effects in sub-groups of patients (14).

Research ethics and ethical transgressions

Experiment and investigation have been a part of medicine since the beginning of modern history, although they have often not been ethically based. Several dark chapters in the history of research stimulated the establishment of international research ethical documents and guidelines in the 20th century, such as the Nuremberg Code and the subsequent Declaration of Helsinki. Those dark chapters should continue to be studied to avoid the recurrence of problems in the future. Today, the established ethical principles for research

help ensure that research subjects are not harmed and that the historical inhumanities do not recur. Several ethical principles should be taken into consideration when clinical trials are planned. Central among these principles is the requirement that participation is voluntary and that the participants know about the risks and purposes of the trials.

In 1981, The New York Times published an article titled, '*Bad Blood. The Tuskegee Syphilis Experiment*', which explained details on the study and called it the '*longest nontherapeutic experiment on human beings in medical history*' (15). The Tuskegee syphilis study lasted from the 1930s to the 1970s. Almost 400 black men with syphilis participated, in addition to 201 men in the control group who were not diagnosed. These men were told that they were being treated for 'bad blood', not that they suffered from syphilis, even though syphilis is a serious disease causing such health problems as arthritis, brain damage, insanity, blindness and death if it is left untreated. The study was carried out in collaboration with the hospital at the Tuskegee Institute with the aim of analysing the natural course of syphilis over time. The research participants were provided with few details of the study purpose, but were offered a daily free meal and free medical treatment. Even when penicillin became standard treatment for syphilis in 1947, it was withheld for both participants and control subjects as part of the study. During this time many men died and many of their wives, girlfriends and children were infected. It was not until 1972, when an investigative journalist, Jean Heller, broke the story and published an article, that effective action was taken (16).

During the Second World War, Nazi physicians conducted four types of cruel medical research on prisoners: racial-anthropological research, brain research and neurology, military medical research and genetic experiments (17). For example, living tuberculosis (TB) bacteria were injected directly into prisoners' lungs to see if any natural immunity would occur, with the result that the majority died of TB (18). Others, as Russian prisoners, were injected with poison as part of an experiment to develop new methods of execution.

Unethical experiments on humans were also performed in Sweden, after the Second World War. At the beginning of the 20th century, there was a high prevalence of dental caries among children, and detection of the cario-static results of fluoride rapidly encouraged a number of research projects (19), one of which was *The Vipeholm Dental Caries Study* (20). Between 1945 and 1955, about 800 intellectually disabled or severely mentally retarded children and adults housed at the Vipeholm Hospital were included in the study, with the aim of examining whether sugar affected dental caries. Patients were randomized to a control group or to regularly drink sugar syrups, eat bread with sugar, or eat chocolate or sticky toffees made especially for the study. The amount of sugar in the saliva was measured frequently, at times every fifteen minutes (21). The teeth of fifty of the subjects in the ex-

periment had been completely ruined. In 2001, one of the dental researchers, Professor Krasse, concluded that the Vipeholm Study at least provided the patient with a sense of meaningfulness in their daily occupations (21). The link between sugar and bad teeth became evident and led to the Swedish tradition of limiting sweets to one day in the week ('Saturday Candy' or 'lördagsgodis'). However, that does not justify carrying out the study on people who could not defend themselves or choose whether they wanted to participate. The patients participating in the study had not given their informed consent, regardless of their capacity to do so.

We have learned from this unethical research, and there are now several international guidelines on ethical principles for medical research involving human subjects. The Nuremberg Code of 1947 emphasized, among other things, the individual's consent and that the risks of experiments must never be greater than the potential benefit to mankind. The Helsinki Declaration, which was issued by the World Medical Association in 1964, has since been revised many times to provide an up-to-date ethical standard for research ethics.

Regulations

Before clinical research can be conducted, the risk-benefit ratio must be found; the potential benefits must exceed the individual risk for participants and, in later phase trials, there should be genuine uncertainty about what constitutes the best treatment (17, 22). Additionally, the participant's well-being is always to be prioritized over scientific or public interests. Such principles have been codified in a legal requirement known as Good Clinical Practice (GCP), provided by the International Conference on Harmonization (ICH) (23).

In general, two instruments are put in place to protect human subjects in clinical trials: the study must be passed by an ethical review board and voluntary informed consent must be obtained from the research subjects prior to their participation (24).

In Sweden, there is a requirement by law that certain research must undergo ethical review before it can commence (25). The regional ethics review boards are independent, formally designated committees that consist of ten members with scientific competence, a judge and five lay members of the community, with the aim of approving and reviewing research that involves humans. In addition to the regional boards, there is a central ethics board whose main task is to assess any appeals on the regional ethics review boards' decisions.

Approval by an ethics board is based on six basic conditions:

1. that the study can be carried out with respect for human dignity;
2. that there is an acceptable balance between human rights and fundamental freedoms and the value of the gained knowledge;
3. that the scientific value of the knowledge gained compensates for all risks concerning health, security and integrity;
4. that the results cannot be achieved by less risky means;
5. that a scientifically competent researcher is in charge;
6. that research on living persons complies with statutes on informed consent.

Clinical trials in humans also need to be carried out according to international, EU and national laws, rules, directives, policies, declarations, codes and guidelines. Important documents for conducting research on humans in Sweden are listed in Table 1.

Table 1. Important regulations, laws and guidelines relevant to clinical research on human subjects in Sweden (26)

| Regulatory framework | Type of rule | Issued by | Year |
|--|--|---|----------------------------|
| Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects | Professional code of conduct | World Medical Association | 1964, latest revision 2013 |
| International ethical guidelines for biomedical research involving human subjects | Ethical guidelines | Council for International Organizations of Medical Sciences | 1982, latest revision 2002 |
| Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: Convention on human rights and biomedicine, ETS No. 164 | International convention signed but not yet ratified by Sweden | Council of Europe | 1997 |
| Universal Declaration on Bioethics and Human Rights | International declaration | UNESCO | 2005 |
| ICH Harmonized Tripartite Guideline for Good Clinical Practice, E6 (R1) | Guidelines on trial performance, quality and ethics | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use - ICH | 1996 |

| | | | |
|---|--------------------|--|----------------------------|
| Commission Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products | EU Directive | European Union | 2005 |
| The rules governing medicinal products in the European Union, Volume 10: Clinical Trials Guidelines | EU legislation | European Union | 2006-2013 |
| The Swedish Medical Products Agency's regulations on clinical trials in humans - LVFS 2011:19 | Swedish regulation | The Swedish Medical Products Agency | 2011 |
| Swedish Medicines Act – SFS 1992:859 | Swedish law | The Ministry of Health and Social Affairs | 1992 |
| The Act concerning the Ethical Review of Research Involving Humans - SFS 2003:460 | Swedish law | The Ministry of Education and Cultural Affairs | 2003, latest revision 2008 |
| Swedish Patient Data Act - SFS 2008:355 | Swedish law | The Ministry of Health and Social Affairs | 2008 |

Personal autonomy in research and medicine

Autonomy can be defined in several ways: 1) as a concept, 2) as a value or principle, and 3) as pertaining to autonomous persons or decisions.

First, the common thread in the various ways of describing autonomy as a concept is the notion that people are self-governing agents. Autonomy is derived from the Greek roots *autos* (meaning 'self') and *nomon* (meaning 'rule' or 'law'). This can be interpreted as an ideal involving governance of oneself according to moral law (Kantian ethics) but has more commonly been taken to mean the capacity of people to choose and act on the basis of their own independent preferences. Because of the numerous variations in interpretation, autonomy is a good example of an essentially contested concept.

Autonomy, as noted, is often used in reference to persons (personal autonomy) and can be seen as a normative principle that requires respect for the decision-making capacity of competent adults. According to Beauchamp and Childress, autonomy presupposes an aspect of ability, and can be described as follows:

“Personal autonomy encompasses, at a minimum, self-rule that is free from both controlling interference by others and from certain limitations such as inadequate understanding that prevents meaningful choice. The autonomous individual acts freely in accordance with a self-chosen plan, analogous to the way an independent government manages its territories and sets its policies.

A person of diminished autonomy, by contrast, is in some respect controlled by others or incapable of deliberating or acting on the basis of his or her desires and plans. For example, cognitively challenged individuals or prisoners often have diminished autonomy” (27 pp.99-100).

Personal autonomy can thus be understood as self-rule, without being controlled by others and without limitations such as insufficient understanding (28). Autonomy here functions as a moral, political and social idea or concept. In all these areas, there is a value associated with autonomy; because it is valuable, others have an obligation to promote autonomy. This line of reasoning results in the conclusion that we should make sure anyone participating in research is as informed as possible, so that they can use their capacity for self-determination to the fullest extent possible.

Beauchamp and Childress also saw autonomy as a principle (27). The moral philosopher Immanuel Kant argued that respect of autonomy has its origin in the recognition that “all persons have unconditional worth, each having the capacity to determine their own moral destiny” (27 p.103). This is also in line with Kant’s theory that people should not use anyone as a mere means, but see them as ends in themselves. As a principle, then, autonomy often encompasses respect for autonomous decisions, i.e. that one is obliged to respect the will of someone who has made up his or her mind, even if that decision was made on the basis of insufficient understanding or knowledge.

Much emphasis has been placed on the role of authenticity in autonomy. If one is to make a decision worthy of respect, it must be a decision with which one identifies at a deep level, which is important. The concept of first- and second-order wishes can help to explain this (29). First-order wishes are what we want, and second-order wishes are wishes regarding our first-order wishes (30, 31). To illustrate, a smoker might wish for a cigarette, but on the higher, second-order level, he or she has the more authentic wish of quitting his or her smoking, based on ideals of health, etc. A wish to smoke that cohere with a second-order wish (to in fact be a smoker) is more authentic than a first-order wish to smoke that conflicts with a second order wish (to not be a smoker). So authenticity is basically a matter of coherence between wishes of different order.

From this notion of authenticity can be distinguished the more basic prerequisite of competence. In order to govern oneself, a person must have the ability to act rationally on the information he or she has, and also to comprehend the consequences of his or her decision. This ability is called decision-making competence.

Further, for a decision to qualify as autonomous, it needs to be made i) intentionally, and ii) without controlling influences that affect the decision (27). This is not usually a problem in healthcare situations, where the patient can clearly demonstrate that the information given has been comprehended and can specify their will. However, when a patient is in crisis, their ability

to take in and process information is reduced and their will can change. In some situations, such as when a patient is undergoing cancer treatment or when the choice is complex and life altering, their capacity to understand information, make a decision and then stick to that decision can be distorted, and consequently autonomy may be diminished (32). Relationships with others may also affect individual autonomy: interactions with other people and socio-cultural relationships can influence a decision, and thus be a threat to autonomy.

The purpose of obtaining informed consent from a patient for a specific treatment is commonly and historically understood to be based on respect for the individual's autonomous decision (33). This is clearly stated in The Declaration of Helsinki, a set of ethical principles for medical research involving human subjects, where respect for personal autonomy and informed consent are particularly important (34).

Informed consent

The practice of obtaining informed consent was designed to protect the autonomy of patients in making their own choices according to their own preferences. The consent process is an essential ethical and practical part of both medical practice and clinical research; this process is most often justified with reference to the patient's or subject's legal and ethical right to autonomy (34-37). Informed consent for research consists of five elements: first, participants need to have adequate decision-making competence. Second, they must be given relevant and understandable information about the important aspects of the research. Third, the potential participant must sufficiently comprehend the information provided. Fourth, the consent must be truly voluntary and the participants need to understand that they can withdraw at any point without it affecting their routine medical care. Lastly, the participants need to authorize the researcher to carry out the research-related interventions and observations (27).

Informed consent is more than a signature on a document; it involves an educational process that includes information on various trial details, such as the purpose, duration, risks and burdens of the research, the potential benefits of the trial, voluntarism, and the names and contact details of the people responsible for the trial. A subject can give voluntary consent only when he or she has based his or her decision on adequate, relevant information and comprehension. Thus, a subject who misunderstands the aim of the study and believes that the aim of the research is to benefit him or her personally cannot give voluntary autonomous consent (27).

According to the Declaration of Helsinki, the following information should be given to the potential participants (articles 25 and 26).

“Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject’s freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed” (34).

