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Informed consent documents for cancer research

Textual and contextual factors of relevance for understanding

Doctoral Thesis

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Thesis for the degree of Philosophiae Doctor
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Informed consent documents for cancer research: textual and contextual factors of relevance for understanding

For at pasienter eller friske personer skal kunne delta i medisinsk forskning, må de gi sitt informerte samtykke til denne deltakelsen. Et informert samtykke innebærer at deltakerne har fått grundig informasjon om hva forskningen går ut på, hva som er konsekvensene av å delta, og at de forstår denne informasjonen. Til slutt må de signere en samtykkeerklæring dersom de sier seg villig til å delta.

Informasjonen til deltakere i forskning blir gitt både muntlig og skriftlig. Den skriftlige informasjonen kalles pasientinformasjonsskriv, og slike skriv er temaet for denne avhandlingen. Innholdet i skrivene er regulert av internasjonale etiske retningslinjer for medisinsk forskning og av nasjonale lovverk og retningslinjer. Regional komite for medisinsk og helsefaglig forskningsetikk (REK) vurderer og godkjenner pasientinformasjonsskrivet før forskningsprosjektet kan starte. Skrivene kan ha et komplisert innhold, og kan dermed være vanskelige å forstå for leserne. Målet med denne avhandlingen har vært å studere forhold som er av betydning for pasienters forståelse av pasientinformasjonsskriv.

Det er viktig at pasienten forstår pasientinformasjonsskrivet, men hva betyr det egentlig å forstå en tekst, og hvordan skal man måle om leseren har forstått den? Vi sammenlignet 34 studier av pasienters forståelse av informasjonsskriv, og fant at svært få av forskerne i dette forskningsfeltet har definert hva forståelse er. Måten forståelse er målt på, varierte også i stor grad fra studie til studie. Disse variasjonene gjør det umulig å sammenligne resultater av forskjellige studier om det samme fenomenet. Dette forhindrer at kunnskapen man kommer fram til i hver enkelt studie, kan brukes til å forbedre innholdet basert på hva som fungerer best for pasientene.

For å undersøke hvordan pasientinformasjonsskriv er skrevet, og om de er leservennlige ble det foretatt to studier av informasjonsskriv. Den første var en undersøkelse av lengde og antall innholdselementer i 87 pasientinformasjonsskriv skrevet mellom 1985 og 2007. Gjennomsnittlig antall ord i skrivene var nesten tredoblet i løpet av denne perioden, mens antall innholdselementer var mer enn fordoblet.

I en oppfølgingsstudie ble de ti eldste og de ti nyeste av de 87 skrivene analysert for å finne ut hvordan skrivemåten påvirker leservennligheten, og om skrivene dermed oppfyller sin funksjon som informasjon som forsøkspersonen kan bruke for å velge om han vil delta i forskningen eller ikke. På den ene siden var de nye skrivene mer funksjonelle enn de gamle fordi det var tydeligere at de handlet om forskning, og de ga dessuten leseren tydeligere instruksjoner om hvordan de skulle gå fram dersom de ønsket å delta. De eldste skrivene handlet mer om pasientens sykdom og behandling, noe som kan gjøre det vanskeligere for leseren å forstå at skrivet først og fremst er informasjon om forskning. På den andre siden inneholdt de nye skrivene flere tema og detaljer enn de gamle, noe som også kan gjøre det vanskeligere for leseren å forstå hovedpoenget i skrivet. De gamle skrivene hadde dessuten en tydeligere interaksjon mellom leser og skriver.

Hvordan pasienter selv opplever innholdet i pasientinformasjonsskriv, studerte vi i en intervjustudie av lungekreftpasienter. De var mest opptatt av praktisk informasjon om sin egen sykdom og behandling, mens de var mindre opptatt av formell informasjon om forskningsprosjektet. De fleste var likevel klar over det overordna målet med forskning, dvs. å generere ny kunnskap som kan komme framtidige pasienter til gode.

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Ovennevnte avhandling er funnet verdig til å forsvares offentlig
for graden ph.d. i palliativ medisin.
Disputas finner sted i auditorium MTA i Medisinsk teknisk forskningssenter (MTFS)
fredag 16.november 2012 kl. 12.15

This thesis has been assessed to be worthy of being defended
for the degree of PhD in palliative care.
The public defense takes place at auditorium MTA in Medical Technical Research Centre
Friday 16 November at 12.15 pm

Norwegian summary

Dersom pasienter eller friske personer er villige til å delta i medisinsk forskning, må de gi sitt informerte samtykke til denne deltakelsen. Informert samtykke innebærer at de har fått grundig informasjon om hva forskningen går ut på, og hva som er konsekvensene av å delta. Etter at de har mottatt muntlig og skriftlig informasjon, bekrefter pasientene at de er informert, og at de ønsker å delta i forskningen ved å signere en samtykkeerklæring.

Den skriftlige informasjonen, pasientinformasjonsskrivet, er temaet for denne avhandlingen. Innholdet i slike skriv er regulert av internasjonale etiske retningslinjer for medisinsk forskning (hvorav den mest innflytelsesrike er Helsinkideklarasjonen utviklet av Verdens legeforening), nasjonalt lovverk og nasjonale og regionale retningslinjer, for eksempel fra regional komite for medisinsk og helsefaglig forskningsetikk (REK). REK skal også vurdere og godkjenne pasientinformasjonsskrivet før forskningsprosjektet kan starte.

Målet med denne avhandlingen har vært å undersøke forhold som kan påvirke pasienters forståelse av pasientinformasjonsskriv, og hvordan tidligere forskning har målt pasienters forståelse av informasjonen de har fått i samtykkeprosessen.

Kravene til hva pasientinformasjonsskriv skal inneholde er omfattende, og man kan spørre seg om skriv som etterfølger alle kravene, blir så kompliserte at det blir vanskelig for leserne å sortere ut hva som er det viktigste budskapet. Selv om reguleringene av innhold er laget i pasientenes interesse, så er det tenkelig at mange av innholdselementene ikke er relevante for leserne. Gjennom å intervjue lungekreftpasienter fant vi at pasientene var mest opptatt av praktisk informasjon om sin egen sykdom og behandling, og at kontekstuelle aspekter ved lesesituasjonen gjorde det vanskeligere å forstå skrivene. Pasientene var mindre opptatt av formell informasjonen om forskningsprosessen. De fleste var likevel klar over det overordna målet med forskning, dvs. å generere ny kunnskap som kan komme framtidige pasienter til gode.

For å undersøke hvordan pasientinformasjonsskriv er skrevet, og om de er leservennlige ble det foretatt to dokumentanalyser. Den første var en undersøkelse av lengde og antall innholdselementer i 87 pasientinformasjonsskriv godkjent for bruk i studier mellom 1985 og 2007. Analysene viste at antall ord var nesten tredoblet i løpet av denne perioden, og at antall innholdselementer var mer en fordoblet. Antallet innholdselementer angående såkalte

formaliteter, dvs. juridisk informasjon, finansiering, lagring av innsamlet materiale, erstatningsordninger, hadde økt mest.

Problemer med å forstå et informasjonsskriv kan også skyldes skrivets lesbarhet, som i tidligere forskning har vært analysert vha. kvantitative lesbarhetsformler. I tillegg kan faktorer som tekststruktur, overskrifter og ordvalg være relevante for om skrivene er lesbare eller funksjonelle for de som faktisk skal lese og forstå dem. I en oppfølgingsstudie ble de ti eldste og de ti nyeste pasientinformasjonsskrivene av utvalget i ovennevnte studie analysert med mål om å finne ut hvilke tekstuelle faktorer som bidrar til funksjonelle pasientinformasjonsskriv og å sammenligne gamle og nye skriv i så måte. Resultatene viste at nye, lange informasjonsskriv ikke nødvendigvis var mindre funksjonelle enn de kortere, gamle skrivene. Nye informasjonsskriv var for eksempel mer rettet mot hovedtemaet i informasjonen (forskningen) og den viktigste handlingen som gjøres i skrivet (å spørre leseren om han er villig til å delta). Gamle informasjonsskriv var mer orientert mot pasientens sykdom og behandling, noe som ikke er funksjonelt som hovedtema i en tekst om medisinsk forskning.

I Helsinkideklarasjonen påpekes det at legen har ansvar for at pasienten forstår informasjonen, men det utdypes ikke noe videre hva det egentlig innebærer å forstå informasjon om medisinsk forskning. En systematisk review av tidligere studier om forståelse ble gjennomført for å vise hvordan begrepet forståelse er definert og målt. Resultatene viste at tidligere studier ikke er basert på en felles definisjon av forståelse, at de fleste målemetodene er utviklet for hver enkelt studie, og at målemetodene er forskjellige med tanke på antall spørsmål og innholdet de dekker. Dette gjør det vanskelig å sammenligne tidligere studier for å finne ut hva som kjennetegner effektiv informasjon til forskningsdeltakere.

Oppsummert viser studiene i denne avhandlingen at norske pasientinformasjonsskriv har blitt lengre og lengre de siste årene, og at de inneholder flere innholdselementer, men at de likevel ikke nødvendigvis blitt mindre leservennlige. Intervjuanalyser tydet på at innholdet i skrivene ikke var tilpasset det som pasientene var mest opptatt av. I forskningsfeltet mangler det dessuten standardmetoder for å måle pasienters forståelse av informasjon, samt en felles definisjon 'forståelse'.

Summary

Participation in medical research must be completely voluntary, and a patient's or healthy volunteers' decision to take part must be documented through an *informed consent*. Informed consent is the process in which the patient makes his/her decision about whether to participate or not based upon thorough information about the procedures of the research and the consequences of participating. After receiving oral and written information, the patients confirm that they are informed and that they are willing to participate in research by signing a consent form.

The written information, the *informed consent document* (ICD), is the topic of this thesis. The contents of the ICDs are regulated by international ethical guidelines for medical research (the Declaration of Helsinki, developed by the World Medical Association, is the most important), national laws, and national and regional regulations, for instance developed by the Regional Committees for Medical and Health Research Ethics (REC) in Norway. An ICD is approved by REC before the actual reader receives it. The overall aim of this thesis has been to investigate factors that can affect patients' understanding of informed consent documents, and how previous research has assessed patients' understanding of consent information.

The regulations regarding mandatory content of ICDs are extensive, and one might consider whether ICDs written according to the guidelines contain so much information that it becomes difficult for the reader to grasp the overall message. Even if lists of mandatory content in ICDs have been developed in the patient's best interest, it is conceivable that several of the content elements are of no particular interest for the patients. Through semi-structured interviews, we found that lung cancer patients were mostly concerned with information about their own treatment and prognoses, and that aspects surrounding the ICD reading situation might hamper the patient's ability to understand it. The patients were less concerned with formal information about the research process.

In order to investigate how the Norwegian ICDs are written, and whether they are patient-oriented, two document analyses were performed. In the first one, the length and content of a sample of 87 ICDs approved for use in research from 1987 to 2007 were investigated. The results showed that there had been a threefold increase in the number of words in ICDs during this period, and that the number of content elements was more than doubled. The presence of

formal content elements (juridical information, financing, insurance and storage of data) increased the most.

However, difficulties with the understanding of ICDs might also be caused by the readability of the documents, which previously has been analysed by quantitative readability formulas. Additionally, aspects such as text structure, headings and vocabulary are possible contributing factors for making documents readable or functional for the actual audience. In order to investigate the functional readability of ICDs, the ten oldest and the ten newest ICDs from the above-mentioned study were analysed in order to find out which textual characteristics might contribute to making ICDs readable, and to compare the readability in old and new ICDs. The findings indicate that even though newer ICDs are longer than the old ones, they are not necessarily less readable. New ICDs were, for instance, more oriented towards the main topic of an ICD (the research) and the main function (to ask the patient to take part). The older ICDs were more oriented towards the patient's disease and treatment, which are not functional as main topics in an ICD for medical research.

The Declaration of Helsinki states that the physician must ensure that the potential research subject has understood the information. However, no further instructions are given to clarify what this means and how it should be done. A systematic review was conducted on the concept of understanding and how patients' understanding of research information has been measured. The findings confirmed that a definition of the term "understanding" is lacking, and there is a large degree of variation between the measuring instruments, for instance concerning the number of questions and the content they cover. This variation hinders comparisons of findings, thus making it impossible to improve ICDs based upon the results of these empirical studies.

In summary, the studies in this thesis showed that Norwegian ICDs had become increasingly longer during the last years, and that they contain more information, bur that newer ICDs not necessarily less readable than old ones. The interview analysis suggested that the content in the ICDs were not adjusted to the patients' preferences. In the field of research, there is also a lack of standardized methods for measuring patients' understanding of information and a common definition of the term 'understanding'.

Contents

Acknowledgements

The work in this thesis has been carried out at Department of Cancer Research and Molecular Medicine, within the Pain and Palliative Research Group and the European Palliative Care Research Center (PRC) which was established during the project period. The studies have been financed by Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU) and the Norwegian Cancer Society. The possibility to carry out this thesis would never have happened without the support from the head of the research group and the PRC, Professor Stein Kaasa. Thank you so much for taking the chance on hiring an applied linguist and for being a supportive co-supervisor throughout the project period.

My main supervisor, Jon Håvard Loge, has been interested and supportive from the beginning of the project, and I am very grateful for your patience, for always being constructive, and for appreciating the linguistic approach in our project. I give my sincere thanks to my generous co-supervisor Nancy Lea Eik-Nes for illuminating discussions, for giving me the right tasks to solve to move forward, and for being available all the time. Thanks to my co-supervisor Bjørn Henning Grønberg for being one of the initiators for the project, and for valuable feedback in the finalizing process of the thesis.

Also a very special thanks to Gunhild Åm Vatn for uttering the magic words in our very first meeting with the oncologists: "And I assume this will be a PhD-project for Kari" – a very important first step of the process.

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I am especially grateful for the contribution of the patients who shared their thoughts and reflections with me in interviews while going through a difficult time of their lives. I also wish to thank to the secretariat in the Regional Committee for Medical and Health Research Ethics (REC) in Central Norway for their help during the data collection and for always taking the time to answer intricate questions about the committees' work.

I want to thank my parents for always being supportive despite my rather vaguely defined direction of education, and for being the best babysitters in the world. Last but not least, I would like to thank my wonderful supporters at home, Lise, Lars and Øyvind. Even the largest work related frustration is forgotten in the moment I come home to your hugs and dinner. Thank you so much for waiting patiently for this thesis to be finished.

Dear Lise, I would like to answer your big question once more – "Mummy, are there a thousand million pages left to write?" – with an updated answer: "No, honey, there are no pages left to write".

Trondheim, May 2012
Kari Sand

List of original papers

This thesis is based on the following papers:

I Sand K, Loge JH, Berger O, Grønberg BH, Kaasa S: Lung cancer patients' perceptions of informed consent documents. *Patient Education and Counseling*, 2008, 73(2), pp 313-317

II Sand K, Kaasa S, Loge JH: The understanding of informed consent information - definitions and measurements in empirical studies. *AJOB Primary Research*, 2010, 1(2), pp 4-24

III Berger O, Grønberg BH, Sand K, Kaasa S, Loge JH: The length of consent documents in oncological trials is doubled in twenty years. *Annals of Oncology*, 2009, 20(2), pp 379-385

IV Sand K, Eik-Nes NL, Loge JH: Readability of informed consent documents (1987-2007) – a linguistic approach. Under review, June 2012

This paper was accepted for publication on 2 September 2009. It will be published in *Journal of Empirical Research on Human Research Ethics*, volume 7, issue 4, pp 67-78. The title has been changed to "Readability of informed consent documents (1987-2007) in clinical trials: a linguistic analysis" due to comments from the reviewers.

1 Introduction

Early in the 20th century, the American lawyer Benjamin Cardozo stated that *"Every human being of adult years and sound mind has a right to determine what shall be done with his own body"* [126]. This right of self-determination refers to one of the main principles of medical ethics: the respect for patient autonomy [16]. To respect the patient's autonomy implies that the physician has a duty to enable the patient to make informed decisions concerning his/her health care, without any kind of coercion and with sufficient understanding of the relevant information.

One central implementation of respecting patient autonomy in medical care and research is the **informed consent** as a premise for patients' decision-making. Regarding medical research, informed consent refers to the process in which a patient or a healthy volunteer declares himself/herself willing to take part in medical research after being informed about the relevant consequences of participation [62]. The consent process includes a disclosure of both oral[1] and written information about all the relevant aspects of the study to the eligible participant. The information is the basis for the patients' decision concerning participation. The present thesis deals with one aspect of the informed consent process for clinical research: the written informed consent document (ICD). The ICD consists of information about the study, the request to participate, and a consent form where both the researcher providing the information and the one being informed have to sign the form if the patient is willing to participate. Thus, the ICD is also a juridical contract between the two parties.

The content of ICDs is regulated by international and national ethical guidelines for research involving human participants. The most influential international ethical regulation is the Declaration of Helsinki, developed by the World Medical Association in 1964 [224]. Derived from this, other ethical guidelines include more or less detailed lists of mandatory content of information to research participants. Also national authorities and sponsors involved in clinical research might make demands concerning the content of the information. Further, ICDs for medical research have to be approved by an ethical review board before the target reader, i.e. the eligible research participant (most often a patient), may receive it. The

[1] In the literature in this field, the term "verbal" is often used in the sense of oral. In this thesis, the term "oral" is used because the term "verbal" is rather understood as both spoken and written communication, as opposed to non-verbal communication.

members of the ethical review boards make sure that the ICD include all the relevant mandatory content.

The present work on ICDs was based on a concern among clinical researchers who wrote and presented research information to potential participants at the oncology department at St. Olavs Hospital, Trondheim University Hospital, Norway. They experienced that the ICDs were difficult to understand for many cancer patients, particularly those who were elderly and in poor general health. This raised some ethical concerns. It was discussed whether regulatory demands in a too high degree influence the content of the ICDs in a direction of "an impossible" document for the patients to cognitively process. If that was the case, we questioned the validity of the consent given by the patients.

The cancer researchers also noticed that the ICDs had to be much longer in 2005 than ten years earlier in order to get the necessary approval from the ethical review board, and started to wonder why. Based upon these experiences and questions, they embarked upon studying ICDs in order to find out: Why had they become longer? Why are they difficult to read and understand? How do the readers perceive all the information? The present thesis is the result of the investigations addressing these questions.

An initial step in the work was to get in touch with a different field of expertise – the field of applied linguistics – in order to find a collaborator with a background in communication research. This collaborator was me, who at the time was teaching bachelor students in document analysis. Applied linguistics is based on the need for communication research in order to solve communication problems, and immediately after the first phone call, my enthusiasm for the ICD project arose realizing this was an opportunity to delve into a current, genuinely experienced communication problem: ICDs which seemed to be becoming less and less reader-friendly. Hopefully, our studies of ICD content, ICD language, readers' perceptions and the concept of understanding might form the basis of relevant suggestions for how to write ICDs in a way that the patients can understand them and thus enable patients to make a truly informed consent to medical research.

2 Background

2.1 The ethical foundation of informed consent

Ethical theories are the foundation of both ethical principles/guidelines for medical research and for legal obligations related to medical research [51]. In order to ensure a high quality of medical research and that the safety of the participants is taken care of, several international guidelines and recommendations have been published from the end of the Second World War and up until today. The guidelines include recommendations for what information should be conveyed to potential research subjects in the process of obtaining informed consent.

