Patients in Clinical Cancer Trials. Information, Understanding and Decision-Making

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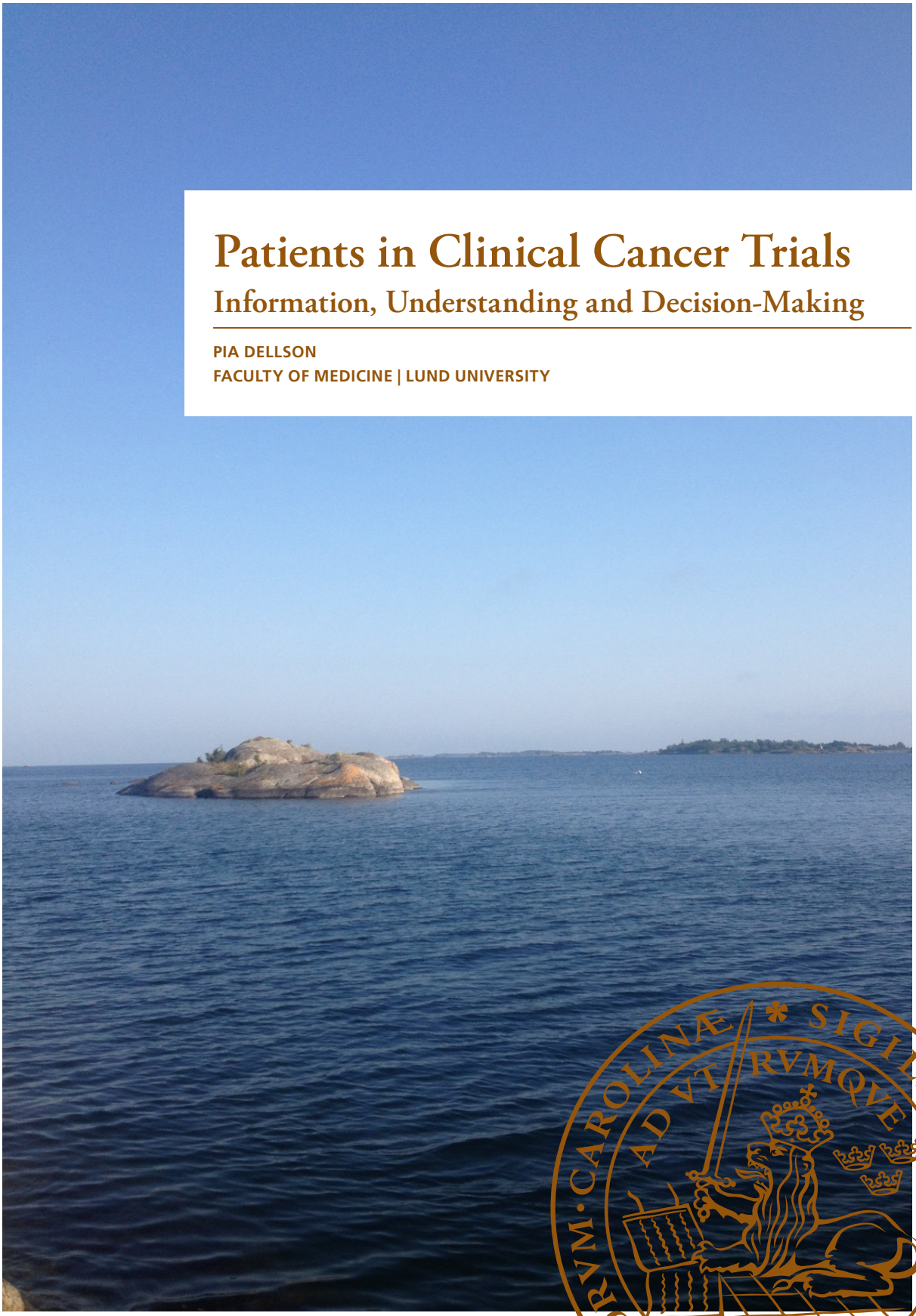

Patients in Clinical Cancer Trials

Information, Understanding and Decision-Making

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Pia Dellson, MD, BA

LUND
UNIVERSITY

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Information, Understanding and Decision-Making

Abstract
The informed consent process for clinical trials (CTs) is complex. Patients must be able to understand the information given to be able to make an informed decision. This thesis aimed to explore patients' and patient representatives' views, factual knowledge, and perceived understanding of patient information in clinical cancer trials, and to investigate how patients' understanding may be correlated to their decision-making and their physicians' assessment of their understanding.

In Studies I and II, focus group interviews were conducted in which patient representatives with experience of breast and colorectal cancer respectively examined informed consent documents (ICDs). Their suggestions for improving breast cancer ICDs were validated by an independent group of patient representatives. These results were then presented as a guide for writing ICDs. The main conclusion was that ICDs need better graphic design in order to facilitate readers' orientation in and processing of information. All ICDs should therefore be designed by a team including patient representatives, professional writers and graphic designers.

Study III was a questionnaire pilot study which showed that patients consider their understanding to be higher than the patient understanding assessed by their informing physicians. Neither the patients' nor their physicians' ratings correlated with the patients' factual knowledge, as measured by the instrument Q-PUR. This pilot study needs validation in an independent setting. The main conclusion was that the informed consent process would benefit from informing physicians acquiring and applying specific communication skills in order to assess patient understanding more precisely, the better to tailor the information given to the needs of the individual patient.

In Study IV, patients who had decided to participate in a CT were interviewed individually about how they reasoned when making this decision. The results showed that the decision to participate was often immediate and guided by emotions and a trusting relationship with health care professionals. Important factors for the decision-making process included knowledge of the right to withdraw from the CT and explicit comparisons between the treatment alternatives included, and also those not included, in the CT. Patients in palliative situations were sometimes unaware of the fact that their disease was no longer curable. For CTs in the palliative setting, the treatment alternative 'best supportive care' should therefore be stated as one option. The main conclusion was that these factors need to be addressed specifically in the informed consent conversations.

The overall conclusions are that better graphic design of ICDs is essential and that informing physicians must acquire and apply specific communication skills in order to improve the informed consent process.

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Clinical cancer trials, informed consent documents, patient understanding, decision-making

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Information, Understanding and Decision-Making

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En som prövar sig fram, det är en människa.

Kerstin Ekman

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List of papers

This thesis is based on the following original publications, which will be referred to in the text by their Roman numerals:

I. **Dellson P**, Nilbert M, Bendahl PO, Malmström P, Carlsson C.
Towards optimised information about clinical trials; identification and validation of key issues in collaboration with cancer patient advocates.
European Journal of Cancer Care (Engl) 2011;20(4):445-54.

II. **Dellson P**, Nilbert M, Carlsson C.
Patient representatives' views on patient information in clinical cancer trials.
BMC Health Services Research 2016;16:36.

III. **Dellson P**, Carlsson C, Nilbert M, Jernström H.
Patients' and physicians' disagreement on patients' understanding of clinical cancer trial information. A pairwise pilot study of mirroring subjective assessments compared with objective measurements.
Manuscript submitted.

IV. **Dellson P**, Nilsson K, Jernström H, Carlsson C.
Patients' reasoning regarding the decision to participate in clinical cancer trials – an interview study.
Trials 2018;19:528.

Preface

In order truly to help someone else, I must understand more than he
– but certainly first and foremost understand what he understands.

Søren Kierkegaard

Communication is a complex matter. For information to result in understanding it needs not only to be transmitted but also to be received. And there's the rub. Physicians often relay information without knowing how and to what degree the patient understands it, or even registers it. They are often not to blame; the medical curriculum has traditionally contained very little education on this subject.

Choices are important, above all in oncology, where a choice can result in life or death. We cure more patients than ever before, but cancer can still be life-threatening. Many live longer and better, many are cured, but none of the treatments we give are harmless; every one of them comes with a price. And it is sometimes hard to tell if it will be worth it. With unknown treatments, such as in clinical trials, the choice can be even harder.

One individual values the treatment possibilities that a clinical trial can offer; another values the absence of eventual side effects more highly. Hope and fear, and doing everything that can be done, come into the equation as well. As physicians, we can never know what path a person will decide to take. We can only try to facilitate people's understanding of the facts and options, and help them come to a decision that is in line with whom they are and how they want to live their lives; a decision that is meaningful to them.

As an oncologist and psychiatrist, working clinically in psychosocial oncology and cancer rehabilitation, I have met many cancer patients struggling to understand their diagnosis and prognosis, and to make choices about their treatments. I have worked as a psychotherapist and as a communication skills trainer for physicians, and these two approaches have made me acutely aware of the intricacies and pitfalls of human communication. This thesis is an effort to make use of all of my own knowledge and experience, together with the voices and assessments of the patients, in an attempt to further the understanding of how patients understand information and make meaningful decisions concerning clinical cancer trials.

Lund, March 2019

Abbreviations

ACT	Acceptance and Commitment Therapy
ARCAD	Aide et Recherche en Cancérologie Digestive
CIOMS	The Council for International Organizations of Medical Sciences
CT	Clinical Trial
GCP	Good Clinical Practice
HCP	Health Care Professionals
ICC	Informed Consent Conversation
ICD	Informed Consent Document
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
LIX	Läsbarhetsindex
NIH	National Institute of Health
NVivo™	Software programme for qualitative analysis (Trade Mark)
Q-PUR	Questionnaire – Patients' Understanding of Research (name of questionnaire)
QuIC	Quality of Informed Consent (name of questionnaire)
RCT	Randomised Clinical Trial
SCB	Statistiska centralbyrån
SFS	Svensk författningssamling
WHO	World Health Organization
WMA	World Medical Association
7Q-PAT	Patients' assessment of perceived understanding, seven mirroring questions (part of a questionnaire)
7Q-PHYS	Physicians' assessment of their patients' understanding, seven mirroring questions (part of a questionnaire)

Thesis at a glance

	Study I	Study II	Study III	Study IV
Study aim	To explore patient representatives' opinions of 3 ICDs for breast cancer clinical trials + Validation of the key findings	To explore patient representatives' views on 4 ICDs for colorectal cancer clinical trials	To compare self-assessed patient understanding of clinical trial information, with paired physician assessment + Measuring of patients' factual knowledge	To explore patients' decision-making process for participating in a clinical trial
Method	Mixed methods	Qualitative	Quantitative	Qualitative
Participants and data collection	1 focus group with 5 breast cancer patient representatives discussed 3 ICDs = 3 interviews + 18 breast cancer patient representatives completed questionnaires	14 colorectal cancer patient representatives, in 3 focus groups discussed 4 ICDs = 12 interviews	17 physicians, paired with 46 patients with different cancers; 92 paired questionnaires	27 patients with different cancers participating in clinical trials were interviewed
Data analysis	Inductive content analysis and descriptive statistics	Inductive content analysis	McNemar's test, Spearman's rank correlation and descriptive statistics	Inductive content analysis
Results and conclusions	21 suggestions for improved ICDs were identified; 18 of the 21 suggestions were validated as important. Most important issues: clearly structured information; explanations of medical terms; emotionally neutral expressions; accurate descriptions of side effects and their treatments; explicit comparisons between treatments included, and also those not included, in the clinical trial (e.g. regarding hospital time, examinations and long term follow-up).	Plain language and layout application, such as colours, fact boxes and illustrations, facilitate understanding. The ICDs should be designed by a team including patient representatives, professional writers, and graphic designers.	The informing physicians estimate the patients' understanding to be lower than the patients themselves estimate it. There was no correlation between assessed patient understanding and patient knowledge, as measured by the Q-PUR. The study needs validation in an independent setting.	The decision to participate in a clinical trial was often immediate and guided by emotions and a trusting relationship with health care professionals. An honest dialogue is vital about positive and negative trial effects, including options such as 'best supportive care' in the palliative setting.
Implications	Better graphic design of ICDs is essential and informing physicians must acquire and apply specific communication skills in order to improve the informed consent process.			

ICD: Informed Consent Document

Q-PUR: Questionnaire – Patient Understanding of Research

Background

Introduction to the thesis

Medical research has during the last decades undergone a development from regarding patients as research subjects to seeing them as partners, actively collaborating in clinical trials (Duffett, 2017). The studies in this thesis originated in an interest to investigate information about clinical cancer trials from the perspective of the patients. Hence all four studies focused on the patients, even when the study participants were physicians, as they were asked to assess the understanding of their patients. All of the studies were also explorative, both in their qualitative and their quantitative study designs.

When the project began, there were only a few qualitative studies exploring the patient perspective on informed consent documents (ICDs) and the patient decision-making process (Bell and Balneaves, 2015). There were also no direct comparisons between patient understanding and physicians' assessments of patient understanding, which we considered an important aspect of the information process. The thesis adds to the research on patient information in clinical cancer trials, presenting views, opinions, assessments, experiences and reasoning from a patient perspective. Hopefully this new knowledge can further the understanding of vital communication issues in clinical trials, such as: How is information best presented and transformed into understanding? And: How is that understanding used for making a decision to participate or not in a clinical cancer trial?