Information, knowledge and comprehension regarding research

It has been reported that the complex design of clinical cancer trials is difficult for participants to understand (38). Although participants in clinical trials are enrolled after having given informed consent, some investigators have found that they may have incomplete understanding of the research purposes and methods (39, 40). In contrast, others have reported that research participants have high levels of knowledge and a thorough comprehension of what is entailed in participation in RCTs (35, 41, 42). However, although participants can consider themselves satisfied with and well informed by the consent process, misconceptions can be frequent. These misunderstandings and knowledge gaps are related to the nature of the procedures involved in clinical trials, such as randomization, potential adverse reactions, any benefits to themselves, and the unproven nature of outcomes in clinical trials (43-48).

Such misunderstandings can increase the risk of “therapeutic misconception”. The term therapeutic misconception was coined by Appelbaum et al. in 1982 (41). Therapeutic misconception has been described as the misunderstanding that arises when a *“research subject fails to appreciate the distinction between the imperatives of clinical research and of standard care, and therefore inaccurately attributes therapeutic intent to research procedures”* (49 p.55).

This characterization has been reworded and validated by the National Bioethics Advisory Commission in 2001 as *“when individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial bene-*

fit from the intervention under study or from other aspects of the clinical trial” (50 p.325).

Participants in trials who fail to understand that research and clinical care are not the same, and believe that the research is mainly aimed at benefitting the individual patient according to the principle of “personal care”, are subject to therapeutic misconception (Fig. 2).

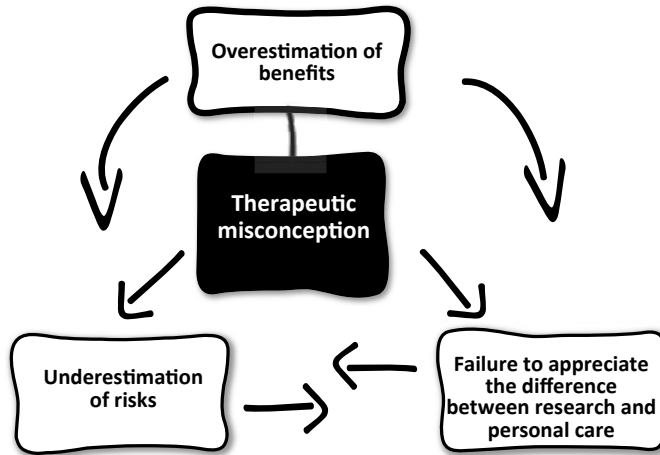


Fig. 2 Description of therapeutic misconception (inspired by a figure by Christine Grady).

Motivation for accepting or declining trial participation

There are many factors that may influence the patient's decision to participate in a clinical trial. Nevertheless, one reason is often more important than others. The following potential motivations summarized in Table 2 are based on the available literature relevant to this area of clinical research.

Table 2. Factors influencing the decision to participate

| Motivation for accepting participation | References |
|--|--|
| The hope for personal therapeutic benefit from access to new and better treatments not yet available to the general population (often the most important reason for enrolment in clinical trials) | Appelbaum et al. (51) Cheng et al. (52) Truong et al. (53) Nurgat et al. (54) |
| Helping future patients | Ellis et al. (55) White et al. (56) |
| Prolonged survival | Kohara et al. (57) |
| The hope for indirect health benefits from access to medical experts and high-quality care, in terms of tests and examinations that could possibly improve their clinical symptoms or provide access to close monitoring for possible adverse events | Italiano et al. (58) Jenkins et al. (59) Cohen et al. (60) Ellis et al. (55) Wright et al. (61) Jenkins et al. (43) |
| Feeling special and cared for | Cox (62) |
| Contributing to medical knowledge | Ellis et al. (55) Madsen et al. (63) |
| | |
| Wanting to follow their doctors' wishes | Jenkins et al.(64) Townsend. (65) |
| Factors involving trust in the doctor or the nurses, positively framed trial descriptions by the physicians, or the belief that clinicians must be acting in the patient's best interest by offering participation in the trial | Ellis et al.(55) Catt., 2011 (66) Nurgat et al.(54) Wang et al.(67) |
| External factors, such as family or significant others | Jenkins et al. (64) De Melo-Martin (68) Jenkins et al. (69) Mills et al. (70) Wright et al. (61) |

There are many factors that may influence the patient to decline to participate in a clinical trial. Barriers to participation may be related to the protocol, the patient or the physicians (70). The reasons below are the most cited potential barriers to participation, and are based on the available literature relevant to this area of clinical research.

Table 3. Factors influencing the decision to decline to participate

| Motivation for declining participation | References |
|--|---|
| Worries about the concept of randomization of patients to treatment or control groups on the basis of chance | Jenkins et al. (59) Kerr et al. (71) Catania et al. (72) Mancini et al. (73) |
| Belief that the new drug may not be the best option | Mills et al. (70) Townslwy. (65) van der Biessen (74) |
| Factors associated with unknown, potentially harmful adverse reactions | Lilford et al. (75) Avis et al. (76) Mills et al. (70) Rondiana et al. (77) |
| More visits to the hospital, travel time, out-of-pocket costs in terms of meals, parking fees and lower income when sick leave from work. Loss of time, in that the patients thought it better to spend their time outside of health-care institutions | Ellis et al. (55) Avis et al. (76) |
| Fear of reduced quality of life | Jenkins et al. (69) Harrison et al. (78) |
| Fear of being an anonymous research subject (being treated as 'guinea pigs') | Biedrzycki et al. (79) Mathews et al. (80) |
| Lack of family support | Ellis et al. (81) |
| Advice from their physician not to participate | Jenkins et al. (59) |

Demographic factors can also influence the decision on whether to participate in a clinical trial. Gender, age, education level and ethnicity have been found to have an influence. Women are less likely to participate in clinical trials, as are younger persons (43, 77), and patients with lower income and education (79, 82). Additionally, ethnic minorities are less likely to participate and less likely to be asked to participate (83).

Shared decision-making

Most research participants prefer to make the decision on whether to participate in a clinical trial on their own; others prefer to share their decision-making with their doctor or significant others (82, 84). Those of younger age and with higher education prefer to play a more active role in decision-making (79, 85). It is uncommon for research subjects to feel pressure from their significant others or the researchers to participate in phase 1 trials, but

they do feel pressure to get treatment for their cancer (86). The decision to participate is often taken immediately after being asked to participate in the trial (87). Those who consent to participation immediately after being asked have been found to be less satisfied with their decision than late signers (61, 88, 89). Nevertheless, most patients are satisfied with their decision to participate in a clinical trial (46, 90). Patients in phase 1 trials have reported that participation made them feel special, privileged, lucky and honoured, because they were given the chance to participate in research (90).

Impact of hope for therapeutic benefit

Hope for a miracle cure is often an important influencing motivation for participating in phase 1 cancer trials (62, 66). Many patients are willing to choose aggressive anticancer treatments in return for a small benefit in their health outcomes. They often overestimate the probability of therapeutic benefit and underestimate the adverse effects (62, 66, 86, 91). As many as eight of ten incurable cancer patients treated with chemotherapy overestimated their chances of benefit in one study (92). When patients hope and put their trust in a cancer treatment unlikely to be active against the disease, this could be understood as an unrealistic hope, an optimistic coping strategy or an unsuccessful consent process (93, 94). Hope centred on cure can be unrealistic, because of the small chance of therapeutic benefit, and is therefore problematic (92, 93, 95). Unrealistic hope can also spring from a refusal to accept one's situation. Unrealistic hope may not be literally false, but may be in conflict with other more important wishes of the patient. Hope plays an important role for cancer patients deciding whether to participate in cancer clinical trials and the healthcare scenario might actually embrace a culture where hope is triggered, enhanced or modified (96, 97). Findings also suggest that hope as a coping strategy can offer patients with incurable cancer access to a meaningful and structured, routinized, everyday life and at the same time provide access to treatment.

The rationale for this thesis

In Sweden, every third person will at some time during their life suffer from cancer. Thousands of these patients will participate in cancer trials, which is a prerequisite for developing new treatments. The importance of focusing on the patients' perspectives and increasing their involvement in, and influence over, their own participation in cancer trials has previously been highlighted by *Myndigheten för vårdanalys* in the report *Starka tillsammans* ("Stronger together" (98), the purpose of which was to investigate the need for national coordination of clinical trials. The report underlined the importance of identifying the patients' perspectives and the need for increasing the patients'

influence over their participation in clinical trials. Despite this, there is a lack of empirical data regarding the understanding of consent, and regarding the motivations and experiences of cancer patients who have consented to participate in cancer trials in Sweden. It is therefore important to study the patients' decision-making processes, including the influence of hope on their decisions.

Overall and specific aims

The overall aims of this thesis were to empirically investigate trial participants' understanding of, motivation for participating in and experiences while participating in cancer clinical trials, with a particular focus on the role of hope, and to reflect on the subject and the results of the empirical studies from an ethical standpoint.

Specific aims of Studies I, II, III and IV:

- | | |
|-----------|---|
| Study I | To investigate patients' motivations for participating in phase 1 cancer trials and their understanding of the trial. |
| Study II | To analyse different forms of hope and to investigate institutional norms for providing hope to patients participating in phase 1 cancer trials. |
| Study III | To investigate patients' motivations for participating in phase 3 randomized controlled cancer trials, their perception of the information given and their experiences related to trial participation. |
| Study IV | To investigate whether there are differences in understanding the trials and in the motivations for participating among participants in phase 3 cancer trials in relation to gender, age, education levels and former trial experience. |

Methods

Patient participation in phase 1 and phase 3 cancer trials is a multidimensional topic; because there are different kinds of research questions, they cannot easily be answered using one particular research method. However, limitations associated with one method can be compensated for by strengths associated with another. The use of different designs, approaches and methods can thus compensate for specific methodological limitations, while providing a wider understanding of the research question than each approach by itself. Therefore, two empirical methods and one theoretical method were used to address the research questions asked in this thesis. The empirical studies consisted of: i) an inductive interview study with a selected sample of cancer patients in phase 1 trials, and ii) a questionnaire study with patients in phase 3 RCTs. The theoretical study contributed to the ethical discussion by examining the role of hope in phase 1 studies. The methodological approaches used in papers 1-IV are summarized in Fig. 3.

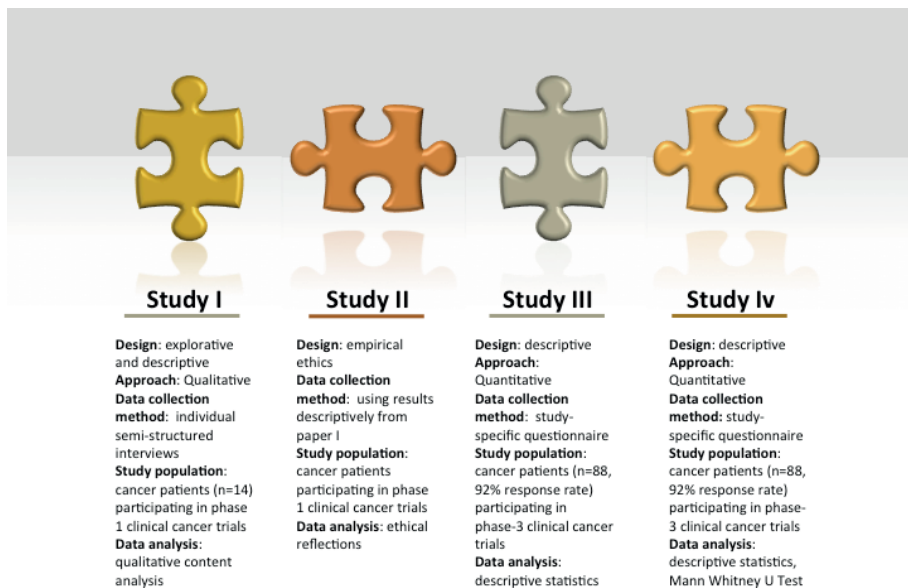


Fig. 3 Description of Studies I, II, III and IV.

Study I

In planning the first study, it was assumed that trial participation and living with a serious cancer that was not responding to conventional therapy indicated that these patients had had long experience of being patients and were used to discussing their experiences. It was thought that they could thus provide key information about their motivation for participating, their knowledge about clinical cancer trials and their decision-making related to participation. Moreover, it was important to obtain an in-depth understanding of how they made sense of their experiences during, motivations for and views of participation in the trial. Arguably, motivations, experiences and attitudes are all part of 'lived experiences' and not just facts about someone, which is why interviews were used to collect data. This method is recommended where there is limited knowledge and where the aim is to obtain a more in-depth understanding of people's experiences and attitudes (99). It allows the informants to state what was significant for them in their own words, and allows the researcher to explore the question more deeply by posing follow-up questions specifically oriented to the respective participant (100).