2.1.1 Principles of medical ethics

Ethical theories of autonomy provide the moral foundation for obtaining informed consent in health care and research settings [51]. Respect for autonomy is one of the four main principles of biomedical ethics, as described by Thomas Beauchamp and James Childress in their classic text-book, *Principles of Biomedical Ethics*, first published in 1979 and currently available in the 6th edition from 2009 [13, 16]:

- respect for autonomy, i.e. the obligation to respect the decision making capacity of autonomous persons
- non-maleficence, i.e. the obligation to avoid causing harm
- beneficence, i.e. the obligations to provide benefits and to balance benefits against risks
- justice, i.e. obligations of fairness in the distribution of benefits and risks [14, 15]

For the studies in this thesis, the principle of respect for autonomy is the most relevant of the four. Autonomy refers to self-governance. According to Faden and Beauchamp [63], the principle of respect for autonomy means that "[p]ersons should be free to choose and act without controlling constrains imposed by others". In medical settings, this implies that patients should take part in the decisions – act autonomously – concerning their health care or their participation in research. In practice, this is for instance done by obtaining *informed consent* from patients before decisions are made in research and clinical contexts [14, 78, 158], i.e. decisions concerning treatment alternatives or taking part in medical research.

Professor of Medical Ethics Raanan Gillon, who wrote a 26 part series about medical ethics in the BMJ in the middle of the 1980s [77], specified that to act autonomously is not just merely

to do what one wants, but to do it *based on thought and reasoning*. This implies that in order to be autonomous, the patient's choices in health care and research have to be based on adequate information and understanding. Ideally, the thorough information disclosed to patients during the consent process enables them to make an autonomous choice concerning participation. In clinical research it is also important to balance the benefits (beneficence) and to avoid harm to patients (non-maleficence). These two principles are also important to have in mind when clinical research is planned and conducted as well as when writing the ICD.

Principles of informed consent

Since obtaining informed consent for a medical research consists of other aspects than merely informing and consenting, several attempts have been made to describe the consent process stepwise [(16)]. Beauchamp and Childress, for example, present a seven-step process in the latest edition of *Principles of Biomedical Ethics* (italics added):

I. **Threshold elements** (preconditions)

1. Competence (to understand and decide)
2. Voluntariness (in deciding)

II. **Information elements**

3. *Disclosure* (of material information)
4. Recommendation of a plan
5. *Understanding* (of 3 and 4)

III. **Consent elements**

6. Decision (in favour of a plan)
7. Authorization (of the chosen plan)

Notably, Beauchamp and Childress differentiate between "disclosure" in step 3, and "understanding" in step 5, recognizing that that what is disclosed is not necessarily what is understood [(99), page 120].The present thesis deals mainly with these two steps: disclosure of information (in information consent documents) and the patients' understanding of this information.

The *disclosure* of information about the research to the eligible participants is given orally and written by the investigator, often the treating physician. The kind of information the investigator conveys, is regulated by ethical guidelines for biomedical research involving

human subjects, for instance the Declaration of Helsinki [224] (see section 2.1.2 for details of the regulations of the content of ICDs).

The ideal consent process is described in the following manner by Falagas and colleagues: "*Appropriate information* given to a *competent individual* will *promote understanding* and, in this regard, sensible *decision making* without coercion" (italics added). They immediately add that the reality is more complicated than this, since *understanding* is not a homogenous process, but dependent of the patient's psychological and intellectual characteristics, and of his/her educational status, level of general knowledge, and personal attitudes (the latter are also affected by the morals and customs of the society). A further complicating aspect of the understanding process in a doctor-patient-setting is that "[t]he communication of medical information to patients is even more demanding because of the need to explain scientific issues with plain language" [64]. Beauchamp and Childress mention additional conditions such as illness, irrationality, and immaturity that might limit the patients' ability to understand information [14].

Further complicating the step "understanding" is trying to determine what level of understanding is sufficient for enabling a patient to give an informed consent. The necessary level of understanding has been defined rather vaguely as for instance "adequate" [16] or "appropriate" [165] for the eligible participant to make a voluntary decision.

The ideal informed consent process should both convey the relevant information and promote understanding. However, the ethical regulations that prescribe the content of the information to eligible research participants do not include instructions concerning *how* this vast amount of content should be presented in order to be adequate or appropriate for the subjects. Several studies have addressed this topic by comparing different methods of information disclosure [44, 50, 99, 150, 152, 185] (see section 2.3.1 for references) without reaching a consensus of what is the best method of informing eligible research participants about medical research.

2.1.2 Formal regulations of the content of ICDs

In order to ensure that the prospective research subjects receive sufficient information about the research, the ethical guidelines for medical research have through the last decades listed more or less detailed instructions to researchers about what to tell the subjects.

The Declaration of Helsinki is the "most widely accepted guidance worldwide on medical research involving human participants" [30], and written by doctors in the World Medical Association. Other organizations have also developed guidelines for medical research during the 1980s and 1990s, for instance World Health Organization (WHO), The Council for International Organizations of Medical Sciences (CIOMS), and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (guidelines presented below). The Declaration of Helsinki has been the foundation for the others, as illustrated in the introduction of the *CIOMS Guidelines* from 1993 which stated that "The Declaration of Helsinki (…) is the fundamental document in the field of ethics in biomedical research and has had considerable influence on the formulation of international, regional and national legislation and codes of conduct" [39]. The Declaration of Helsinki constitutes a framework of principles which are expressed in more concrete, often rather detailed, terms in the other guidelines [108]. However, the Declaration of Helsinki was not the first international guidelines of ethics for research involving human subjects – the first was the Nuremberg Code.

The Nuremberg Code

The Nuremberg Code was the first systematic international statement of the subjects' rights and physicians' obligations in medical research [5, 153]. The code was developed by the judges who condemned the Nazi physicians for their horrifying experiments on human beings in the concentration camps during the Second World War [181] in order to prevent similar experiments in the future [5]. The judgement of the 23 Nazi physicians and scientists was concluded with enumeration of the 10-point code of human experimentation [5]. The first directive of the Nuremberg Code states that voluntary consent from human subjects is absolutely essential, and elaborates by referring to the information which is necessary for giving a voluntary consent: *the person involved (…) should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision* [153], page 181.

The Declaration of Helsinki

In 1964, the World Medical Association (WMA) – after a decade of planning, drafting and revising – launched the Declaration of Helsinki [217], which is still the most influential ethical guideline for medical research (the current version is the Seoul revision from 2008 [224]). The

Declaration of Helsinki is both a set of ethical precepts and a guide to the protection of human rights in human experimentation [108].

In the 1964 version, the mandatory information to eligible research participants was stated as follows:

> *The nature, the purpose and the risk of clinical research must be explained to the subject by the doctor* [217]

In the first revision, from 1975, the requirements for informed consent were significantly elaborated [26], and included benefits – not only risks – and also the two main participants' rights: the right to refuse and the right to withdraw:

> *In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it might entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time* [218]

The revisions from 1983, 1989 and 1996 [219-221] did not involve any changes in the paragraph concerning prescribed content of the information to potential research subjects. The most substantial revision of the Declaration of Helsinki is the Edinburgh version from 2000 [222]. The following elements were added to the paragraph of mandatory content elements: *sources of funding*, *any possible conflicts of interest*, *and the institutional affiliations of the researcher*. In addition, the physician's obligation to ensure that the subject has understood the information is stated in the Declaration for the first time:

> *After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing* [222]

The revision from 2004 [223] did not involve relevant changes concerning the informed consent. The latest revision of the Declaration of Helsinki from 2008 neither adds further mandatory content, except the broad "*any other relevant aspects of the study*" [224]. However, a few details have changed in the paragraph (marked in bold in the quotation below):

> *In medical research involving **competent** human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible*

> *conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail,* ***and any other relevant aspects of the study****. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal.* ***Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.*** *After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed* [(224)]

For the first time, the Declaration of Helsinki also touches upon the manner of informing, not just the content. However, the phrase "Special attention should be given (…) to the methods used to deliver the information" is rather vague and does not give the researcher specific recommendations about how to present the content to the eligible participants in the most efficient way.

CIOMS' International Ethical Guidelines for Biomedical Research Involving Human Subjects

The Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO) initiated a new set of ethical guidelines in the late 1970s due to the challenges of applying the Nuremberg Code and the Declaration of Helsinki in developing countries [(40)]. In 1982 CIOMS published their *Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects* [(38)]. The *Proposed guidelines* are based on the Declaration of Helsinki, and are drawn up as specific recommendations which indicate how the ethical principles in the Declaration can be effectively applied, particularly in the developing countries [(38)].

The *Proposed Guidelines* refer to the prescribed information to research subjects as stated in the Declaration of Helsinki (the 1975 revision [(218)]) and discuss the challenges of informed consent related to vulnerable groups: *There are many individuals, including children, adults who are mentally ill or defective, and those who are totally unfamiliar with modern medical concepts, who are incapable of giving adequate consent* [(38)].

Following the two revisions of the Declaration of Helsinki in the 1980s, a revision of the CIOMS' *Proposed Guidelines* was initiated in the late 1980s. In 1993, *The International Ethical Guidelines for Biomedical Research Involving Human Subjects* were published. This revision included specific and detailed recommendations of "essential information for prospective research subjects" in eight bullet points. It is also stated that the information should be given "in language that he or she is capable of understanding" [(39)]. The list of essential information is far more extensive and detailed than in the Declaration of Helsinki and comprise *the invitation to participate as a subject in research*, *aims*, *methods*, *duration* and *benefits*; *risks* or *discomfort*; *alternative procedures or treatment*; *confidentiality*; *the investigator's responsibility to provide medical services to the subject*; *that therapy will be provided free of charge for specified types of research-related injury*; *compensation for injury*; *the right to refuse and to withdraw*.

Ethical issues related to controlled clinical trials with external sponsors and investigators, carried out in low-resource countries lead to the need for a further update of the CIOMS' guidelines [(40)]. In the late 1990s, the work of a second revision were initiated, and resulted in the so far latest version published in 2002. In this revision the eight bullet points are extended to 26 points of essential information that "the investigator must provide" to the prospective research subject:

1. that the individual is invited to participate in research, the reasons for considering the individual suitable for the research, and that participation is voluntary;

2. that the individual is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she would otherwise be entitled;

3. the purpose of the research, the procedures to be carried out by the investigator and the subject, and an explanation of how the research differs from routine medical care;

4. for controlled trials, an explanation of features of the research design (e.g., randomization, double-blinding), and that the subject will not be told of the assigned treatment until the study has been completed and the blind has been broken;

5. the expected duration of the individual's participation (including number and duration of visits to the research centre and the total time involved) and the possibility of early termination of the trial or of the individual's participation in it;

6. whether money or other forms of material goods will be provided in return for the individual's participation and, if so, the kind and amount;

7. that, after the completion of the study, subjects will be informed of the findings of the research in general, and individual subjects will be informed of any finding that relates to their particular health status;

8. that subjects have the right of access to their data on demand, even if these data lack immediate clinical utility (unless the ethical review committee has approved temporary or permanent non-disclosure of data, in which case the subject should be informed of, and given, the reasons for such non-disclosure);

9. any foreseeable risks, pain or discomfort, or inconvenience to the individual (or others) associated with participation in the research, including risks to the health or well-being of a subject's spouse or partner;

10. the direct benefits, if any, expected to result to subjects from participating in the research

11. the expected benefits of the research to the community or to society at large, or contributions to scientific knowledge;

12. whether, when and how any products or interventions proven by the research to be safe and effective will be made available to subjects after they have completed their participation in the research, and whether they will be expected to pay for them;

13. any currently available alternative interventions or courses of treatment;

14. the provisions that will be made to ensure respect for the privacy of subjects and for the confidentiality of records in which subjects are identified;

15. the limits, legal or other, to the investigators' ability to safeguard confidentiality, and the possible consequences of breaches of confidentiality;

16. policy with regard to the use of results of genetic tests and familial genetic information, and the precautions in place to prevent disclosure of the results of a subject's genetic tests to immediate family relatives or to others (e.g., insurance companies or employers) without the consent of the subject;

17. the sponsors of the research, the institutional affiliation of the investigators, and the nature and sources of funding for the research;

18. the possible research uses, direct or secondary, of the subject`s medical records and of biological specimens taken in the course of clinical care (See also Guidelines 4 and 18 Commentaries);

19. whether it is planned that biological specimens collected in the research will be destroyed at its conclusion, and, if not, details about their storage (where, how, for how long, and final disposition) and possible future use, and that subjects have the right to decide about such future use, to refuse storage, and to have the material destroyed (See Guideline 4 Commentary);

20. whether commercial products may be developed from biological specimens, and whether the participant will receive monetary or other benefits from the development of such products;

21. whether the investigator is serving only as an investigator or as both investigator and the subject`s physician;

22. the extent of the investigator's responsibility to provide medical services to the participant;

23. that treatment will be provided free of charge for specified types of research-related injury or for complications associated with the research, the nature and duration of such care, the name of the organization or individual that will provide the treatment, and whether there is any uncertainty regarding funding of such treatment.

24. in what way, and by what organization, the subject or the subject`s family or dependants will be compensated for disability or death resulting from such injury (or, when indicated, that there are no plans to provide such compensation);

25. whether or not, in the country in which the prospective subject is invited to participate in research, the right to compensation is legally guaranteed;

26. that an ethical review committee has approved or cleared the research protocol.

The ICH guideline for Good Clinical Practice

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was convened by the EEC (today's EU) in 1990 in order to harmonize the regulations and guidelines for drug development from different national authorities and pharmaceutical industry in Europe, Japan and the US (with WHO, Canada, Australia, and the Nordic countries as observers). The *ICH Guideline for Good Clinical Practice* (GCP), based on principles originating in the Declaration of Helsinki, was finalized in 1996 [(62)] (and has to our knowledge not been modified since then).

The ICH GCP guideline also includes a list of mandatory content of information for potential research participants. In the introduction to this list, the ICH GCP, as the only guideline, refers specifically to giving information both orally and in writing: "Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following":

(a) That the trial involves research

(b) The purpose of the trial.
(c) The trial treatment(s) and the probability for random assignment to each treatment.
(d) The trial procedures to be followed, including all invasive procedures.
(e) The subject's responsibilities.
(f) Those aspects of the trial that are experimental.
(g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
(h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
(j) The compensation and/or treatment available to the subject in the event of trial-related injury.
(k) The anticipated prorated payment, if any, to the subject for participating in the trial.
(l) The anticipated expenses, if any, to the subject for participating in the trial.
(m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
(o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
(p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
(q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
(r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
(s) The expected duration of the subject's participation in the trial.
(t) The approximate number of subjects involved in the trial.

Norwegian regulations

Clinical researchers in Norway have probably most often written their ICDs in accordance with various instructions received from Regional Committees for Medical and Health

Research Ethics (REC). Thereafter, the committee reviewed and recommended (or not) the ICDs before they could be used in the consent process[2].

In the review process, the REC might have given the researcher/author instructions concerning how to modify the content or wording of the ICD, and the researcher/author has been strongly advised to follow the instructions before giving the ICD to the eligible research participants. Thus, the Norwegian RECs have had a dual role regarding informed consent documents: (1) They have developed instructions for how the ICDs should be written, and (2) They recommend/approve the ICDs before the eligible research participants receive them.

Additionally, other agencies beyond the REC might have given the researcher/author feedback concerning the content and design of the ICD. Dependent of the type of study, the Norwegian Medicines Agency, the Norwegian Directory of Health, Norwegian Social Science Data Services (NSD), the Data Inspectorate, and the Ministry of Health and Care Services might have been involved in the review process (personal communication with Arild Hals, secretariat of REC Central Norway and Sigmund Simonsen, Department of Health and General Practice, NTNU).

2.2 ICDs as part of the consent process

The informed consent documents (ICDs) are only one part of a communication process called the consent process. The aim of the process is to convey sufficient information about the study to the eligible research participant, in order to enable him/her to make a truly informed consent to participate or to refuse. There are several challenges related to achieving the aim of the consent process. The communicating actors in the process often have dual roles: The physician is both a physician and a researcher and the patient is both a patient and a potential research participant, something which might be confusing. Further, in the case of clinical trials, the information about the trial has to be disclosed in a situation where the patient's disease quite often is progressing, and his/her situation is characterized by anxiety, despair or confusion. The patients' cognitive capacity might be reduced due to the disease. For many patients, this is obviously not the optimal point of time for acquire new knowledge about a medical study – a topic that is unfamiliar for many patients.

[2] After the implementation of the Health Research Act in 2009, REC *approves* the ICDs, not only recommends, see section 6.3.

In clinical settings, the oral communication between physicians and patients are also a very important part of the consent process. The patient is often asked to join a study during an oral consultation before he/she receives the ICD. However, the oral information is not regulated to the same extent as the written ICD, since, for instance, no approval is needed for oral information. The regulations of content and the consequences of the regulations for the ICDs are the starting point for the studies in this thesis. In this section, the ethical foundation of the informed consent will be presented, mainly focusing on autonomy. Thereafter, the development of ethical regulations of the content of ICDs will be presented.

2.3 Previous research on informed consent documents (ICDs)

There are currently a vast number of ethical regulations available that prescribe what kind of information eligible research participants should receive in the consent process. The regulations seem to have become increasingly detailed during the last two decades. The regulations are developed with the aim of ensuring that the consents are truly *informed*. Still, the question of whether the information is actually understandable for patients has been the subject of a considerable number of empirical studies. The empirical studies in the field can be divided into three main types: (1) studies of whether the patients understand the information about the study [64, 72], (2) studies of participants' satisfaction and information preferences concerning the entire consent process or parts of it [69, 205], and (3) studies of the documents readability, length and/or and content [12, 179]. Combinations of outcomes are common in previous studies, for instance understanding and readability [22] and patients' experiences and readability and length of ICDs [204]. The three directions of research are presented in separate sections below.

2.3.1 Participants' understanding of ICDs

Several previous studies have been conducted in order to measure research participants' understanding of consent information [8, 11, 18, 46, 48, 61, 66, 67, 80, 85, 92, 94, 98, 111, 114, 115, 118, 128, 130, 156, 162, 166, 170, 174, 175]. A review by Falagas and colleagues [64] evaluating patients' understanding of several aspects of the informed consent process, including studies from 1961 to 2006, concluded that participants may not clearly understand the investigative nature of clinical research. They found, for instance, that participants had an adequate comprehension of the aim of the research in only half of the studies that provided relevant data. In an updated

review including studies from 1996 to 2007, Cohn and Larson confirmed previous findings concerning research participants' limited level of understanding consent information [35]. Cohn and Larson pointed out that despite an increase of regulations and attention to the consent process, no improvement in comprehension of informed consent could be detected, even in more recent studies.

The studies of patients' level of understanding are frequently based upon "the fact" that previous studies have shown research participants' poor understanding of information, for instance: "One area that is consistently identified in the literature as being a problem is that patients often do not understand key components of the research trial" [2], and "many studies have shown that clinical research consent forms are too difficult for patients to understand" [52]. However, when looking into the specific studies, it seems more precise to describe the results in previous research as Griffin and colleagues did: "Previous studies report mixed results about how much information study participants actually can read, understand and retain" [85]. In quite a few studies, the respondents were found to have a fairly good understanding of the information they had received during the consent procedures [11, 18, 92, 109, 111, 114, 175, 200].

Other studies showed that patients had high level of understanding of some aspects of the information and poor understanding of other aspects [46, 49, 61]. For instance, Criscione and colleagues found that all the respondents understood that the trial was a medical experiment, and that a majority answered correctly regarding placebo and masking and also regarding voluntariness and the right to withdraw, while they showed less understanding of randomization and risks [46]. A low level of understanding of risks was previously found in the study by Estey and colleagues, who also found that almost half of the participants did not have a clear understanding of the concept of confidentiality [61]. On the other hand, in the study by Daugherty and colleagues, a majority of the participants remembered one or more of the risks, while few were able to state the research purpose [49]. The participants' in Daugherty et al's study were eligible for phase I trials. A review of consent consultations in phase I trials confirmed that the majority of the participants answered the question about the aim of the study correctly [42]. On the whole, only a few previous the studies of participants' understanding showed overall poor participant understanding [8, 166]. Riecken & Ravich found that only about 10 % of the participants could give a lucid account of the purpose of the study [166] and Appelbaum and colleagues found that the majority of the participants manifested

some degree of misconception about personal benefit and individualized decision about their care [8]

Comparisons of different methods for conveying information

A subcategory of the studies of understanding is randomized trials in which the effect of different methods of providing information have been compared in order to examine which method was most effective in promoting the participants' understanding. The interventions have involved either modifications of the informed consent documents [2, 22, 23, 27, 44, 50, 52, 60, 134, 149, 150, 160, 171, 190, 197, 198, 227] or other information interventions, most often the use of multimedia such as videotapes or DVDs [99, 109, 152, 185, 192, 200, 213, 230]. The results of such studies are compared thoroughly in review articles [1, 35, 54, 56, 72], with different approaches and conclusions. The main conclusion in the systematic review by Flory and Emanuel [72] was that to spend more time talking to a study member or neutral educator appeared to be the most efficient available way of improving participants' understanding, while Edwards and colleagues [56] concluded in a similar, but broader manner that "more information results in greater knowledge". Other interventions, such as multimedia interventions or enhanced ICDs, did not lead to significantly increased level of understanding [72]. On the other hand, in the review by Dunn and Jeste, the authors concluded that 11 of 16 studies were "positive", since they demonstrated increased understanding among participants in the intervention groups.