Clinical cancer trials

Clinical trials are the mainstay of treatment development for cancer diagnoses. The usual time frame for developing a new drug up to clinical use is ordinarily about ten years, and it is a costly procedure, including several clinical trials. Clinical trials of oncological drugs are usually conducted in three to four steps, divided into phases I-IV (Friedman et al., 2015).

In phase I, the drug is tested on a small number of healthy volunteers, and the primary aim of the trial is to document the safety of the drug in humans. In phase

II, the drug is tested on a small group of actual patients, and here the aim is to define a safe dose range and mode of administration, and possibly receive an indication of whether the drug has a treatment effect. The drugs that are found interesting enough can proceed to a full-scale phase III trial, which is commonly a randomised trial. The aim here is to compare the new drug to standard treatment in order to evaluate which is the most effective treatment. This often requires a large number of participants to show statistically significant effects. Phase IV trials are long-term follow-ups of the drug in order to identify eventual adverse events not yet documented in the earlier phases (Stolberg, 2004).

Clinical trials are usually initiated by a sponsor, most frequently a pharmaceutical company, which selects and cooperates with medically trained investigators such as physicians with appropriate specialities (ICH, 2016). There may be several investigators, particularly in the case of multi-centre trials. Clinical trials follow a strict protocol that includes ethical procedures such as obtaining informed consent from all participating patients.

Informed consent

A large number of regulations have been developed since the Second World War to protect participants in clinical trials. The first ethical code originated from the crimes committed by the Nazis, who conducted horrible experiments in the name of science. In order to prevent the recurrence of such atrocities, the Nuremberg Code was formulated, which is considered the cornerstone of research ethics, even though it is not legally binding (Markman and Markman, 2007). The first sentence establishes that 'The voluntary consent of the human subject is absolutely essential' (Government, 1949).

This code was followed in 1964 by the Declaration of Helsinki, which was developed by the World Medical Association, and which further clarified and interpreted the principles of ethical research (WMA, 1964/2013). In 1982, the Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization (WHO), developed the International Ethical Guidelines for Biomedical Research Involving Human Subjects. These guidelines were broadened in 2016 to encompass other aspects of research as well, and the title was changed to International Ethical Guidelines for Health-related Research Involving Humans (CIOMS, 2016).

Finally, in 1996, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) developed the Guideline for Good Clinical Practice, abbreviated GCP (ICH, 2016). This guideline was developed in order to provide a standard for the conducting and reporting of

clinical trials, and also to facilitate the harmonisation of legal procedures across the European Union, Japan, and the United States.

In addition to these guidelines, research conduct is also regulated by a number of national laws. In Sweden there are notably the Swedish Medicines Act (SFS 2015:315), and the Swedish Ethical Review Act (SFS 2003:460). Further, the Swedish Medical Products Agency must approve all clinical trials of medical products on humans. Worldwide, all clinical trials must be approved by a research ethics committee before commencing the recruitment of participants (Chin, 2008). In Sweden, a new authority, the Swedish Ethical Review Authority, has replaced the regional ethics committees and organises all ethical reviews since 1 January 2019.

All these guidelines and regulations include the requirement that the researcher must obtain informed consent from every potential research participant. Valid informed consent must include a minimum of five components (Beauchamp and Childress, 2013; del Carmen and Joffe, 2005):

- **Capacity**
  Potential research participants must be capable of making health care decisions, i.e. be able to process information rationally and appreciate the consequences of their decisions.
- **Voluntariness**
  Potential research participants must be free from coercion and able to act autonomously according to their own free will.
- **Information**
  Researchers are obliged to provide potential research participants with the information needed to understand the procedures in the trial, including risks, benefits and available alternatives.
- **Understanding**
  Understanding requires that potential research participants comprehend the information provided and can appreciate its consequences in their individual situations.
- **Decision**
  Potential research participants must present a decision authorising researchers to execute the proposed intervention.

The first two elements, capacity and voluntariness, are preconditions without which no informed consent can be considered valid. The following three elements, information, understanding and decision-making, are intimately linked and can be considered to constitute a stepwise process leading up to the aim of supplying an informed decision to participate or not in the proposed clinical trial. This thesis focuses on these three steps.

Information

All potential research participants must receive adequate information about a suggested clinical trial, and this information is usually given both in written and oral form. The amount of information should be adjusted according to the patients' needs and they should be given enough time to consider the information and make a decision (Behrendt et al., 2011). There is however no consensus on how much and what type of information are needed for it to be adequate. Originally, the standard of information was considered to be best determined by the professional community's customary practices, but the perspective has gradually shifted towards legal jurisdictions in combination with a reasonable person's standard, that is, the amount and type of information a reasonable person would consider important (Beauchamp and Childress, 2013). There is further development towards a subjective standard of information provision, which holds that it should be based on the specific needs of the individual person receiving it.

The written information is called an Informed Consent Document (ICD) and is produced by the sponsor and the investigators of the clinical trial in cooperation. All ICDs are then reviewed and approved by a research ethics committee, which in Sweden also includes members who are laymen, in order to supply this perspective to the review process (Etikprövningsmyndigheten, 2019). The oral information is usually provided by a physician during an informed consent conversation with the patient. However, research nurses often assist by confirming the information and answering any subsequent questions. Finally, if the patient decides to participate in the trial, he or she must sign the ICD before commencing any treatment.

Written patient information

Content

For decades there have been reports of Informed Consent Documents (ICDs) being too difficult and technical for patients to understand properly, which has obstructed the informed consent process (Albala et al., 2010). Furthermore, the elements enlisted in the guidelines above as facts to include in the ICDs, have become increasingly numerous with time, which has resulted in ever longer and more complex ICDs (Berger et al., 2009). Some researchers have even questioned the possibility of fulfilling the requirements of a fully informed consent due to this fact (Jayson and Harris, 2006). A number of papers suggest ways to shorten and simplify ICDs (Bleiberg et al., 2017; Jefford and Moore, 2008). Several studies have reported that shortened and simplified ICDs increased patient satisfaction but without improving understanding (Coyne et al., 2003; Davis et al., 1998), whereas some also showed improved understanding (Kim and Kim, 2015).

Readability

As the readability of ICDs has been questioned so frequently, a number of methods have been used to investigate the readability of ICDs and establish the optimal, or at least the maximum, level of difficulty suitable for ICDs. In English, the scale most frequently used is the Flesch-Kincaid Reading Grade Level scale (Kincaid, 1975). This scale presents a score as a U.S. grade level, thus indicating the number of years of education that the reader needs in order to be able to read the text. The average reading skill level of adult Americans is at about the eighth grade level, whereas the readability level of ICDs for cancer is frequently at the college level or above (thirteenth grade) (Doak et al., 1998). The mismatch is thus often five grade levels. Another study compared the templates for ICDs produced by research ethics committees with their own recommended reading grade levels (Paasche-Orlow et al., 2003). This study showed that the readability of the templates exceeded the recommended standard by 2.8 grade levels, and suggested that a reading level of fourth to sixth grade may be a suitable target.

In Sweden, the most common scale for deciding the readability level of a text is the LIX test (Björnsson, 1983): LIX = Sentence length + word length. This scale renders a score from 0 to 100, where the higher the score the higher the level of reading difficulty. A Flesch-Kincaid Grade Level score corresponding to the eighth grade is equivalent to a LIX score of 35-40 (Björnsson, 1968).

Layout

Very few of the guidelines mentioned give any instructions on the layout of the ICDs, even though there are indications regarding the importance of graphics and illustrations for improving learning and understanding, especially for low-literacy readers (Clark and Lyons, 2010; Kools et al., 2006; Austin et al., 1995). Sometimes the use of graphic layout elements is recommended, such as headlines, bold text or bullet points (Jefford and Moore, 2008; NIH, 2018). Studies of patients' preferences indicate that graphic representations are appreciated both for clarification of the information and for making the information more appealing and more easily accessible (Shneerson et al., 2013). There is however only a few studies on the evidence of layout and illustrations in ICDs (Bunge et al., 2010).

In education, research graphics have been studied more extensively, as presented by Clark and Lyons in their textbook Graphics for Learning (Clark and Lyons, 2010). Here, graphics are classified according to their functions, such as communication function or psychological function. Communication functions can among others be representational, as when depicting an object realistically, or relational, as when presenting a pie chart showing quantitative relationships.

Further, psychological functions of graphics can be to direct attention, minimise cognitive load, build mental models or support motivation. It is vital to analyse the

function of the intended graphic elements for them to be effective. Distracting illustrations, that do not direct readers towards the information goal of the text, can depress learning and should be avoided. On the other hand, low-complexity line drawings of a procedure together with a short text can be very effective, as they manage memory load by maximising the limited capacity of the readers' working memory.

In cognitive science, researchers define two modes in which written information can be expressed: formulation and visualisation (Holšánová, 2010). These two modes have different communication potential depending on the message, the recipients and the context. A central principle of reader-friendly design is the signalling principle, which states that a reader will take in more of a message if given cues to how the material is organised (Holšánová, 2010). Such cue structures can be rhetorical and graphic, such as key words and fact boxes. The function of cues is to structure the content, orientate the reader on the page, and direct the reader's attention to relevant parts of the information.

Oral patient information

Another important part of the informed consent process is the Informed Consent Conversation (ICC), in which the physician orally presents information about the clinical trial (Baer et al., 2011). Oral information can be tailored to the individual needs of the patient, allowing questions and concerns to be addressed. Physicians also tend to use more understandable language when talking to patients in comparison with the language of written information (Koyfman et al., 2016). Thus extended ICCs seem to be more effective than written trial information in improving patient understanding of clinical trial information (Flory and Emanuel, 2004).

Specific communication techniques can be used to enable patients to articulate concerns, such as agenda-setting, open questions and pauses (Back et al., 2009). Eliciting patient preferences or issues systematically and addressing them specifically can also ensure that patients have understood every important aspect of the alternatives in the clinical trial (Wade et al., 2009). Such communication skills need to be trained, and communication training has been shown to improve the quality of informed consent and patient satisfaction with ICCs (Hietanen et al., 2007). However, even though oral communication is such an important part of the informed consent process, none of the guidelines mentioned above addresses the matter of how ICCs should be conducted.

Understanding

There is no consensus in the literature on the nature and level of understanding needed for a person to give informed consent (Beauchamp and Childress, 2013), nor is there any consensus on the definition of understanding (Sand et al., 2010). There are also partly overlapping concepts for understanding, such as comprehension and knowledge, which are often used interchangeably in research literature, rendering the comparison of studies difficult. Some authors, however, consider understanding to comprise something more than knowledge:

> Understanding is an active process. It requires the connecting of facts, the relating of newly acquired information to what is already known, the weaving of bits of knowledge into an integrated and cohesive whole. In short, it requires not only having knowledge but also doing something with it. (Nickerson, 1985)

Understanding thus requires information processing, which can be challenging under clinical circumstances in cancer care. A patient may recently have received news of a cancer diagnosis or recurrence, and may sometimes be overwhelmed by emotions, which renders the taking-in and processing of information difficult (Back, 2006). To consider additional information about a clinical trial under these circumstances is an even more complex procedure (Thorne et al., 2013).

Furthermore, certain concepts, such as randomisation and equipoise, have been shown to be more difficult for patients to understand than others (Featherstone and Donovan, 2002). The basic condition for a randomised clinical trial is that researchers do not know which of the treatment alternatives investigated is the best, there is equipoise between them, and the reason to conduct the trial is to answer this research question (Friedman et al., 2015). In order to make a decisive comparison, the groups of patients compared need to be free from selection bias, and therefore the patients are randomly allotted to the treatment alternatives. However, patients have repeatedly been shown to confuse these research aims with the aims of clinical care, a phenomenon named ‘the therapeutic misconception’ (Appelbaum et al., 1987). Many patients seem to prefer to think that the physician is selecting the best treatment for them rather than to realise that no one actually knows as yet which is the best option (Stead et al., 2005).

Measuring instruments for understanding

Despite the lack of a common definition of patient understanding in clinical trials, a large number of studies have tried to measure this phenomenon, and they have come to mixed conclusions on how well patients understand various aspects of clinical trials (Griffin et al., 2006). A large number of interventions have been

tried to improve patient understanding (Flory and Emanuel, 2004; Kao et al., 2017). Enhanced ICDs and extended ICC interventions have been shown to improve knowledge outcomes (Nishimura et al., 2013), but according to a review by Tam et al., the proportion of participants who understood informed consent had not increased over 30 years (Tam et al., 2015).

Various methods have been used to investigate patient understanding, such as open-ended or semi-structured interviews, assessments of filmed patient-physician interactions, and a number of questionnaires of which most have been constructed for the purpose of being used in individual studies (Sand et al., 2010). Regarding the understanding of clinical cancer trials, only two validated questionnaires have to our knowledge been published with thorough descriptions of the questionnaire, its development, and testing. These two are the 'Quality of Informed Consent' (QuIC) (Joffe et al., 2001b) and the 'Questionnaire – Patient Understanding of Research' (Q-PUR) (Hutchison et al., 2007b).