Participants

The 14 patients included (Table 2) comprised nine men and five women aged between 51 and 81 years (median 63 years). Five patients had been educated to university level, three to high school and six to primary school. The patients had a variety of advanced cancers; most had lung cancer or prostate cancer that was not responding to conventional therapy. Of the 14 patients, eleven were outpatients and three stayed at the hospital for inpatient care and treatment: one because of performance status deterioration, one because of pain and one because of respiratory distress. Two of the outpatients were so affected by the disease (pain and respiratory distress) that it was agreed to ask the main questions briefly and then end the interview.

Procedure

Patients participating in phase 1 clinical trials were identified by the clinical research nurses at Uppsala University Hospital, and were then recruited over an eight-month data collection period (April to November 2011).

At first, 61 patients were identified for possible participation. However, 45 patients died or were too ill to participate in the interviews. Fourteen patients were asked to participate. Two declined to participate and twelve consented. The two declining patients reported poor performance status in combination with practical difficulties as their reasons for declining. Although the inter-

viewer concluded that no new information seemed to be forthcoming based on the interviews of these 12 patients, it could not be excluded that added interviews might provide richer data; therefore, a number of patients from the Karolinska University Hospital in Stockholm were asked to participate. Thus, over a period of two months, two more patients agreed to participate in the interview study. The patients were given verbal and written information describing the purpose and design of the study, and they then gave their informed consent. All informants were free to refuse to answer any question at any time without giving a reason. They were also free to end the interview at any time.

Data collection method

Data were collected through individual semi-structured interviews, which were based on theoretical assumptions from the literature (101). The interview guide was based on the categories of information and informed consent, influential factors and the decision-making process, and included the following questions: “What did you think about the information you received before you decided to participate?” “How did you make your decision to participate in the clinical trial?” “Did you discuss the decision with someone?” “What do you think the advantages and disadvantages (or risks) are of participating in such an early trial?” Once the initial interview guide was developed, a pilot test was conducted with a research subject participating in a cancer trial.

All informants were asked the same set of questions, but the interviews were structured to allow the informants to talk freely on the subject of decision-making and participation in clinical trials. The interviews were audiotaped and transcribed, and were then analysed by TG.

Analysis

A descriptive and explorative qualitative analytical method was chosen and the results were reported in a structured form, following the qualitative content analysis described by Graneheim and Lundman (102).

Study II

Study I indicated that some patients choose to participate in phase 1 trials because they hope for therapeutic benefit in terms of a miracle cure. Study II discussed these ethically challenging results, focusing on the concept of hope and its meaning for cancer patients. This study was, therefore, more of a discussion paper than Studies I, III and IV, and was designed to seek reason-

able interpretations of and normative conclusions from the results of Study I. Study II used empirical bioethics, in which the ethical reasoning was based on a problem that was made visible through an empirical study (103). The empirical data did not provide evidence or support for the conclusions, as in a purely empirical study. Rather, they showed that the problem was anchored in reality and highlighted the need for ethical reflection.

In this study, conceptual and normative issues in the context of phase 1 trials were addressed and discussed, with the focus on issues of hope and communicative norms, and the clinical implications of these. The methods used were conceptual and argumentative analysis (104).

Studies III and IV

The aim of Study III, a single-institution cohort study, was to understand the motivations behind the participation of cancer patients in clinical phase 3 trials in Sweden, to understand how they perceived the information concerning the trials, and to describe their attitudes and experiences related to participation. In this study, study-specific, self-administered questionnaires were used as the data collection method, because a questionnaire was thought to allow a larger sample to be studied than interviews and to have the capacity to examine a large number of variables.

The aims of Study IV were to investigate differences in trial knowledge and motivations for participation among participants in phase 3 cancer trials, with respect to gender, age, education level and former trial experience.

Participants

Adult cancer patients participating in one of nine ongoing academic or pharmaceutical company-sponsored phase 3 RCTs at the Department of Oncology, Uppsala University Hospital, were asked to participate (Table 2). Seven of the trials were in an adjuvant setting (two breast cancer, two gastrointestinal cancer, one prostate cancer, one melanoma, and one gastric cancer). The other two trials were for palliative treatment of metastatic colorectal cancer and lymphoma.

Of the total 88 participating patients (response rate 92%), 53 were women and 35 men, with an age range of 31 - 80 years (median 61 years). In this study population, nearly half (48%) of the patients had been educated to university level and the majority (74%) were married/cohabitating.

Procedures

The clinical research nurses identified ninety-six patients participating in these ongoing phase 3 trials between 2009 and 2012 who fulfilled the inclu-

sion criteria of age over 18 years and being able to understand Swedish. Over the period of January to April 2012, the patients were asked to fill in the questionnaire. The patients consented to participate in the study by returning the completed questionnaire by mail.

Eighty-eight patients completed the questionnaire; of these, 52% were women with breast cancer. The distribution of women and men who responded to the questionnaire was similar to that in the population of patients participating in the clinical trials during the period. Eight patients (four women and four men; 8%) did not respond to the questionnaire. Of the non-respondents, three had breast cancer, two had prostate cancer, two had malignant melanoma and one had colon cancer. There were no obvious differences between the respondents and the non-respondents in terms of demographic characteristics (age, education, married/cohabiting and children).

Data collection method

The questionnaire *Cancer patients' views on participation in drug trials* (Appendix 1) is a study-specific questionnaire designed for participants in phase 3 clinical trials. The following steps were used in order to design the questionnaire, in line with the design recommended by Charlton (105) and Streiner and Norman (106) (Fig 4). The overall aim and research questions were first defined. The planning phase included identifying knowledge and ethics issues relevant to cancer trials from the literature and previously used questionnaires. A draft questionnaire was developed, followed by focus group interviews with participants in phase 3 trials. After pre-testing and revision of the questionnaire, experts (an oncologist, a psychologist, a philosopher, a bioethicist and a nurse) analysed the items and discussed scale design. Finally, after modifications had been made, a pilot version of the questionnaire was conducted: five patients who were participating in cancer trials were asked to comment on the wording and discuss their impressions of the items on the questionnaire.

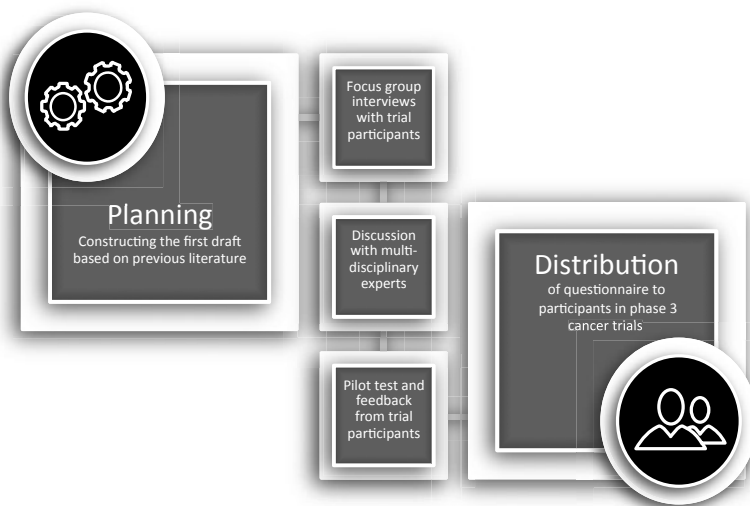


Fig. 4 Flowchart of the questionnaire design, in line with recommendations from Charlton (107) and Streiner et al. (106).

The questionnaire consisted of:

1. Demographic data (gender, age, marital status, whether they had children, whether their children were aged <18 years, education and occupation) and whether they had previous experience of participating in a clinical trial (8 items).
2. Items allowing answers on a six-grade scale [endpoints from ‘don’t agree at all’ (1) to ‘completely agree’ (6)]. These questions measured the participants' understanding of the trials, along with their attitudes and experiences related to participation. It was possible to add a comment to some of these items (49 items).
3. Items to be answered on a visual analogue scale [endpoints from ‘not important’ (0 mm) to ‘very important’ (100 mm)]; the questions were about their motivations for participating in the clinical trial (8 items).
4. Items to be answered on a seven-grade scale [endpoints from ‘very poor’ (1) to ‘excellent’ (7)]; the questions were about health and quality of life during the past week these questions were taken from EORTC QLQ-C30 [(108); (2 items)].

Data analysis

The Statistics Package for the Social Sciences (SPSSv20) was used for analysing the results and descriptive statistics were used for the descriptive aims (Study III).

To investigate factors that may have influenced differences in participants' understanding of and motivations for participating in phase 3 cancer trials, the patients' gender, age (<65 years or ≥65 years), level of education (12 years of education or university level), and previous experience of clinical trial participation (yes/no) were analysed using the Mann-Whitney test (Study IV). A p value <0.05 was considered statistically significant. Stratification of patients by age, <65 or ≥65 years, is in line with the definition of older or elderly persons used in most developed countries (109).

Table 1. Patient characteristics are presented in absolute numbers (n=102). Lack of data indicates that the subjects were not asked.

| Participants in phase 1 (study I) and phase 3 (studies III and IV) clinical cancer trials | | | | |
|--|-----------------|-------|-----------------|-------|
| | Phase 1 n=14 | | Phase 3 n=88 | |
| Age, years | | | | |
| Mean | | 63 | | 61.1 |
| Range | | 51-81 | | 39-80 |
| Gender | | | | |
| Male | 9 | | 35 | |
| Female | 5 | | 53 | |
| Marital status | | | | |
| Married/ cohabitating | | | 66 | |
| In relationship, but living apart | | | 9 | |
| Single | | | 13 | |
| Have children | | | 81 | |
| Children < 18 years | | | 16 | |
| Lack of data | 14 | | | |
| Education | | | | |
| Below university level | 9 | | 45 | |
| University level | 5 | | 42 | |
| Missing | | | 1 | |
| Current main occupation | | | | |
| Employed | | | 34 | |
| On sick leave | | | 8 | |
| Unemployed | | | 2 | |
| Disability pension | | | 5 | |
| Retired | | | 38 | |
| Lack of data | 14 | | 1 | |

| | | | | |
|----------------------------------|----|--|----|--|
| Types of cancer | | | | |
| Breast | | | 48 | |
| Prostate | 4 | | 20 | |
| Colorectal | | | 8 | |
| Pancreas, lymphoma or stomach | 1 | | 4 | |
| Malign melanoma | 5 | | 8 | |
| Lung | 4 | | 0 | |
| Previous trial experience | | | | |
| Yes | 2 | | 32 | |
| No | 12 | | 56 | |

Ethical considerations

Patients diagnosed with cancer are in a very vulnerable position; respect and consideration were shown to all participants. Research in trial participants with advanced incurable cancer (Study I) can bring up important ethical issues, because the participants are in a vulnerable situation and in great need of medical care. One of the issues is the extent to which it is an unnecessary burden for patients to participate in an interview study. On the one hand, they would be contributing to worthwhile knowledge and, on the other hand, they are being brought into a situation where emotional reactions can arise, because a cancer diagnosis always has an existential character. However, emotional reactions are not necessarily only negative. Trial participants in Study 1 were asked in person at the oncology clinic or the research centre if they would participate. Participants were given oral and written information. The information described the purpose and design of the study, that it was voluntary, that they could withdraw from the study at any time, and that all answers would be handled confidentially. They were also given an individual information letter with the e-mail addresses and telephone numbers of the researchers, so that they could contact the researchers if they had any concerns about the study. Participants were also allowed to bring along a support person to the interview if they so wished. Before the start of the interview, written informed consent was obtained. After the end of the interview, the researcher made sure that the informants were as well as could be expected; some stayed to reflect for a moment when they were sure that the recording was finished.

In the questionnaire study, informed consent was given by returning the questionnaire, as specified in the patient information.

This thesis was performed in agreement with Swedish law (110) and the Declaration of Helsinki (34). The Regional Ethics Review Board in Uppsala, Sweden, granted ethical approval for the studies included in the thesis (Dnr 2011/018). Because of inclusion difficulties in Study I, an additional application was submitted to the Ethics Review Board in Uppsala concerning the addition of a number of patients from the Karolinska University Hospital in Stockholm.

Summary of findings

Study I

Two categories and eight sub-categories emerged during the process of qualitative content analysis (102). The interview results were summarized under the theme heading *Renewed hope by participation in phase 1 clinical trials*. The categories and subcategories are included in the theme and the results are presented in the text below.