The differences between these reviews were to a certain degree caused by different aims in the reviews, some variations on which studies have been included and the time period for inclusion. However, the main cause of the different review results was that the review authors had not interpreted the results of the included studies in the same way, and that they had not assessed the quality of the studies with the same degree of thoroughness. For instance, the results of two of the studies characterized as "positive studies" by Dunn and Jeste [22, 54, 227] were questioned by Flory and Emanuel since they evaluated simulated consent processes [72]. Further, two studies of a supplementary video intervention [76, 208] were interpreted as "positive studies" by Dunn and Jeste [54] while Flory and Emanuel included these two studies in their overall conclusion regarding multimedia interventions: they "often failed to improve research participants' understanding" [72].

Why then, could two reviews make the opposite conclusions about the results of the same two studies? The so-called "positive" result in the two abovementioned studies regarded long-term retention of the information. No differences were found between the intervention groups and the control groups regarding the comprehension scores directly after the consent information had been disclosed. Flory and Emanuel commented in a footnote that long-term improvement in retention showed that the intervention improved *memory* and not *comprehension* at the time of information disclosure [72].

Weaknesses in the studies concerning a lack of consistence regarding definition, operationalization and assessments, especially the confusion of recall/memory with understanding [1, 54, 56, 143] has been discussed by other authors of systematic reviews as well, and Edwards and colleagues stated that "[s]imple recall of information is potentially misleading, since memory per se is an imperfect indicator of understanding" [56].

Two interview studies illustrate the differences between recall and understanding, one by Katie Featherstone and Jenny Donovan [66, 67] and one by Claire Snowdon and colleagues [187]. In both, the research participants' understanding and recall of randomization was explored. The results in both studies showed that the participants had a fairly good recall of the allocation process or seemed familiar with the terms "random" and "randomization", while they on the other hand revealed uncertainty and misunderstanding of the same terms. Patricia Agre and colleagues referred to the lack of consistence regarding the "gold standard" of understanding and summarized basic unanswered questions in the field in 2003:

> *[W]hat is or should be the "gold standard" of understanding? What should we expect people to know? Many of the intervention studies used knowledge quizzes to assess understanding, but what should qualify as adequate performance on such a quiz? […] Do scores on knowledge quizzes actually reflect and understanding of the information provided? Are all of the elements of equal importance, and if not, which are most important?* [1]

2.3.2 Participants' satisfaction and information preferences in the informed consent process

The other main direction in the field of research on the information given in the consent process, is the studies of participants' satisfaction and preferences – which also are crucial

aspects of a successful consent process. These studies have been aimed at a variety of aspects regarding the information presented.

Studies have included subjective evaluations of understanding (i.e. evaluation of one's own understanding) of the information / the ICD [69] and participants' evaluations of various aspects of the consent process, for instance overall satisfaction with the information or evaluation of the quality of information [114, 164, 201, 206], whether the information was perceived as useful in the decision-making process [93, 162], and also evaluations of the amount of information [19, 69, 132, 156, 164, 201, 209] and the time provided to consider the decision [19, 20]. Readers' preferences concerning the description of randomization have also been addressed [113].

Overall, research participants have reported to be satisfied with the information process and disclosure, and they often prefer to be thoroughly informed [37, 73, 209]. However, in two studies, the results showed increased level of anxiety after receiving thorough information about all relevant aspects of the study [185] and similar lower level of anxiety when receiving an easy-to-read ICD [44]. Even if many patients express a preference for detailed information in the informed consent process, the large amount of information might still cause misunderstandings or problems sorting out the main message of the information, supported by a tendency for patients to overestimate their own understanding [115].

Fewer studies have been oriented towards the participants' needs and preferences concerning the content of information (i.e. studies of what the patients want to know before making a decision) [28, 151, 194]. The reasons for investigating information needs have partly been related to recruitment aspects, i.e. what information is important for patients who consents [194] or how much information do eligible participants prefer [6], and partly to basic ethical aspects of research with human participants, for instance the need to include "patient satisfaction" as a necessary condition for quality the informed consent process [205]. In their study of subjects' information needs in clinical pain research, Casarett and colleagues described the ICD authors' challenges related to fulfilling the content requirements. The requirements allow the writers of ICDs to disclose a large amount of information to the subjects eligible for a medical study. However, there is uncertainty about which part of this information the patients actually want. For instance, it is not known which risks or potential benefits that are important for patients when they make their decision about participating in clinical pain research. Neither is

it known how much information the patients want to receive. Casarett et al discovered that the patients had different concerns about the study: about contingency plans, about addiction to opioids and about study-related changes in medication, dose, or dosage schedule. The authors claim that by adjusting the information to these concerns, the recruitment to pain research might increase.[28].

As far as we know, there is only one previous study in which patients have been asked to indicate what contents they found pertinent for a decision to agree to or refuse participation [194]. The patients in this study indicated what they found to be pertinent by underlining the most relevant information in a hypothetical ICD. The result showed that the ideal consent process of patients "weighing" the pros and cons of participation before reaching an autonomous decision, is not the picture of an actual consent process. Only 13 of the 50 participants underlined both benefits and risks as important information for their decision. This indicated that a substantial number of patients did not weigh risks and benefits as part of their decision-making process. The results of the study further showed that patients assigned very different meanings to the same information [194].

Even though patient preferences and experiences regarding the consent process has been the topic of quite a few studies, no previous study have investigated how actual eligible research participants' assess the mandatory content of the information in the consent process. As presented in section 2.1.2, ethical regulations of medical research have been updated and expanded during the 1980s and 1990s and new regulations have been published, resulting in a steady increase of the amount of instructions about what to tell the patients in the consent process. The increasing amount of content regulations makes it relevant to question which content elements are most relevant for the patients who are supposed to use the ICDs as part of their decision-making process. The reader's evaluation of the content would be of relevance for how to organize the topics of ICDs so that the information is made relevant for the readers and at the same time covers all the necessary content.

2.3.3 Document analysis of ICDs

The third main direction within the field of research in information in consent processes is analysis of the documents themselves. For more than 25 years, researchers have noted that informed consent documents might be written inappropriately [87, 88, 179]. In previous research,

one might identify two main approaches to document studies of ICDs: (1) readability studies and (2) content analyses.

Readability studies

Readability is what makes some texts easier to read than others, and is usually measured with quantitative instruments based on the use of long and short words and/or word familiarity and frequency. Since the beginning of the 20th century, a large amount of formulas have been developed for testing of readability, and approximately 200 formulas are available today [53]. When analysing documents by use of readability formulas, the results are numbers on a scale which indicates whether the documents are easy or difficult to understand, for instance a Flesch Reading Ease Formula scale ranging from 0 to 100 – the higher the number, the easier the text is to read [71].

The readability of ICDs has been measured in several previous empirical studies. The most frequent way of reporting the results are the so-called "grade level", i.e. a number indicating the years of education needed to be able to understand the document. In 20 observational studies of readability conducted between 1989 and 2007, identified through a MEDLINE literature search, the grade level was over 13 in nine of the studies (equivalent to about the first year of college/university in the USA) and over 10 in all but one (about junior high in the USA) [12, 25, 31, 74, 79, 82, 87, 90, 97, 104, 129, 131, 142, 155, 167, 179, 183, 196, 210, 211].

The scores in the mentioned readability studies are not directly comparable, since the results would be different by the use of the Flesch-Kincaid Grade Level Index (FKGL) compared to Fry Graph Readability Formula (the Fry graph) or the Gunning's Fog Index Readability Formula (the Fog index). The study by Christopher and colleagues, the result showed a 12th-grade reading level using the FKGL, a 13.9th-grade reading level when using the Fry graph, and a 14.5th-grade reading level when using the Fog Index [31].

However, the results indicate that based on quantitative readability indexes, the ICDs for clinical research are written on a level that is far too complicated for the majority of the population to understand. The International Adult Literacy Survey (IALS) was conducted in several countries between 1994 and 1998. The results showed that low literacy skills were not found only among marginalised groups but also among "significant proportions of the adult populations in all countries surveyed. Between one-quarter and three-quarters of adults fail to

attain literacy Level 3, considered by experts as a suitable minimum skill level for coping with the demands of modern life and work."[154]. The recommended level for provision of patient medical information is at US grade 6 (11–12 years) [214].

There is, however, no scientific evidence that ICDs written at a high readability level actually would be better understood by the readers [102]. Mark Hochhauser has pointed to the large amount of mandatory information in the ICDs as a more plausible source of the problems of understanding than words and reading grade levels [102]. It is relevant to investigate how the increasing amount of content regulations (section 2.1.2) has affected the ICDs.

Content, terminology and text structure

Some researchers within the field of consent information have recently turned their focus towards content and language analyses in addition to, or as an alternative to, traditional readability analysis. Content analyses of documents involves using or developing a set of categories and to count the number of instances that fall into each category [182), page 159]. Content analyses of ICDs have typically used some kind of recommendations for content as a basis for the predefined categories – either one or a few elements, or a whole list [12, 107, 183, 204, 210]. The three oldest of these studies showed that basic elements were omitted in the documents [107, 183, 210] while the two newest studies showed that the ICDs mostly contained the necessary information [12, 204]. For instance, in Hull et al.'s content analysis of ICDs for genetic research, they conclude that there were examples of critical omissions and unnecessary inclusions in the over 250 documents included. On the other hand, Verastegui, in her analysis of Mexican ICDs found the all the ten ICDs included all the basic elements required by international ethical guidelines.

The terminology in ICDs has been investigated in different ways. For instance, identification of which terms were used for the subject, the investigator and the study agent was done in two studies of ICDs from gene transfer studies [120, 121]. The results showed that treatment terminology ("patient", "doctor" or "treatment") were often used instead of or interchangeably with research terminology ("research subject", "investigator" or "study drug") in the ICDs.

The main result in the study by King and colleagues was that potential benefits in the ICDs were not presented in a clear and unambiguous way. The analysis revealed vagueness,

inconsistency, and overstatement, and thus it is probable that the readers might misinterpret what to expect from taking part in the research [121]. Ambiguous language might cause confusion concerning what to do, about who is going to do what and about the implications of participating, for instance the degree of personal benefit.

Mark Hochhauser has looked into potential difficult words used in ICDs, another aspect that is not covered by traditional readability formulas: “those formulas don’t specify specific words or phrases that average readers might find hard to understand” [101]. As recommendations to IRB members, Hochhauser suggested alternative words and phrases for several common ICD terms, for instance “to swallow a pill” instead of “oral administration”, “you might have these six problems” instead of “foreseeable risks and discomforts, and “will not cure” instead of “no medical benefits”.

Few studies of ICDs have included the structure of information in the analysis, i.e. the placement of the information in the text and/or use of headings. Horng and colleagues [105] pointed to the impact of placing relevant information in the beginning of the document. In about 85% of the ICDs in their study, a statement indicating that the study was *research* was considered to be "prominent" based on its placement in the beginning of the document (and that it was easy to identify and repeated). Strategic placement of information is way of highlighting important information. To place important information in the beginning of a document is a way of framing the subsequent information, i.e. indicating for the reader how to interpret the rest of the document [195].

The study by Sandra Philipson and colleagues [163] is one of very few studies that have made use of a broad framework including other aspect of readability than word length, sentence length and content. The Readability and Processability Form (RPF) used for analysis include the Fry readability scale, but also 19 other areas of analysis. The RPF is based on reading comprehension theories and developed to evaluate areas of comprehension that critical for reading and understanding expository material. Areas included in the study were for instance vocabulary related elements (presence of difficult terms, the use of exemplifications, highlighting of important terms by italics or bold), the need to state main ideas clearly, to use familiar syntactic patterns and to address the reader by personal pronoun rather than in third person. In order to help the reader understanding the information, it was considered helpful if the text enabled the reader to create vivid mental images of the procedures used in the

described study. The results showed that many ICD were written more appropriate for a medical audience than the lay public because they were written in a technical style that lead to a loss of personal tone. Further, the ICDs were found to probably cause confusion due to ambiguous sentences and overall lack of clarity.

The content of ICDs is included in increasingly more studies, while other textual aspects still are limitedly investigated. In the search for answers to the overall question - how to write understandable ICDs – it is necessary to investigate several textual characteristics of ICDs, such as structure and vocabulary.

2.3.4 Summary

Previous research in the field of informed consent and readers understanding of the information in consent processes have shown that research participants in some cases do not have a sufficient level of understanding of the information to be able to give a valid consent to participation. However, it has also been pointed out that the studies measuring patients' understanding has been very heterogeneously conducted, something which makes it difficult to compare previous studies. There is a need for systematizing the methodologies in the field in order to conduct future studies of understanding in a more standardized manner.

The number of guidelines for consent information and their level of detail have been steadily increasing during the past years, and in the light of this it is relevant to investigate both 1) how actual readers relate to all the information and 2) how the informed consent documents have changed during the years of expansive guidelines. Since most of the previous analysis of ICDs have made use of quantitative readability formulas, there is furthermore a need for broadening the analytic approaches that take into consideration aspects such as who is the ICD actually written for, what is the main message and function of the ICD, and how should this be conveyed in a comprehensible manner to the reader?

3 Aims of the study

The overall aim of this thesis was to investigate factors that can affect patients' understanding of informed consent documents, and how previous research has assessed patients' understanding of consent information

In order to investigate this, we conducted four separate studies with the following research questions:

- Which contents of the ICDs did the patients consider relevant or important? (Paper I)
- How did the patients assess the amount of information in the ICDs – did they find any of the information redundant, or did they want additional information? (Paper I)
- How has 'understanding' been defined in empirical studies of trial participants' understanding of consent information? (Paper II)
- How has 'understanding' been measured in empirical studies of trial participants' understanding of consent information? (Paper II)
- Has the length and amount of content elements of ICDs for oncological trials increased from 1987 to 2007? (Paper III)
- If length and amount of content elements have increased in the ICDs, what information has been added during the period 1987 to 2007? (Paper III)
- What textual characteristics contribute to *functional linguistic readability* of ICDs? (Paper IV)
- How has *functional linguistic readability* of ICDs developed during the last 20 years? (Paper IV)

4 Material and methods

Descriptions of the samples and methods for each study are presented separately below. (An overview is given in table 1, see attachment on the next page).

4.1 Paper I: Interview study

4.1.1 Participants and ICDs

The patients participating in the interview study (the *'POP'* trial) were eligible for a randomized, phase III study by the Norwegian Lung Cancer Group comparing pemetrexed plus carboplatin versus gemcitabine plus carboplatin as first line chemotherapy for patients with stage IIIB/IV non-small cell lung cancer (the *'PEG'* trial), at St. Olavs Hospital, Trondheim, Norway [86]. The patients were eligible for the *POP* trial if they fulfilled all the inclusion criteria for the *PEG* trial, except "signing of consent form", since they signed consent form for the *PEG* trial *after* they had participated in the *POP* trial. Further inclusion criteria were: chemotherapy naïve, over 18 years old and a WHO performance status of 0-2 [86], indicating that patients were self-caring and ambulatory, but not necessarily able to carry out work activities.

The patients were included between September 2005 and July 2006. After being informed about the *PEG* trial by their physicians, the eligible participants were also asked if they were willing to take part in an interview study, and given a separate informed consent document for this. If willing to participate, the patients signed a separate consent form for the *POP* trial. In the *POP* ICD, the patients were informed that the investigators wanted to find out what information the patients would prefer to read in an ICD for a clinical trial.

The *POP* trial was a randomized, explorative study in which patients' perceptions of two versions of an ICD were compared. The ICD described a clinical trial for which the patients were actually eligible (the *PEG* trial). A shortened version of the ICD for the *PEG* trial was developed for this study. The original ICD consisted of 1118 words and was approved by Regional Committee for Medical and Health Research Ethics (REC) in Central Norway in 2004. The shortened version contained 508 words and was based on a shorter ICD approved for a similar study ten years earlier.

Table 1 Material and methods in the four studies

	Paper I (POP trial)	Paper II (Systematic review)	Paper III (Length and content study)	Paper IV (Linguistic readability study)
Samples	Lung cancer patients (n=22)	Previous empirical studies (n=35)	ICDs from oncological studies (1987-2007) (n=87)	ICDs selected from the sample of 87 in paper III (n=20)
Methods 1 Procedures	Intervention: shortened version of the ICD Randomizing participants to read the standard or the shortened version Semi-structured interviews Transcribing	Literature search in four databases Hand search Scanning titles, abstracts and publication types of 1139 papers 60 full text papers were read 35 included	ICDs scanned into word format and proofread A list of 47 mandatory elements in ICDs were developed based on guidelines for medical research Computer counting of words in ICDs Manuel counting of the presence of each mandatory content element (= quantitative content analysis)	The Evaluative Linguistic Framework (ELF), items: (1) generic structure, (2) rhetorical functions, (3) reader-writer relationship, (4) metadiscourse, (5) headings, (6) expert language, (7) visual elements
Methods 2 Analyses	Qualitative content analysis Deductive and indicative categories	Development of data extraction scheme. Categories: (1) Study design, number of participants, data collected, what information was the basis for the testing; (2) What kind of information did the patients receive before the testing was done; (3) What was measured (aims/outcomes); (4) How many tests were conducted; (5) Which topics were covered in the instrument Reading of the included papers. Identifying study characteristics in accordance with the extraction scheme	Descriptive frequency analysis	Reading and re-reading all the 20 ICDs for each item in the ELF. Extracting and marking relevant words, sentences or paragraphs directly in the electronic documents or on printed versions Counting instances. Placing into preliminary tables and/or writing summaries Comparing the findings in old and new ICDs

Both versions of the ICD consisted of information about the treatment and research procedures. The original ICD were longer mainly due to more information about:

- what will happen to the collected data (storing, deleting, confidentiality and publishing)
- who is responsible for the study
- funding of the study
- approving authorities; information termed "formalities".

The distribution of the main categories of content in the two versions of the ICD is given in table 2

Table 2 Medical aspects and formalities in the two versions of the ICD used in the POP trial

	The original document	The shortened document
The medical aspects	823 words	458 words
The formalities	259 words (23.2 %)	50 words (9.8 %)
Other	36 words	
Sum	1118 words	508 words

4.1.2 Semi-structured interviews

The included patients were randomly assigned to two equal groups: one group received the original consent document, and one group received the shortened version. After reading the standard or the shortened ICD for the *PEG* trial, the patients participated in semi-structured interviews. All the interviews were undertaken by the same interviewer, the first author, who was an applied linguist, i.e. was not health professional or involved in the treatment of the patients. The interviews took place at a minimum of 90 minutes and a maximum of 30 hours after the patient had received the ICD. Twenty-one of the interviews were performed at the hospital, and most of them in the patient's room (often while the patient was lying or sitting in bed), while some were performed in a sitting area nearby. The last interview was performed in the patient's own home. The patients had the ICD available during the interview. All patients later read and signed the original ICD before they were enrolled in the *PEG* trial.