The QuIC has two parts, one for patients' perceived understanding and one for their factual knowledge of clinical trials. The QuIC has been used in several studies, (Paris et al., 2006; Hietanen et al., 2007; Bergenmar et al., 2008; Bergenmar et al., 2011; Bergenmar et al., 2014; Brandberg et al., 2016; Spellecy et al., 2018). The Q-PUR consists of 12 questions on patients' factual knowledge, and has only been used in one study by the author who constructed the instrument (Hutchison et al., 2007a).

Physicians' assessment of patient understanding has to our knowledge rarely been measured. We have found only two examples, where the first is that in one of the studies regarding the QuIC, physicians were asked to assess their patients' general understanding of the clinical trial presented (Joffe et al., 2001a). Further, a study of an educational DVD presented data on a questionnaire in which physicians assessed whether or not their patients were able to make an appropriately informed decision on trial participation (Strevel et al., 2007). However, there are very few studies on physicians' assessments of patient understanding. The quality of these assessments is fundamental for physicians' ability to tailor their information to the individual needs of the patient.

In Studies I-IV in this thesis we use 'understanding' as meaning the subjective understanding perceived by an individual, and 'knowledge' as meaning the objectively measured knowledge of facts.

Decision-making

Factors influencing patients' participation in clinical trials

A number of factors influencing patients' decision to accept or decline participation in clinical trials have been identified. Acceptance is associated with a positive belief about the benefits of participating in clinical trials, such as treatment effects or an altruistic desire to help others (Godskesen et al., 2015; Truong et al., 2011; Jenkins et al., 2013). A trusting relationship with the physician presenting the clinical trial is also important, as is advice from family members to accept inclusion (Bell and Balneaves, 2015; Albrecht et al., 2008). High levels of perceived understanding and factual knowledge of the clinical trial information has also been shown to be associated with accepting participation (Brandberg et al., 2016). Declining participation is associated with patients having negative beliefs about clinical trials, such as concerns about the experimental nature of the treatment or about side effects, or lack of belief in treatment effects (Weckstein et al., 2011; Manne et al., 2015). Further, understanding and accepting the concepts of randomisation and equipoise also seem to be important, and have been shown to have a direct influence on the decision to participate in a clinical trial (Mills et al., 2003). Patients with a strong preference for one of the treatment arms in a clinical trial, when this treatment is also available outside the clinical trial, may decline participation in order to preserve their right to choose a particular treatment (Harrop et al., 2016a).

Decision-making models and theories

Making a decision is a process including both cognitive and emotional components. Medical research literature has traditionally focused mostly on the cognitive and factual aspects of decision-making. In psychology research and related cognitive science, the emotional aspects of decision-making have been studied intensely during recent decades, and emotions are now considered a vital part of decision-making and risk perceptions (Lacasse, 2017). A number of dual processing theories have emerged, which have in common the idea that there exist two different modes of processing regarding decisions. The most neutral terms are 'System I and System II processes', made well-known by Kahneman in his book 'Thinking, fast and slow' (Kahneman, 2011).

System I processes are categorised by being unconscious, automated, rapid and emotionally influenced (Evans, 2008). These processes are highly efficient in making everyday decisions with a minimum of effort, or rapid decisions under stress or threat. They have a high working capacity and are considered to be the

evolutionarily oldest default processes in humans as well as animals, since they are non-verbal and instinctive. System II processes, on the other hand, are conscious, deliberate, slow and energy-consuming. These processes have a low working capacity and are not used unless there is need for them, and time enough to implement them. They are uniquely human as they are linked to language and logical abilities. In stressful situations, people tend to apply System I processes more, as they are automatic and instinctive.

Another aspect of decision-making is found in the theories of Acceptance and Commitment Therapy (ACT), one of the most recent developments of cognitive psychotherapy. During ACT, the therapists help patients to become aware of their fundamental values in various areas of their lives, such as relations, work, and health (Hayes et al., 2012). These fundamental values are often connected to emotions, and carry information about which activities humans find it meaningful to engage in. When patients have identified a fundamental value they can start acting in accordance with it, thus enhancing their sense of meaningfulness and well-being. For example, many cancer patients mention a will to help others as a reason for entering a clinical trial (Godskesen et al., 2015). Such altruism may thus be a fundamental value in their lives, and acting in accordance with it, they create meaning in the difficult situation of illness.

Decision aids

Decision aids are interventions that help individuals to make treatment choices. They incorporate both the cognitive and the emotional aspects of decision-making, as they consist of two essential components. The first aims to improve patients' knowledge about the clinical trial and its treatment alternatives, often including visual representations of risks and benefits. The second component aims to clarify the patients' individual values and attitudes about the treatment alternatives and their consequences, often in the form of value exercises and various scenarios for the patient to consider (Bekker et al., 2003; Abhyankar et al., 2011).

Decision aids have been shown to be effective in the context of cancer treatment and screening decisions, increasing patient knowledge and satisfaction with the decision-making process as well as sometimes decreasing decisional conflict (Waljee et al., 2007; Martinez-Alonso et al., 2017). There are a few studies on decision aids for clinical trial decisions that have also been shown to improve knowledge and counteract decisional conflict or regret (Sundaresan et al., 2017; Politi et al., 2016; Juraskova et al., 2014).

Aims

The overall aim of the work presented in this thesis was to explore patients' and patient representatives' views, factual knowledge, and perceived understanding of patient information in clinical cancer trials, and to investigate how this may be correlated to their decision-making and their physicians' assessment of their understanding.

The specific aims were:

- To study patient representatives' opinions of the written patient information used in clinical trials for breast cancer and validate the key findings in an independent group (Paper I)
- To explore patient representatives' views and perceptions of the written patient information used in clinical trials for colorectal cancer (Paper II)
- To investigate how patients invited to take part in a clinical trial rated their own understanding of the clinical trial information, and to compare the results with the paired physician assessments of patient understanding (Paper III)
- To correlate these assessments with patients' factual knowledge of the oral and written clinical trial information provided (Paper III)
- To explore the process of patients' reasoning regarding the decision to participate in a clinical cancer trial (Paper IV)

Materials and methods

Säll är den som har till rättesnöre
att man bör noga tänka efter före.

Tage Danielsson

The focus of this thesis has been to investigate different aspects of patient information, understanding and decision-making concerning participation in clinical cancer trials. To capture various perspectives, and depending on the research question, a combination of data collection methods as well as data analysis methods were used, on a number of different materials and participants, both patients and physicians. This ensured that the object of investigation was elucidated from a variety of angles, in order to broaden the picture.

Participants and materials

Cancer is an umbrella term for a large number of different diagnoses, and cancer patients are therefore constitute a very heterogenic group, or rather a number of subgroups. Further, clinical cancer trials are conducted in many different settings, such as Phases I to IV, or with adjuvant or palliative purposes. In order to capture a range of aspects, potential participants with experience of different cancer diagnoses and in different trial settings were approached. In Study III, the physicians informing the patients were also included.

For the first two studies, cancer patient representatives (here called informants) were recruited through different patient associations. Two of the largest diagnosis groups were approached, breast and colorectal cancer, represented by the southern Swedish breast cancer patient associations (https://brostcancerforbundet.se/om-oss/), and the two Swedish patient associations for gastrointestinal diseases, Ilco (www.ilco.nu) and Mag- och tarmförbundet (www.magotarm.se) (Studies I and II).

Study I can be seen as a pilot study for Study II. In Study I, the female breast cancer informants discussed their opinions on three ICDs from randomised, double blind, phase III breast cancer trials, whereas Study II included informants of both

sexes with experience of colorectal cancer. To broaden the scope even further, the ICDs were selected from colorectal cancer trials in different settings, varying in research phases, treatment options, and reading level, both randomised and non-randomised. The clinical trials were de-identified so that the names of specific drugs or pharmaceutical companies were exchanged for 'the drug/treatment regimen' or 'the company' in brackets.

Details of the ICDs used in Studies I and II are described in Table 2. The recommended Flesch Kincaid Grade Level should not exceed eighth grade (NIH, 2018; Weber et al., 2017). The equivalent score of the Swedish LIX test should be 35–40 to be considered readable by most patients. These ICDs are seen to be in the upper part of 'medium difficulty, such as newspaper text' (score 40–50), bordering on or at the level of 'difficult, such as official texts' (score 50–60) (Björnsson, 1983). All the ICDs are therefore assessed as being texts that are too complicated.

Table 2. Features of the clinical trials and the ICDs in Studies I and II

ICD code	Phase	Treatment intention	Arms/ randomi-sation	Words	Head-lines	Medical terms: explained/ not explained	Flesch - Kincaid reading grade level	LIX score
1A	III	Adjuvant	2/+	1242	6	7/7	12	50
1B	III	Palliative	2/+	978	9	2/2	11	47
1C	III	Palliative	2/+	788	1	1/3	13	51
2A	I-II	Neoadjuvant	1/-	2075	20	14/53	12	45
2B	III	Palliative	2/+	1090	9	3/50	11	47
2C	I-II	Palliative	1/-	1032	13	0/15	12	46
2D	III	Adjuvant	2/+	748	1	3/16	12	47

In the last two studies, cancer patients were included who had been offered participation in a randomised phase III trial (Study III) or had accepted participation in a clinical trial (Study IV). The patients in both studies were diagnosed with a range of different cancers. Study III also included the physicians who had been informing the patients. Each physician could participate a maximum number of five times in the study, to avoid any single individual dominating the study material.

Methodological considerations on participants and materials

Participants

In Studies I and II, the informants were patient representatives as described above, recruited through patient associations, where the presidents contacted members

who they thought would be interested in participating in the studies. This kind of self-selecting sample may result in a subgroup of participants with above average engagement and knowledge. There is also no information on dropout, if any, thus limiting the possibilities of evaluating to what extent these informants represent the respective cancer populations. Further, how patients in a real situation might understand the ICDs may differ from how these patient representatives actually did, who were not in fact considering a suggested clinical trial.

In Studies III and IV, the participants were actual cancer patients considering a specific clinical trial. Here, recruitment was carried out by the research nurses responsible for carrying out clinical trials at the clinic. There was a column on the study list of participation for reporting patients or physicians who declined participation. However, no such cases were reported. In Study IV, it was decided only to include patients accepting participation in the clinical cancer trial offered. This limits the results, as is further discussed in the ethics section.

The sample sizes for the interviews in Studies I, II and IV may be questioned. They may seem small, but sample size in qualitative research is less important than the content of the interviews (Henricson, 2017). The researchers aim at interviewing the broadest available selection of informants, and at finding persons with experience of the phenomenon studied who are willing and able to formulate their experiences and views as thoroughly as possible (Morse, 2015). The goal is to shed light from a maximum number of angles on the phenomenon studied, in order to explore it exhaustively. Depth and variation are therefore more important than quantity.

We do not claim that the findings in these studies are universally generalisable, which is also true of other qualitative studies. However, with the limitations described in this section, it should be possible to transfer these findings to similar contexts in other western countries.

Considering the generalisability of the findings of Study III, 70 % of the physicians were male, which is a larger proportion than the average at the two clinics. On the other hand, 80 % of the patients were female. This reflects the diagnoses treated in trials at the two clinics, where breast and ovarian cancer trials were most active at the time of inclusion in this study. However, in total more males than females are diagnosed with cancer in Sweden (Socialstyrelsen, 2018).

The education level of the patients in Study III was high, and 50 % of them had a university education. For Sweden as a whole, 27 % of the population has a university education (SCB, 2018). Thus the findings from this population may not be generalisable to Sweden as a whole. Further, only patients considering participation in a clinical phase III trial could come into question, not the patients who declined. Moreover, the patients had to be asked to participate in our study by

the research nurse. Thus the group of participants in Study III may not be representative for all cancer patients considering participation in a clinical trial.

Finally, one limitation of the generalisability of the results in this thesis is the fact that all the patients in the four studies were Swedish-speaking. Hence no experiences and perceptions of clinical trials were captured from participants from linguistically more diverse populations. This fact may limit the results to being representative mainly for Swedish-speaking persons.

Materials

The ICDs selected for examination by the focus groups represented many different types of clinical cancer trials, as well as different text lengths and complexity. This gave the informants the opportunity to discuss different aspects of ICD understanding and design. The patient representatives and the ICDs were however only concerned with either breast or colorectal cancer, and persons with experience of other cancer diagnoses, or examining ICDs regarding other cancer diagnoses, might express different views.

In Studies III and IV, the clinical cancer trials that the patients were offered or had accepted participation in, were selected to give as broad a range as possible with regard to aspects such as cancer diagnoses, treatment intention (adjuvant/palliative) and treatment modalities. In Study III, all the clinical trials were phase III; they needed to be randomised trials as the questionnaire selected to measure patients' factual knowledge of clinical trials (Q-PUR) was designed for this type of trial. In Study IV, the trials were phase I-III. This was decided in order to make the variation as broad as possible, as the studies had an explorative intent.