The decision-making process and trial comprehension

- Trust in the doctor
- Comprehension of the information
- Easy decision
- Alternatives to participation
- Shared decision-making with relatives
- Clutching at straws

Experience of participation

- Feeling notable
- Feeling cared for

The informants often did not have an optimal or clear understanding of the trial's purpose. Some informants thought that they had had no real option other than to participate, as they were not responding to conventional therapy and had a short life expectancy. Some informants related participation to clutching at straws in a desperate situation in which no treatment options were effective. The act of reaching out to experimental research was likened to stretching for a solution, no matter how rational the choice was. The clinical trial nurtured their hope in a worrisome and desperate situation, and made them feel seen and cared for. Most of the informants reported that they trusted the doctor and his/her medical competence. None of them had discussed alternatives to participating in the trial with the oncologist, but some of the informants had talked with their relatives about participation.

Study II

Hope of a miracle cure is one motive for participating in phase 1 clinical cancer trials. Communication of hope may encourage patients to participate and may enhance their quality of life. However, participation in the trial may also deprive them of an opportunity to spend the remainder of their lives as they would otherwise have wished. Much depends on the kind of hope involved. There were three forms of hope entertained by trial participants: i) hope that provided a sense of meaning in itself, ii) realistic hope, and, iii) hope that could be seen as clutching at straws. The first two forms are not ethically problematic; on the contrary it may be important that patients have and can sustain these kinds of hope, and healthcare professionals have an important role to play here. The third form of hope, on the other hand, could be ethically suspect in the context of phase 1 trials since it is indicative of misconceptions concerning the trial. Study II advocated a cautious approach when informing patients about a trial.

Study III

It was also apparent that most of the patients (80%) were satisfied with the information they had received (Table 3). When asked if the doctor took her/his time in explaining the content of the trial, circa three quarters of the respondents thought the doctor did so (Table 3). More than 60% perceived the doctors and nurses as interested in the participants' experiences. About half of the respondents agreed with the statement 'contact with the research nurse has allowed me to receive better care than I would have received outside the trial' (Table 3). Most (60%) understood what adverse reactions the treatment could cause, but some (20 %) were not aware of the possibility of adverse drug reactions (Table 4). Additionally, they understood the most basic aspects of the design (86%), and the concept of randomization (Table 4). Finally, they were positive toward and satisfied with trial participation, had trust in the medical system, and preferred to share the decision-making process with their relatives or the clinicians. Some patients (20%), however, required more information on what participation entailed and found it hard to ask questions because they did not know what to ask about (Table 4). Almost one third of the patients stated incorrectly that new treatments are tested on patients only if it is believed that the new treatment has no adverse effects, whereas 46% of the patients answered correctly, that treatments are tested even if adverse effects might occur (Table 4).

Hope for a cure and contributing to research that can help future patients were reported as the most salient reasons for participation in the phase 3 cancer trials (Table 5). The patients participated in the hope of personal health benefits, but were also motivated by contributing to research that

could help future patients. Access to better examinations was also an important factor for participation. When finally asked “Which of these reasons was the *most important* to you?” hope for personal medical benefit was the most frequently cited motivation (41%). Contributing to research that could help other people was the second most significant reason given by the respondents (28%). Nearly 20% of respondents reported two to four sets of reasons for participating in the clinical trial (combinations of getting well, helping others, access to examinations, giving something back in return and a duty to help).

Table 3. Overview of items regarding experiences of participation

| Experience of participation response rate in numbers N= (%) | Agree | Disagree |
|---|--------------|-----------------|
| My experience of participating in the trial has corresponded well with the information I have received about the trial (84) | 67 (80) | 3 (3) |
| The doctor took his time in explaining the content of the trial (83) | 60 (73) | 7 (8) |
| Based on my experience, I would recommend to others that they participate in cancer treatment trials (80) | 65 (82) | 5(6) |
| The research nurse has been interested in my experiences of the treatment in the trial (82) | 56 (69) | 9 (11) |
| The doctors have been interested in my experiences of the treatment in the trial (84) | 54 (64) | 11 (13) |
| Contact with the research nurse has allowed me to receive better care than I would have received outside the trial (80) | 38 (48) | 20 (25) |
| I am taken better care of within healthcare because I am participating in a trial (84) | 29 (35) | 38 (45) |
| If a pharmaceutical company finances a trial, my desire to participate is lower compared to if it is healthcare/society conducting a trial (84) | 25 (30) | 41(49) |
| I sensed expectation from the doctor that I would consent to participate in the trial (87) | 10 (12) | 61(70) |
| I worry that participation in the trial can hurt me (85) | 7 (8) | 62 (74) |
| I worry that my participation in the trial carries a risk that I will receive lower quality treatment than I otherwise would have received (86) | 2 (2) | 80 (93) |
| I have regretted consenting to participate in the trial (83) | 1 (1) | 80 (96) |

Table 4. Scores for knowledge about participation in clinical trials in all participants and between-groups comparisons

| Items† | All participants (n=88) | | Male (n=31-34) | | Female (n=51-54) | | <65 y (n=47-48) | | ≥ 65 y (n=35-40) | | Education below university level (n=41-43) | | Education at university level (n=39-40) | | Formal trial experience (n=31-32) | | No former trial experience (n=51-54) | | |
|--|----------------------------|-------------------|--------------------|--------------------|---------------------|--------------------|--------------------|-------------|---------------------|-------------|--|--------------------|---|--------------------|--|--------------------|---|--------------|-------------|
| | Agree n (%) | Disagree n (%) | Median (Q1; Q3) | Median (Q1; Q3) | Median (Q1; Q3) | Median (Q1; Q3) | Mean (SD)‡ | Mean (SD)‡ | Mean (SD)‡ | Mean (SD)‡ | Median (Q1; Q3) | Median (Q1; Q3) | Median (Q1; Q3) | Median (Q1; Q3) | Median (Q1; Q3) | Median (Q1; Q3) | Mean (SD)‡ | Mean (SD)‡ | |
| | | | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | |
| If I don't want to participate in a trial I will be offered treatment that is normally given for precisely my disease | 82(99) | 0(0) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | |
| The most important purpose of conducting a trial like the one I'm participating in is to improve the treatment methods | 84(98) | 1(1) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | |
| In a randomized trial, patients are randomly allocated to different treatment alternatives in order to compare effects and side-effects between the different treatment alternatives | 78(90) | 3(4) | 6 (6;6) | 6 (5;6) | 6 (5;6) | 6 (5;6) | 5.42 (1.16) | 6 (6;5)* | 6 (6;5)* | 6 (6;5)* | 6 (5;5;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (5;6) | 6 (5;6) | 6 (6;6) | 6 (6;6) | |
| Participating in a trial is voluntary – completely without conditions | 82(95) | 2(2) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | |
| I can withdraw from a trial at any time – without giving a reason | 7(9) | 72(86) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (5;6) | 4.97 (1.88) | 6 (6;6)* | 5.67 (1) | |
| The treatment I receive in the trial is determined randomly (called randomization) | 74(86) | 10(12) | 4 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 6 (6;6) | 5 (1;6) | 5 (1;6) | 5 (1;5) | 1 (1;5) | |
| New treatments are tested on patients only if it is believed that the new treatment has no side-effects | 28(34) | 38(46) | 6 (2;5) | 3 (1;5) | 3 (1;5) | 3 (1;5) | 3 (1;5) | 3 (1;5) | 3 (1;5) | 3 (1;5) | 4 (1;5) | 3 (1;5) | 3 (1;5) | 3 (1;5) | 3 (1;5) | 3 (1;5) | 3 (1;5) | 3 (1;5) | |
| I can withdraw from a trial only if I just experience side-side effects | 19(22) | 64(76) | 1 (1;5) | 1 (1;1) | 1 (1;1) | 1 (1;4) | 1 (1;2) | 1 (1;4) | 1 (1;4) | 1 (1;4) | 1 (1;2) | 1 (1;4) | 1 (1;4) | 1 (1;4) | 1 (1;5) | 1 (1;5) | 1 (1;5) | 1 (1;2) | |
| I can only withdraw from a trial if I have a good reason | 7(9) | 72(86) | 1 (1;2) | 1 (1;1) | 1 (1;1) | 1 (1;1) | 1 (1;1) | 1 (1;1) | 1 (1;1) | 1 (1;1) | 1 (1;1) | 1 (1;1) | 1 (1;1) | 1 (1;1) | 1 (1;3) | 1 (1;3) | 1 (1;3) | 1 (1;1)** | |
| | | | | | | | | | | | | | | | | | | 2.06 (1.72) | 1.31 (1.12) |

†Higher values indicate higher knowledge (maximum value 6). For the last two statements, lower values indicate higher knowledge (maximum value 6).

‡For statistically significant differences

*p < 0.05 ** p < 0.01

Table 5. Why patients agreed to participate and between-groups comparisons of scores of motives for participation in phase 3 clinical trials

| Items† | All participants (n=88) | | Male (n=31-34) | | Female (n=51-54) | | <65 y (n=47-48) | | ≥ 65 y (n=35-40) | | Education below university level (n=41-43) | | Education at university level (n=39-40) | | Formal trial experience (n=31-32) | | No former trial experience (n=51-54) | |
|--|-------------------------|----------------------|-----------------------|-----------------|------------------|-----------------|-----------------|-----------------|------------------|-----------------|--|-----------------|---|-----------------|-----------------------------------|-----------------|--------------------------------------|--|
| | Mean value | Not important n= (%) | Very important n= (%) | Median (Q1; Q3) | | Median (Q1; Q3) | | Median (Q1; Q3) | | Median (Q1; Q3) | | Median (Q1; Q3) | | Median (Q1; Q3) | | Median (Q1; Q3) | | |
| | | | | Mean (SD)‡ | Mean (SD)‡ | Mean (SD)‡ | Mean (SD)‡ | Mean (SD)‡ | Mean (SD)‡ | Mean (SD)‡ | | | | | | | | |
| The hope of getting well/slowing the disease | 9.7 | 0(0) | 26(30) | 9.7 (8.9;9.9) | 9.6 (7.8;10) | 9.7 (5.3;10) | 9.7 (9.4;10) | 9.7 (9.4;10) | 9.7 (9.4;10) | 9.7 (9.4;10) | 9.7 (9.4;10) | 9.7 (9.4;10) | 9.7 (9.4;10) | 9.7 (9.4;10) | 9.5 (8.2;10) | 9.7 (8.4;10) | | |
| That I was contributing to research that can help others in the future | 9.7 | 0(0) | 21(24) | 9.5 (8.6;9.8) | 9.7 (9.1;10) | 9.6 (8.6;9.9) | 9.7 (9.3;10) | 9.7 (9.3;10) | 9.7 (9.3;10) | 9.7 (9.3;10) | 9.7 (9.3;10) | 9.7 (9.3;10) | 9.7 (9.3;10) | 9.7 (9.3;10) | 9.4 (8.7;9.8) | 9.7 (9.1;10) | | |
| That I had access to extra exams | 8.7 | 0(0) | 8(10) | 9.0 (5.9;9.7) | 8.7 (6.3;9.7) | 7.8 (4.5;9.6) | 9.0 (5.3;9.7) | 9.0 (5.3;9.7) | 9.0 (5.3;9.7) | 9.0 (5.3;9.7) | 9.0 (5.3;9.7) | 9.0 (5.3;9.7) | 9.0 (5.3;9.7) | 9.0 (5.3;9.7) | 7.6 (5.4;9.3) | 9.2 (6.8;9.7) | | |
| That I would have access to better care within healthcare | 6.2 | 2(2) | 4(5) | 7.2 (1.8;9.0) | 5.2 (2.7;8.3) | 7.8 (4.5;9.6) | 9.0 (7.9;9.7) | 9.0 (7.9;9.7) | 9.0 (7.9;9.7) | 9.0 (7.9;9.7) | 9.0 (7.9;9.7) | 9.0 (7.9;9.7) | 9.0 (7.9;9.7) | 9.0 (7.9;9.7) | 6.5 (1.6;8.6) | 6.0 (2.5;9.1) | | |
| To give something back in return for the help I've received from healthcare/ society | 4.6 | 8(9) | 5(7) | 5.6 (2.7;9.4) | 2.0 (0.4;6.8)* | 1.7 (0.3;6.5) | 5.0 (2.0;9.4)* | 5.0 (2.0;9.4)* | 5.0 (2.0;9.4)* | 5.0 (2.0;9.4)* | 5.0 (2.0;9.4)* | 5.0 (2.0;9.4)* | 5.0 (2.0;9.4)* | 5.0 (2.0;9.4)* | 4.8 (1.2;9.2) | 4.4 (0.5; 7.3) | | |
| That my doctor thought so | 4.1 | 7(8) | 0(0) | 4.6 (1.2;6.1) | 2.5 (0.3;7.0) | 2.6 (0.4;5.7) | 4.8 (0.6;6.8) | 4.8 (0.6;6.8) | 4.8 (0.6;6.8) | 4.8 (0.6;6.8) | 4.8 (0.6;6.8) | 4.8 (0.6;6.8) | 4.8 (0.6;6.8) | 4.8 (0.6;6.8) | 4.2 (0.9;5.7) | 3.2 (0.3;6.8) | | |
| That those close to me thought I should | 2.4 | 8(9) | 6(1) | 5.2 (1.6;7.8) | 0.9 (0.2;4.9)** | 1.0 (0.2;5.1) | 5.0 (1.2;7.3)** | 5.0 (1.2;7.3)** | 5.0 (1.2;7.3)** | 5.0 (1.2;7.3)** | 5.0 (1.2;7.3)** | 5.0 (1.2;7.3)** | 5.0 (1.2;7.3)** | 5.0 (1.2;7.3)** | 1.4 (0.5;5.6) | 2.8 (0.3;6.5) | | |
| It felt I had a duty to help | 0.7 | 14(17) | 1(1) | 1.7 (0.5;3.9) | 0.5 (0.2;1.0)* | 0.5 (0.0;2.2) | 1.0 (0.4;6.0)* | 1.0 (0.4;6.0)* | 1.0 (0.4;6.0)* | 1.0 (0.4;6.0)* | 1.0 (0.4;6.0)* | 1.0 (0.4;6.0)* | 1.0 (0.4;6.0)* | 1.0 (0.4;6.0)* | 1.1 (0.4;2.9) | 0.5 (0.2;2.5) | | |