The interview guide consisted of six questions, which were meant to be a thematic guide for the interviewer, not a list to follow strictly from start to end. The questions were intended as

initiatives to discussions with the patients. Follow-up questions were used for clarifications and elaborations. The three first questions concerned the amount of information in the ICDs the patients had read: whether the information was sufficient, whether some information could be removed and whether the patients wanted some additional information. After the third question, a brief explanation was given by the interviewer about the regulations of content in ICDs and the mandatory information about research formalities and the fourth questions concerned the patients' information needs concerning these formalities. The fifth question addressed the patients' evaluation of the language in the ICD, and the final question addressed what the patients found to be the most important factors for their decision-making.

Eighteen of the interviews were audio taped and transcribed verbatim by the first author. Technical problems made the audio tapes unusable for the remaining three interviews, but thorough notes had been taken during and/or after these interviews.

4.1.3 Qualitative content analysis

The interviews were analysed through qualitative methods of content analysis; these methods comprised subjective and systematic interpretations of the content of text data (here transcriptions) through identification and categorization of essential themes and patterns [106, 177, 226]. The data were analysed and interpreted by the principle investigator and one of the co-authors.

The preparation phase of the analysis comprised reading and re-reading of the transcribed interviews in order to get an overall impression of what was said, both answers to the interview questions and other topics that were brought up. Brief summaries of each interview were written, and both the summaries and the recordings were used in the further analytic process.

The analysis was based on both deductive (predefined) and inductive categories [139]. The deductive categories were developed based on the research questions of the study, which were applied on the text (transcriptions). The inductive part of the analysis comprised deriving categories from the data itself, i.e. the themes the informants themselves brought up, not decided in advance by the investigators [58]. The inductive categories included both topics that were related to the research question and topics that were related to the context of the patients' experiences which were relevant for interpreting how the patients understood the

ICD and the situation. Both the deductive and the inductive categories were developed through discussion between the authors.

The deductive content analysis comprised the first part of the analysis. The deductive categories concerned the patients' perceptions of content in the ICDs. Operationalization of the research questions were manifested in the interview guide, and therefore the guide was used as a preliminary categorisation matrix [58]. The application of the matrix implied to apply to identify the patients' answers, and to code and systematize them [139]. During the process, the topic "language in ICDs" was removed from the analysis, due to practically no information yielded about this from the participants.

The deductive phase also involved to compare the results from the two groups, those who read the original ICD and those who read the shortened. No considerable differences were identified concerning how the patients assessed the content of the ICDs, and therefore the second part of the analysis was based on the all the interviews as a whole.

The second part of the analysis had an inductive approach, meaning that categories were developed based on topics that emerged during the interviews [58]. Overall, the basis for the inductive categories are also the research questions and the theoretical background of the study [139]. The inductive categories in the *POP* interviews were developed from what the patients said concerning relevant contextual aspects that might illustrate why they related to the ICD the way they did. Contrary to the deductive phase, the coding process in this phase was more open, including to extract relevant headings related to all the content of the interviews [58]. Such headings were further used for developing categories relevant for describing the phenomenon of investigation, i.e. the patients' evaluation of ICDs.

4.2 Paper II: Systematic review

Paper II is a systematic review of previous research concerning evaluation, testing or measurement of regular trial participants' understanding of information provided during the consent procedures for medical research.

Relevant empirical, original research studies were identified through a literature search in four databases: MedLine, Embase (1980–2007 week 39), ISIWeb of Science, and PsycINFO. The

search terms used were *(informed consent OR consent forms) AND (clinical trials OR clinical research) AND (comprehension OR understanding*). The hand search was performed by searching the reference lists of all the included papers, and of relevant review papers. The literature search yielded 1139 papers.

Studies were included if:

- the participants were eligible for, or already participating in, actual medical research
- the participants were regarded competent to make a decision regarding consent to medical research
- written in English

Studies were excluded if:

- they were investigations of patients' satisfaction with or subjective evaluations of the consent procedure
- they were hypothetical
- the participants were healthy volunteers
- the participants belonged to so-called vulnerable or underrepresented groups of participants (psychiatric patients, geriatric patients, patients with dementia or Alzheimer's disease, participants from developing countries or ethnic minorities, parents consenting for their children, or subjects in emergency situations)

4.2.1 Data extraction and analysis

Relevant categories for analysis were identified and used by the first author and a co-author to develop a data extraction scheme. The starting point for the scheme was the research questions concerning definitions and measurements of understanding. The initial examination of the included studied comprised identifying which definitions and which assessment tools were used in the studies, in addition to study design.

During this first phase of data extraction, the category "definition of understanding" was replaced, since most of the papers did not include such a definition. Instead, it was decided to extract information about the aim of the study, since this gave an opportunity to identify the terms the investigators used to refer to what they were measuring, and information about what kind of information the patients had received in advance (conversation, an ICD or both).

Furthermore, it was decided to extract details regarding the assessment tools, and thus this category was broken down into three categories (see the list below).

The focus in the review was on methodology, and thus the results of the studies were not included in the data extraction scheme. The full-length papers were read (by the first author) and categorized according to the following headings and subheadings in the final data extraction scheme:

I. Overall characterization of the study:

    1. Design of the study (randomized or observational)
    2. Number of participants
    3. Materials collected (pre- and or post-test of understanding and when the test(s) was performed)

II. What was measured?

    4. Whether the participants had received oral and/or written information before the test
    5. Aims of the study, including the words used for the phenomenon being tested, e.g. "understanding", "recall", "knowledge" etc.

III. How was it measured?

    6. Assessment tool (i.e. questionnaire or interview, structured (MCQ, true/false, agree/disagree) or semi-structured)
    7. The number of measurements conducted
    8. Topics covered in the assessment tool

The extracted data were presented in tabular format and thereafter synthesized into descriptions in order to make conclusions concerning the main research questions concerning the definition of understanding and how understanding has been measured in previous research [225].

4.3 Paper III and IV: Document analyses

Two document analyses are included in the thesis: one quantitative content and length analysis (paper III) and one qualitative linguistic analysis (paper IV). The sample of ICDs used in the first document analyses (paper III) was the corpus from which the subsample for the linguistic analysis in paper IV was selected.

4.3.1 Sample of ICDs

The sample in the quantitative document analysis of ICDs (paper III) consisted of 87 ICDs from oncological research approved by The Regional Ethical Committee in Central Norway (REC) in the period from 1987 to 2007. Approval for using the ICDs for analyses was given by the secretariat of REC and the documents were found by searching the committee's archives from its establishment in 1985. A total of 253 oncology studies were identified, and a subsample was drawn from these. The subsample consisted of ICDs from all the phase II and III studies of medical therapy for cancer patients evenly distributed throughout the years (a total of 41). From the remaining projects, ICDs from three studies per year (a total of 46) were selected randomly, yielding a total of 87. When less than three ICDs were available, all the documents from that year were included (from 1985 and 1986 no one was included). These studies included investigation/donation of biological material, testing of medical equipment, and observational studies of quality of life.

The ICDs were scanned by using the Scansoft's Omnipage SE® text recognition program into Microsoft Word® format. All the documents were proofread before analysis was performed to ensure that no words were misinterpreted by the scanning software.

The sample in the qualitative follow-up study (paper IV) consisted of the ten oldest and the ten newest ICDs from the original sample of 87 ICDs. Among the ten oldest, six were phase II/phase III clinical trials, and among the ten newest, five were phase II/phase III clinical trials.

4.3.2 Quantitative content analysis (paper III)

Coding scheme

The coding scheme for the quantitative content analysis of ICDs was a list of mandatory elements in ICDs. This list was based on the required content of consent information from the

Declaration of Helsinki [224], a three-page long guidance for authors developed by REC and a checklist of content elements developed by a working group nominated by the Ministry of Health and Social Affairs. A total of 45 content elements were derived from these sources. Thereafter, two other lists of essential content in ICDs were checked: The CIOMS' International Ethical Guidelines for Biomedical Research Involving Human Subjects [40] and ICH Guideline for Good Clinical Practice [62]. Two further elements were identified in these lists; yielding a total of 47 possibly mandatory content elements in ICDs (noting that not all elements are mandatory in all types of studies).

During the analysis, two investigators discussed the categories further when comparing scores for a selected number of ICDs. The comparison was made to ensure a reliable scoring. Agreement was found in 88% of the cases. For the rest of the cases, agreement was reached after a further discussion, which also contributed to refining the categories.

One hypothesis behind the study was that there were some elements of content in ICDs that were of less relevance for patients. Based on this hypothesis, the content elements on the list were categorised in two overall categories: "basic components" providing information about fundamental medical and ethical aspects of the study and "formal components" giving information about formalities such as juridical aspects, financing, insurance and storage of data [17].

Word count and content analysis

A word count of the ICDs was performed by the Microsoft Word 2003 ® word count function.

The presence or absence of the 47 mandatory elements was identified in each of the ICDs and scored 0 (not present) or 1 (present), by the first author. In order to ensure reliability, a subsample of the documents (all ICDs from two of the periods) was re-scored by a co-author. The two investigators agreed in 88% of the cases, and the disagreement was discussed until an agreed-upon score was obtained. The rest of the ICDs were scored by one of the investigators on the basis of this process.

The total scores were added up for each ICD, and also the scores for basic components and formal components respectively. Average number of elements and average number of words

were presented for three-years-periods in tabular format, and the development of number of elements and words were presented in scatter diagrams.

4.3.3 Linguistic analysis of functional readability (paper IV)

The Evaluative Linguistic Framework (ELF)

A linguistic framework, the Evaluative Linguistic Framework (ELF) [34], developed for studying text quality of written health information for patients, was chosen for the analysis of functional readability in paper IV. The framework was used to analyse the ICD's readability, in other words, the ICD's functionality in the specific situation it is used. The ELF was developed by Clerehan and colleagues to analyse the quality and possible shortcomings of drug information leaflets related to rheumatoid arthritis [32-34], by identifying those features that may or may not contribute to the fulfilment of writer and reader objectives [33]. The ELF consists of nine items, and seven of these were used in the analysis. The two items excluded were *lexical density* and *factual content*. Lexical density was excluded, since – as far as we know – a number for average lexical density does not exist for the Norwegian written language, moreover this is a quantitative measure which is not considered relevant for the present analysis. Analysis of factual content was excluded since this kind of analysis demands specific medical and research expertise concerning the specific studies presented in the material.

The ELF items, descriptions of them and corresponding assessment questions used to operationalize the framework are shown in Table 3 [34].

Table 3 The Evaluative Linguistic Framework for evaluating healthcare text

Item	Description	Assessment
Overall generic structure	Series of themes in a document (e.g. "purpose of the trial", "study procedures" or "participants' rights")	What identifiable main topics are present? What is the order of the topics?
The rhetorical functions	The interactive functions performed for each theme (to inform, to instruct and to explain)	What is linguistically being done? Is there clear guidance about what to do with the presented information?
The writer-reader relationship	Nature of the relationship between the writer and reader	How are the intended audience and the writer addressed?

		Is it clear who the writer and intended audience are? Is the relationship between writer and reader clear and consistent? Is the person who is expected to take responsibility for any actions clear?
Metadiscourse	Description of the purpose and/or structure of the text	Is there a clear description of the purpose of the text?
Headings	Signposts in the text for the reader	Are headings (main headings and subheadings) present? If present, are they appropriate?
Technicality of the vocabulary	The technicality of the expert terminology that is used	What characterizes the expert terminology in the text? Are technical terms explained in lay terms?
Visual aspects	Aspects such as layout, font size, style, and use of visual material	What is the length, layout, font size and the visual aspect of the document?

Linguistic document analysis

Using the ELF to analyse the ICDs comprised two main steps. Each of the seven items from the framework was analysed separately. The first step in the analysis was reading and re-reading all the 20 ICDs, and extracting and marking relevant words, sentences or paragraphs directly in the electronic documents or on printed versions of the ICDs.

The second step was counting instances and placing the results into preliminary tables for each item in the ELF. Also, summaries of the identified textual characteristics were written. The preliminary tables and the summaries for the old and the new ICDs were compared.

The analysis was mainly performed by the first author. When necessary, instances of uncertainty concerning the classification and interpretation of the textual elements were discussed by the first author and the second author until consensus was reached.

- The analysis of *generic structure* was done by identifying and naming the main themes in the ICDs. A "theme" was defined according to the examples and findings presented in the studies by Clerehan and colleagues [32, 34]. Themes are overall content units (for instance "information about study procedures" or "study background"). A

list of the identified themes was compiled for each ICD. The lists also included repetitions of themes and their placement within documents.

- The analysis of *rhetorical functions* was done by investigating the linguistic and relational function regarding each identified theme (e.g. was the text informing or instructing?).
- The analysis of the *reader-writer-relationship* was done in two steps. First, actors were identified as visible (explicit) or not visible (implicit); secondly, the ways of addressing and portraying the reader and writer were identified, and additional actors who were neither the reader nor the writer were also identified.
- The analysis of *technicality of language* was conducted by identifying all words, phrases and sentences in which medical expert terminology or research expert terminology was used, and to determine whether the terminology was explained in lay terms.
- The analysis of *metadiscourse* was performed by identifying descriptions of the ICDs' purpose and/or function and directions about how to read and interpret the text.
- The analysis of *headings* was done by identifying the main headings and subheadings and determining the headings' appropriateness by comparing the topic in the headings with the subsequent content.
- The final item, *visual aspects*, was analysed by counting the number of pages and identifying the graphical elements in the ICDs.

Finally, the readability of the identified and categorised textual characteristics was interpreted as “more readable” or “less readable” based on theoretical premises of reading comprehension that are the basis of the ELF.

4.4 Ethics

The *POP* trial (paper I) was approved by the Regional Committee for Medical Research Ethics, Health Region Central Norway, and the participants in paper I gave written informed consent (the signed consent forms have been destroyed in compliance with the instructions from the privacy ombudsman for research). The document analysis (paper III and IV) did not need an approval of the ethical committee. The committee secretariat gave the permission to use the ICDs from the archive.

4.5 Financial support

The studies in this thesis have been supported by the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology, and by the Norwegian Cancer Society.

There were no conflicts of interest in this work.

5 Summary of papers

Paper I

Lung cancer patients' perceptions of informed consent documents

The participants in the study were patients eligible for a trial of palliative chemotherapy for lung cancer (N = 22). They were randomized to receive either a original ICD or a shortened version. Semi-structured interviews were conducted after the patients had read the ICDs. The interviews were based on a broad interview-guide with questions concerning the patients' perception of the content and language in the ICDs. A qualitative content analysis was performed, including both deductive and inductive categories.

Overall, the analysis showed few differences between the patients who read the original ICD and those who read the modified version with respect to their subjective assessment of the amount of information, whether some of the content was perceived as redundant, or whether they would have preferred some additional information. Most of the participants seemed to have problems with talking extensively about their own assessment of the content in the ICDs and to evaluate what kind of information they wanted or not. They mostly gave short answers, for instance that the text was all right, easily understood, and not complicated to read, giving the impression that they were satisfied with the document. Seven patients said they wanted additional information. Three of these specified this by referring to more information about the treatment and side effects. Over half of the patients said that the most important information was to know that they are contributing to science and helping future patients.

When asked specifically about their opinion of the research formalities in the ICDs, half of the patients stated that reading about the research formalities were unnecessary, while seven patients thought it was relevant or interesting information (three did not answer).

One of the inductive categories in the study is made up by questions the participants posed to the interviewer during the interviews. Fourteen of the patients asked quite a few questions to the interviewer, showing that they took initiatives, they contributed to the dialogue and they were active in trying to get the information they wanted. These questions were an indication of which aspects that the patients would like to know more about (i.e. what we were looking

for by asking them questions about what further information they would have wanted). The main topic in these questions was treatment procedures such as: “at which hospital will I receive my treatment”, “who will perform the blood tests”, “who can I call if something happens” and “will I lose my hair?”.

Two other inductive categories were identified during the analysis, which might contribute to the total picture of the informed consent process: The unfamiliar situation and the trust in health care professionals. Being seriously ill and being at a hospital was unfamiliar for many of the patients, feelings that might influence their ability to understand written information. Eight patients expressed their complete confidence in the physician and the hospital, and this trust was related to their lack of interest in research formalities. It was not crucial to remember every detail in the ICD as long as they trusted the physician. Even though most of the patients gave the impression of understanding that the main purpose of is to contribute to generate new knowledge that would benefit future patients, they also felt confident that the physician acted in the patient’s best interest.

This study showed that the patients were most interested in the practical information about the study procedures and the information that was most directly related to themselves and their situation. This indicates that the patients’ information preferences do not correspond to the ethical guidelines prescribing a wide range of research-related content in ICDs.

Paper II

The Understanding of Informed Consent Information – Definitions and Measurements in Empirical Studies

Eleven hundred and nine titles, abstracts, and publication types were screened for relevant studies, of which 306 were duplicates. Sixty full-text articles were retrieved and read. 31 of these met the inclusion criteria, while the hand search yielded four additional publications. Thus, 35 papers met the inclusion criteria. Since two of these reported the same data collection, the number of reviewed studies, was 34. Eleven of the studies were randomized, while 23 were observational studies. The number of subjects in the studies ranged from 8 to 1789, with a median of 62 and a mean of 146. In 27 of the studies, understanding was measured once (in a post-test), while in seven studies understanding was measured more than once.

Several different terms were assigned to the variable to be measured, for instance "understanding," "comprehension," "recall", "knowledge", "perception", "retention," "awareness", and "recognition". Four to six different terms were used within the same paper in several occasions. However, a definition of what these terms implied or the distinctions between them was seldom given.

Only four of the studies included some sort of definition of and/or distinction between terms, for instance a distinction between memory and comprehension. In these studies, comprehension was seen as the most relevant variable to measure, since the authors found it less relevant to investigate what the patient *remembers* a certain period after having read the ICDs. Comprehension is vaguely referred to as "what is known at the time the consent was obtained".

Exactly what kind of information the measurement was related to varied to a certain degree between the studies. Most common was to investigate the subjects' understanding of research in general or related to the specific study. Two studies measured the subjects' understanding of a specific aspect of the information, while three studies specified a wide range of information aspects the test addressed.

Most of the studies used questionnaires or structured interviews for measuring the subjects' understanding. The questionnaires were in most cases developed specifically for each study. The questionnaires differed substantially with regard to number of items, which topics were covered, and time of measurement. The number of items varied from 2 to 23 (median 9 ½). The content of the items were divided into two main categories: (1) *Generic questions* (concerned research in general, for instance what is the reason for doing clinical research) and (2) *Trial-specific questions*. The latter category included questions either specifically related to research aspects ("all women in the study will get the same cancer-fighting drugs" true/false) or not ("which of the following side effects could be caused by the drug you are taking?"). The time of measurement varied from one hour after consent interview to two years after the closure of the study.

In 15 of the studies, no description of the development of the measurement tool was given. Only two studies described the entire development and testing of the questionnaire. The rest to a varying degree described the rationale for the items, for instance that the items were based on guidelines for consent information or on the information the subjects actually had received.

The findings of this review confirm a lack of definition of the term "understanding" and large degree of variation in regard to how it was measured. This variation hinders comparisons of findings and thus the improvement of ICDs based upon empirical findings. In order to find out what makes ICDs difficult to understand, a crucial initial step is to answer the question "What does is imply to understand an ICD?".

Paper III

The length of consent documents in oncological trials is doubled in twenty years

The material in this study consisted of 87 ICDs from oncological trials approved by the Regional Committee for Medical and Health Research Ethics (REC) in the central region of Norway between 1987 and 2007. Based on the guidelines for content in ICDs, a list of 47 mandatory content components was derived. Seventeen of these were categorized as "basic components" (i.e. fundamental medical and ethical aspects) and 30 were categorized as "formal components" (i.e. juridical and financial matters, insurance and data safety and storage). The analysis was performed by counting the number of words in each ICD and the presence of each content element were registered for all ICDs.