Study design and data collection methods

A number of different data collection methods were used in the studies included in this thesis, depending on the research questions and study design. Qualitative methods, such as focus group interviews (Studies I and II) and individual interviews (Study IV), were used to explore firstly views and perspectives of written patient information for clinical trials and secondly patients' decision-making process. Quantitative methods in the form of different questionnaires were used both to validate the qualitative results (Study I), and to investigate patients' perceived understanding and factual knowledge of the written and oral information for RCTs, as well as the correlation of these results with the physicians' assessments of the patients' understanding and knowledge of RCTs (Study III).

Focus group interviews (Studies I and II)

In Studies I and II, data was collected through focus group interviews. Such interviews are a well-tried method for collecting a rich set of data on a particular topic from individuals with experience of this topic (Morgan, 1997). This method was therefore chosen for these studies of patient representatives' views and preferences regarding the written patient information for clinical trials. The patient representatives, here called informants, had received the ICDs in advance, and during the focus group interviews they discussed their opinions on how they understood the documents and presented suggestions on how they would have preferred them to be formulated or designed. All interviews were recorded and subsequently transcribed verbatim.

Compared to individual interviews, a focus group interview allows the informants to evolve their opinions in a dialogue and to inspire each other, comparing pros and cons and alternative views, which often results in a more diverse production of data than in the individual setting. The facilitators have an important role in conducting the interview and moderating the discussion so that all informants are able to express themselves, and as many different aspects of the topic as possible are illuminated (Patton, 2015; Henricson, 2017).

Individual interviews (Study IV)

In Study IV, data was collected through individual interviews. Here the research focus was to explore the reasoning of cancer patients who were in the actual situation of having decided to participate in a clinical trial. Individual interviews were chosen for data collection, as this method allowed the patients to express freely any aspect they wanted in as much personal detail as they preferred. Compared to group interviews, individual interviews allow each informant more time to develop their views, and an undisturbed opportunity to express thoughts and emotions about personal experiences (Dicicco-Bloom and Crabtree, 2006). All interviews were recorded and subsequently transcribed verbatim.

Questionnaires (Studies I and III)

In studies I and III, three different questionnaires were used. The questionnaires contained sections that were constructed specifically for these studies and one section that was translated from English to Swedish. The reasons for choosing questionnaires as the data collection method were several and depended on the research questions, and each questionnaire is presented in more detail below.

In Study I, a questionnaire was constructed to validate the primary results from the qualitative part of the study in a larger group of informants. This questionnaire

was constructed out of the themes and suggestions for improvements that the informants in the focus group presented during the interviews. These issues were rephrased as a list of 21 key statements, which could be scored as not/less/quite/very important (scores 1–4). For the validation part of the study, an independent group of 18 informants received the same three ICDs as the focus group informants, together with the questionnaire. The informants were asked to read the texts and to reflect on them while scoring the questionnaire.

Study III comprised two questionnaires, one for patients and one for physicians. The questionnaires contained the following sections.

Patient questionnaire:

1. Demographic section
2. Patients' assessment of perceived understanding, seven mirroring questions (7Q-PAT)
3. Patients' factual knowledge (Q-PUR)

Physician questionnaire:

1. Demographic section
2. Physicians' assessment of their patients' understanding, seven mirroring questions (7Q-PHYS)

Except for the Q-PUR, these questionnaires were constructed by the research team. The 7Q-PAT measured patients' assessment of perceived understanding of written and oral patient information. The 7Q-PHYS was a questionnaire with questions mirroring the ones in 7Q-PAT. The 7Q-PHYS measured how the informing physician assessed the patient's understanding of the information.

The Q-PUR questionnaire in Study III was a validated questionnaire designed by Hutchison et al., which contains 12 multiple-choice questions that measure factual knowledge about clinical trials (Hutchison et al., 2007b). It is called 'Questionnaire – Patients' Understanding of Research', abbreviated Q-PUR. This questionnaire was chosen in order to investigate whether there was any correlation between the patients' factual knowledge and the assessments of patient understanding, according to the patient and the physician respectively, and if so, which assessment was the more correct. The questionnaire was translated to Swedish and re-translated to English by professional translators and further revised by the article authors, to ensure that the questionnaire would be correctly represented in Swedish (Wenemark, 2017).

Mixed methods (Study I)

As described above, we used mixed methods for Study I. This is a research approach aimed at broadening the perspective through combining qualitative and quantitative methods in one study (Morgan, 2007). This can be done in a number of ways, but the combination used in Study I was an explorative sequential design, through qualitative exploration in the first step, and then quantitative validation of the patient representatives' views of written patient information in a second step (Henricson, 2017).

In the first step, focus group interviews were used for primary data collection. The results included a number of themes and suggestions for improvements, and out of these, 21 key issues were identified. In a second step, the key issues were validated through a questionnaire in an independent and larger group of breast cancer patient representatives. Combining qualitative and quantitative methods in this manner can be used to strengthen the results of a study (Johnson, 2004).

Methodological considerations on data collection

Interviews

Interviews were used in three of the studies in this thesis, first in the form of focus group interviews for Studies I and II, and later in the form of individual interviews in Study IV. Collecting data through interviews is time-consuming but renders a rich data set to analyse. Focus groups are often used when the aim is to investigate views and opinions concerning a specific object on which the discussion can focus (Patton, 2015). In a focus group interview, a variety of aspects tend to come up, as the informants inspire each other to associate further, agreeing with or contradicting the previous speaker (Henricson, 2017).

Individual interviews allow more time for each informant and the questions can be individually tailored (Henricson, 2017). The interviews in Study IV were conducted with open-ended questions to allow the patients to speak freely with a large amount of flexibility. The majority of the patients in Study IV presented their decision-making as a short narration of how they were diagnosed with cancer or a recurrence, how they were offered participation in a clinical trial, and how they reasoned when they came to the conclusion to accept participation. The interviewers could then ask subsequent questions.

Questionnaires

Questionnaire construction

The questionnaire in Study I was composed of 21 re-phrased suggestions from the patient representatives interviewed, on aspects of the ICDs they had discussed.

These 21 statements could be graded on a likert scale with four alternatives: ‘very important’, ‘rather important’, less important’, and ‘unimportant’. The scale had no midpoint and hence the respondents needed to ‘choose sides’, as the alternatives could be divided into one agreeing and one disagreeing side (Kline, 2005).

The seven mirroring questions in Study III (7Q-PAT and 7Q-PHYS) could also be answered on a likert scale with four grading alternatives, without a midpoint: ‘fully agree’, ‘partly agree’, ‘do not fully agree’, and ‘disagree’. These alternatives were visually clear but the wording of the two middle alternatives may have been ambiguous and may have caused insecurity about how to grade the answers. In order to avoid any confusion as to the meaning of the wording of the middle alternatives, another way of phrasing the answers might have been to use a polar rating scale numbered 1 to 4, with ‘disagree’ at one end and ‘fully agree’ at the other (Kline, 2005).

The content validity of perceived patient understanding (7Q-PAT and 7Q-PHYS) was addressed in several ways: firstly by choosing questions based on previous research and secondly by involving research nurses and physicians in testing the questionnaire and adjusting the questions according to their feedback (Wenemark, 2017). However, there are additional steps that could have been taken to ensure that the questions represented an accurate measurement of the concept of perceived patient understanding. A more carefully selected panel of content experts who were asked to judge question representativity and completeness in a structured manner might have rendered questions that more precisely measured patients’ perceived understanding (Grant and Davis, 1997).

Another way of improving the phrasing and the response alternatives of the questions may have been to carry out cognitive interviews with a few patients and physicians (Willis, 1999). Cognitive interviewing is a method used to elicit any problems of understanding and answering questions that respondents may have, through discussing how they reason about the task while filling in the forms. Any ambiguities or doubts as to comprehensibility could then have been addressed before a larger number of pairs were collected, which would probably have strengthened the validity of the questionnaire (Wenemark, 2017).

No reliability-testing has been implemented for the questions on perceived patient understanding. This could be amended through a test-retest pilot study in which patients and physicians in five to ten pairs are asked to answer the same questionnaires again two weeks later, to measure the intraclass correlation coefficient between the first and the second administration (Wenemark, 2017).

The Q-PUR and questionnaire translation

Regarding the translation and cultural adaption of the Q-PUR, there are three difficulties. One concerns the translation of ‘randomisation’ in question 3, the second the translation of ‘best supportive care’ in question 7 and the third the cultural appropriateness of question 12.

The word ‘randomisation’ (‘randomisering’) is an unusual and technical term in Swedish. Therefore, in question 3 an explanation in brackets was inserted after the word randomised: ‘(the patients are assigned by lot to one group or the other)’. This may have led to the unexpectedly high rate of correct answers, 98 %, that the treatment is decided by chance.

Question 7 read in its original form: ‘If 'best supportive care' or 'symptom control' is one of the randomisation options in the trial, it means that…’ The Swedish translation of the expression ‘best supportive care’ resulted in terms that are unknown to the general public outside the medical field (‘bästa understödjande behandling’). Therefore, in the Swedish translation the words 'best supportive care' in English were kept in parenthesis after the Swedish translation. The words 'symptom control' were omitted due to the length of the question.

A high proportion of the patients, 35 %, chose an incorrect response alternative to question 7, which may be due to these translational choices being unsuccessful. However, another reason may be that some of the clinical trials presented to the patients concerned curative treatments. In such trials ‘best supportive care’ is never an option, and consequently this aspect would not have been discussed with all patients.

Question 12 concerns financial incentives for the physicians, and was incorrectly answered by a high proportion of the patients, 35 %. The reason may be that recruiting physicians in Sweden never receive any personal fees or other incentives, and the issue is therefore not discussed either in media or in the health care system. Consequently, this question should perhaps have been omitted or replaced with a culturally more relevant question (Beaton et al., 2000).

The Q-PUR is a validated questionnaire in English, but the Swedish version of the questionnaire still remains to be validated. The translation and cultural adaptation process would have benefitted from using the EORTC quality of life group translation procedure (EORTC, 2017). Their recommendation is to perform two forward translations, not just one, reconcile the two versions and then perform two backward translations as well, with an external proof-reader to resolve any discrepancies. Eventually this version is pilot-tested on 5–10 patients for clarity, and their opinions are included in the final version. This process might have produced better solutions to the two confusing translations of ‘randomisation’ and ‘best supportive care’, possibly influencing the results of this study.

Correlation between perceived understanding and factual knowledge

The seven mirroring questions on perceived patient understanding of clinical trials (7Q-PAT and 7Q-PHYS) do not seem to be correlated to the Q-PUR. The lack of correlation may be due to the fact that the two sections were not constructed as a whole. The 7Q-PAT and the 7Q-PHYS contain separate questions on how the written and the oral information were understood, in order to see if there were any differences in how accessible the different types of information were. However, the questions were not chosen to match the Q-PUR, which rendered the subsequent analysis of potential correlations between the two parts more difficult.

Another option for this kind of study might have been to use the QuIC, an instrument developed by Joffe et al. (Joffe et al., 2001b), which includes sections both on patients' perceived understanding and their factual knowledge of clinical trials. However, there are no mirroring questions for physicians, which was an important part of Study III. Theoretically, the 14 questions on perceived patient understanding in the QuIC could have been mirrored to allow for the physicians' perspective. However, taking into consideration the feasibility of the physicians completing the questionnaires, as they are frequently short of time (Medisauskaite and Kamau, 2017), it was decided to keep the number of questions to a minimum. We therefore constructed the seven questions on perceived patient understanding ourselves, and the Q-PUR was chosen for measuring factual knowledge in this study. The feasibility and acceptability of the questionnaires was high, and the response rate for returning the questionnaires was 100 % for both patients and physicians.

Mixed methods

In Study I, two different methods for collecting and analysing data were applied. Firstly, a set of data was collected through focus group discussions of ICDs. These perspectives might however have been particular to the individuals in the focus group. The next step was therefore to take this collection of opinions and suggestions for improvement of the ICDs, and reformulate them as a list of key issues on how an ICD should be designed. An independent group of patient representatives validated these key issues as being important. Finally, this list of key issues was presented as a guide for formulating and designing ICDs, based on patient representatives' views. This combination enabled the research team both to explore and validate aspects of the research topic, which can be considered an advantage of using mixed methods (Johnson, 2004).

Data analyses

Qualitative analyses and considerations (Studies I, II and IV)

The qualitative analyses of studies I, II and IV were carried out using the same method. Regardless of whether the data was from focus group interviews or individual interviews, it was all analysed using inductive content analysis. This method was chosen because it is a descriptive method that can be used at varying levels of abstraction and interpretation (Graneheim and Lundman, 2004; Henricson, 2017).

The research teams read the transcribed interviews repeatedly in order to acquaint themselves with the data. The texts were then either analysed manually (Study I) or imported into NVivo™ (Studies II and IV). NVivo™ is a computer programme for sorting large amounts of data and facilitating the analysis. The first step of the analysis was to identify all meaning units, such as words and sentences, which could be associated with the purpose of the study. Depending on their content, the meaning units received different codes. The research team then reflected together on the combined codes and meaning units and composed subthemes according to their contents. This procedure deepened the understanding of the phenomenon being studied. The contents of the subthemes were further discussed and their scope widened and narrowed, as the analysis moved from a more tangible level towards a more abstract, in a constantly comparative process (Vaismoradi, 2016). Finally, themes were found that encompassed the subthemes, and illustrative quotes from the informants were selected in order to exemplify the themes and subthemes.