† The patients' reason(s) for participating in the cancer trial. The endpoints were scored from 0 (not important) to 10 cm (very important).

‡ For statistically significant differences.

* p < 0.05 ** p < 0.01

Study IV

The results of Study IV showed that the research subjects' understanding of important aspects of the trials was generally high, with only minor, although sometimes statistically significant, differences with respect to gender, age and education (Table 4). Those with previous experience of study participation were significantly less aware that a good reason is not needed to withdraw from the trial ($p=0.04$). They also had less knowledge of the right to withdraw from participation at any time without a reason ($p=0.005$; Table 4). Males more than females, and those ≥ 65 years more than those aged <65 years, were motivated to participate by a desire to give something in return for the help they had received from health care or the community ($p=0.015$ and $p=0.036$, respectively; Table 5). Males and older participants were also significantly more motivated to participate out of duty ($p=0.020$ and $p=0.013$, respectively). Males and older participants also felt it was more important that family or friends thought they should attend ($p=0.001$ and $p=0.003$, respectively; Table 5). Compared with those educated at a university level, those educated below university level were significantly more motivated to participate on the basis of hope for a cure or because of a desire to contribute to research ($p=0.008$; Table 5).

Discussion of key findings

The following discussion is structured in three parts. The first part discusses the empirical results, with additional research results from previously published literature focusing on participation in clinical cancer trials, and the ability of empirical studies to contribute to the wider body of knowledge regarding the consent process. The second part deals with the ethical question of hope and exploitation. The third part discusses the methodology of the studies.

Insight into patients' perspectives about participation

The patients who participated in the cancer trials were reportedly very satisfied with the experience (Studies I, III and IV). This supports previous findings (46). It was also apparent that most of the participants who signed a consent form for participation in a cancer trial were satisfied with the information given and understood enough of the information on the primary elements of a clinical trial to give truly informed consent, regardless of age, gender and education. However, although the information process appeared to work well in general, some results caused concern. The participants' understanding of clinical cancer trials, their motivation for participation and their decision-making processes related to participation will be more extensively discussed below.

Patient understanding of the consent information

Most of the patients in phase 1 trials felt that they had been sufficiently informed, despite some of them not having a clear understanding of the basic aspects of participation, such as the risks and the basic nature of phase 1 trials (Study I). Participants in phase 3 trials were satisfied with the information given in the consent form, and understood the primary elements of a clinical trial sufficiently to give truly informed consent, largely regardless of age, gender or education (Studies III and IV). However, a small group of participants overestimated the benefits, underestimated the risks and found it hard to ask questions, in addition to not understanding the alternatives to study participation (Studies I, III and IV). Obtaining informed consent is a challenging undertaking and patients do not always comprehend the true

nature of clinical trials. Many internal and external factors can influence the process of understanding what is entailed in a trial (61, 79). Some participants may lack focus because of their physical or psychological state, others might not understand because the information was poorly presented or explained.

If research subjects overestimate the possible benefits, underestimate the potential risks, or interpret research as a tailored treatment option, they can be said to be under a therapeutic misconception (Fig. 2). Results similar to those in Studies I and III were obtained in an Australian survey of oncology nurses, most of whom were actively involved in cancer trials (111). The majority of the nurses (>80%, n=192) noticed that research subjects often overestimated the benefits and that more than half underestimated or did not understand the risks and the fundamental nature of cancer trials. These results are also consistent with the findings of Jenkins et al. who studied the informed consent process in phase 1 trials at five UK cancer centres in 2011 (112). They used observation and interviews to study what oncologists said to presumptive participants, what the patients thought the oncologists had said, and what the patients recalled and understood afterwards. The results showed that important information was omitted, for example about the patient's prognosis, and that much of what the oncologists said was incorrectly understood by the patients, resulting in the conclusion that "what clinicians say and what patients hear or interpret can be two different things" (112).

In a study by Weeks et al. in 2012 (92), 1,193 patients with incurable colorectal or lung cancer failed to distinguish research from clinical care. Patients believed that the trial treatment was tailored for them; nearly 80% of the patients overestimated their potential therapeutic benefits (111). Since Studies I, III and IV all showed that patients typically put great trust in their doctors and nurses, the reason for this overestimation could be that research subjects expect their physicians to invite them to participate only if they expect the trial to promote their individual health interests. These results indicate that therapeutic misconceptions exist and that they are a challenge in early research (113). Further empirical studies are needed to identify risk factors for these misconceptions and to clarify how these risk factors can be identified. The fact that physicians often use 'ambiguous words', and that patients often interpret their meaning in an excessively optimistic way, is also of concern (114, 115). Words like 'treatment' appear to have a more positive meaning for patients than for physicians and, even when the physicians explicitly mentioned palliative treatment, the atmosphere of a 'curative aura' gave another impression (114).

The finding that some patients found it difficult to ask questions because they did not know what to ask, and required additional information (Studies I and III), is similar to the results of earlier studies, where some patients were unable to ask questions, mostly because they were too anxious or uncomfortable in the situation (116, 117). The fact that oncologists and research

personnel face considerable levels of stress and time constraints during the information session may be an influential factor here. The stress and time constraints might result in an environment in which patients or relatives do not remember what to ask, or feel that there is no available time to ask questions.

In Study IV, there were no differences among the subgroups (gender, age, education and previous experience of trial participation) after stratifying the data according to these parameters, aside from the finding that those with former trial experience seemed less aware of the facts around their voluntary status and withdrawal from the trial (Study IV). These results differed from those of Jenkins et al. (112) who found that experienced trial participants were more aware of the voluntary nature of their participation and their right to withdraw. Their result seems reasonable, as previously informed participants can be expected to bring this prior knowledge to the consultation. There are several possible explanations for our contrasting result. Patients with previous trial experience were diagnosed with cancer earlier than other patients, and the period between receiving the trial information for the first trial and receiving the trial information and questionnaire for this trial may have caused a memory bias; they may have overestimated how much they knew, and thus failed to pay the same attention to the consent information in our study. It is also possible that the clinicians believed that some patients had sufficient trial knowledge from their previous participation and consequently did not provide as much information as they would have offered patients with no former trial experience.

Since therapeutic misconception can be a barrier to genuine informed consent, the question arises of how to optimize the provision of consent information. Importantly, healthcare professionals should not shy away from discussing existential questions with patients who indicate unrealistic expectations of a miracle cure (118).

As shown in Study I, most trial participants could not remember discussing any alternatives to participation with the doctor. One reason for this finding might be that research subjects in phase 1 trials perceive themselves as fighting their cancer and therefore not requiring palliative care (86). This appears to be related to the view described in the literature that trial participants feel they are in less need of home help or emotional, psychological or spiritual support than other palliative-care patients (119).

In conclusion, early clinical trials seem to offer cancer patients with poor prognosis some form of support for coping with the emotional stress of their situation and for establishing new perspectives on the meaning and purpose of their lives. Efforts have been made to improve this process through changing the format of information delivery as objective assessments suggest that patients cannot recall having received adequate information to make an informed decision. However, further development of the information procedures is required. Improving the process of providing information to obtain

consent for participation in clinical research is of constant concern to regulatory authorities. Recently, the US Food and Drug Administration released draft guidelines for using a new electronic informed consent (E-IC) form for increasing the efficiency of trials and modernizing the application process (120). It is hoped that the E-IC will help prospective participants understand better what participation in a clinical trial entails by optimizing access to information and improving the ease of retrieval of consent. The information may be accessed even more easily by using electronic technology, such as text messages, graphics, audio-visual recordings, podcasts, and interactive websites. However, two systematic reviews have shown that the outcomes from using multimedia and audio-visual interventions as tools for improving the informed consent process for people considering participation in clinical trials remain largely unclear (121, 122). Bergenmar et al. (123) found that knowledge and understanding was not improved in research subjects who were randomized to receive the information required for consent to participate in phase 2 and 3 clinical trials from audio-recordings at home. It is apparent that further work on innovative methods of providing simplified improved consent information to presumptive research subjects is needed.

Reasons for participating in clinical trials

The results of the retrospective studies clearly indicated hope of therapeutic benefit as the most important motivation for patients to participate in phase 1 trials. The decision to participate in a phase 3 trial is likely to be multifactorial, based on hopes of potential therapeutic benefit, altruism and hopes of access to better examinations. Males and older patients were more likely to participate because of internal factors such as duty and external factors such as the influence of family or friends.

The findings of this thesis that participants in phase 1 clinical trials were strongly motivated by a hope for therapeutic advantage and had unrealistic expectations (Study I) echo the findings of other qualitative studies (86, 88), questionnaire-based studies of patients' views (66, 124, 125) and a study of oncology nurses' perspectives (111) also confirm these results. The majority of nurses (>80%) thought that patients sometimes have unrealistic expectations and will participate in anything that offers hope. It has previously been shown that patients with a poor prognosis who are participating in early phase trials are less motivated by altruism than other participants (53). The patients in Study I were willing to accept experimental treatment involving unpleasant procedures and difficult adverse effects in exchange for minor therapeutic self-benefit. This is in general in agreement with the findings of other studies, that patients with advanced cancer often choose aggressive treatment from a perspective of hoping for small medical advantages (88, 93, 111, 125).

Patients with advanced incurable cancer might have a different perspective from patients with curable cancer, as the former are confronting their mortality and might therefore be willing to test drugs with less promise of benefit and a significant risk of toxicity (93). Participants receiving adjuvant treatment (as the majority of patients in Studies III and IV were) might allow themselves to feel more altruistic because the trial drug is given in addition to the primary or initial cancer treatment and their overall prognosis is fairly good. It is possible that participants in phase 1 trials are a self-selected group, who are reacting to hard times by coping optimistically (53, 54, 88).

Participants in phase 1 trials (Study I) were happy to be part of a trial because participation nurtured their hope. Hope is complex and has an important role in life. It can ease suffering and help the patient at the end of their life to focus on positive events (52, 66, 113, 126). When patients appear to be expressing attitudes of optimism and faith (Study I), they could also be harbouring unrealistic hopes (113). Much thus depends on the kind of hope involved. Study II outlines three forms of hope entertained by trial participants: i) hope that provides a sense of meaning in itself, ii) realistic hope, and iii) unrealistic hope. The first two are not associated with ethical problems; in fact, it may be important that patients have and can sustain these kinds of hope, and healthcare professionals can have an important role to play in promoting them. Unrealistic hope, on the other hand, is ethically worrisome in the context of phase 1 cancer trials since it is indicative of misconceptions concerning the trial (113). The decision to participate may be made out of fear of dying that has triggered the patient to believe that any option is better than doing nothing, no matter how small the chances of therapeutic benefit are (88). To prohibit patients at the end of their lives from making a decision about participating in a clinical trial could deeply insult their personal autonomy or personally meaningful values, at a time when honouring those values should be most important. However, it is also important that patients have a realistic sense of the chances of therapeutic benefit from a phase 1 trial, so that they can do what they need to do in their remaining time. Unrealistic hope and optimism can also be the result of healthcare professionals wanting to bring stability to the uncertain lives of patients by keeping them engaged in treatment activities, as explained by the strong need for control in the western world. Such optimism could be seen as benefitting both parties, making the end of life less emotional and more optimistic (114).