The mean length of the ICDs increased from 338 (range 276–464) words in 1987–1990 to 1087 words (range 399–2345) in 2005–2007. The number of words in the entire period ranged from 165 to 2345.

The mean number of components increased from nine in the 1987–1989 period to 25 in 2005–2007. The presence of basic components increased steadily from seven in 1987–1989 to 14 in 2005–2007 while the presence of formal components increased substantially from two to 11. The increased length of the ICDs is mainly explained by an increased complexity of the documents and especially more information about research formalities.

The number of words describing basic elements increased from a mean of 302 (range 184–464) in 1987–1989 to a mean of 833 (range 320–1807) in the 2005–2007 period. The number of words addressing the formalities increased even more with a seven doubling from a mean of 35 words (range 0–92) in 1987–1989 to a mean of 254 words (26–538) in the 2005–2007 period.

When writing ICDs according to the lists of mandatory information, the documents become long and contain a vast amount of information. Thus, the content regulations of ICDs might just as well hamper the patient's understanding as result in well-informed trial participants.

Paper IV

Readability of informed consent documents, 1987-2007 – a linguistic approach

The ICDs' characteristics were identified by use of a linguistic framework previously developed for investigating text quality in written health care information for patients. The items included in the analysis were: Present themes, the order of the themes, the acts performed by language (to inform, to explain, to instruct), the actors present, the interaction between the actors, the use of expert terminology, the use of metainformation (i.e. information about the text) and the use of visual aspects. The broad characteristics of the ICDs were interpreted according to theoretical premises of reading comprehension that are the basis of the framework.

Several aspects were found to contribute to readable ICDs. First, readable ICDs place essential information in the beginning of the text, both in order to highlight the main topics and to create a frame of reference which would help the reader to understand the rest of the document in an appropriate manner. Essential information would be the request to participate in research, that the reader is supposed to make a decision, and that his choice is completely voluntary. Second, readable ICDs maintain focus on *research implications* throughout the document. This implies to also present information about diagnosis and/or treatment as related to research. Third, readable ICDs give a clear picture of the reader and what he/she is supposed to do with the information (use it as a basis for decision-making) and a clear picture of the writer and other actors in the text, and their roles in the research procedures. Forth, readable ICDs use expert terminology in order to be precise, and explain expert terminology in lay terms when necessary.

Finally, readable ICDs include explicit assisting formulations such as instructions to the reader about how to consent, metainformation that presents the main goal and topics, subheadings which help the reader navigate in the document, and visual aspects to emphasize key elements.

The comparison of readability in old and new ICDs showed that the new documents were not clearly more readable or less readable than the old ones. Some textual characteristics would reduce readability while others would increase readability. On the one hand, readability in the

new ICDs was reduced due to more information, more details, and more complex presentations of actors and actions. On the other hand, the new ICDs were more research oriented than the old ones both in the beginning and throughout the text, the new ICDs included instructions to the reader about what to do if he wanted to consent and detailed contact information, aspects that increase the readability. The old ICDs were only one page long. The old ICDs scored higher on presentation of clear interaction between the actors in the document, for instance due to less additional actors. These aspects might increase readability. However, the old ICDs contained a relatively large proportion of information about the reader's diagnosis and treatment, and were thus less oriented towards research, which might reduce the goal-oriented readability.

6 Discussion

The main findings in this thesis were that:

- Patients reading ICDs mostly were concerned with practical information about their own treatment
- There is no consensus concerning what it means to "understand the information in an ICD" and how understanding should be measured.
- ICDs for oncological trials have become longer during the past decades, and the number of topics included has increased
- Despite increased length and amount of information, the textual organization of newer ICDs makes them more functional

To give an informed consent to research is a process that consists of more steps than reading a document and signing it. Particularly the dialogue between the physician and the patient is of great importance. There are reasons to believe that oral information about a medical study is at least as important as the written information for many patients, and perhaps also for physicians. A face-to-face consultation gives the patient the opportunity to ask questions, and the physician the opportunity to respond to the questions, to repeat information, and to assess immediately if the patient has understood [(203)].

A study of reading and signing various legal documents showed that nearly four out of ten participants had signed legal documents without reading them [(216)]. Reasons mentioned for not reading the documents were for instance trust, that the contents had already been explained by someone, or that the document was too difficult to read. On the other hand, the oral information is not standardized, there are possibly large variations between consultations, and there is also a possibility for a certain level of manipulation. Written information ensures that every eligible participant receives the same information, and the document can be kept as documentation of essential information that is always available for the participants [(184)]. The oral information is not the scope of this thesis.

6.1 Discussion of main findings

6.1.1 Patients' assessment of ICD contents (paper I)

Information preferences vs. content regulations

The results of the *POP* trial (paper I) showed that the patients were mostly concerned with information about the practical aspects of their treatment, and less interested in research formalities about the trial for which they were eligible. It seemed difficult for the informants to evaluate the documents extensively, and several of them expressed a high level of trust in the physicians. These results are in accordance with the results in the study by Karen Cox who investigated cancer patients' perceptions of the informed consent process and their descriptions of the decision-making process. The patients in Cox' study seemed to want the kind of information that enabled them to know what is going to happen next, in order to have some control over the situation [43].

The *POP* trial and the Cox study were both oriented towards the relationship between the *content regulations* of the ICDs and the *reader's information preferences* in the consent process. Cox pointed to the challenge of providing information that "ensure that the legal requirements of informed consent are fulfilled on the one hand, and helping patients get the information they want and understand in order to make a genuinely voluntary and informed decision on the other" [43]. The patients' preferences in the *POP* trial indicated that their information preferences were not in accordance with the content regulations concerning medical research, since many of them were mostly concerned with information regarding disease and treatment.

According to David Casarett and colleagues there are at least two challenges regarding how to inform the patient based on the regulations of content [28]. The first is a qualitative challenge: Of all the possible information included in the broad categories of mandatory content, what does the patient want? The other challenge is a quantitative one: How much information does the patient expect? The starting point for the Casarett-study, the *POP* trial, and also for a recent similar study of patients' information needs [124] was the patients' information preferences regarding the mandatory information. Since the qualitative content analysis in the *POP* trial also included inductive categories, it was possible to identify other information preferences than those related to mandatory information. Overall, the patients in the *POP* trial

seemed to be more interested in information *not* related to the mandatory research information than in mandatory formalities. These findings yield a third challenge in the consent process: How to ensure that the patients understand that the information in the consent consultations and ICDs are about research and not about treatment per se?

It is important to point out that to investigate the patients' information preferences in the consent process does *not* imply that the ICDs should contain only the information the patients want, because the patients are not aware of all the contents necessary to convey for enabling patients to make a decision about participating in research. It is necessary to follow guidelines written by experts (medical, juridical, and ethical experts). Still, it is of relevance to find out which content the patients find to be of relevance in order to convey and organise the information in such a manner that it as far as possible meets *both* the patients' needs and the formal requirements.

It is of course not surprising that cancer patients prefer information about their own diagnosis and prognosis. In the consent process, however, it is crucial to clarify that the information first and foremost concerns participating in a medical study, and that participating in a study differs from getting treatment outside of the study. The patient should get all the information he wants about his own situation, but he/she has to relate it to the research implications if the aim is to obtain a valid decision concerning research participation.

Contextual factors of relevance in the consent situation

The *POP* trial revealed contextual factors of relevance for how the patients in the *POP* trial related to the ICD. They were in an unfamiliar situation, they were severely ill and they trusted their physician, some of which might diminish the capacity to comprehend trial information. In a previous study it was shown that patients trusted the physician, the hospital and the research enterprise as a whole, and consequently, the details in the consent form were not particularly relevant for them in their decision-making process [(118)]. Findings concerning contextual factors confirm that investigating actual research participants in actual consent processes is essential for understanding how the information is perceived. As a consequence, contextual factors should be taken into consideration when writing ICDs, when reviewing ICDs and when investigating the effects of different ways of informing patients.

6.1.2 Testing understanding of trial information (Paper II)

A review of methodology gives an overview of potential sources of strengths and weaknesses in a specific field of research. In the field of informed consent, the problems of vague or lacking definitions of understanding and no standardized way of measuring it, had been referred to by previous review authors (see section 2.3.1), but had not been studied systematically prior to the publication of paper II. The findings in this paper showed that previous concerns regarding the heterogeneity and shortcomings in the field certainly were correct. As Appelbaum described it in his editorial accompanying the publication of paper II, the measurement of understanding has been "a conceptual and methodological chaos" [9].

Three main aspects were found to constitute the chaos: **First**, the definition of the term "understanding" (or whatever term was used) was absent in 30 of the 34 included studies. Terms such as understanding, comprehension, knowledge, recall, and retention were used interchangeably. By looking at the items in some of the assessment tools, it seems more accurate to say that recall or memory was measured, not understanding:

- *What special tests will be done while you are in the study? Check only the correct items* (Electrocardiogram / X-ray of the brain / Blood tests / Radioactive liver scan) [18]
- *You will be required to return to the clinic at intervals of*: (one week / two days / one month / two months / two weeks) [152]
- *The phase I trial is an investigational treatment* (agree / disagree) [111]
- *Can I be part of the trial if I am pregnant?* [52]
- *The drugs used in the trial are completely safe* (agree / disagree /don't know) [46]

The reason for recall not being sufficient for giving a truly informed consent is related to the ethical foundation of the informed consent, and not the guidelines regulation the content, which mostly lists the essential content. An ethically valid informed consent requires that participants truly understand and freely decide to participate [70]. As mentioned in 2.1.1, to act autonomously is not just merely to do what one wants, but to do it *based on thought and reasoning* [77], and that implies to understand the implications of the options one have in the consent process – to consent or to refuse – not only remember factual information about the study procedures (see recommendations for items below).

While most of the included studies in paper II did not include definitions or reflections upon what understanding is – or what recall, retention or knowledge is – a few of the studies addressed that there are differences between *remembering* and *understanding* [66, 67, 94, 128, 166]. Hassar and Weintraub stated already in the 1970s that "Some subjects remembered, but misunderstood what they had been told", indicating that *to remember* is not the same as *to understand* [94]. And as shown in section 2.3.1, Featherstone and Donovan [67] found in their interview study that even if their respondents showed good *recall* of randomization, they still did not *understand* the principle of randomization completely (i.e. that recall and understanding is not the same, and that recall does not necessarily lead to understanding): "The case studies of each man showed that all were involved in what was, essentially, a struggle to make sense of their participation". Featherstone and Donovan's findings suggest that to understand could be defined as "to make sense of", and that to measure recall or memory might not be sufficient to find out if the participants have made sense of the information to a sufficient degree to be capable to give informed consent [66, 67].

Related to the question of what to measure, is the question of *when* to measure. The studies included in paper II, showed no consensus concerning the appropriate time between the presentation of information and the assessment. In some of the studies, the assessment took place months or even years after the information was disclosed. [80, 98, 99]. However, the information in the consent process is intended to be used to facilitate decision-making in a specific situation, and for being able to give an informed consent to research, there is simply no need for a patient to remember the information for a long period of time afterwards

Secondly, the included studies showed that there is no consensus about what information must be understood in order to be enabled to make a truly informed consent [9]. One might for instance question whether these three questions actually constitute an assessment tool for assessing the "basic knowledge about the trial" [85]: (1) the purpose of the study, (2) the name of the study medication and, (3) the main side effect from the medication [85]. The purpose of the study would be a basic aspect of importance to recognize for the eligible subjects, while the name of the study drug seems of less importance. To understand what it implies to take part in a medical study are not dependent on whether the participant remembers the word *gemfibrozil*.

Thirdly, the included studies in the review showed a lack of standardized assessment tools for measuring understanding. The assessment tools were for the most part developed for each particular study, something which resulted in a large degree of variation between the assessment tools. The assessment tools consisted of a variable number or items (range 2-23 [172]) and the items covered different contents; some items were related to research in general and some to the specific trial. A systematic overview over the contents of the assessment tools have never been presented prior to paper II. The development of a standardized tool should be based on a common definition of understanding and a consensus about what information that needs to be understood (see suggestions below).

In his editorial, Appelbaum pointed out that the methodologic diversity in the field is not the same as claiming that the individual studies lack value in themselves. Some of the studies of participants' understanding are of high quality [9], it is the comparison of them that is problematic, since comparisons will be of limited value if one does not really know what is measured, and if the methods used to assess understanding are very different [9, 172].

A few questionnaires for testing understanding have been developed and validated meant for further use in other studies [110, 116, 146]. Of these, the Quality of Informed Consent (QuIC) is the only one that has been used by quite a few other investigators [11, 12, 176], and it has been translated to Finnish [99], French [159], and Korean [124], indicating that in the last five years, a certain standardization of the assessment have taken place. However, also during the last five years, investigators have continued to develop new questionnaires for measuring patients' understanding. Three such examples are described as follows: "a 21-item, true/false "Assessment of Understanding" (AoU)" [59], "a comprehension questionnaire which was designed by the study team" [21], and "In an effort to ensure that participants adequately understood study information, investigators developed a 20 item true/false comprehension quiz" [29]. The problem remains that investigators mix up the term understanding with other terms such as knowledge and recall, as exemplified in the following comments: "understanding, including self-perceived understanding and retained knowledge" [138] and "questions were primarily focused on assessing the respondent's recall of key elements of the informed consent, which were understanding the fact that his/her child was participating in a research study […]" [173].

How to operationalize understanding and develop measurements?

To measure understanding of the information in ICDs, there is a need to clarify the major aim of the information. The guidelines for medical research do seldom specify the overall aim of the information. However, in chapter 8 of ICH Good Clinical Practice [62] it is stated the purpose of the "informed consent form" is "to document the informed consent", and that the purpose of "any other written information given to trial subject" is to "document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent". It is plausible that "any other written information" is referring to the actual description of the study (the ICD). In other words, the aim of the ICD is to facilitate the research participant's decision-making.

How could that aim be achieved? There is a need to help the reader to understand what research is and the implications of being a research participant. According to Paul Appelbaum and colleagues, in their presentation of the so-called "therapeutic misconception" (TM) [7], it is crucial for the research participants to understand that the overall aim of research differs from the aim of individual treatment. The aim of research is to generate knowledge which might benefit future patients, and TM might occur when the research participants are not able to distinguish the dual role of their caretaker, being both a physician and an investigator or the implications of this. The TM occurs because the participant has a more or less "therapeutic mind-set towards the study" and thus interpret what they read and experience "as related to their individual needs" [7]. Based on this, it is an aim of the ICDs to facilitate that the reader gets a "research mind-set". This mind-set would help him to interpret the information in the appropriate manner and help him understanding the differences between treatment and research.

Based on the abovementioned definition of understanding, an instrument based on *retelling in own words* might be an approach for measuring understanding, as for instance in the interview studies of Featherstone and Donovan [66, 67]. However, the results of such methods might also be difficult to compare, since there would be a high extent of researcher's interpretation in the analyses, and the sample size would be small.

In order to develop quantitative instruments measuring the ICD reader's understanding, there is a need to include items related to research in general, the overall aims of research, why patients are included in research, the specific study he is asked to participate in, and the

implications of consenting or refusing. One example of a questionnaire including some of these items is the one developed by Strevel and colleagues [192] who initially asked the participants whether they had heard of "clinical trials" and "phase I clinical trials" and about what "a treatment clinical trial" is and what is the goal of a phase I clinical trial. These questions address the participant's background knowledge and the "research mind-set".

A questionnaire developed for measuring clinical trial participants comprehension of ICDs in India is another example of an instrument clearly directed towards the overall aims of research and towards the participant's background knowledge [21, 178]. The questionnaire is divided into four main parts, called Background of the study, Study design, Participants' rights and Miscellaneous. The firsts questions in the questionnaire are: "Do you understand that you are being asked to participate in research?", "Why is this research being done?", "For whom will this information be useful?" and "Why are you being invited to participate in the research" – i.e. basic questions about the goal of performing the study and of the participant's role in it.

6.1.3 ICDs over time: Both more complex and more functional (paper III and IV)

The main results of the analysis in paper III were that the ICDs for cancer trials in Norway had become considerably longer from 1985 to 2007, that they consisted of an increasingly larger number of content elements, especially regarding research formalities (paper III), and that longer documents not necessarily were less readable than the shorter (paper IV).

Continuously increasing length of ICDs

The results in paper III concerning increased length of ICDs confirmed findings from previous studies of the development of ICD length [10, 12, 129] and has also been confirmed later [4]. Increased length of ICDs have been considered to lead to documents that are more difficult to understand [4, 12, 60, 134, 179].

While previous studies have studied length and readability [12, 179], paper III related increased length to increased number of content elements in the ICDs. Not only the length per se, but also a large amount of topics might influence the reader's comprehension process.

Recent studies, from all over the world, have also examined the presence of mandatory content in ICDs [3, 136, 157]. The aim of these studies was to find out whether the ICDs contain the information they should, while the aim of paper III was more descriptive: To investigate the amount of information in the ICDs, whether the amount had increased, and what kind of contents were added during the last years. The increasing number of content elements identified in the ICDs were in accordance with the described development of more extensive regulations of information to medical research participants during the period of investigation (see section 2.1.2), i.e. the more extensive regulations, the more extensive ICDs. The prescription of content are developed in the patients' best interest, and the writers of ICDs obviously do what they are told to do, resulting in long ICDs saturated with information. Baker and Taub addressed the paradox related to this development already in 1983, before the large increase of detailed content regulations took place in the 1990s:

> "*Efforts to protect the rights of research subjects through federal regulations have resulted in presentation of appropriate information, but little progress has been made in ensuring that the information is comprehensible, understood, and used*" [10].

When the challenge of long ICDs with more and more content still is a reality, one might ask whether the next step would be to modify the regulations in a new manner. A modification of regulations could imply both a reduction of the number of mandatory content elements and, and not least, additional instructions about *how to present* the information, i.e. instructions about headings, wording, order of content, how to emphasize information (and what information should be emphasized) etc.

Longer ICDs, but not necessarily less readable

That the included ICDs represented a long period of time and that the results from papers III and IV were compared made it possible to reach a nuanced picture of ICDs which is rather unique in the field of informed consent research. The findings in paper IV showed that even though the ICDs had become longer during the 20-year period, they are not necessarily less readable, in the sense of being functional for their readers. Also according to a recent study by Stunkel and colleagues, there were no correlation between length of the ICD and patient comprehension of study information [193]. This indicates clearly that brevity per se is not a sufficient factor for readable ICDs. Other textual aspects than length and scores on readability formulas contribute to more functional information. The newer ICDs in paper IV were for

instance more oriented towards the topic of research than old ones, and included a clearer request about participation and clearer instructions about what to do if one wants to consent.

Albala and colleagues have later investigated the length and one content element, description of risk, in ICDs in a study with a longitudinal design [4]. The results showed two trends similar to the results in paper IV. Despite an increased length of ICDs during the 25-year-period, the descriptions of risks became less discrepant, suggesting that the writers and reviewers of ICDs are more concerned with accuracy and completeness of the information. Albala et al pointed to the paradox of a greater level of accuracy leading to increased length [4], which, as in paper IV, indicates that longer ICDs are not necessarily less readable than short ones since they might be more precise.

Linguistic analyses of ICDs are rare, but linguistic modifications of ICDs have been done in randomized studies comparing a modified document with the standard document. For instance, Bjorn and colleagues revised the language, style and layout of two ICDs for medical procedure (not medical research), by breaking down the text into smaller segments, adding subheadings dividing long sentences into smaller, and replacing professional language with lay language [22]. This revision was based on linguistic analysis of ten ICDs, and "a number of problems were identified". These problems were, however, not presented in their paper, neither their analytic framework [22], and thus it is impossible to address these problems in future attempts of modifying ICDs. On the contrary, a pre-developed, broad linguistic framework as ELF (paper IV) made it possible to specify possible problems of ICDs, for instance:

- not suitable thematic focus (when research were not thematically highlighted)
- not functional introductions (when the main message of the ICDs were not introduced in the beginning)
- limited use of explanations of expert vocabulary
- unclear presentations of the actors and what they were supposed to do
- inappropriate headings (when the headings does not cover the content in the body text)
- no use of metainformation

The findings in paper IV is therefore of value for specific recommendations for how to write and organize ICDs.