In qualitative studies, the terms validity and reliability are often replaced by the umbrella term trustworthiness, or rigour. Trustworthiness in qualitative studies is often discussed in relation to four aspects: credibility, confirmability, dependability and transferability (Houghton et al., 2013; Shenton, 2004; Lincoln and Guba, 1985). Transferability has already been discussed in the section on participants and materials, and the other three aspects will be discussed below. In the process of interviewing and analysing, credibility was strengthened through the use of open-ended interview questions, which made it possible for the informants to speak freely about their understanding of the ICDs and their reasoning concerning their participation in a clinical cancer trial.

In all research it is necessary to be aware of the researchers' own preconceptions when collecting and analysing the data (Silverman, 2017). However, this awareness is perhaps even more crucial in qualitative research, and therefore the influence of the researchers' own experiences is often discussed (Graneheim et al., 2017). In Studies I, II and IV, the researchers' different fields of experience were

valuable during the process of analysis in reinforcing confirmability, which is the equivalent of avoiding systematic bias in a quantitative study.

In all the Studies I, II and IV, one researcher was a psychiatry and oncology consultant as well as doctoral student, and one was a nurse and a doctor of medicine in the field of consumer perspectives and patients' involvement. In Studies I and II, the third researcher was a consultant and professor of oncology with experience of conducting clinical trials. In Study IV, the third researcher was a nurse and a professor of healthcare pedagogics. These different fields of experience facilitated the researchers' reflexivity concerning preconceptions and interpretations during the analytic process and decreased the risk of questions and preconceptions being taken for granted. The researchers' knowledge and experience of meeting patients in clinical settings contributed to a richer and more developed understanding and interpretation of the patients' reasoning and of the complex phenomenon in focus.

Dependability is supported by the accurate and detailed description of data collection and analysis. The open-ended interviewing contributed to capturing varying and rich descriptions from the informants. In order to reinforce and demonstrate the consistency of the findings, the researchers used detailed quotes from informants to illustrate the themes and subthemes presented in all of the Studies I, II and IV (Graneheim et al., 2017).

Statistical analyses and considerations (Studies I and III)

Studies I and III included questionnaires that were analysed statistically. In Study I, the 18 questionnaires were analysed through mean scores, whereas in Study III the 92 paired questionnaires were analysed using the median scores. In retrospect, median scores would also have been more correct to use in Study I, as the response scale was ordinal, and considered qualitative (Ejlertsson, 2018). However, if median values had been used in Study I, the same three statements (with a score < 2.5 points) would still have been scored as unimportant by the patient representatives. The result that 18 of the 21 statements can be considered validated by the larger group of patient representatives is the main point in Study I, and this result remains.

The correlations between statements were calculated, in Study I using Pearson's correlation coefficient, and in Study III using Spearman's rank correlation coefficient. Again, the scales in both studies were ordinal, and Spearman's rank correlation would have been the correct method (Ejlertsson, 2018). In Study I, the numbers were however very small, and consequently any conclusions based on such small numbers must be considered uncertain. This would have been the case even if Spearman's rank correlation had been used. This uncertainty should have

been explicitly stated. In retrospect, that part of the analysis was too speculative and should not have been included in the paper.

Study III was somewhat larger, with 92 questionnaires, i.e. 46 paired questionnaires, filled out by 46 patients and 17 physicians, where each physician could be included for up to five patients. In the paper on Study III, the authors stated clearly that the study was an exploratory pilot study. Consequently, there was no predesigned plan of analysis, testing a stated hypothesis. Instead, the aim was to explore the new mirroring questionnaires (7Q-PAT and 7Q-PHYS) and to investigate whether the Q-PUR was an adequately correlated measure of patients' factual knowledge, see Figure 1. In an exploratory study, no adjustment should be made for multiple testing as each *P*-value ought to be considered the level of evidence against each null hypothesis (Bender and Lange, 2001).

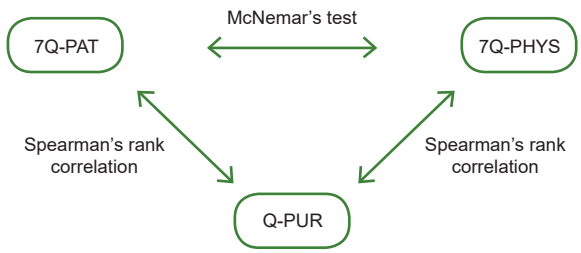

Figure 1. The performed analyses in Study III.

Concerning the analyses of the four response alternatives to the seven mirroring questions on perceived patient understanding (7Q-PAT and 7Q-PHYS), no participants had answered the lowest alternative, and very few the second lowest. The two middle alternatives were therefore merged, and subsequently a new category was created, called 'fully agree' (yes/no). The merging of response alternatives into 'fully agree' (yes/no) enabled McNemar's test to be used for investigating the discordance between the pairs for each question (McNemar, 1947). (See Tables 4A and 4B in Paper IV)

An advantage of using McNemar's test was that when the pairs were discordant, McNemar's test demonstrated whether the discordant pairs were equally distributed between the groups where only the patient, or only the physician, had rated 'fully agree'. Further, by looking at the 2 by 2 tables it was possible to see whether the disagreement leaned towards the patients or the physicians. It was thus possible to see whether the patients or the physicians rated patient understanding higher in the cases where they disagreed. An alternative method might have been to use Cohen's kappa coefficient. This method can be used for measuring the

inter-rater agreement beyond what could be expected by chance. However, the test does not show disagreement or direction of disagreement, which was of interest in this study. Therefore McNemar's test was chosen.

In order to compare the demographic factors with the median Q-PUR score, the Mann-Whitney U test was used for the dichotomous variables, such as sex or previous participation in a research trial. The Mann-Whitney U test is a non-parametric test that can analyse differences between two groups. For the variables with more than two groups, such as age or level of education, the non-parametric Jonckheere-Terpstra test for trend was used. An alternative test might have been the Kruskal-Wallis test, but this test is used when there is no *a priori* ordering of the variables. When there is an ordering, as in the case of age group or level of education, the Jonckheere-Terpstra test has more statistical power, and was therefore chosen here.

In the English version, the Q-PUR has an overall questionnaire score with a Cronbach's alpha of 0.77, which is considered an acceptable value of internal consistency (Kline, 2000). However, looking at the corrected item-total correlation, which is the correlation between each question and a scale score that excludes that question, the correlation is below 0.4 for several questions. These questions were therefore excluded and a new analysis was carried out on the six questions with a value of > 0.4 regarding item-total correlation. However, the comparison of the Q-PUR scores with the patients' perceived understanding and the physicians' rating of their patients' understanding respectively, did not show any correlations between either of them, regardless of whether the comparison used the full 12 questions or the selected six questions. The translated Swedish version of the Q-PUR has not been tested for reliability, and could therefore in theory result in correlations differing from the English original.

Ethical considerations

Informed consent was obtained from all participants in the four studies. The potential participants received a letter explaining the purpose of the study, inviting them to participate, and explaining the voluntary nature of their possible participation. For Studies I, II and IV the patients signed an ICD, and for Study III the returning of a filled-in questionnaire was considered equivalent to consenting.

The requirements of autonomy were fulfilled, as none of the participants in any of the four studies was dependent upon any person in the research team for his or her health care. Confidentiality was ensured through the removal of any names and personal identity numbers from all research material (audio-tapes, transcribed interviews, and questionnaires). Codes were substituted for these names and

numbers and all coding lists were kept separate from the other research material, stored in different safe archives.

Specific concerns of Studies I and II

The most realistic way to study how patients perceive and understand ICDs would be to interview a number of patients faced with making a decision about participation in a clinical trial. However, patients considering treatment options for cancer find this in many cases to be a stressful situation, and it was therefore considered ethically more feasible to ask former cancer patients to constitute the focus groups. These informants would not be in the actual situation of deciding on clinical trial participation, but because of their personal experiences of a cancer diagnosis they were assumed to be able to relate to such a situation.

The informants were not required to be personal or to reveal any personal details regarding their cancer experiences, as the ICDs discussed did not concern them directly. They were informed that they could participate as much or as little as they preferred in the discussions, and that they could end their participation at any time. Further, they were informed that the interviews would be transcribed verbatim but that informants would only be labelled by a random code, and that it would thus not be possible to identify individuals. The researchers facilitating the interviews took care to create a safe climate of conversation, ensuring that all informants had the opportunity to speak and be listened to in a respectful manner.

Specific concerns of Study IV

The fact that Study IV only included patients who had decided to consent to participate in a clinical cancer trial, and not those who had declined to do so, can be questioned. This selection of patients may have contributed to the fact that their reasoning to some extent was surprisingly positive. The reason for our choice was ethical, as we wanted to avoid any risk of non-participating patients feeling that their decision was questioned, or experiencing pressure to participate in a clinical trial. This may have been too cautious, and the findings in Study IV confirm the importance of carrying out a further study with patients who declined to participate. Some of the patients were in a late palliative stage of their cancer disease, but they were motivated to tell their story despite sometimes considerable fatigue. The researchers took care to be considerate of any emotional or other concerns of the participants.

Results and discussion

The results of Studies I-IV will now be presented and discussed in relation to the subheadings of this thesis: Information, Understanding and Decision-making.

Information

Exploring patient representatives' views on Informed Consent Documents (ICDs) was the specific aim of Studies I and II. This section will therefore focus on the results of these studies, which primarily concern the written information. In particular, attention will be given to the cognitive information aspects with bearing on patient understanding. The results are presented under the headlines *Structure and comprehensibility*, and *Layout and graphic presentation*.

Structure and comprehensibility

All informants were agreed that it is important to facilitate the cognitive process of assimilating the written information, as it is often extensive. In this they stressed the importance of clearly structuring the contents, as several of the trial information texts were difficult to follow due to the information being presented in an illogical order. The informants wanted the key messages first, in the following order: Why the patient had been selected for the trial; what participation in the trial implied; and what the treatment alternatives were. They did not want any general information about the cancer disease to be included, only the specific information needed to make a decision about trial participation. (Study I)

When the informants encountered difficult sections, they either interrupted their reading to try and decipher the meaning, which slowed down their reading pace, or they skipped the section altogether despite uncertainty about the content, causing gaps in their knowledge. To avoid this problem, the informants wanted sentences to be short and the language to be easy, avoiding medical jargon and with explanations following any medical terms that needed to be included. (Studies I and II)

The readability of the ICDs studied was eleventh to thirteenth grade, which is well above the recommended readability of sixth to eight grade. This probably added to the informants' difficulties in understanding them. This is a common problem for ICDs, which tend to focus more on fulfilling all formal requirements, such as legal aspects, rather than on aspects relevant to patients such as readability and impact on daily life (Reinert et al., 2014).

Improved readability can be achieved in several ways, most notably by regulating the readability grade level, as described in the background chapter (p. 21). For example, a study by Hadden (Hadden et al., 2017) has shown good effect on the readability of ICDs by producing a template in collaboration with research participants and research ethics committees. The template had a fifth grade readability level and was made available on the website of the research ethics committees for use by investigators planning clinical trials. In addition, the members of the research ethics committees were trained in using the template for approval purposes when reviewing clinical trial applications. The results of the study showed that ICD readability was improved by being lowered from a baseline mean readability of tenth grade to a post intervention readability of seventh grade level.

Increased readability awareness among health care professionals would thus probably result in more appropriate readability levels of ICDs. However, there is also a lack of health care professionals with the necessary editing skills. In another study by Hadden, students in health professions were trained to assess, edit and format written health materials so that they were easier to understand (Hadden, 2015). The initial readability of tenth grade to college level was lowered to sixth grade or below post editing. This study also presents a way to provide an increased number of health care professionals with editing skills and insight into the importance of improved readability of health materials.

Layout and graphic presentation

Focus group informants experienced the first impression of a text as being important for their motivation to continue reading and for their assimilation of the information. Thus the layout plays an emotional and motivational part in raising an interest in the subject of the text and improving its accessibility. When encountering a compact and evenly distributed text without use of layout techniques to facilitated orientation, some informants reported that they simply gave up any attempt to try reading it. (Study II)

Informants stressed the importance of the layout for facilitating their reading. Headlines followed by short passages, typographical emphasis (such as bold and italics), frames and fields in different colours, bullet points and fact boxes, were

found to promote readers' ability to orientate themselves and relocate parts they might want to re-read. (Study II)

Misunderstanding of treatment

The treatment alternatives were often difficult to follow, making it hard for readers to understand which treatment arms patients would be randomised between. One part of the treatment description in trial text 1B (Study I) caused a long discussion in which none of the informants was sure of the correct administration, and four incorrect interpretations were presented of how the drug would be given. The text read:

> (The name of the drug) is also given as an injection in a vein for a period of 5–10 min 2 times, at an interval of 1 week, and the treatment is repeated after 3 weeks.