This also ties in with findings from an empirical study by Olsson et al. (126) on the experience of hope among cancer patients, which found that hope helped patients at the end of life. Four types of hope were identified from the patient's perspective: 'convinced hope'; 'simulated hope'; 'seize-the-day hope' and 'gradually extinct hope'. With 'convinced hope', the patients were focusing on positive events and felt they had something to look forward to. They had energy to fight the illness and some even hoped for a

miracle cure. 'Simulated hope' included being absorbed by grasping for hope, even if the strategy and the things they hoped for were unrealistic. With 'seize-the-day hope', the patients tried to appreciate each moment of hope as it appeared; even if it was only fragmentary and increased their awareness of the limited time remaining, they still focused on seizing the day. With 'gradually extinct hope', the patients experienced slowly fading hope and decreasing physiological and psychological energy for finding meaning in life. The results of Olsson et al. (126) are largely supported by the results of Studies I and II in this thesis, although 'gradually extinct hope' was not reported in Study II. This may have been because of the distinction between the early and late palliative phases, since patients residing in palliative care facilities are closer to death and have thus progressed further in their processing of hope.

The forms of hope entertained might also partly be the result of social or institutional norms. "Giving-in and losing hope are frowned upon as socially unacceptable ways of dealing with disease" (86 p.743) and patients who are active in the battle against the disease might be influenced by cultural expectations inside or outside of health care (96, 97, 127). Such expectations can work as a two-edged sword. Communication of hope may stimulate patients to participate and may enhance their quality of life; however, participation in the trial may also deprive them of an opportunity to spend the remainder of their lives as they would have wished. A culture of hope within a research setting can nurture the research participant's hope for a miracle cure. The advice of Ambroise Paré, for example, to "always give the patient hope, even when death seems at hand" has influenced healthcare professionals worldwide and could be seen as a norm, with the aim of protecting the patient, but which lacks a clear notion of what giving hope really entails. This could be seen as an "unexamined, taken-for-granted practice of hope that may exert undue influence on the decision-making/informed consent for cancer research participation" (96).

The patients themselves were mostly positive about joining the study as a result of their hope. They indicated that they felt emotionally cared for and had a sense of wellbeing from participating, and that the clinical realities involved a good communication climate that was helpful in their daily life. They also related to researchers/clinicians as friends and enjoyed the familiar talk, check-ups and telephone calls (Study I). Previous research on patient satisfaction shows that individualized and personal support and information generally affects patient responses to and satisfaction with healthcare, but also affects compliance with medical treatment (57, 128). Well-being and hope can also be seen as helping patients to continue to fight their cancer and supporting them in living on instead of giving in to death (60, 129). However, this close relationship with the healthcare personnel also makes it important to ensure that patients are aware of the distinction between the re-

spective purposes of clinical care and research, in order to minimize the risk of therapeutic misconception.

The motivations for participation were sensitive to the effects of gender and older age. Male participants and those aged 65 years or older were significantly more driven by a wish to repay society for the help they had received, out of a sense of obligation and because of the influence of close relatives or friends (Study IV). The findings supplement previous interview-based studies that showed similar results (130, 131). Preferences for ‘helping’ or acting for the good of others, as an important motivator for participating in a clinical trial for older participants, have also been confirmed in a quantitative survey (132). The majority of participants preferred to share the decision-making whether or not to participate with their significant others, the physicians and/or the nurses (Studies I, III and IV). Earlier research also indicates that patients prefer a collaborative role with their significant others in treatment decisions (84, 133).

From knowing that participants in phase 1 clinical trials at times have inadequate knowledge about the primary purpose of the trial and alternatives to participating in research, they might suffer from therapeutic misconception. The question arises if these circumstances make the risk of exploitation likely.

Are patients in phase 1 clinical cancer trials vulnerable and exploited?

It has been established that therapeutic misconception can result from inadequate knowledge about the primary purpose of phase 1 trials and alternatives to participating in research. The question arises whether these circumstances increase the risk of exploitation.

Does the risk of unrealistic hope make phase 1 trial patients vulnerable? The concept seems to designate persons of lesser fortune, since the word ‘vulnerable’ has its origin in the word for wounded or harmed. Agrawal et al. (88) argue that typical participants in clinical cancer trials do not seem vulnerable, since they are often white, well-educated, with higher incomes, and such populations are not characteristically seen as vulnerable groups. These participant characteristics were also prevalent in our studies; the patients were white, aged between 31 and 80 years, and over half of them were educated to university level and were married/cohabitating (Studies I, III and IV). However, it may be that having an incurable disease makes one vulnerable.

The *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)* suggests that this is true:

“Vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, and patients in emergencies, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent” (134).

The ICH also define vulnerable research subjects as:

“Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate” (135).

According to Martin et al. (136):

1. All participants in research studies are vulnerable. That is why laws and guidelines provide a framework for research that protects the rights of participants.
2. Those in phase 1 cancer trials are at risk of being particularly vulnerable, because of the stress associated with expecting benefit from the study and their heavy dependency on others; therefore, they are in need of additional protection.

It seems reasonable to perceive patients in phase 1 clinical trials as being particularly vulnerable with regard to their possible overestimation of benefits, underestimation of risks and lack of knowledge of alternatives to participating in the research. As exploitation is usually thought of as taking advantage of someone’s vulnerability, an ethical challenge arises: are these particular subjects at risk of being exploited through participating in phase 1 trials? If so, what is an appropriate response?

Exploitation is the act of taking unfair advantage of others [Stanford Encyclopedia (137)].

When Stanford Encyclopedia explains the concept of exploitation, it looks misleadingly simple. This explanation only requires that the exploiter (A) should take unfair advantage of the exploited (B). While this notion is widespread, it has been contested. According to Goodin (138), four essential conditions define exploitation:

1. An asymmetrical relationship between A and B
2. B is in need of resources that B believes A can supply
3. B is particularly dependent upon A for the supply of these resources
4. A is in control of the resources that B believes he/she needs

It can be argued that 1 is superfluous, as conditions 2-4 provide the same content. Further, in order to fully represent the preconditions for exploitation, another condition must be added:

5. A uses their position (defined by conditions 2-4) to take unfair advantage of B.

It then becomes necessary to define 'unfair'. If both A and B agree to a transaction, and both feel that the outcome is beneficial, is it really unfair? When discussing exploitation in the context of research, Alan Wertheimer in Emanuel, 2008 (17) has suggested that there are two types of exploitation:

1. *Non-consensual and harmful* – in which the exploiter (A) is benefited and the exploited (B) is harmed and does not give valid voluntary consent;
2. *Consensual and mutually advantageous* – in which both the exploiter (A) and the exploited (B) benefit, and (B) provides valid voluntary consent (138).

An example of the first kind would be the Nazi medical experiments. The second type of exploitation can be exemplified by a third world woman who voluntarily agrees to be a surrogate mother, but who may be motivated by an economic incentive caused by poverty and deprivation and led by entrepreneurs and the fertility industry.

Clinical research performed in industrialized countries probably involves few research subjects who are exposed to exploitation in the form of non-consensual and harmful research. Consensual and mutually advantageous clinical trials are based on advantageous mutual benefits and valid informed consent. The ethical dilemma in the context of phase 1 oncology trials is that subjects often have the impression that the research is devised to benefit them personally because they do not appreciate the distinction between re-

search and standard care. In such a situation, we need to add two more risk factors for exploitation to Wertheimer's list:

3. *Consensual and non-mutually advantageous* – this situation is beneficial for A, but provides only a small chance of benefit for B, who has given valid voluntary consent.
4. *Non-consensual and non-mutually advantageous* – this situation is beneficial for A, but provides only an illusion that it is advantageous for B. B agrees to partake, but has not given valid consent, since it is based on misunderstandings or misinterpretations (therapeutic misconception).

In the third category, the research subject gives valid voluntary consent, based on information disclosure and comprehension, but participation is not advantageous in terms of potential therapeutic benefit. In the fourth category, the research subject will probably participate in anything that offers hope and is therefore at risk of being exploited (111). However, research subjects can also wish to participate without expecting therapeutic benefit. This is discussed further below.

In the fourth category, which is non-consensual and non-mutually advantageous, A benefits in terms of performing an investigation, but the research subjects (B) have not truly consented, because they believe that they will benefit. Various factors can affect a patient's ability to make an autonomous choice. Patients with end-stage cancer are dependent on their caregivers and can be unduly influenced by their expectations of how a 'good' patient behaves, justified or not. Other confounders include therapeutic misconception, hope for a miracle cure or misinformation (Study I). When informed consent is based on incorrect information or misunderstanding, it is not valid and is thus non-consensual.

Although patients in phase 1 cancer trials are in a risky situation where they can be taken advantage of, it has not been shown thus far that this actually happens. To do that, one has to show that criterion no. 5 above is fulfilled, i.e. that healthcare bodies or drug companies take unfair advantage of patients. Further discussion about unfairness is thus required. Some distinctions might aid this endeavour. What can be said is that patients at the end of life are vulnerable to exploitation. The vulnerability occurs because they are in a non-advantageous situation related to their small chances of responding to the treatment, even though they have consented to joining the trial and know how to withdraw. These patients are research subjects with unrealistic hopes who will probably consent to anything that offers them hope (111). Those who conduct the research are, however, in an advantageous position.

Methodological considerations

The studies in this thesis used a mix of qualitative, quantitative and philosophical methods. One of the main strengths of the studies was that participants were broadly selected; they came from several different clinical trials (three in Study I and nine in Studies III and IV) and, in Study I, they were recruited from two sites (university hospitals). Further, in Studies III and IV, the response rate was 92%.

Establishing trustworthiness

Studying the motivation and experiences of patients participating in phase 1 cancer trials raises both methodological and ethical issues. It is important to have access to rich study material that captures many different nuances and aspects in order to gain an understanding of how patients reason and how they experience these trials.

To establish credibility, some steps were taken in Study I to minimize potential distress. The following ‘safety’ factors are from Finlay et al. (119):

- The participants were allowed to talk freely, and to share the burdensome experiences without risking the aim of the study.
- The interviewer had a clinical background – so as to deal with patient information concerns.
- The patients were able to address feedback to one of the co-authors. In the consent paper, names, telephone numbers and e-mail addresses were included.

Presenting the participants’ quotes and describing the research process carefully achieved dependability. To improve the conformability, the authors discussed the analysis together and it was also discussed and scrutinized at a research seminar. The transferability was improved by participants being recruited from two different hospitals and by carefully describing the research context and the sample. It is possible that research subjects in phase 1 trials comprise a self-selected group that has the characteristics of being positive and embracing an active problem-focused coping mechanism. The number of phase 1 clinical trials in cancer in Sweden is relatively low and the recruitment process is complex. The median duration of survival in phase 1 study participants is slightly more than ten weeks, with a range of 1 to 119 weeks, according to Fussenich et al. (2). Most potential patients in this study died during the study period or were in too poor health to participate. The small number of ongoing phase 1 trials at the time of recruitment and the short survival of cancer patients participating in phase 1 trials could explain the most important enrolment difficulties in this interview study. Neverthe-

less, 14 patients from three different phase 1 trials, at two different hospitals, participated.

Establishing instrument validity and reliability

The relevant literature was analysed and previous questionnaires were studied. We found no validated instruments that addressed questions about the motivation behind participation in clinical cancer trials, the information provided and patients' experiences related to participation that were appropriate for a Swedish context. Therefore, the questionnaire used was developed specifically for this study.