Jefford and Moore summarizes a part of the field of research of ICDs by referring to the language modifications, such as modification of content, writing style, format, or length of ICDs, that have had limited effect on the readers' understanding [112]. Still, they do believe that "attention must continue to be paid to the language of consent forms". The refer to terms such as "simplification" of ICDs and "simplified" language when they present what have been done in previous research or recommendations for what should be done in future writing of ICDs. However, the solution for writing understandable ICDs is perhaps not "a simple language" comprised of shorter sentences, shorter words and lay terms only, but, as the results in paper IV indicates, a better organized information with a clearer focus on the main message of the ICD. Furthermore, the specific problem areas of ICDs, as identified in paper IV, makes it relevant to suggest that guidelines for information to eligible research participants should comprise instructions about *how to inform*, not only *what to say*, as is the case in many of the current guidelines (see section 2.1.2).

6.2 Methodological considerations

Three of the studies in this thesis are qualitative studies (papers I, II and IV), thus, the main methodological considerations were how to achieve validity and reliability in these qualitative studies. It was important to recognize the differences between qualitative and quantitative research in the way reliability and validity are defined.

6.2.1 Research quality assessment: Validity and reliability

The rigour and trustworthiness of research are demonstrated by the validity and reliability of the procedures [168]. The strategies for establishing validity and reliability differs in qualitative and quantitative research [212]. Since the 1980s, there has been an on-going extensive debate concerning whether the terms reliability and validity are useful in qualitative research, whether other terms should be used instead, and, in that case, which terms, or whether the terms should be treated as a whole under a term such as trustworthiness [148]. This debate is out of the scope of this thesis (see for instance [36, 91, 148]). In this thesis, the terms reliability and validity are used in accordance with those who have argued that the terms reliability and validity are appropriate for all kinds of research, since the aim is to obtain rigour independent of research questions and methods (see for instance Janice Morse and colleagues [148]).)

Validity in qualitative research concerns similar aspects of research as in quantitative research: To ensure that one measures what one purports to measure [65] so that the study produces valid results. This has been referred to as "internal validity", while "external validity" refers to in what degree the results are generalizable to a more general set of circumstances than the specific population under investigation [202]. In this thesis, the term "validity" is used for the former and "generalizability" or "transferability" for the latter.

In quantitative research, validity is closely related to the study design and to the measurement methods, and strategies such as randomization and blinding are used prevent biased results. Validity is also ensured by estimating the sample size needed for enabling generalizable results [191]. In qualitative research, validity to a larger degree concerns the entire research process. There are some overall, key elements of a valid qualitative research process: First, it is important to select an appropriate method for investigating the research questions and to apply the method in a coherent and rigorous way [36, 148].

Secondly, regarding sampling strategies, one might ensure validity by including the participants that best represents what the investigator is interested in and who have knowledge of the research topic [148] or by choosing participants with various experiences to get a broad spectre of perspectives on the research topic [84]. Thirdly, the researcher in qualitative studies is not a neutral part in the investigation, and it is not an aim to remove every aspect of investigator biases. However, the investigator needs to be keenly aware of how he/she influences the data collection, analysis and results [122, 140].

Other strategies for validation of qualitative studies:

- *Triangulation*: to use multiple research methods, for instance collecting different kinds of data, combining qualitative and quantitative methods or collaboration of analysis between the investigators [89, 180, 199]. The aim of triangulation is to increase the investigators' ability to interpret the findings [199], and is most often not regarded as a test of validity [140].
- *Iteration*: to move back and forth between data and analysis have been considered to be the essence of attaining reliability and validity in qualitative studies [148].
- *Informant validation or member checking*: to compare the researcher's account with the informant [140]. This procedure is not a part of this thesis, since the researcher's

account are regarded as interpretations of entire data sets, and not necessarily something patients or ICDs writers recognize as "correct".

Generalizability is also relevant for qualitative studies. Even if the aim of qualitative research is not to generate knowledge that could be generalized to a larger population [135], the results should have a certain degree of transferability beyond the investigated situation [133]. To facilitate transferability, the investigator should give a clear description of the situation of data collection, the selection and characteristics of the participants and of the analytic process [84].

Reliability has been argued to be less suitable for qualitative research than for quantitative research [81], since the term is related to accurate representations of the natural world [36] and reproducibility – aspects that are not in accordance with the aims and procedures of most qualitative research. The aim is to broaden the understanding of the investigated phenomenon [125]). Thus, reliability in the qualitative paradigm does not mean to obtain exactly the same result time after time, but to achieve consistent results [36, 125]. However, this is not to say that the aim of qualitative analysis is a total consensus of how to interpret the data. Reliability can be achieved, for instance, by choosing analytic procedures that are well-known and validated [36]. The procedures should be performed and described in detail.

Inter-rater reliability or co-researcher dialogue has been argued to enhance reliability of qualitative analysis, i.e. dialogues between two or more of the involved investigators to ensure consensus in coding, to identify topics or patterns that one investigator may have missed, or for completing the interpretations [47, 58, 84]. The co-researcher dialogue is not supposed to remove the level of subjective interpretations in the analytic process, because this is exactly what characterizes qualitative research: the extensive interaction between the researcher and the data. The researcher's "in-depth familiarity will undoubtedly affect the subsequent interpretation" [47]. In developing a data extraction scheme, the categories must be as precise and replicable as possible [182] to ensure reliability, and co-researcher dialogue may be used. Reliability is also enhanced by giving clear, transparent descriptions of the process of data collection and analysis [122, 140].

6.2.2 Sample representativeness

This thesis is concerned with the ICDs related to cancer research and thus cancer patients. Cancer patients are a heterogeneous group with large variations in age, gender and education with different diseases treated quite differently and with considerable variation in expected outcome. Also comorbities vary between cancer patients and effect upon the health state of cancer patients.

Patients (paper I)

It is considered a strength that the sample in paper I consisted of patients who were actually eligible for a clinical trial and who were interviewed about an authentic ICD. An appropriate sample, consisting of participants who best represent or have knowledge of the research topic is one of several verification strategies that ensure reliability and validity in qualitative studies [(148)]. Although there are several studies of hypothetical scenarios in the field of informed consent, including patients or healthy volunteers being informed about hypothetical trials [(55, 68, 83, 119, 169, 188, 207)], such studies are less likely to be representative and valid for cancer patients.

The study cohort in the *POP* trial is not necessarily representative for a general cancer patient population, due to several factors:

- The sample size was small
- The patients had advanced, incurable/inoperable lung cancer
- The patients were diagnosed at one hospital only
- The patients' performance status was good enough for being referred to chemotherapy, indicating that they were more fit than many other patients advanced disease
- The patients had consented to the *POP* trial, i.e. consented to take part in an interview

During the 10 month inclusion period for the POP study, it was estimated that approximately 70 patients were diagnosed with advanced NSCLC in the county in which the *POP* study were conducted [(24)][3], suggesting that less than 2/3 of all potentially eligible patients were

[3] Data from the Cancer Registry of Norway has been used. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.

asked to participate in the trial. The participants in the *POP* trial are considered to be representative for this selected group of lung cancer patients, i.e. the results represents how these patients assess the content of an ICD for an actual clinical trial.

However, background variables of gender, age and level of education reflect some general characteristics of lung cancer patients.

- Gender: There was a slight preponderance of men among the *POP* participants (54.5%), as there was similar preponderance of men among new cases of lung cancer patients in 2006 (one of the years in the inclusion period) (59 %) [(24)].
- Age: Median age of the *POP* participants were 69 years, which is close to median age for lung cancer debut (median 72 years [(57)]).
- Education: The *POP* trial participants' level of education was lower than in the general population [(189)], which is common for lung cancer patients. In Northern Europe and Germany, there is a correlation between low education level and lung cancer in large mediated through smoking [(145)].

The sample might to some extent also be regarded as representative for a general lung cancer population. This means that the findings in the study might be a basis for what to bear in mind when writing/reviewing an ICD for severely ill, low educated lung cancer patients who have smoked their entire adult life.

Sampling strategy

The *POP* trial was a randomized, add-on study of an RCT of chemotherapy for advanced non-small cell lung cancer (the *PEG* trial). The sampling strategy of the *POP* trial followed the same principles as in the parent RCT, i.e. a sampling strategy for quantitative studies in which the participants were selected from a larger group of patients with the aim of creating a representative sample of a specific group of lung cancer patients fitting the inclusion criteria for a chemotherapy trial [(135)]. Sampling processes in qualitative research is most often not aiming at drawing a representative sample for generalizations of results. Participants in qualitative studies are rather selected intentionally or strategically, i.e. the investigator invites participants according to their knowledge about the topic investigated in order to include informants that represent the most typical or the maximum variation of the field of

investigation [161, page 230 ff.]. In other words, in qualitative sampling processes, the investigator usually searches for the participants he needs, whether it is all kinds of patients or only those who probably have sufficient experience to give relevant information about the topic of research.

Different sampling strategies might be chosen within qualitative research. Since the aim of the *POP* trial was to explore the experiences of a particular group of patients – severely ill cancer patients – a so-called homogenous sampling would probably have been used, i.e. selecting informants due to their similar characteristics relevant for the research question [103, 122]. This would probably have resulted in a sample quite similar to the one actually drawn in the *POP* trial.

Also regarding the number of participants, the principles for quantitative research were followed, since the number of patients was decided in advance based upon power calculations for the *PEG* trial In qualitative research the inclusion process are usually closed when one reaches saturation [135]. Since quite a few of the interviews did not provide sufficiently rich information about the topic, it is considered that saturation probably not was reached when the inclusion period was over. However, that saturation was not reached was probably not a result of the sample size being too small, but of some limiting aspects of the interviewing process (see section 6.2.3). Furthermore, the principle of saturation is not the most suitable for all qualitative studies. In the *POP* trial, the final number of participants was decided due to the pragmatic aspect of how many eligible informants were available in the project period.

Eleven of the eligible participants were either not asked or refused to take part in the POP trial. No further information was collected about the characteristics of these patients, their reasons for refusing or the reasons for someone not being asked. The inclusion criteria for the *PEG* trial, and thus the *POP* trial, were rather stringent, and the eleven patients were thus probably quite similar to the included patients.

Documents (papers III and IV)

The samples of ICDs used in the two document studies in this thesis (paper III and IV) were collected from the archives at the regional ethical review board in the Central Norway, and thus represent only one region of the country. All the ICDs were related to cancer research, and might not be representative for ICDs from other medical fields.

The 87 ICDs in paper III

The study in paper III is a quantitative study, and the sample of 87 ICDs was randomly drawn to comprise a representative subsection of cancer research ICDs submitted to this ethical committee, and is regarded representative for all cancer research ICDs approved by this committee in the entire period from its establishment until 2007 when the data collection was done. It is not considered representative for ICDs approved later than the inclusion period, since a considerable change in the national regulations of ICDs took place in 2009 when a template was developed (see section 6.3).

The sample of ICDs is not necessarily representative for ICDs submitted to the other Norwegian regional ethical committees, since the procedures for reviewing ICDs may vary between the different committees, and the cancer research activity within the four Norwegian health regions might also differ. However, the variation was probably larger in the beginning of the period, and reduced over the years due to an increasing level of standardisation of regulations concerning the content of ICDs.

Neither is the sample regarded representative for international ICDs since the procedures for writing and reviewing ICDs may vary between countries, even though the international ethical regulations for clinical research are the same across the world and have strongly influenced the Norwegian regulations in the field [(96)].

The 20 ICDs in paper IV

The size of the sample for the follow-up study (paper IV) was based on the number of documents analysed in the studies by Clerehan and colleagues [(32, 33)] who developed and made use of the Evaluative Linguistic Framework (ELF). They included a sample of 18 documents from a previously examined corpus of 91 [(33)]. The selection of 20 ICDs in paper IV was regarded as both a manageable and large enough number of documents for the broad linguistic analysis of text quality. The sample was not selected to be representative but to shed light on the development over time [(135)].

As mentioned above, the variation between the ICDs approved in different committees was probably larger in the beginning of the inclusion period. Thus, the 10 oldest ICDs in the sample are less likely to be representative for other ICDs in country, while the 10 newest are

more likely to be representative for all ICDs approved in the region, and also all Norwegian ICDs, from 2006-2007. Additionally, the 10 oldest ICDs in paper IV were rather homogenous and it was often obvious that they were written by researchers belonging to the same research group (based on the names and institutions mentioned in the ICDs). The consequences of using a homogenous sample of ICDs might be that aspects of functional readability in earlier ICDs would not be identified. Samples consisting of ICDs from other committees or other countries may have resulted in identifying other aspects that contributed to increased or decreased readability.

Previous empirical studies (paper II)

The four databases chosen for the literature search were regarded as relevant databases and a sufficient number of databases to retrieve as many empirical studies as possible. Still, one cannot guarantee that some articles were missed in the search. One might assume a database like CINAHL could have yielded additional relevant paper, since studies of informed consent often have been published in nursing research journals [11, 75, 127, 141-143, 186]. A literature search in CINAHL with the same search terms and within the same period as in paper II actually yielded 81 hits, of which 25 were not identified in the original search. However, none of these were eligible for the systematic review.

The search term *understanding* was used in the search string because the Declaration of Helsinki states that it is the physician's responsibility to ensure "that the potential subject has understood the information" [224]. The term *comprehension* was included because it is the MeSH-term that covers *understanding*. In the included studies the respondents were asked to answer questions regarding what they had grasped from the information that had been disclosed to them concerning the study they were participating in or were eligible for. As described in paper II, several terms and descriptions were used for the phenomenon being measured, and most often without a definition, for instance recall, retention and knowledge, even if these were not included in the search string. In retrospect, one might question why the search was not altered to include these terms as well. An extended MEDLINE search for studies published the same period as the included studies, and with the terms knowledge, recall, retention, and memory was therefore performed, and this search yielded 1552 hits. A comparison was made between the hits in two time periods, 1995-1996 and 2005-2006, in the original search and in the extended search. The extended literature search yielded a total of 453 hits in the two time periods, compared to 187 in the original search limited to the same

period. However, only two includable papers were identified, of which one had already been identified in the ISI Web of knowledge and one through the hand search. In conclusion, it is thus most probable that the initial literature search and hand search identified the vast majority of the relevant papers in the field published between 1969 and 2007.

6.2.3 Interview validity (paper I)

The interview guide was not developed by the interviewer, but by the co-authors. It consisted of questions assumed to be useful for initiating a discussion with the patient about the informed consent document (presented in section 4.1.2). Most questions in the guide were closed-ended questions (yes/no). It might have yielded richer information if open questions had been used. However, the follow-up questions were used to allow the informants to elaborate upon their views.

The interview guide was developed based on an image of a patient who was able to express various aspects of his/her experiences and reflections related to reading the ICD. In the interviews it turned out that it was rather difficult for many of the patients to answer the questions, and the material turned out to be not as rich as assumed. Rich information or "thick descriptions" are a condition for a higher degree of transferability of qualitative research results [45]. The question about the language in the ICDs did not yield any substantial answers, and is left out of the presentation of results in paper I.

After the first interview, the interviewer changed the guide so that each interview started out with one open-ended question about what the patient thought of reading the ICD. A trained interviewer would probably have altered the interview guide to a greater extent in advance, for instance to systematically include more open questions related to the ICD and the consent consultation (such as "who gave you the ICD?", "when did you receive it?", "what did the doctor tell you?"). This might have helped the patients to think through the entire process as a basis for answering the questions and also contributed to placing the patients' answers into a broader context during analysis.

In the *POP* trial it was regarded suitable that the first author with a background from communication research undertook the interviews, and not a physician or nurse. This was assumed to contribute to staying focused on the topic at hand during the interviews (the content of the ICDs) and prevent talking about diagnosis and treatment.

However, since most of the interviews were conducted at the lung department, the interviewer was instructed to wear a white coat. This coat probably affected the conversation, since several of the informants seemed to talk to the interviewer as a health care professional, i.e. asked questions related to treatment procedures, even though the interviewer presented herself and explained that she was *not* a nurse or a physician. The patients answer might have differed if the interviews had taken place outside the lung department or the hospital. On the other hand, the patients asked several questions which seemed to be directed to a nurse/physician which indicated clearly what kind of information they wanted – and to learn what the patient wanted was a major aim in the *POP* trial.

In order to ensure a consistent, reliable data set, the same person conducted all the interviews. The interviewer also transcribed all the interviews. Transcription reliability was maintained by doing a verbatim transcription, not a retelling or summary, and by always going back to recordings during the rest of the analytic process when uncertainly occurred concerning what had been said.

6.2.4 Data extraction schemes (paper II, III and IV)

Three different data extraction schemes were used in this thesis, one in the systematic review (paper II) and in the two document analyses (paper III and IV). For the two document analyses, relevant available methods for data extraction were not found. In paper III, an ad hoc scheme for content analysis was developed by the investigators, while in paper IV, a framework developed for a similar research setting involving written patient information [32-34] was used.

Data extraction scheme for systematic review (paper II)

In accordance with the aim of the systematic review, the data extraction scheme needed to be extensive and detailed in order to achieve a reliable method and a valid analysis. This would enable the investigator to identify the differences concerning the terms and the instruments used. A scheme with fewer, overall categories would not have given the possibility to describe the nuances in the included studies.

The 47-point list of mandatory content in ICDs (paper III)

In the process of developing the 47-point data extraction scheme in paper III, the guidelines from the Oviedo Convention from the Council of Europe[4] was not addressed. Regarding the content of ICDs, the most relevant part of the Oviedo Convention is *The Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research* [(41)], which was published in 2005. The investigators were not aware of this publication at the time of the data extraction. *The Additional Protocol* contains a list of mandatory information for persons being asked to participate in research. Most of the elements in the Oviedo-list were already covered by the 47-point list. However, element (iii) "arrangements for responding to adverse events or the concerns of research participants" and element (vii) "any foreseen potential further uses, including commercial uses, of the research results, data or biological materials" do not have clear corresponding items in the list used in paper III. Including these would have increased the validity of the data extraction scheme, since the list would have been slightly more representative for the actual guidelines. However, it is considered that including these elements in the scheme would not have changed the results of the analysis.

In a subsequent study, the 47-point-list was used to develop a questionnaire [(117)]. Through a Delphi-process [(95)], the number of elements was reduced from 47 to 30 . During this procedure, it became clear that there were quite a few overlapping elements in the original list of 47 items that had not been excluded during the initial discussions. This means that a few elements in the 47-point list were not sufficiently precise.

A limitation regarding the 47-point-list is that it comprised of mandatory elements from about 2005 – when the analysis was initiated – while it was used for analysing ICDs from the entire period (1985-2007). However, it would have been nearly impossible to analyse the ICDs from each period in accordance with the corresponding guidelines, since the development and management of ethical guidelines are a continuous processes which are not possible to date accurately.

The Evaluative Linguistic Framework (ELF) (Paper IV)

The ELF's face validity was assessed by the co-authors and found quite satisfactory. The items included in ELF were considered appropriate for analysing ICDs in order to identify what constitutes text quality, functional topic organization and also possible sources of

[4] The guidelines from the European Convention on Human Rights and Biomedicine of 1997

confusing information, i.e. information not functional, for the eligible research participant reading it. Despite similarities, there are, however, some key differences between the two genres: A drug information leaflet is written to provide supplementary information about a particular therapy [33], while an ICD is written to facilitate the readers' choice concerning taking part in medical research. However, the different aims do not make the ELF unsuitable for investigation of ICDs.