The correct treatment procedure is illustrated in Figure 2. Contrary to this procedure, one informant interpreted the text as if the drug would be given once a week, during two subsequent weeks, and then there would be a pause of three weeks before starting the next cycle (Figure 2, incorrect interpretation 1). Another informant thought the drug would be given once a week, during two subsequent weeks, and then the treatment would be completed (Figure 2, incorrect interpretation 2). Two additional interpretations were that the drug would be given twice on the same day. In one of the interpretations, it was assumed there would then be a three weeks' pause before repeating the cycle, in the other that the next cycle would start in week number three, that is, without any pause (Figure 2, incorrect interpretations 3 and 4). (Study I)

The different schemes in Figure 2 describe a range of treatment intensities, with hospital visits varying in frequency from either every other week, every two weeks or two weeks out of three. This shows how difficult it can be to describe timelines with words alone. The informants in both Studies I and II suggested that treatments should also be presented in a graphic form as this gives quick and accurate information and a better overview of the treatment chronology. (Studies I and II)

An additional suggestion was to show all the treatment events, including blood samples and other investigation procedures, in a checklist or timeline in which it would be possible to see how far along the way the patient had come and what the next step would be. On the timeline, the patient could tick off one step after another, see the progress made, and be able to plan everyday life. (Study II)

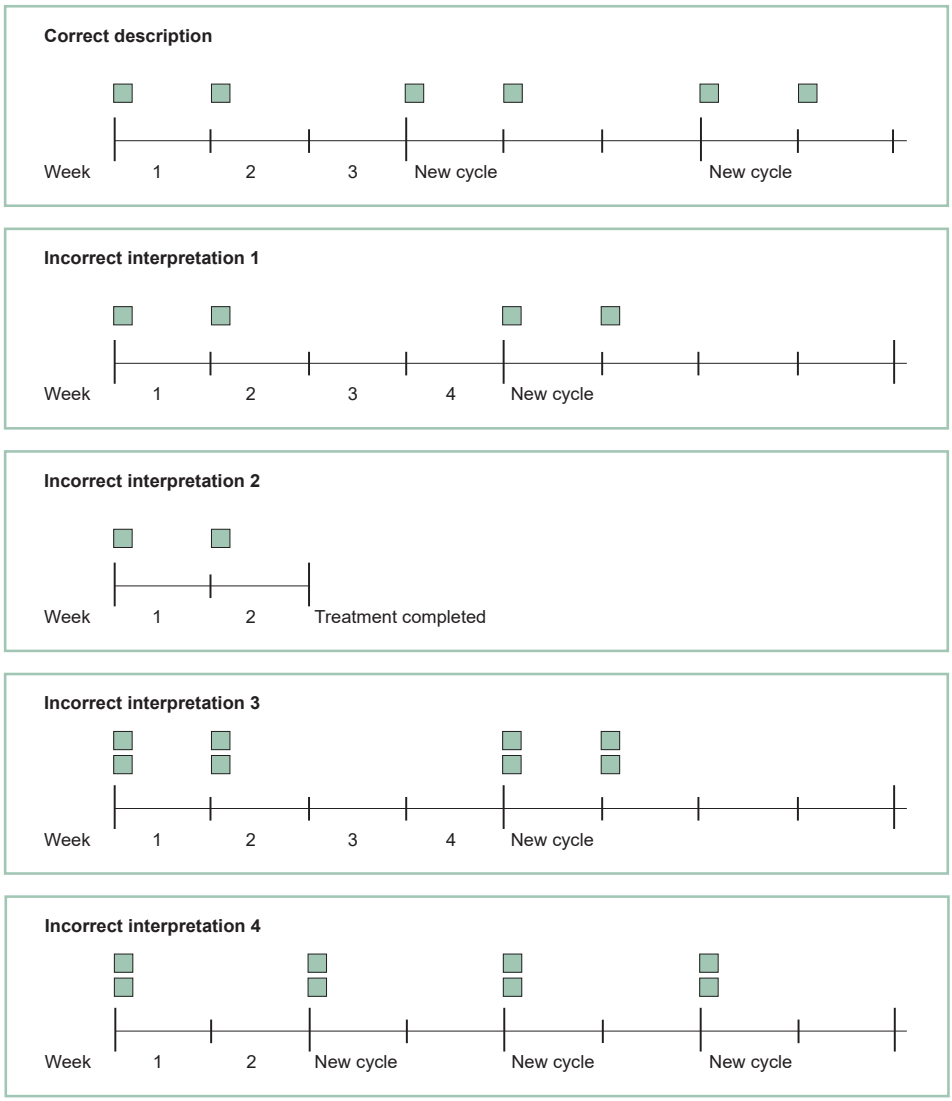

Figure 2. Graphic presentation of the correct description and the four incorrect interpretations of the treatment in trial 1B.

In Study I, the suggestions from the informants were converted into a questionnaire with 21 statements that were rated by an independent sample of patient representatives. Eighteen of these issues were validated as important and the list of suggestions was presented as a guide for designing ICDs. It is notable, however, that the theme of graphic illustrations of e.g. treatment plans came up in

the focus group discussion, but was not validated as important in the questionnaire. The reason for this may have been that the questionnaire with key issues merely asked whether an ICD should 'include illustrative figures/pictures'. The 18 independent patient representatives filled in their questionnaires in solitude, without partaking in the focus group discussion leading up to the suggestion of including graphic illustrations, and may therefore have imagined any kind of merely decorative illustration. This would be a fair assumption, as decorative pictures are often used for the purpose of raising motivation to process the information in everyday texts, such as advertisements.

The patient representatives' views on cognitive aspects and graphic design are in line with other research showing that patient suggestions for enhancing the readability of ICDs often include graphically redesigning them (Manta et al., 2016). A growing body of research demonstrates that the layout is of great importance for accessing written information, in particular for patients with poor reading skills (Doak CC, 1996). Studies have shown that simplified ICDs using graphic cue structures and illustrations can improve readability and understanding of informed consent information (Kim and Kim, 2015; Tait et al., 2005). Pictographs combined with spoken medical instructions can have a dramatic effect on enhancing memory, raising correct recall from 14 % to 85 % (Houts et al., 1998). These effects were later shown to be retained for a significant time and were valid also for people with low literacy skills (Houts et al., 2001). Text producers are therefore advised to use for example simple drawings without distracting details and to link them closely to short plain language messages (Houts et al., 2006). In conclusion, producers of ICDs should make use of graphic presentations, which necessitates involving professional communicators and graphic designers, as well as patient representatives in the writing and designing of ICDs (Knapp et al., 2011).

Suggested treatment illustration

Here is an example of two treatment alternatives described in one of the ICDs, first presented in its original form as text only, and secondly with the addition of a suggested graphic presentation of the treatment scheme (see Figure 3):

> **Treatment A:** You will be treated with Drug X. The next treatment occasion will take place 3 weeks later. Before this, you will do a blood test. If the test is normal and you have not had any side effects, you will start the next cycle.
>
> **Treatment B:** On the first treatment occasion, you will be treated with both Drug X and Drug Y on the same day. During the two following weeks, you will receive only Drug Y once a week. After 3 weeks of treatment you will start a new cycle. Before this, you will do a blood test. If the test is normal and you have not had any side effects, you will start the next cycle.

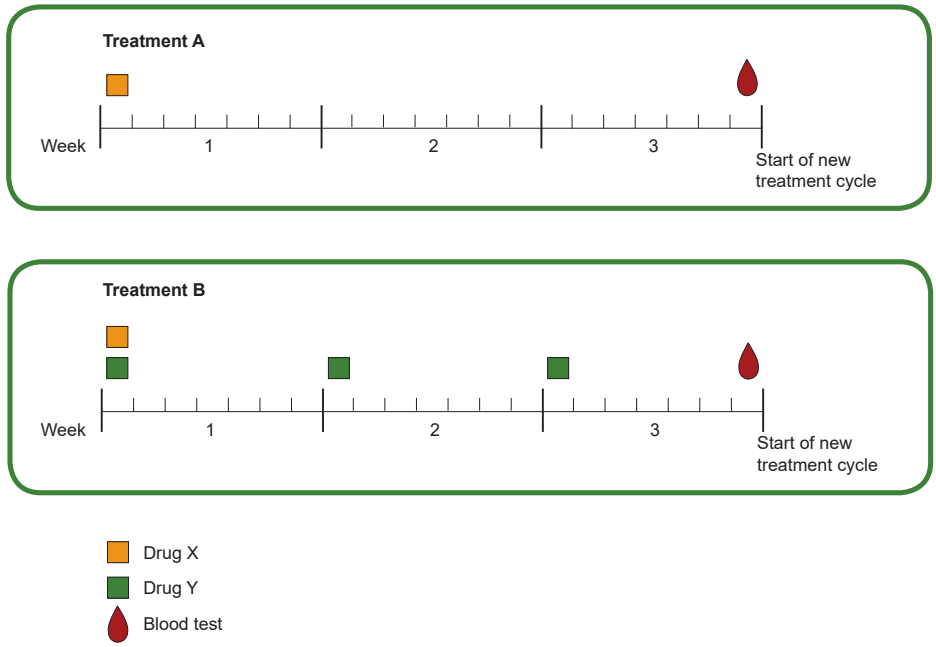

Figure 3. Suggested graphic illustration of treatment scheme.

Reading the text only requires careful consideration in order to understand how the treatments are given, whereas the graphic presentation effectively illustrates the differences and assists the readers' working memory in managing the information load.

Templates for ICDs are available, but they tend to focus on content and completeness of medical and legal information, rather than presentation format and comprehensibility. None of the large organisations in the medical field, such as WHO or CIOMS provides advice in their guidelines on the layout of ICDs (WHO, 2018; CIOMS, 2016). Not even a recent paper specifically dedicated to improving ICDs, entitled 'A need to simplify informed consent documents in cancer clinical trials', produced by an international group of oncologists (ARCAD) in 2017, mentions the impact that the layout can have (Bleiberg et al., 2017).

Written information in society at large has undergone considerable development the last decades, both in terms of simplifications of wording and the use of graphics for guiding the reader. The Swedish Language Act (SFS 2009:600), states that authorities' language should be correct, simple and understandable. Major state authorities, such as the Swedish Social Insurance Agency (Försäkringskassan) or the Swedish Tax Agency (Skatteverket), have made huge

efforts to make their information more accessible and comprehensible (Ryttge, 2016; Ehrenberg-Sundin, 2015).

ICDs in clinical trials do not seem to be keeping in step with this development, and hence risk giving an unprofessional and unnecessarily reader-unfriendly impression. They are not intended not look alluring or persuasive, but it ought to be possible to find a balance between the extremes, with the aim of helping patients understand the information better. Cognitive scientists state that no text producers can ignore visual design; visual design aids them in giving their readers the guidance they need to read and understand the message (Holšánová, 2010; Clark and Lyons, 2010). Consequently, this is a topic that needs to be considered more deeply by health care professionals when designing written patient information. The development of ICDs used to focus on including more and more content (Berger et al., 2009), but now has to focus more on how to package information to make it accessible for patients. Otherwise ICDs risk resembling the terms and conditions on websites where many customers immediately click 'accept' without reading anything of the text (Steinfeld, 2016).

There is also a growing demand for patient involvement in research, which is often a prerequisite in applications for funding (Salamone et al., 2018). For producers of ICDs, Studies I and II show that focus group interviews with patient representatives are a feasible method for including the patient perspective. Such focus group interviews also work well for collecting views and suggestions for the improvement of ICDs regarding their comprehensibility, content, and layout. This method can therefore be useful when piloting a new ICD, in order to improve it with consideration to the potential recipients of its information.

Other expertise than the medical is also paramount to such improvements (Bossert and Strech, 2017). Taken together, these findings seem to suggest the need of a new standard for the production of ICDs in clinical trials, stipulating that production teams for ICDs should include patient representatives, professional writers, and graphic designers. Testing and developing ICDs using such procedures has been shown to improve patient understanding significantly (Knapp et al., 2011). To implement this new standard in practice, we suggest that it be a requirement of the Swedish Ethical Review Authority that ICDs be produced according to these standards, in order for a research application to be approved.

Understanding

Understanding was addressed in various ways in all four of our studies, but here in particular the results from Studies III and IV will be presented and discussed.

Perceived patient understanding and factual knowledge

The results of Study III showed a trend in which participating physicians rated patients' understanding as being lower than the patients did themselves. This was the case with all seven questions on perceived patient understanding (7Q-PAT and 7Q-PHYS). For each of the seven questions, the patients and the physicians agreed in around half of the pairs. For the disagreeing half, the physicians in a majority of cases assessed patient understanding as lower than in the patients' own assessments. Consequently, the patients perceived themselves as understanding more than the physicians estimated. Concerning factual knowledge, no correlation was found between the patients' factual knowledge as measured by the Q-PUR and the assessment of perceived patient understanding, either for the patients or for the physicians (7Q-PAT and 7Q-PHYS, respectively). (Study III)

The results of this pilot study must be viewed with caution, due to the small number of participants and the explorative analysis. However, there are very few studies that have directly compared physicians' assessments of patients' understanding with the patients' own assessments, and hence the results are interesting. A pairwise comparison with mirroring questions as in Study III has to our knowledge never been made before.