Validation includes establishing that the questionnaire produces data that are reliable and factual and that measure what they were supposed to measure (139 p.196). Extensive validation or psychometric testing of the instrument was not carried out, but a draft questionnaire was developed, tested and retested in a sample of patients participating in a cancer trial, which is in line with the test-retest method recommended by Streiner and Norman (106). The final questionnaire instrument consisted of 66 questions and addressed themes in relation to trial participation: the decision-making process, the information received, understanding the information and any associated experiences. Internal validity (accuracy of the results) was ensured by the inclusion of open-ended questions in the questionnaire, which offered the participants an opportunity to comment freely on issues related to participation. The open-ended answers were, however, not included in the analysis. Similar items that measured the same aspects were also tested, and these showed internal consistency. The questionnaire seemed to be measuring what it was supposed to measure. However, one question [“In the trial I am participating in, the doctor chooses the treatment for me” (question 33)] was thought to be ambiguous, and related to additional possible answers. The question was intended to encourage respondents to say whether they believed the doctor could influence the randomization process (to treatment group vs control group). However, the question could also mean that the doctor chooses the non-research cancer treatment, or the doctor chooses whether the patient is eligible for the study (meets the inclusion criteria).

One of the problems with questionnaires is that the closed questions are standardized, and all participants are asked the same questions whether they are relevant or not. The benefits are that questionnaires are cost effective and are a useful way of gathering a lot of information from a large group of people and reaching a representative picture of the attitudes and characteristics of a large group. It was assumed that a self-administered questionnaire would result in a higher response rate than interviews would have because it would be less time-consuming.

There is always a risk of bias in research (139). Recall bias and reporting bias are two related biases that can threaten the internal validity of self-reported questionnaires. Recall bias is the most serious potential problem, because the ability to recall information is an important concern when assessing knowledge. Reporting bias occurs when people adjust their answers in order to give a 'better' answer. It is possible that participants in Study III and IV answered the questionnaire in a way that they thought was right, socially accepted or based on the questioner's perspective, rather than sharing their real opinions. This can be a particular problem with cancer participants, since they are in a vulnerable situation and in a dependent position related to the need of professional care; social desirability bias can be a problem in this situation. However, when respondents found it difficult to answer because they did not know, they often answered in free text that they did not know, e.g. regarding questions about the implementation of the trial (questions 36 and 37), and many answered in the margin that they did not know if the trial was conducted by healthcare departments alone or in collaboration with a pharmaceutical company.

The questionnaire was not tested for reliability, i.e. for the degree to which it would produce the same result if administered again and the degree to which the results would be transferable to populations other than the target population (140). However, the studies appear to be representative of the population. Ninety-two percent of the 96 possible participants (n=88) responded to the questionnaire. Of these, 60 % (n=53) were women, and of these 35% were older than 65 years. Forty percent were men, and of these 64% were older than 65 years. Patients were recruited from many different clinical trials and a number of diagnoses were included. In this study population, nearly half of the patients (48%) had education to university level and the majority was married/cohabitating (74%). These analyses were based on Swedish speaking, mostly well educated cancer patients from homogeneous ethnic backgrounds, who had actively consented to participate; the generalizability to cancer patients in other cancer trials and other ethnic groups is unknown. These results may not be representative of all patients in clinical cancer trials, but are representative of patients in clinical cancer trials in Sweden.

Empirical ethics

In study I, some patients agreed to participate in phase I trials in the hope of a cure, without understanding the primary purpose of the trial. This raised ethical questions that were not deliberated further in Study I but were examined in Study II. Ethical deliberation can make use of empirical findings to challenge our understanding of the moral issues involved. In bioethics, the focus on empirical ethics has also called for context-sensitivity (141). There is an emphasis on starting with accurate facts (Study I), and focus is also

placed on the relevant moral issues for those in the situation, beginning with an understanding of the moral positions actually held by those affected (Study II). Empirical ethics can often be seen as an example of what Thomson called institutional ethics, “which focuses on the ethical problems created or significantly shaped by the institutional setting in which they occur” (142). This kind of ethical problem has not received as much attention as problems at the individual level. Empirical results can provide bioethics with more precise means of understanding and discussing institutionally based moral conflicts such as those occurring, for example, when there is a conflict between respect for patient autonomy and concerns for the well-being of the patients. Ethical deliberation needs conceptual development, relevant collaborated facts as a basis, and critical discussion of the norms and values that are operative in a practice.

Conclusions and clinical implications

The main conclusions and clinical implications that can be drawn from the studies in this thesis are summarized here:

- This thesis found that most participants in phase 1 clinical cancer trials neither have any clear understanding of the primary scientific aim of the clinical trial nor of the small potential for treatment benefit.
- The participants in phase 1 trials were strongly motivated by the generally unrealistic hope for therapeutic benefit. When the chances of a cure are miniscule, as for participants with end-stage cancer in phase 1 trials, hope can play and provide meaning. However, unrealistic hopes could deprive patients of the opportunity to spend their remaining lives as they would otherwise choose.
- Phase 3 trial participants mostly understood the basis for the trials, although there were some knowledge gaps about side effects and the right to withdraw. Some participants also found it hard to ask questions and felt they needed more information about what it entails participating.
- The reasons for participating in phase 3 RCTs are likely to be multifactorial, with an emphasis on potential therapeutic benefit, altruism and access to better examinations. Men and the elderly participated more markedly from the motives to give back for the help they had received in care and to share the decision with significant others or physician.
- These results imply that the informed consent process work mostly well, with good results within most subgroups. However, improvements to the consent process should be sought for patients with end-stage cancer who are participating in phase 1 trials. This is a vulnerable group as they have very little potential for treatment benefit and risk harm from participating. Additional information about alternatives to research participation also needs to be clarified in the consent dialogue so that the patients can make informed decisions about the end of their lives.

Future research

Further studies are suggested in the following areas to complete the research presented in this thesis:

- Because only patients were included in this thesis, future research should focus on the physicians' and nurses' perspectives and how they view their roles in the informed-consent process.
- It is also important to consider physicians' and research nurses' understanding of how they inform and counsel patients in the decision-making process in terms of the results of this thesis.
- Follow-up studies should analyse the internal and external factors affecting participation according to relevant subgroups in order to gain more knowledge about motivation for participation.
- Future interviews and questionnaire studies should also explore the motivation behind the decision to decline participation and investigate trial knowledge in cancer populations in general.
- It is recommended that, in order to protect participants' autonomy and improve their understanding of the process and the aims of the trial, the informed-consent process should become an evidence-based discipline like other practices in health care (17 p.658). Future research should therefore evaluate written consent documents for phase 1 trials with the aim of improving the consent process.

Svensk sammanfattning (Swedish summary)

Bakgrund

Få sjukdomar har så stor påverkan på det moderna samhället som cancer. Enligt Socialstyrelsen (2009) kommer var tredje person under sin livstid att drabbas av cancer. I Sverige har antalet diagnostiserade cancerfall ökat kraftigt under de senaste årtiondena. Denna uppgång kan delvis förklaras med att befolkningen har blivit äldre, men även när man tar hänsyn till detta har många typer av cancer blivit vanligare. Socialstyrelsen presenterar i en rapport, *Cancervården i Sverige* (143) en ny prognos som tyder på att det under de närmaste 10 – 15 åren kommer att ske en betydande ökning av olika cancersjukdomar. Enligt Möller et al. (144) förväntas en prevalensökning med ungefär 30 procent fram till 2020. Prognosen är mycket varierad för olika typer av cancersjukdomar, dock är idag överlevnaden tio år efter diagnos betydligt bättre än under de senaste decennierna.

Tusentals framtida patienter kommer att delta i kliniska läkemedelsprövningar, vilket är en förutsättning för att utveckla nya behandlingar. Trots det finns väldigt lite forskning på patientperspektiv. Detta har uppmärksammats bland annat av Myndigheten för vårdanalys i betänkandet *Starka tillsammans* (98) som har till syfte att utreda behovet av en nationell samordning av kliniska studier i Sverige. I betänkandet framhålls vikten av att tillvarata patientperspektivet och att öka patientens delaktighet i och inflytande över sitt deltagande i klinisk läkemedelsforskning. Det är således viktigt att få ökad insikt i varför patienter väljer att delta i kliniska prövningar för läkemedel och hur de upplever sitt deltagande.

Syfte

Syftet med denna avhandling var att beskriva och analysera kunskap, beslutsfattande och hopp hos cancerpatienter som deltar i kliniska läkemedelsprövningar.

Metod

För att uppfylla det övergripandet syftet med avhandlingen behandlar de fyra delarbetena olika perspektiv kring deltagandet och inkluderar både empirisk (kvalitativ och kvantitativ metod) och etisk metod. Studierna har godkänts av den Regionala etikprövningsnämnden i Uppsala (Dnr 2011/018). Patienter rekryterades från de onkologiska enheterna vid Akademiska sjukhuset i Uppsala och Karolinska universitetssjukhuset i Stockholm (delstudie I).

I den första delstudien var intervjuer den mest lämpliga metoden för insamling av det empiriska materialet. Under den 11 månader långa datainsamlingen identifierades 61 patienter av forskningssjuksköterskor vid två svenska universitetssjukhus som potentiella deltagare till studien. Alla patienter hade långt framskriden cancer, svarade inte längre på standardbehandling och var inskrivna i en av tre pågående prövningar (fas-1). Av dessa 61 patienter kunde 45 inte delta p.g.a. för dålig hälsa eller för att de avled. Fjorton patienter samtyckte till att delta och data samlades in med hjälp av semi-strukturerade individuella intervjuer. I denna studie har intervjuerna analyserats med hjälp av kvalitativ innehållsanalys (102).

I den andra delstudien gjordes en etisk analys av vetenskapliga, etiska och sociala dimensioner av hopp som motiv vid deltagande i fas-1-prövningar.

I den tredje och fjärde delstudien användes ett studiespecifikt frågeformulär, då inget befintligt frågeformulär fanns tillgängligt för att inhämta hela den mängd empiriskt kvantifierbara data som efterfrågades.

Frågeformuläret skickades till 96 cancerpatienter som deltog i en av nio randomiserade kliniska studier som pågick vid Akademiska sjukhuset i Uppsala. Åttioåtta patienter besvarade enkäten (92 %); 95 % av dessa var patienter i adjuvant behandling och 5 % deltog i kliniska prövningar inom ramen för palliativ vård. För att beskriva och analysera materialet användes Statistics Package for the Social Sciences (SPSS v20).

Sammanfattning av resultaten

I den första delstudien var syftet att undersöka om patienterna hade förstått patientinformationen och vilka motiv patienter hade för sitt deltagande i fas-1-prövningar. Resultaten visade att informanterna primärt var motiverade av ett hopp om bot. De var positiva till sitt deltagande och uppskattade den me-

dicinska och psykologiska uppmärksamhet de fått, vilken fick dem att känna sig speciella och viktiga. Patienterna hade emellertid orealistiska förväntningar om terapeutiska fördelar och en bristande förståelse av det vetenskapliga syftet med fas-1-prövningar.

I den andra delstudien låg fokus på hoppets roll för cancerpatienter som deltar i fas-1-prövningar. Hopp om en mirakelkur är ofta ett viktigt motiv för att delta i fas-1-prövningar. Att hysa hopp kan förbättra livskvaliteten, men det kan också beröva svårt sjuka patienter möjligheten att tillbringa slutet av sitt liv enligt sina egna förutsättningar och val. Mycket beror på vilken typ av hopp som är inblandad. Institutionella normer för att kommunicera hopp i hälso- och sjukvården kan påverka patientens beslut. Dessa resultat har båda normativa och kliniska implikationer.

I den tredje delstudien var syftet att undersöka motiv för deltagande i cancer RCTs, bedöma om patienterna förstod informationen de fick, och beskriva patienternas upplevelser av deltagande i läkemedelsprövning. Två viktiga motiv identifierades för deltagande i en prövning: hopp om bot och altruism. Bättre tillgång till cancer-specifika undersökningar var också ett viktigt motiv.

Patienterna ansåg att de hade fått tillräcklig med information och betänketid, och var positiva till att delta och hade förtroende för sjukvården. Majoriteten tog beslutet att delta i samråd med sina familjer eller/och läkare. En tredjedel av deltagarna instämde i det felaktiga påståendet att nya behandlingar testas på patienter bara om de tros sakna biverkningar.