The ELF was developed through re-examinations of different documents within the same genre, of subsamples and of extended material [32-34, 100]. Two studies were conducted to validate the framework by the constructors. The results in the first one showed that patients preferred documents written in accordance with ELF, with respect to both linguistic and design considerations [100], while the conclusion in the other one was that: "We believe that use of our framework may be both valid and valuable for assessing and enhancing the quality of other medication information documents" [34].

At least one relevant aspect of ICDs was not covered by ELF: the *amount* of information given for each topic, something which turned out to be of relevance for analysing text quality of ICDs. Not only an increasing number of topics, but also an increasing number of details contributed to the new ICDs being longer. The old and new ICDs differed considerably when it came to the presenting details about study procedures. However, the ELF was not designed to cover this aspect. Still, the ELF is considered suitable for analysing text quality of ICDs in a more functional manner than quantitative readability indexes, which was the aim in paper IV.

6.2.5 Triangulation

Deductive and inductive analysis of interview (paper I)

To combine deductive and inductive categories in the analysis of the interviews were considered a strength since it made it possible to identify both the informants' perspectives concerning the content of the ICDs and the most relevant surrounding aspects that could explain why the informants acted and reflected the way they did. To investigate the interaction between the phenomenon being studied and its context is especially important in qualitative research which is oriented towards understanding what has happened in a specific situation than towards producing results that are generalizable to larger populations [81].

Quantitative and qualitative document analyses (papers III and IV)

Combined, the two document analyses (papers III and IV) might be seen as a methodological or analytical triangulation of the same phenomenon [199]. The aim of combining methodological strategies in the analyses of ICD was not to reach identical results or to confirm the initial finding with the next. Rather, inconsistent or even contradictory findings are to be expected when triangulation methods for analysing the same data [137], and the aim was to complete investigators' understanding of the content and design of ICDs [180]. The results on the two studies were to a certain extent contradictory. The new ICDs were longer than the old ones, an aspect that previously has been related to reduced readability [12]. However, the longer new ICDs were found be *more* readable in certain aspects than the shorter, old ones. Since the length of documents was not an item in the framework used in paper IV, the combination of methods gave a more complete picture of ICDs.

During the analysis using the ELF in paper IV it was discovered that the level of details concerning each topic would have been a relevant additional item for the study of text quality of ICDs. The document analyses showed an increased number of topics in the ICDs, which might explain why they have become longer. However, the extended level of details and elaborations regarding some of the topics in the newer ICDs is probably also an important part of the explanation of the increased length. Neither of the methods employed in paper III and IV covered this aspect.

Co-researcher dialogue (all studies)

The use of co-researcher dialogue (also called investigator triangulation [199]) was used to various degrees in the studies in this thesis. The data extraction in all the studies was mostly done by the first author alone[5], while it preferably should have been at least two co-workers collaborating also in this stage of the analytic process. Regarding for instance the use of ELF (paper IV), the application of the framework for a different document genre than is was originally developed should have included a critical review of each item and a collaborative data extraction.

Two authors discussed all the proposed elements in the list in order to reach an agreement about how to interpret them. A couple of elements were deleted from the list during this

[5] The first author was not the same person in paper III as in the other papers

process because discussion revealed that some categories were not actually content elements but style elements and thus not appropriate for the study.

The interpretation phases of the analysis were done collaboratively. For instance, in paper I, two co-authors with different professional positions, communication and medicine, discussions resulted in the inclusion of an inductive analytic phase. It was considered useful for addressing the research question to include the patients' contextual experiences. This approach has been called "directed content analysis" [106, 228], meaning that the initial coding starts with a theory or relevant research findings, and then the researchers during the analysis immerse themselves in the data and allow themes to emerge from the data. In paper IV, the interpretation of textual aspects as increasing or reducing readability was done through discussions between two authors.

6.3 ICDs – present status

In Norway, instructions about how to write ICDs are given in two new ICD templates developed by a working group within the ethical committees in 2009 (one general template and one for clinical trial ICDs). Thus, current ICDs might differ from the ones included in this thesis and that ICDs now are more standardized.

In addition to content instructions, the templates include a suggestion for main heading (*Request for participation in a clinical trial*) and several subheadings (*Background and purpose*; *What does the study involve?*; *Potential advantages, disadvantages and serious adverse events*; *What will happen to the samples and your personal information?* and *Voluntary participation*). The templates consist of "fill in-sections" (with instructions regarding which content to insert) and of ready-prepared formulations which the writer might use in his ICD, for instance

- *This is an invitation for you to participate in a research study which involves testing of the medicine*
- *The samples and data that are registered about you will only be used in accordance with the purpose of the study as described above*
- *Participation in the study is voluntary. You can withdraw your consent to participate in the study at any time and without stating any particular reason*

The template consists of three parts. The first part is a description of the main procedures and the participant's main rights, and is supposed to give the reader sufficient information to make a decision. Part two and three are appendixes with elaborations for readers who want more information. Part two is meant for elaboration of what the study involves while part three is meant for information about data privacy, biobank, funding and insurance. There are no further instructions given to the author about what to include in the appendixes. The consent declaration is placed in the end, after the second appendix. Thus, an increasing amount of instructions about what and how to write are provided to Norwegian writers of ICDs. The vast majority of the instructions concern the ICDs' content, not the shape.

Another major change in the field of research ethics in Norway in 2009 was the implementation of the new Act on medical and health research (Health Research Act) [(147)] . The Health Research Act contains the first general, statutory provision of consent to medical research in Norway and states that, as the main rule, the consent should be informed, voluntary, explicit and documentable [(147)] (chapter 4, § 13). However, the Act does not specify how one might ensure that participants are informed.

The practical implications for the writing of ICDs are that fewer authorities now are involved in the process of approving the documents, but still there are quite a few possible involved parts in the process of approving an ICD, especially regarding clinical trials (drug testing). For studies involving drug testing, the researcher is required to send an application to the Norwegian Medicines Agency which might comment upon the ICD, and which rather often does (personal communication with Kari Steig, Norwegian Directory of Health). Studies involving clinical testing of medical equipment have to be reported to the Norwegian Directory of Health, which also might make objections concerning the content and language in the ICD, but which rather seldom does (personal communication with Ingvild Aaløkken, Norwegian Medicines Agency). Finally, pharmaceutical companies initiating clinical trials have developed their own templates for content and design of ICDs which might differ from the new template.

Even though paper IV showed that length is not a sufficient factor for predicting readability, it is still considered a problem that the ICDs are long. Norwegian ICDs have usually been shorter than ICDs from several other countries (ICDs from about 35 countries were collected for a planned comparative study with a similar design as in paper III), but have still been

considered too long. The new template for ICDs was designed to give the reader a relatively short overview of the most important information. However, the possibility to include elaborations in part two and three had led to ICDs becoming much longer than before (personal communication with Arild Hals, REC Central Norway). And the placement of the actual consent declaration, i.e. the place for the signature, after the two appendixes, might indicate to the reader that the entire information should be read before a decision is made. A thorough oral explanation of how to deal with the ICD would be necessary.

6.4 Study implications

Implications for practice and implications for future research are presented below.

6.4.1 Implications for practice

In this section, some implications for those who review and approve/disapprove of the ICD, i.e. members of ethical review boards (called REC members), and those who write ICDs, i.e. medical researchers, are presented.

Implications for ethical review boards

- The results in paper I showed that some contextual aspects are of great relevance for how severely ill patients might perceive the ICD. The unfamiliar and frightening situation they were in and their confidence in their physician made the information in the ICD of less importance for them in the consent process. Thus, also REC members should take the contextual aspects into considerations in their review of the ICDs.
- The results of the document studies (paper III and IV) indicated that REC members need to take into considerations a broad range of textual characteristics in their review of ICDs, for instance overall thematic consistency, emphasizing important messages, suitable headings and subheadings and clarity of interaction between the actors.

REC members administer ethical guidelines such as the Declaration of Helsinki, ICH Good Clinical Practice and the Oviedo Convention. Thus, one might say that in order to enhance the ICDs, there is a need to revise these guidelines as well, not only recommend changes in the REC review process.

The guidelines for authors of ICDs often comprise lists of essential/mandatory content elements (examples shown in section 2.1.2). In these lists each content element seems to be

equally important, since no information is given regarding what is the most important information or the overall message to the reader of the ICD.

Based on the findings of studies, the following would be possible elaborations of the guidelines for trial information to eligible trial participants: There is a need:

- to specify what is the main objective or function of the information to eligible research participants (in order to orient the content and design of the information towards this)
- for a certain ranking of the required content elements in order to specify which are the main topics
- to include more guidelines concerning *how* to present the content, i.e. how to present a large amount of required content in an adequate manner for a patient audience
- to elaborate how the physician is supposed to ensure that the patient has understood the information and a specification of what is the most important information to understand

A more radical approach related to the challenges of writing understandable ICDs, is the question of whether written information at all is an appropriate solution for obtaining informed consent. Alan Meisel argues that ICDs are merely formalistic and that what is needed is methods of informing patients adjusted to each person's needs and learning styles [(144)]. Consequently, this means to aim for individualization of information rather than standardization of the information. Individualization is not achieved through written information, but through "good, old-fashioned conversations", according to Meisel [(144)]. Other investigators in the field of informed consent has also found or argued in favour of conversation as the way of ensuring the patients' understanding during the consent process [(215, 229)]. While it is unlikely that written information would be totally replaced by oral, these points of view suggest that the guidelines for information to eligible research participants also might specify how to inform the eligible participants orally.

Implications for writers

The results of the studies in this thesis and previous research might contribute to suggestions for what to bear in mind when writing ICDs for potential research participants. A consistent

and functional ICD should be oriented to the overall aim of the informed consent process. The ICD might have different aims for the writer and reader, but ideally, the ICD is written for the eligible research participant, and the aim is to enable the reader to make a truly informed decision about participating in research. In order to write a functional ICD, one might:

- Emphasize research as main topic in the ICD, i.e. present the request to participate, the study procedures (not the treatment per se), the choices the reader has, the implications of choosing one or the other, including the reader's rights. Patients might want a lot of information about their disease, treatment and prognosis. In the consent process, however, this information should be framed as part of a research setting in order to be functional.
- Clarify the relationship between the reader, the writer and any additional actors in the document, for instance by explaining the dual roles of the physician and patient (i.e. that they are also an investigator and an eligible research participant).
- Emphasize the request to participate as main function. The information in the consent process is related to subsequent actions, first and foremost the consenting (or refusing), performed by the reader. The main function might be clarified by placing a request in the beginning of the ICD, by repeating the request, and by giving the reader clear instructions about how to proceed if he/she wants to consent.
- Clarify what actions the different persons are supposed to perform might be clarified by writing in the active voice and include subjects in the sentences.
- Orient the ICD towards the target reader, i.e. the eligible research participant, not "only a patient" and not the ethical review board.

Furthermore, since it is the investigator's responsibility to ensure that the trial participant has understood the information, a test of participants' understanding might also be used as part of the actual consent process [213]. Relevant questions in such an assessment tool should address the overall aspects of research and the study, for instance the aim of research, the aim of the specific study, and how research differs from regular treatment. There are some examples of questions of this kind in studies included in paper II:

- Items regarding the goals of the study were for instance included in the questionnaire developed by Strevel et al: *Please state whether each of the following is a goal of a phase I clinical trial*: *a) decide how much of a new drug can be given safely (yes/no), b) decide how often a new drug needs to be given*

(yes/no), decide if a new drug is more effective than an old drug (yes/no), decide what the side effects of a new drug are (yes/no) [192].

- The questionnaire developed by Joffe and colleagues, the QuIC, addressed the main aim of cancer clinical trials, and emphasized the important aspect of trials being performed to benefit future patients (*A2. The main reason cancer clinical trials are done is to improve the treatment of future cancer patients (Disagree, unsure, agree*)) [116].
- The questionnaire developed and validated by Hutchison and colleagues consisted entirely of questions about research (since it is designed to test patient understanding of research). Questions in the questionnaire look like this: *The main reason for carrying out research with patients is … (a) to improve current treatments; (b) to find treatments with no side effects; (c) to help pay for cancer treatments; (d) don't know*.
- Hutchison et al's questionnaire also addressed the crucial differences between therapy and trials in the options for response in the following question: *When a trial is 'randomized . . .(a) the process selects the best treatment for you; (b) you have exactly the same chance of receiving the new treatment (or not receiving it), as any other patient taking part; (c) the doctor decides which treatment is the right one for you; (d) don't know.*

6.4.2 Implications for research

Future research of ICDs would have to imply the studies of both the readers, writers, approval authorities and the documents in order to facilitate the readers' understanding of the information to a sufficient level for voluntary decision-making.

- There is a need to investigate how to organise the information so that the readers are capable of sorting out the main message of an ICD.
- In order to compare the level of understanding of documents with the same objective, there is a need for a standardized assessment tool based on a common definition of the term "understanding". In order to measure the participants' understanding of the information, there is also a need to specify the overall message and the overall aim of ICDs. (See recommendations in section 6.4.1.)
- A broader approach to the consent process would also have to include research on the oral information about medical research to the eligible participants.

- Two important organizational changes have occurred since the data collection in this thesis was done: The introduction of an ICD template and the implementation of the Health Research Act (see 6.3). The direct consequence of writers using the template is that the ICDs become even more standardized, but the template per se is no guarantee for more readable ICDs. Thus, a relevant subsequent research question is how these changes have affected the length and the functionality, including the readability, of Norwegian ICDs?
- It is still not known what kind of ICD modifications/revisions that increases the reader's level of understanding. Further studies would have to imply intervention studies of linguistically based modifications of ICDs and of information oriented towards patient's information preferences
- Future modifications of ICDs should be completed with performance-based approach as for instance user testing. To combine performance-based user testing with expertise in writing for patients and information design resulted in a significantly improved and preferred information sheet in a study by Knapp and colleagues [(123)].

7 Conclusions

The following conclusions are the answers to the research questions addressed in the thesis:

- After reading an ICD, the patients were most concerned with practical and detailed information about the treatment they were about to receive – summarized as ”who will do what, when and where”. They were, however, aware of their participation in research and that the overall goal of research is to generate new knowledge which might benefit future patients. The patients expressed less interest in information about research formalities.

- Both the patients who read the standard ICD and those who read the shortened version, expressed satisfaction with the amount of information. Few patients were able to state which information was redundant and what they would have preferred to read more about. The two participants with higher education were the only ones who were able to state their opinion about redundant information.

- The term ‘understanding’ has seldom been defined in previous studies of research participants’ understanding of information. Previous studies showed a large varition in the terms used for the phenomenon measured; terms such as understanding, comprehension, recall, knowledge, awareness, preception, retention etc. were often used synonymously within the same paper.

- Previous studies of understanding were very heteregeneous in terms of participants included, number of participants, the timing of mesuring and not least the assessment tools used, which in most cases was developed for each study. The most frequent assessment tool was questionnaires, and they differed substantially regarding the number of questions, the content of the items and the time of testing related to the time of information.

- A threefold increase of length was found in Norwegian ICDs between 1987 and 2007.

- The number of content elements in Norwegian ICDs increased considerably from 1987 to 2007. The presence of both basic elements and formal elements had increased, with the largest increase identified for the formalities.

- Overall textual characteristics that might contribute to increased readability of ICDs are: to introduce the document be clearly referring to the main message of research

participation and implications, to maintain this thematic focus throughout the entire ICD, and to write for the main reader – i.e. the eligible research participant, not merely a patient and not the ethical review board

- Even if the new ICDs were longer than the old ones, they were not necessarily less readable. New ICDs were more clearly oriented towards the main topic and function of ICDs, since the request to participate were placed in the beginning of the documents, and since the entire documents were more oriented towards research procedures and implications. The old ICDs, on the other hand, presented a clearer interaction between the actors in the document, for instance due to less additional actors.

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Lung cancer patients' perceptions of informed consent documents

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ABSTRACT

Objective: To compare patients' perceptions and preferences of two different versions of informed consent documents.
Methods: Patients eligible for a trial of palliative chemotherapy for lung cancer ($N = 22$) were randomly assigned to receive either an original consent document or a shortened version written for the present study. Semi-structured interviews were conducted after the patients had read the consent documents. The interviews were transcribed verbatim and analysed using qualitative content analysis.
Results: Few differences between the two groups were found with respect to patients' assessment of the amount of content and the most important information in the documents. Information about disease and treatment seemed to be of most interest for the patients, while information about research aspects of the study such as financing, confidentiality and publishing (formalities) was judged to be of lesser relevance. Two patients who read the original document indicated that they treated the formalities as secondary.
Conclusion: Patients seemed to pay little attention to the research aspects, and thus risked to misunderstand the main point of the consent document.
Practice implications: The structure of consent documents should clarify for the readers that they are asked to take part in research, and that participation is voluntary.

1. Introduction

Before inclusion into biomedical research, researchers must obtain the informed consent of the eligible patients. The information in the trial includes both verbal and written elements, and a truly informed consent presupposes that the patients can understand written information before signing the consent document.

The Declaration of Helsinki recommends that the consent document should include information about the purpose of the trial, procedures, possible risks and benefits, sources of finance, potential conflicts of interest and the researchers' institutional affiliation [1]. In addition, the documents should be written in accordance with directions from the Regional Committee for Medical Research Ethics, the Norwegian Social Science Data Services, and the Norwegian Medicines Agencies. The amount of directions for content in the consent documents has increased over the last years, and it could be a challenge to comply with all these instructions when writing a consent document.

Previous studies have revealed that many participants in clinical research fail to understand or recall central aspects in the information disclosed during the consent process [2], like risks, the right to withdraw [3], confidentiality [4], side effects [5] and the purpose of the trial [6]. Suggested explanations for this have been low literacy in some patient groups (e.g. high age and lower education), low health literacy among typical underrepresented groups in clinical research (e.g. ethnic minorities), the patients' reduced health status, and technical and scientific language in the consent documents [5,7,8].

Another explanation for participants' lack of understanding might be that the extensive instructions for writing consent documents result in complex documents consisting of too many elements of information. The amount of information could limit the readers' ability to understand the main point of the consent document and to give a truly informed consent.

In order to enhance informed consent documents, it is important to study how the patients themselves perceive the documents. To our knowledge no studies have addressed which of the information elements the patients perceive as most relevant and important. Further, most patients are severely ill and elderly,

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and little is known about how sick, weak or old people perceive complex consent documents and which of the content elements they regard to most relevant.

In the present study, we compared patients' perceptions and preferences of two different versions of informed consent documents written according to a set of formal requirements. Our primary research question was which content the patients considered relevant or important. A secondary question concerned the amount of information—did the patients find any of the information redundant? Or did they prefer additional information?

2. Methods

2.1. Intervention

The subjects were eligible for a randomized, phase III study by the Norwegian Lung Cancer Group comparing pemetrexed plus carboplatin versus gemcitabine plus carboplatin as first line chemotherapy of patients with stage IIIB/IV non-small cell lung cancer (the 'PEG' trial) [9]. The original consent document for the trial contained 1118 words, and was approved by all regulatory authorities (the Regional Committee for Medical Research Ethics, the Norwegian Medicines Agency, Norwegian Social Science Data Services, and the Directorate for Health and Social Affairs) in 2004. For the purpose of the present study a shortened version of the consent document, containing 508 words, was written. The shortened version was based on a consent document written for a study with the same design in the same patient group approved by the Regional Committee for Medical Research Ethics in 1994. The content was modified in accordance with the PEG trial.

The two consent documents consisted mainly of two categories of information. We have chosen to term the information concerning the study treatment and the study related procedures as *medical aspects*, and the information not directly related to treatment and procedures as *formalities*. Formalities would be for instance information about confidentiality, storage and possible re-use of data, consequences of refusal or withdrawal of consent (alternative treatment, whether collected data will be deleted or not), access to the results after the trial is closed, and insurance. The distribution of the two main categories of content in the two consent documents is shown in Table 1.