Patients often seem to consider themselves well informed, even if they misunderstand some key aspects of research (Bergenmar et al., 2008). However, it is interesting that the patients in Study III assessed their understanding as significantly higher than the physicians did for five of the seven questions. The differences were nominally statistically significant, but are they clinically significant? This is a difficult issue to determine, as there is no definition of how much knowledge is needed for a patient to give informed consent (Sand et al., 2010). Further, there was no definition in the questionnaire of what was implied by answering 'fully agree' to the questions on perceived understanding compared with the adjacent alternative 'partly agree'. However, the questions were mirrored for patients and physicians and were thus directly comparable.

The fact that the physicians considered their patients' knowledge to be lower is in concordance with a study showing that 30 % of physicians did not consider their patient capable of making an informed decision on participation in the clinical trial in question (Strevel et al., 2007). The question then arises why the physicians were satisfied although their patients did not fully understand the information?

Did the physicians assume that their patients knew enough to make a decision even though they did not understand everything, or did they assume that the patients knew what was most important to them? However, it may just have been the case that the physicians lacked the time or the communication skills to check their patients' understanding, and therefore omitted to do so.

Regarding factual knowledge, the patients' scores on the Q-PUR can be considered as relatively high. Only six patients out of 46 (13 %) scored below nine out of 12 points (75 % correct answers). However, these six individuals would perhaps have benefitted if their physician had noted their low level of knowledge and addressed it. One suggestion based on the results of Study III is possibly that physicians would benefit from communication skills training in which they could practise assessing patients' understanding more accurately. Such training would increase physicians' ability to tailor their information to the needs of individual patients. This would further improve the informed consent process. A larger study is needed to investigate this issue.

Therapeutic misconceptions

In Study IV, a recurring opinion voiced by the patients was that participation in a clinical trial (CT) implied a chance of receiving better treatments than in ordinary cancer care. Some of the patients who were in a palliative situation felt that they had no other choice than to participate, since it was the only possibility to receive a new treatment, and these patients sometimes had unrealistic hopes of cure or improvement. Often, but not always, this hope was simultaneously expressed as a hope for helping future cancer patients and furthering research. Most patients stated that they were not concerned with risks or side effects. (Study IV)

One of the most common misunderstandings in CTs is that patients tend to overestimate the expected benefit of participating in a CT and underestimate the risks, confusing the research intent of investigating treatment alternatives on a group level with the clinical intent of the doctor choosing the best treatment for the patient on an individual level. It may however be the case that a CT might not ensure the best treatment for an individual patient, for example if the CT includes a placebo arm, or is a phase I CT, which is primarily designed not to see treatment effects but only to investigate whether or not a new treatment is safe to administer. The notion of confusing research intentions with clinical care has been labelled 'the therapeutic misconception' by Appelbaum et al. (Appelbaum et al., 1987).

The results of Study IV are in line with other research. Patients enrolling in CTs because of unrealistic hopes for treatment benefits, particularly in palliative situations and for phase I CTs, have been consistently reported for over 30 years according to a review by Gad (Gad et al., 2018). This review also showed that a

mean of 61 % of patients in 17 studies expected treatment effects in a phase I CT and a mean of 21 % in 6 studies expected to be cured (Gad et al., 2018). In one study of patients considering participation in a phase I CT, a high proportion of patients, about 45 %, expected their cancer to shrink, and this proportion was maintained after their first consultation with the oncologist (Dolly et al., 2016). Either the oncologist had presented overly optimistic information, or the patients' optimism was not primarily based on information, but was rather a form of coping strategy. Salander et al. use the expression 'creative illusion' about the strategy to simultaneously know the realities of a cancer disease and still disavow or play down the implications of these realities (Salander, 2012; Salander, 2003). If a patient's optimistic view is essential to his or her psychological wellbeing, it may be difficult to correct through more information, or in fact any information.

In addition, one can argue that hoping for personal treatment benefits may be realistic, particularly in phase II-III trials, where the drug tested has shown some promise in earlier phases (Locock and Smith, 2011). In the palliative setting, Horng and Grady identify three different kinds of misunderstanding of research, labelling them Therapeutic Misconception, Therapeutic Misestimation and Therapeutic Optimism (Horng and Grady, 2003). Many patients may make a Therapeutic Misestimation, when they are aware that the CT is not aimed at optimising their individual treatment, but nevertheless significantly misestimate the chances of effect significantly, believing them to be unrealistically high compared with preliminary estimations by the researchers conducting the CT. Patients displaying Therapeutic Optimism are realistic about their chances of treatment benefits but still hope they will be one of the few who will be benefitted. In view of these variations, what exactly patients mean by benefit needs to be further investigated, in order to judge what kind of individualised information may be useful for them to make an informed decision to participate or not in a CT.

Interesting work by Lidz et al. suggests that one reason for therapeutic misconception is that researchers and patients use different and incongruent cognitive frames when understanding the concept of clinical trials (Lidz et al., 2015). Researchers have a cognitive frame that views the clinical trial as a means of answering the research question of which is the best treatment for a whole group of patients. Patients, on the other hand, have a cognitive frame that views the CT as a means of receiving the best treatment and care for them personally, and even when they receive information to the contrary, they squeeze those facts into their existing frame, distorting the facts into a therapeutic misunderstanding. The authors suggest that the informed consent procedure needs to start with a scientific reframing of participation in a CT. Such a scientific reframing has been attempted in a recent randomised trial of a reframing intervention, resulting in a reduction of therapeutic misconception (Christopher et al., 2017). This method may be useful for improving the future communication of information in CTs.

Decision-making

Results regarding decision-making were most evident in Studies I and IV. Four aspects especially merit discussion: *An immediate decision based on gut feeling and trust; Comparing treatment alternatives*; *The right to withdraw from a clinical trial*; and *Advantages and meaning of clinical trial participation.*

An immediate decision based on gut feeling and trust

In Study IV, many of the patients considered it to be an obvious, immediate and easy decision to participate in a clinical trial, even if some of them had received pre-information about the trial from their referring physician, which prepared them for the question and gave them time to consider it in advance. Their decision was often based mainly on their positive gut feeling and a trusting relationship with the health care professionals. They did not worry about the possible side effects. Many of the patients only skimmed through the ICDs, and registered fragments of the oral information, being too preoccupied with thoughts and emotions regarding their cancer to process cognitively any large amount of facts. Thus the patients did not seem to base their decisions on the factual information, but were rather guided by their emotions. However, some reported reading the ICD afterwards, to confirm their decision. (Study IV)

These results indicate that the patients' decision-making process was instant and intuitional, and guided by their gut feeling and trust in their physician. The decision being easy and taken immediately after hearing about the clinical trial has been reported earlier in a few studies (Godskesen et al., 2013; Cox, 2002). This immediacy may be in line with theories of dual processing in higher cognition (Kahneman, 2011; Evans, 2008). The immediate and intuitive System I may have been guiding the patients' decision-making, so that when they experienced an intuitively good and trustful feeling about the physician and the clinical trial treatment, they instantly decided to agree to the physician's proposal of clinical trial participation. The patients may also have come to the ICC with a cognitive frame assuming that physicians always suggest the best treatment and care for the individual patient, and researchers are to be trusted. This cognitive frame would further have inclined patients to decide on participating in the clinical trial, perhaps without a thorough deliberation on the pros and cons.

Written information seems here to have been less important than presumed, and even in the informed consent discussion, the informing physician often seems to have lost the attention of the patient. However, the advantage of a conversation is that the physician can interact with the patient in ways not possible in writing, in order to ensure that the information is received. There are communication skills

specifically aimed at capturing and retaining the patient's attention when disclosing emotionally impacting information, where one example is the SPIKES method (Baile et al., 2000). By orally preparing each step in the conversation, flexibly following patients' trains of thought, and giving adequate space and support for emotional reactions, physicians can facilitate patients' cognitive processing of factual information.

The oral information is sometimes considered more important than the written (Cox, 2002). In any case it is important not to regard the informed consent process as merely a one-way transmission of information: it should rather be viewed as a co-operative discussion (Locock and Smith, 2011). Unfortunately, there exist no official guidelines for how the ICCs should be conducted, as is the case for the contents of the ICDs (Sand et al., 2008). Hence informing physicians are often left to their own devices. However, communication skills training has been shown to improve important communication skills for physicians, such as providing individually tailored information, responding to emotions, and applying shared decision-making (Henselmans et al., 2018; Fallowfield et al., 2002). Further, recommendations for the improvement of informed consent procedures for clinical trials have begun to include advice that recruiters should attend communication skills training programmes (Lentz et al., 2016; Anandaiah and Rock, 2018).

Comparing treatment alternatives

The patient representatives in Study I repeatedly stressed the importance of being able to compare the treatment alternatives in order to decide whether or not to participate in a trial. They would have liked the treatment alternatives outside of the clinical trial to be listed in this comparison as well. Above all, they wanted to know the impact that the different treatment alternatives would have on their everyday lives. Information on drugs, side effects, and additional investigations was considered important, and was included for all of the studied ICDs. However, cancer treatments often run over a long period of time and the informants also wanted to know the time allocation for treatments, investigations and follow-up, and in this they considered it particularly important to specify time bound to the hospital. This kind of information was sometimes missing or incomplete. They would also have like the treatment alternatives outside of the trial to include these factors. (Study I)

The informants repeatedly stated that individuals differ in how they value different aspects of a trial when making a decision about participation. They exemplified that to one individual the treatment frequency is the most important factor, to another the side effects. One person may feel that extra investigations give extra security; another cannot bear the stressful waiting for those extra results. Furthermore, the disease situation matters, and a patient facing a palliative

situation may be willing to accept greater risks than someone in a curative situation. One informant explained that she needed information to estimate what the worst-case treatment scenario, in her opinion, would imply, in order to make a decision. She wanted specifications of the time required for the treatment procedures in the different trial arms, and what the anticipated differences in side effects would be. If the worst-case scenario was acceptable to her, then she could decide to participate in the trial. (Study I)

Information on the impact of treatments on daily life, and restrictions on food or exercise are among the frequently asked questions by patients considering treatment choices, but these aspects are rarely addressed in ICDs (Reinert et al., 2014). Also, alternatives to the clinical trials offered are frequently missing in ICDs (Resnik et al., 2010). Further, when discussing clinical trials, physicians tend to omit palliative care, or no tumour specific treatment at all, as alternatives to participation, even in the informed consent conversations (Miller et al., 2014; Hlubocky et al., 2018). If this information is not included in ICDs, there may therefore be a risk that patients will not receive it at all. One suggestion may be to require phase I trials in particular to include information about 'best supportive care' in ICDs. This may affect trial accrual negatively, as patients who become aware that palliative care may be their best treatment option may decline inclusion (Bell and Balneaves, 2015). However, some patients will still choose inclusion, as they may perceive active tumour treatment to be their preferred coping strategy. The point would be that they choose this while conscious of an alternative, which could be said to constitute better informed consent.

The right to withdraw from a clinical trial

Many of the informants in Study I and the patients in Study IV considered it very important that they had the right to leave a trial at any time without explanation, and without it affecting their quality of care. This knowledge made it possible to give a clinical trial a try, and yet have a safe door if side effects or time consumption turned out to be unacceptable (Studies I and IV). The right to withdraw enabled the patients in Study IV to reason that they had nothing to lose by participating, which made them feel secure in their decisions. (Study IV)

According to our results, the right to withdraw was considered an essential aspect of the decision to participate in a clinical trial. This is in line with the ethical guidelines stating that all ICDs must inform potential participants that they have the right to withdraw at any time without needing a particular reason for their withdrawal. Further, all ICDs must inform participants that if they withdraw from a clinical trial implying cancer treatment, they will receive the standard treatment for their type of cancer, and the withdrawal will not affect their care negatively (WMA, 1964/2013). However, patients have been reported as misunderstanding or

misinterpreting these rights, in particular by believing they need to have a cause for withdrawing (Godskesen et al., 2016). The signing of a consent form may add to this notion, as it may be perceived as a contract, implying that the patient is taking on responsibilities. The risk exists that patients may decline participation on erroneous grounds if they do not comprehend that they can withdraw at any time without providing a reason. Consequently, all the aspects mentioned of the right to withdraw need to be stated clearly in ICDs and informing physicians must ensure potential clinical trial participants' understanding of them.

Advantages and meaning of clinical trial participation

The informants in Study I and the patients in Study IV saw a number of advantages in participating in a clinical trial, such as accessing treatments otherwise not available and receiving better care, with easy access to their own research nurse and longer and more frequent follow-up (Studies I and IV). Many patients in Study IV also stated that they wanted to contribute to the treatments of future patients and cancer research in general. (Study IV)

The tendency for patients in Study IV to see advantages in clinical trial participation and not worry about side effects is also in line with other research showing that acceptors tend to focus on treatment effect and decliners on adverse effects (Madsen et al., 2007). Worry about side effects is a common reason for patients to decline participation in clinical trials (Weckstein et al., 2011; Bell and Balneaves, 2015), and since the patients in Study IV had all accepted participation, this seems to be one reason why they did not raise such concerns. clinical trial participation has been reported to be a positive experience by many patients, who sometimes even argue that patients should have a right to participate in clinical trials (Harrop et al., 2016b; Locock and Smith, 2011).