I den fjärde delstudien var syftet att undersöka om det finns skillnader i kunskaper och motiv för att delta i fas-3-prövningar, med hänsyn till kön, ålder, utbildningsnivå och tidigare erfarenhet av prövningar. Resultaten visade att patienters kunskap om viktiga aspekter kring sådana prövningar var hög, med smärre skillnader med avseende på kön, ålder och utbildning. Deltagare ≥ 65 år och de med tidigare erfarenhet av studier hade mindre kunskap om rätten att avbryta medverkan. Jämfört med kvinnliga deltagare och män < 65 år så motiverades äldre män i större utsträckning till att delta utifrån en önskan om att betala tillbaka för den hjälp de fått av sjukvården/samhället, av plikt, eller för att deras familj eller vänner ansåg att de skulle delta. Jämfört med högskoleutbildade deltagare var de utan högskoleutbildning mer motiverade att delta utifrån ett hopp om bot eller en önskan om att bidra till forskning.

Slutsats

I detta projekt har vi erhållit en djupare kunskap om varför patienter väljer att delta i läkemedelsprövningar, hur de ser på sitt deltagande och samtyckesprocessen, samt hoppets roll i beslutsprocessen. Resultaten visade att samtyckesprocessen verkar fungera relativt väl, med goda resultat inom de flesta subgrupper. Majoriteten av deltagarna ansåg att de hade fått tillräcklig med information och betänketid. Många patienter som deltog i fas-1-prövningar hade däremot en bristande förståelse av det vetenskapliga syftet med fas-1-prövningar och orealistiska förväntningar om bot. Majoriteten av patienterna i fas-3-prövningar var främst motiverade av att delta på grund av ett hopp om bot eller för att hjälpa framtida patienter. Hopp om en mirakelkur kan förbättra livskvaliteten, men det kan också beröva svårt sjuka patienter möjligheten att tillbringa slutet av sitt liv enligt sina egna förutsättningar och val. Patienter med cancer som deltar i fas 1-studie är en utsatt grupp eftersom de har mycket liten behandlingspotential i kombination med en påtaglig risk för skada och kräver därför speciell uppmärksamhet.

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UPPSALA
UNIVERSITET



ATT DELTA I FORSKNING

*En enkät om medverkan i
läkemedelsstudier*

Ansvariga för studien är:

Centrum för forsknings- & bioetik, Uppsala universitet

Klinisk forsknings- och utvecklingsenhet, Onkologkliniken, Akademiska sjukhuset

Cancerpatienters syn på medverkan i läkemedelsprövningar

– frågan om medverkan i en undersökning

Det saknas kunskap om varför cancerpatienter väljer att delta i läkemedelsprövningar, och syftet med denna undersökning är att fylla denna kunskapslucka. Därför skickar vi ut detta frågeformulär till Dig, som medverkar i en läkemedelsprövning.

Din medverkan är frivillig. Dina uppgifter kommer inte att användas i något annat syfte än för detta forskningsprojekt. Ditt svar kommer att vara kodat och endast undertecknade har tillgång till kodnyckeln. I de svar som redovisas framgår aldrig vad enskilda personer har svarat.

Personuppgiftsansvarig är Uppsala universitet. Den information Du lämnar till oss kommer att hanteras enligt gällande sekretessbestämmelser och Personuppgiftslagens (PuL) regler. Enligt personuppgiftslagen (PuL) har Du rätt att gratis en gång per år ta del av de uppgifter om Dig som hanteras och vid behov få eventuella fel rättade. Studien är godkänd av den regionala etikprövningsnämnden i Uppsala.

Data insamlas bara vid detta tillfälle och beräknas ta ca 15 minuter. Ingen ersättning utgår. Genom att returnera frågeformuläret ifyllt samtycker Du samtidigt till att delta i denna enkätstudie.

Tveka inte att ringa eller maila oss om Du har frågor. Ansvariga för undersökningen är:

Tove Godskesen, leg sjuksköterska och doktorand, Centrum för forsknings- & bioetik, Uppsala universitet.
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Telefon: 018-471 62 33. E-post: ulrik.kihlbom@crb.uu.se

Ett stort tack på förhand för din medverkan!

Frågor om din livssituation

Dagens datum / 20

Jag är

- () Man
- () Kvinna

Ålder år

Mitt civilstånd

- () Ensamstående
- () Särbo
- () Gift/sammanboende med partner

Egna barn

- () Nej
- () Ja, jag har (ange antal) Ange antal barn under 18 år som bor hemma

Jag har tidigare deltagit i en forskningsstudie (även kallad klinisk prövning) utöver den jag nu deltar i

- () Ja
- () Nej

Jag har följande utbildning

- () Grundskola
- () Gymnasieutbildning eller yrkesutbildning
- () Utbildning på högskola eller universitet

Min huvudsakliga sysselsättning för tillfället?

- () Förvärsarbetande
- () Sjukskriven
- () Arbetslös
- () Sjukpensionär
- () Pensionär
- () Student

Mitt yrke

Frågor om deltagande i forskningsstudier

Läs följande påståenden och sätt ett kryss (X) i rutan vid det svar som stämmer bäst för dig

Frågor om informationen inför deltagande i studien

Instämmer
inte alls

Instämmer
helt

▼ ▼ ▼ ▼ ▼ ▼

- | | | | | | | |
|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. Jag förstod den muntliga informationen | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Jag förstod den skriftliga informationen | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Jag förstod alla ord och uttryck som läkaren använde vid informationen | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Jag tyckte att den information jag har fick var tillräcklig | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. Jag skulle önskat mer information om vad det innebär att delta i studien | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. Jag fick hjälp av någon (i eller utanför familjen) att förstå den skriftliga informationen | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. Jag fick hjälp av min läkare/forskningssjuksköterska att förstå den skriftliga informationen | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 8. Det var svårt att ställa frågor på grund av att jag inte visste vad jag skulle fråga om | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 9. Läkaren tog sig god tid att förklara innebörden av studien | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 10. Läkaren kopplad till studien var den som gav mig bäst information om studien | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 11. Forskningssjuksköterskan kopplad till studien var den som gav mig bäst information om studien | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

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12. Om du inte tyckte informationen var tillräcklig, försök att precisera vad du saknade

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Frågor om ditt beslut att delta i forskningsstudien

Instämmer
inte alls

Instämmer
helt

| | ▼ | ▼ | ▼ | ▼ | ▼ | ▼ |
|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 13. Jag beslutade mig för att medverka i studien i samråd med mina anhöriga | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 14. Jag beslutade mig för att medverka i studien i samråd med läkaren | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 15. Jag beslutade mig för att medverka i studien i samråd med forskningssjuksköterskan | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 16. Jag tycker att jag fick tillräckligt med tid för att bestämma mig för om jag ville delta eller inte | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 17. Jag överlämnade beslutet att delta i studien till läkaren | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 18. Jag beslutade mig för att medverka i studien helt utan samråd med andra | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 19. Jag kände en förväntan från läkaren att tacka ja till deltagande i studien | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ |

Frågor om medverkan i en forskningsstudie

Instämmer
inte alls

Instämmer
helt

| | ▼ | ▼ | ▼ | ▼ | ▼ | ▼ |
|--|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 20. Jag oroar mig för att mitt deltagande i studien gör att jag riskerar att få en sämre behandling än jag annars skulle ha fått | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 21. Jag förstod vilka biverkningar behandlingen i studien kan ge | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 22. Jag oroar mig för att deltagandet i studien kan skada mig | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 23. Jag tycker att risken för biverkningar är en nackdel med studiedeltagande | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 24. Att delta i en studie är frivilligt – helt utan villkor | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 25. Att delta i en studie förväntas av mig | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ |

Frågor om medverkan i en forskningsstudie

| | Instämmer inte alls | | | | | Instämmer helt |
|--|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| | ▼ | ▼ | ▼ | ▼ | ▼ | ▼ |
| 26. Jag kan gå ur en studie bara om jag får biverkningar | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 27. Jag kan gå ur en studie när som helst - utan att ange skäl | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 28. Jag kan gå ur en studie bara om jag har bra skäl | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 29. Om jag inte vill delta i en studie kommer jag att erbjudas den behandling man brukar ge för just min sjukdom | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ |

Frågor om genomförandet av studien

| | Instämmer inte alls | | | | | Instämmer helt |
|--|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| | ▼ | ▼ | ▼ | ▼ | ▼ | ▼ |
| 30. Det viktigaste syftet med att genomföra en studie av den typ jag deltar i är att förbättra behandlingsmetoderna | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 31. Nya behandlingar testas på patienter bara om man tror att den nya behandlingen inte har några biverkningar | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 32. Den behandling jag får i studien bestäms av slumpen (kallad lottning eller randomisering) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 33. I den studie jag deltar i väljer läkaren behandling åt mig | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 34. Jag förstod hur behandlingen skulle genomföras och följas upp | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 35. I en randomiserad studie lottas patienterna till olika behandlingsalternativ för att jämföra effekt och biverkningar mellan de olika behandlingsalternativen | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 36. Den studie jag deltar i genomförs i samarbete med läkemedelsföretag | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 37. Den studie jag deltar i genomförs av sjukvården/samhället utan medverkan av läkemedelsföretag | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ |

Frågor om dina förväntningar och åsikter om forskningsstudier

| | Instämmer inte alls | | | | | Instämmer helt |
|--|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| | ▼ | ▼ | ▼ | ▼ | ▼ | ▼ |
| 38. Jag får en bättre medicinsk vård genom deltagande i studien än genom behandling utanför studien | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 39. Jag får ett bättre omhändertagande i sjukvården genom att jag deltar i en studie | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 40. Om ett läkemedelsföretag finansierar en studie minskar min vilja att delta jämfört med om det är sjukvården/samhället som genomför en studie | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 41. Om ett läkemedelsföretag finansierar en studie för att utveckla ett nytt cancerläkemedel bör de betala en ersättning till mig för "sveda och värk" och den extra tid jag lägger på studiedeltagandet | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 42. Om sjukvården/samhället finansierar en studie för att förbättra cancervården bör de betala en ersättning till mig för "sveda och värk" och den extra tid jag lägger på studiedeltagandet | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ |

Dina erfarenheter av medverkan i forskningsstudien

| | Instämmer inte alls | | | | | Instämmer helt |
|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| | ▼ | ▼ | ▼ | ▼ | ▼ | ▼ |
| 43. Läkarna har varit intresserade av mina erfarenheter av behandlingen i studien | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 44. Forskningssjuksköterskan har varit intresserad av erfarenheter av behandlingen i studien | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 45. Kontakt med forskningssjuksköterskan har gjort att jag fått ett bättre omhändertagande än jag hade fått utanför studien | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 46. Min erfarenhet av att delta i studien har stämt väl överens med den information jag har fått om studien | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 47. Jag har ångrat att jag tackade ja till att delta i studien | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 48. Jag skulle utifrån min erfarenhet rekommendera andra att delta i studier av cancerbehandling | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ |
| 49. Om du upplever fördelar med att delta i studien, försök precisera vilka | | | | | | |

Hur viktiga var följande skäl när du bestämde dig för att medverka i studien?

Här vill vi att du markerar på skalan med ett kryss (X) 0 = inte viktigt, 10 = mycket viktigt. Markera vad som stämmer bäst för Dig. Se exempel nedan.

0 _____ X _____ 10

50. Hoppet om att bli frisk/ sjukdomsförloppet skulle bromsas
0 _____ 10
51. Att jag bidrog till forskningen som kan hjälpa andra i framtiden
0 _____ 10
52. Att betala tillbaka för den hjälp jag har fått från sjukvården/samhället
0 _____ 10
53. Att jag fick tillgång till extra undersökningar
0 _____ 10
54. Att jag skulle få tillgång till bättre omhändertagande i sjukvården
0 _____ 10
55. Att mina anhöriga tyckte så
0 _____ 10
56. Att min läkare ansåg det
0 _____ 10
57. Det upplevdes som en plikt att ställa upp
0 _____ 10
58. Vilket av dessa skäl var viktigast för dig?
.....

Din hälsa och livskvalitet under senaste veckan

Sätt en ring runt den siffra mellan 1 och 7 som stämmer bäst in på dig för följande frågor

59. Hur skulle du vilja beskriva din **hälsa** totalt sett under den vecka som gått?

| | | | | | | |
|----------------------|---|---|---|---|---|----------------|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Mycket dåligt | | | | | | Utmärkt |

60. Hur skulle du vilja beskriva din totala **livskvalitet** under den vecka som gått?

| | | | | | | |
|----------------------|---|---|---|---|---|----------------|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Mycket dåligt | | | | | | Utmärkt |

Om du har synpunkter på någon enskild fråga eller kommentarer till detta frågeformulär kan du göra det här

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Tack för att din medverkan!

Acta Universitatis Upsaliensis

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from the Faculty of Medicine 1112*

Editor: The Dean of the Faculty of Medicine

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