Patients often attribute a sense of meaning to their participation in a clinical trial, a meaning that can sometimes change during the course of the trial, depending on the treatment effects. Participants may first have hoped for either a cure or reduced symptoms, but if that is not the case they may re-evaluate the meaning of their participation in the clinical trial, and focus more on the altruistic aspects of helping future patients (Wootten et al., 2011). Finding a sense of meaning in an otherwise meaningless disease experience seems to be an important part of patients' strategies for coping with their cancer (Godskesen and Kihlbom, 2017). Using their cancer to achieve something meaningful, if only for future patients, is one way to create such meaning. Helping others is for some patients a fundamental value that guides their actions in the important matters of life.

For the decision on clinical trial participation to be experienced by patients as a good decision, it seems important for it to be in line with their fundamental values

in life, sometimes termed the patients' 'valued living' (Wilson et al., 2010). These core values are sometimes not evident even to the patient and an important part of the informed consent conversation may be to find and articulate them in order to provide a base for the patient's decision. For example, if a patient values spending time with the family, and trial participation will entail extra time in hospital, the patient may realise that declining participation is the best option for that reason. Or else the patient might value the principle of never giving in despite a palliative situation, and accepting participation in a clinical trial may be the option best aligned with this value. An important aspect of the informed consent conversation is thus to find out what patients' core values in life are, and to facilitate aligning their clinical trial decisions with these values.

A means to structure and facilitate this process is to use a decision aid. Decision aids are a kind of written patient information consisting of two parts: one part contains information about the clinical trial and the other part contains values exercises to help patients formulate which values are most important in their lives. A central function of decision aids is to help the patients to deliberate about their personal values in life and become clear about whether participation in a particular clinical trial is in line with these values (Abhyankar et al., 2011). Further, using a decision aid has been shown to lower significantly the level of subsequent decisional conflict for patients (Sundaresan et al., 2017; Juraskova et al., 2014). Studies report that decision aids can give patients improved knowledge of clinical trials, with more realistic expectations of risks and benefits, and a clearer view of what matters most to them, as well as involving them more in the decision-making (Spatz et al., 2016; Politi et al., 2016).

One suggestion may therefore be that clinical trials would benefit from including decision aids as part of their ICDs, together with providing training for informing physicians in using these aids, to enable patients to reach well-founded decisions. This way, clinical trial decision-making would be a collaborative effort by patient and physician to add a sense of personal meaning to factual knowledge, and to use this sense of meaning in deciding how best to act.

Conclusions

In conclusion, this thesis adds to the research on patient perspectives regarding three main issues of the informed consent process in clinical cancer trials: Information, Understanding and Decision-Making.

Patient representatives' views and suggestions included aspects on comprehensibility, content, and layout, which resulted in a guide for writing informed consent documents.

- Informed consent documents should be designed and illustrated in such a way that patients can easily orientate themselves and easily find the aspects they consider most important in their decision-making process. Informed consent documents should therefore be written in cooperation with patient representatives, professional writers, and graphic designers.

The comparison of perceived understanding between patients and physicians through mirroring questions showed that patients perceived themselves as understanding clinical trial information better than physicians perceived them as doing.

- Physicians would benefit from communication skills training, during which they would practise more accurate assessment of patients' understanding and how to tailor their information to the needs of the individual patient. This would further improve the informed consent process.

Neither patients' nor physicians' assessments of perceived understanding correlated with the patients' factual knowledge scores, as measured by the Q-PUR.

- It is unclear whether patients have the factual knowledge they need to make an informed decision about participation in a clinical trial. Informing physicians must ensure more explicitly than at present that patients have understood the factual knowledge received and thus also the implications for them of the clinical trial in question.

Patients' decision to participate in a clinical trial was often immediate and guided by emotions and a trusting relationship with health care professionals. Preoccupation with thoughts and emotions regarding their cancer rendered cognitive processing of the clinical trial information difficult.

- The informed consent conversation is therefore crucial, enabling the physician to interact with the patient, and to ensure that the information is received and taken in. Informed consent conversations need to be further developed through the definition of essential communication skills and how to acquire and apply these skills in clinical practice.

Factors that were deemed important for the decision-making process included knowledge of the right to withdraw from the clinical trial and explicit comparisons between treatment alternatives included, and also those not included, in the clinical trial.

- These factors therefore need to be specifically addressed in the informed consent conversation. Patients in palliative situations were sometimes unaware of the fact that their disease was no longer curable. For clinical trials in the palliative setting, the treatment alternative 'best supportive care' should therefore be stated as one option.

Implications

The conclusions in this thesis may have implications for how the information should be presented to patients eligible for a clinical trial. There are possible implications for both the written and oral information.

Written information

- We suggest a new standard for producing informed consent documents, entailing that the production teams of informed consent documents should include:
    - Patient representatives
    - Professional writers
    - Graphic designers

- To implement this standard in practice, we suggest that the Swedish Ethical Review Authority should stipulate the requirement that informed consent documents must be produced according to this new standard, for research applications to be approved.
- Guidelines for the production of informed consent documents should include instructions not only on the content but also on the graphic design. These instructions should be based on cognitive science evidence for optimising readability.
- Informed consent documents should include accurate descriptions of all treatment alternatives, elucidated with graphic illustrations. The treatment alternative ‘best supportive care’ should be stated as one option in all clinical trials where this alternative is applicable.

Oral information

The conducting of informed consent conversations needs to be further developed. We suggest that informing physicians should acquire and apply specific communication skills in order to:

- Capture and retain the patient's attention when disclosing emotionally impacting information.
- Assess patient understanding and tailor the information according to each patient's individual needs.
- Ensure the patient's understanding of all aspects of the right to refuse participation without consequences for their care, and to withdraw at any time without needing to provide a reason.
- Have an honest discussion about other treatment alternatives not included in the trial, when informing about palliative clinical trials, including palliative options such as 'best supportive care' where applicable.

Future perspectives

The development of informed consent documents for clinical trials has previously been focused on including more and more content. Now it is important to focus on how to package this information, to maximise accessibility for the patients. Cognitive science has made considerable advances over the last decades and interdisciplinary research using these advances when developing informed consent documents for clinical cancer trials would be a new and interesting field of research. For example, it is important to cast light on the production of informed consent documents according to cognitive science evidence on layout and readability scoring, and to investigate the effects these enhanced informed consent documents may have on patient understanding, knowledge, and preferences.

Further research is also warranted on how to optimise informed consent conversations and how best to train informing physicians' communication skills. The most important question regarding informed consent is perhaps not exactly which facts about the clinical trial the patient understands and to what degree, but which facts about the clinical trial the individual patient considers most important as a basis for his or her decision. Communication skills training should therefore focus on improving physicians' ability to assess and adjust to what patients consider the most important issues to understand in a clinical trial, and what their motives are for participating or not, in order to help them align their decisions with their core values. Research on how this can be accomplished in a structured manner, and what effects it would have on e.g. patient decision-making and satisfaction with the decision, or clinical trial recruitment, would be of interest.

In addition, the role of research nurses and the impact of their communication on the informed consent process are aspects that are largely unexplored, and which would be important to study. Finally, patient aspects that need to be further investigated are in particular the views and motives of patients who decline participation in clinical trials.

Populärvetenskaplig sammanfattning

Forskningsstudier, så kallade kliniska prövningar, är mycket viktiga för att kunna utveckla nya behandlingar mot exempelvis cancer. För att vara med i en klinisk prövning måste potentiella deltagare först ge sitt informerade samtycke. Det innebär att de behöver få information om den kliniska prövningens syfte, och vilka fördelar och risker den kan innebära. När de förstått detta kan de ge ett välinformerat samtycke till att delta. Informationen ska ges både skriftligen och muntligen. Tidigare studier har dock visat att den skriftliga informationen ofta är svårläst och att patienter även kan missuppfatta den muntliga informationen. Därför har vi genomfört fyra undersökningar för att om möjligt förbättra informationsprocessen vid kliniska prövningar. Vi ville få svar på vad patienter tycker om informationen, hur de hade velat ha den, hur mycket de förstår av den och vad som var viktigt när de fattade beslut om att gå med i en klinisk prövning.

Den första studien handlade om skriftlig information, och visade att patienter vill ha tydligt strukturerad skriftlig patientinformation, med förklaringar av alla medicinska termer. I informationen ska biverkningarna anges noga men också följas av en beskrivning för hur de kan behandlas. Alla behandlingsalternativ i den kliniska prövningen ska visas på ett överskådligt sätt, så att de lätt kan jämföras, gärna med en enkel grafisk illustration som visar vad som ska hända och när. I beskrivningen ska ingå hur behandlingarna påverkar vardagen, med exempelvis bunden tid på sjukhus, olika undersökningar samt hur kontrollerna efteråt går till. Det bör också framgå vilka behandlingsalternativ som finns om man tackar nej till att delta i den kliniska prövningen, och hur de är upplagda. Dessa patientförslag listades i en guide för författare av skriftliga patientinformationer.

I den andra studien hade patienterna många synpunkter på den grafiska formgivningen, eller layouten, av de skriftliga informationerna. De uppfattades som svårlästa och omoderna, eftersom de inte utnyttjade grafiska hjälpmedel, exempelvis olika färger eller faktarutor. Sådant hade underlättat för läsaren att få en överblick över informationen och snabbt kunna hitta olika fakta. De hade heller inga illustrationer som visade exempelvis tidslinjer för behandlingar och undersökningar. Slutsatsen blev att skriftliga patientinformationer skulle kunna bli mer läsvänliga om de tas fram av team som också innehåller patientrepresentanter, kommunikatörer och grafiska formgivare. Ett förslag är att detta ska bli ett krav för att den nya Etikprövningsmyndigheten ska godkänna forskningsansökningar.

I den tredje studien fick patienter skatta sin egen förståelse av information om kliniska prövningar, och sedan jämfördes detta med hur väl patientens läkare tyckte att patienten förstått informationen. Patienterna fick också besvara ett kunskapsprov, som visade hur mycket de faktiskt förstod. Resultatet visade att patienterna ofta skattar att de förstår bättre än vad deras läkare skattar att de förstår. Varken patienternas eller läkarnas skattning av patientförståelsen visade något samband med patientens resultat på kunskapsprovet. Patienterna tycker alltså att de förstår bättre än läkarna tror de gör, men vi vet inte vem av dem som har rätt. Den här studien var liten och man behöver göra om den i större skala för att kunna dra några säkra slutsatser. Ett förslag är ändå att de informerande läkarna skulle behöva bli bättre på att stämma av patienternas förståelse, så att de kan anpassa informationssamtalet efter patientens individuella behov.

I den fjärde och sista studien intervjuades patienter om hur de fattade beslutet att gå med i en klinisk prövning. Resultaten visade att patienterna hade svårt att ta in all information de fick, så beslutet styrdes mest av magkänsla och tillit till vårdteamet. Patienterna fattade ofta beslutet snabbt och bekymrade sig inte så mycket över eventuella biverkningar, utan hoppades få nytta av nya behandlingar och kunna bidra till att föra cancerforskningen framåt. De tyckte det var viktigt att veta att de hade rätt att gå ur prövningen när som helst. Det gjorde att de vågade prova en ny behandling, eftersom de visste att den gick att avbryta, om de skulle få biverkningar exempelvis. Patienter med icke botbar cancer hade inte alltid förstått detta, utan hoppades att den nya behandlingen skulle kunna bota dem.

Slutsatserna från den fjärde studien är att informationssamtalet är betydelsefullt, för då kan läkaren ta reda på vad patienten föreställer sig och tycker är viktigt. I dialogen kan de tillsammans räta ut eventuella missförstånd och se vilket beslut som stämmer bäst överens med patientens önskemål. Det finns olika samtalstekniska färdigheter som kan underlätta att genomföra informationssamtalen på ett optimalt sätt, och som informerande läkare skulle behöva träna sig på att använda. Det är också viktigt att läkaren ärligt diskuterar behandlingsmöjligheterna, både de som ingår i den kliniska prövningen och de som inte gör det. Vid en icke botbar cancersjukdom borde läkaren även ta upp möjligheten att ge rent symptomlindrande behandling, vilket ibland kan vara det bästa alternativet i den situationen.

Den här avhandlingen har lett till två övergripande slutsatser för att förbättra informationen vid kliniska prövningar. Dels att grafisk formgivning skulle kunna förbättra den skriftliga patientinformationen, och dels att informerande läkare behöver tillägna sig och använda specifika kommunikationsfärdigheter för att optimera den muntliga patientinformationen.

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Patients in Clinical Cancer Trials

Information, Understanding and Decision-Making

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