Both documents consisted of detailed information about the treatment procedures: beforehand procedures, how information about the patients will be recorded, randomization, frequency and duration of the treatment, medication not to be taken during treatment, which information will be collected from the patients, and exclusion criteria. The original document in addition consisted of thorough information about what will happen to the collected data (storing, deleting, confidentiality and publishing), about who is responsible for and financing the study, and about the different approving authorities.

2.2. Interviews

After having received verbal information about their malignant disease, recommended treatment and the purpose of the PEG trial from their physician, consecutive patients eligible for the PEG trial at St. Olavs Hospital, Trondheim, Norway between September 2005 and July 2006 were asked to participate in a semi-structured interview. Of the 33 eligible patients, 22 agreed to participate in the interviews. They were randomly assigned to receive either the original consent document or the shortened version before the interview. The eleven others were either not asked or refused to participate.

All the interviews were undertaken by the same interviewer (K.S.). The interviews took place at a minimum of 90 min and a maximum of 30 h after the patient had received the informed consent document. One of the interviews took place 3 months after enrolment, and was later excluded. This yielded a final material of 21 interviews. The patients had the consent document available during the interview. All patients read and signed the original consent document before they were enrolled in the PEG trial.

The six-item interview guide was designed for this study to elicit the patients' own assessments of the information in the consent document (Fig. 1). Follow-up questions were used for clarifications and elaborations. According to the semi-structured design, the items were used as topics to guide a discussion with the patients.

Eighteen of the interviews were audio taped and transcribed verbatim by K.S. For the remaining three, technical problems made the audiotapes unusable, but thorough notes were taken during or after these interviews.

2.3. Ethics

The study was approved by the Regional Committee for Medical Research Ethics.

2.4. Analysis

Data were analysed using methods of qualitative content analysis, which included subjective and systematic interpretations

Table 1
Medical aspects and formalities in the two consent documents

	The original document	The shortened document
The medical aspects	823 words	458 words
The formalities	259 words (23.2%)	50 words (9.8%)
Other	36 words	
Sum	1118 words	508 words

The interview guide

- Do you think that the informed consent document give you the information you need in order to decide whether you want to participate in the trial or not?
- Could some of the information in the document be left out?
- Would you want any further information in document?

Give the patient information about the guidelines for writing and approval of informed consent documents, and give examples of required formalities like insurance, confidentiality and that the researchers do not have financial interests of conducting the trial.

- How much do you feel you need to know about such research regulations?
- What do you think about the language in the document?
- Which information is the most important for you when you decide whether or not to participate in the trial?

Fig. 1. The interview guide about here.

of the content of text data through identification and categorization of essential themes and patterns [10–12]. The data was analysed and interpreted by the interviewer (K.S.) and one of the co-authors (J.H.L.). The analysis was based on both deductive and inductive categories [13]. The deductive categories were predefined according to our research questions, and concerned the patients' perceptions of the consent documents. The inductive categories were developed in terms of the material itself. Both kinds of categories were developed through cooperation between the authors.

Initially the transcripts were read and re-read in order to get an overall impression of the content. Thereafter, brief summaries of each interview were written. Based on the summaries and the recordings we identified and condensed the patients' answers to the questions outlined in the interview guide into overall answers (the deductive categories). According to the randomized design of the study these answers were compared for the two groups of patients in order to detect possible differences. The second part of the analysis was based on the sample as a whole, and included recurrent themes that emerged as a result of inductive category development [13].

3. Results

3.1. Patients

Twelve men and nine women participated. Ten received the standard consent document and eleven the shortened version. Background information about the participants in the two groups is presented in Table 2. The subjects' median age was 69 years (range 44–84). All patients were considered decision-competent by their physicians. The interviews lasted between 6 and 42 min (median 12 min).

3.2. Deductive categories

Most participants were not able to assess the content in the documents when they were questioned directly about their own perception. Most gave short answers, for instance that the text was all right, easily understood, and not complicated to read.

Interviewer:	Do you think the document gives you the information you need in order to find out whether you want to participate in the study or not?
Patient:	No I don't know. . .not really
Interviewer:	You would have wanted some more information?
Patient:	mm
Interviewer:	About what. . .could you say something about that?
Patient:	No. . .I don't think so

Table 2
Background variables in the two groups

	Standard informasjon	Short information
Age (median, range)	73.5 (53–84)	68 (44–80)
Gender (males/females)	8/2	4/7
Education		
Primary and/or lower secondary school	5	5
Between 1 and 3 years of upper secondary education	4	5
More than 4 years of higher education	1	1

When asked what was the most important information in the consent document over half the participants said that it was important to know that they are contributing to science and helping future patients. Other aspects that were brought up as important information from the patient's point of view were hopes for better treatment (three patients), practical information about the procedures of the trial (two patients), and information about that the two treatment alternatives are equal (one patient). Formalities, like voluntariness and the right to withdraw, were also mentioned as the most important information. Some mentioned more than one element as important, for instance both to help others and to achieve personal benefits.

3.2.1. Assessment of the amount of content

Seven patients answered that they wanted further information. Three wanted more information about the medication/treatment and the (side) effects of it. One was interested in the results of the study. One wanted information about who he could contact, and another wanted an explanation of the term "your doctor". The last patient was not able to specify what kind of further information she wanted, but said she would have preferred the text to be better oriented for the general reader.

Two patients had a comment concerning redundant information (the only two with higher education). Both of them read the original version of the consent document. One said that some elements probably could be removed from the text, but that it would depend on each patient's degree of illness what kind of information that would be experienced as unnecessary. The other found the detailed explanations in the document unnecessary.

3.2.2. Assessments of the formalities

Eleven patients stated they did not need to read about the formalities. Seven other patients said that the formalities were interesting or relevant. Some of them added that they preferred to receive as much information as possible, but most of them did not extend their opinions about the formalities any further. The last three patients did not have a clear answer to the question.

Two patients, who read the original consent document, reflected any further on the formalities on their own initiative. One characterized the formalities by saying: "*The rest of the text* [i.e. the formalities] *is something that I haven't tried to memorize or assess. It is that kind* [*of information*] *that I will deal with if necessary*", thus indicating that he had not read the formalities as thoroughly as the rest of the text. The other brought up the formalities while explaining how she would have separated the two parts, and put the medical aspects on one page and the formalities on another—"*because then you could choose to read what was the most relevant for you*".

She also reflected on how she thought the average patient would read the formalities of the documents, by saying: "When they read it. . .there are a lot of questions that they don't ask anybody. They don't. I don't think so. It doesn't occur to them that they can ask about this. Where it [the data] will be stored for 15 years—it doesn't matter".

For the rest of the patients, the formalities were not perceived as a problem, but rather as insignificant. None of them brought up issues like publishing, financing, insurance, or approving authorities, which are required elements in a consent document.

3.3. Inductive categories

Three essential themes were identified during the inductive analysis of the interviews: the patients' trust in their physicians, the unfamiliar situation at the hospital and the questions raised by the patients during the interviews.

3.3.1. Trust

Eight patients expressed complete confidence in the physicians and the hospital. When asked whether he wanted any further information, patient 11 said "No, there is not (. . .) because I am in the best hands when I take part in this". Other patients said that they felt they were they could leave everything to the physicians or that they knew the physicians would act in the patients' best interest. Some added that it was not crucial for them to remember every detail of the consent document due to this confidence.

The patients' trust in the physicians was the most frequent reason stated for their lack of interest in the research formalities in the document. Seven of the eight patients who expressed confidence in the physicians, said that they did not need or want to read about research formalities in the consent document.

3.3.2. The unfamiliar situation

The patients' answers showed that being seriously ill and being at a hospital was unfamiliar, something which might influence their ability to understand written information. One said that the consent document could be difficult to understand because "all this is new for me (. . .) and therefore it is difficult to understand at first". Another answered that the much of the language in the document was "completely Greek to me, I don't have a clue about chemotherapy". A third said that he left the illness to the doctors, and "I don't care. I have been healthy for 70 years, so this is somewhat unfamiliar".

3.3.3. Questions raised by the patients during the interviews

The interview data did not yield direct expressions of what kind of information the patients found relevant or irrelevant in the informed consent documents. When questioned whether they wanted any further information in the consent documents, most of the patients answered no. However, during the interviews 14 patients spontaneously posed a number of questions to the interviewer, something which indicated that they actually *did* prefer some further information, and also which information they were most interested in.

Most of the patients' questions dealt with the treatment procedures. The most frequent question was at which hospital the patient would receive his/her chemotherapy. Other typical questions were: "Who can I call if something happens?", "How often will I get treatment?", "Is my personal physician performing the blood tests?", "What are my prognoses?", and "Will I lose my hair?". Practically none of the patients' questions addressed the formalities in the consent documents.

4. Discussion and conclusion

4.1. Discussion

The present study indicated that the information in the consent document concerning research formalities was perceived of as less relevant compared to information about disease and treatment.

The comparison between patients who read the original consent document and patients who read a shortened consent document with fewer formalities showed few differences regarding the patients' perceptions of the documents. However, the answers from two patients who read the original document indicated that the detailed information about formalities is perceived as of lesser importance in this particular reading situation.

Which information a reader notices and remembers in a document, can be related to *textual* aspects like the structure and organization of words, paragraphs and information elements [14]. However, it can also be related to *contextual* aspects, like the reading situation. The patients included in the present study read the documents while facing a life-threatening disease. One patient characterized the situation like this:

> "because what you are interested in is *me. . .here. . .now. . .*that is what concerns you (. . .) the only thing people are interested in is. . .what would this imply for me?"

It is of course important that the patients understand the procedures of the treatment they are about to receive. However, there are central differences between receiving treatment inside and outside of a clinical trial, which are crucial for patients to be aware of before accepting or refusing to participate in a trial. Research is conducted to generate knowledge that could benefit future patients, and not necessarily the patients that participate in the actual trial. When patients are not able to see this distinction between treatment and research, the result could be the so-called therapeutic misconception [15]. Therapeutic misconception exists when the subjects do not understand that the overall purpose of clinical research is to produce generalizable knowledge, regardless of the individual's personal benefit [16].

The patients in our study expressed confidence in the health professionals, something that made it less important for them to understand the consent document in detail. Previous studies have also revealed the same degree of confidence in the physicians [17,18]. Kass et al. [17] found that many of the subjects had made up their mind about participation before they were given the information, and that a difficult document did not matter. They perceived the details of the document as irrelevant. This was also the case for the subjects in our study. In some cases the answers to the patient's questions were clearly expressed in the consent document. This indicated that not all of them read the document thoroughly or that they did not notice, understand or remember it. Still, they wanted to participate in the PEG trial.

It might seem that patients' relation to their physician is of greater importance than the informed consent document in their decision making process. One might therefore question why the formulation of the consent documents is strongly emphasised in the research approval process, while the verbal information is not. There exist no guidelines or approval of the verbal information, as is the case for written information. Especially for poor readers, one might question whether other strategies than clarifying the consent document could be used for ensuring understanding. Further research might examine patients' perceptions of verbal and written information, respectively. The information can also be presented in more interactive ways than the static informed consent document by use of modern information technology. Possible improvements need to be documented by empirical research.

Some aspects of the present study might have influenced the findings. Firstly, due to the sample size we have limited possibilities to make generalizations.

Secondly, the sample consisted of a homogeneous group of patients, i.e. elderly patients with advanced lung cancer. The perception of the content in the informed consent documents could have been different in other patient groups, for instance younger and/or less severely ill patients, or healthy volunteers. Schaeffer et al. [19] found that subjects with diseases of different severities focused on and retained different aspects of experimental protocols.

Thirdly, some of the interviews were short. It seemed difficult for some of the patients to talk about their own reading of a document. Many of them might never have reflected upon shortages or irrelevant aspects of a document. Consequently, it might be challenging to talk extensively about these matters in an

interview. To overcome this, future studies can address more specifically the relevance of each content element. In order to make comparisons between different information strategies, future studies with a randomized design will probably benefit from using standardized assessment methods for measurement of understanding [20].

4.2. Conclusions

The consent documents did not seem to function as intended since many patients seemed to pay little attention to the research aspects, and thus risked to misunderstand the main point of the consent document. Statements from two of the patients indicated that the information of the formalities is perceived as of lesser importance than the information about medical procedures. The formalities are not necessary information for making a decision about participating in the trial, but could be relevant later.

4.3. Practice implications

The physician in charge of the treatment should be aware of his/her importance for the patients in their decision making about whether to consent to participation in clinical trials. This points to the necessity of ensuring the quality of the oral information disclosed during the consent process.

It is also necessary to rethink the structure of the consent documents. Writing a consent document should primarily be based on the readers' ability to understand and to give consent instead of a list of required information. The structure of the documents should clarify what the eligible patients agree to when signing the consent form: that they are asked to participate in medical research and that the decision to participate is voluntary. A possible structure could imply to place the formalities as a separate part of the document.

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Paper II

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Paper III

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Paper IV

Readability of informed consent documents (1987–2007) – a linguistic analysis

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Abstract

The goal of an informed consent document (ICD) is to ask the reader to participate in research, and to explain the implications of being a research participant. An ICD is readable if it achieves this overall goal. The aim of this study was to investigate the readability of ICDs linguistically and to compare old and new ICDs in this respect. Twenty ICDs (ten from 1987–1992 and ten from 2006–2007) were included. The Evaluative Linguistic Framework (ELF) was used to analyse the texts. ELF includes the following items: main themes, order of themes, rhetorical functions, the relationship between reader and writer, metadiscourse, headings, expert terminology, and visual aspects. The new ICDs were found to be more readable than the old ones as they were more oriented towards research, contained instructions about how to consent, and provided clear contact information. Aspects that reduced the readability of the new ICDs were the large number of topics, details and actors presented. The readability of the old ICDs was enhanced by few topics, a clear presentation of the involved actors, and brevity. However, their readability was reduced by the inclusion of a vast amount of information about the reader's diagnosis and treatment.

Introduction

Informed consent documents (ICDs) are a central component of the consent process in clinical trials. Previous research has shown that eligible trial participants often have difficulties understanding the information provided in the ICDs (Criscione, Sugarman, Sanders, Pisetsky, & St Clair, 2003; Joffe, Cook, Cleary, Clark, & Weeks, 2001; Lynoe, Sandlund, Dahlqvist, & Jacobsson, 1991; Schultz, Pardee, & Ensinck, 1975), which might lead to invalid consent. For the patient to comprehend the ICD, the document has to be readable. Traditionally, readability has been measured by use of indexes/formulas (Baker & Taub, 1983; Goldstein, Frasier, Curtis, Reid, & Kreher, 1996; Grossman, Piantadosi, & Covahey, 1994; LoVerde, Prochazka, & Byyny, 1989; Meade & Howser, 1992; Murphy, Gamble, & Sharpe, 1994; Ogloff & Otto, 1991; Philipson, Doyle, Gabram, Nightingale, & Philipson, 1995; Rivera, Reed, & Menius, 1992; Sharp, 2004; Tarnowski, Allen, Mayhall, & Kelly, 1990), i.e. quantitative measurements based on, for instance, number of letters per word and number of words and syllables per sentence (e.g. the Flesch reading ease score (Flesch, 1948), the Gunning Fog Index (Gunning, 1952) and the Fry scale (Fry, 1968)). Readability studies have also often included a measure of the ICDs' total length.

However, traditional readability formulas fail to cover a variety of aspects of a document's readability, for instance the organization of content, visual design, and choice of vocabulary. Such aspects may also go beyond the text to encompass the readers' motivation and interest for reading, as well as background knowledge about the topics presented in the text (Finnie, Felder, Linder, & Mullen, 2010; Meade & Smith, 1991; Peterson, Clancy, Champion, & McLarty, 1992; Pichert & Elam, 1985).

An aspect that further complicates the reading of ICDs, is that the initial reader of the document is not the eligible trial participant, but the members of an ethical review board who must approve the content and design of an ICD before the text can be presented to the actual target reader, the

person who is to give his/her consent. These will often differ from the primary reader on aspects such as age, education level, emotional status and motivation.

In the present study of ICDs, readability is defined as a matter of a document's functionality for its audience in a particular situation. This implies that an ICD is readable when the textual characteristics – i.e. the content, the structure, the terminology, and the interaction between the actors in the text – contribute to fulfilling the goal of the communication. The goal from a patient's perspective is to be enabled to give a consent/refusal that is actually informed (Erlen, 2010). This implies that the reader must be able to comprehend that he is being asked to participate in research, that he is supposed to make a voluntary decision, the implications of consent or refusal, and that participating in research differs from receiving standard treatment.

In a previous study, we showed that the length of ICDs and the number of content elements had increased considerably over the last two decades (Berger, Grønberg, Sand, Kaasa, & Loge, 2009). These two aspects might contribute to reduced readability. In the present study, the aims are to evaluate the functional readability of ICDs and to compare old ICDs (1987–1992) with new ICDs (2006–2007) in order to investigate whether the new, longer ICDs are more or less readable than the old, shorter ones.

Materials and methods

Material

The material in this study consisted of 20 ICDs selected from a sample of 87 documents used in a previous quantitative study of ICDs' length and content (Berger, et al., 2009). The ICDs were from oncological trials approved by the Regional Committee for Medical and Health Research Ethics in the central region of Norway from 1987 to 2007. For the present study, the 10 oldest ICDs (1987–1992) and the 10 most recent (2006–2007) ICDs were selected for analysis.

Analytic framework

In order to investigate readability of the ICDs beyond the traditional readability indexes, a linguistic framework developed for studying text quality of written health information for patients was chosen, the Evaluative Linguistic Framework (ELF) (Clerehan, Hirsch, & Buchbinder, 2009). ELF was developed by Clerehan and colleagues to analyse the quality and possible shortcomings of drug information leaflets (Clerehan & Buchbinder, 2006; Clerehan, Buchbinder, & Moodie, 2005; Clerehan, et al., 2009). Seven items from the ELF were used in the present analysis (presented below). Two of the items from ELF were not included. Lexical density was excluded, since – as far as we know – a number for average lexical density does not exist for the Norwegian written language; moreover this is a quantitative measure which is not considered relevant for the present analysis. Further, analysis of factual content was excluded since this kind of analysis demands specific medical and research expertise concerning the specific trials presented in the material. The included items were as follows:

(1) *Generic structure* refers to (a) the overall themes (e.g. "purpose of the trial", "study procedures", and "participants' rights") and (b) the order in which the themes are presented. A document is considered readable when the reader's expectations concerning content are met, i.e. when the reader recognizes a conventional set of themes and the order in which they are presented (Clerehan & Buchbinder, 2006).

(2) *Rhetorical functions* in a document influence how the reader deals with the text. (Clerehan, et al., 2009). These functions may be to inform, to explain and to instruct. A document is considered readable when the reader knows what to do with the information – merely read it and comprehend it, or act upon it.

(3) *Reader-writer relationship* refers to (a) how the actors are addressed and (b) who is given the responsibility to carry out the actions mentioned in the document. A document is considered readable when the actors and the relationship between them are presented consistently and adequately (Clerehan, et al., 2005).

(4) *Metadiscourse* refers to "language about the text itself" (Clerehan, et al., 2005), and signals to the reader what he is supposed to do with the information, e.g. "The purpose of this document is to give you information about the trial called (…)".

(5) *Headings* refer to (a) the use of main heading and subheadings in a document and (b) their appropriateness related to the content. A document is considered readable when headings give the reader an impression of the main themes and when the headings and the subsequent

content are thematically related (Clerehan & Buchbinder, 2006).

(6) *Technicality of the vocabulary* refers to (a) the use of expert terminology in the document and (b) the use of explanations of expert terms. A document is considered readable when the terminology is familiar to the reader and/or when explanations in lay terms are used

(7) *Visual aspects* are limited in the present analysis to length and layout (i.e. how the text is organized on the pages). A document is considered readable when visual aspects, such as illustrations, bullet lists and other typographic cues are used to emphasize key information and to facilitate the reader's scanning of the document (Schriver, 1997).

Procedure

The analysis of ICDs was performed in accordance with the framework developed by Clerehan and colleagues (Clerehan, et al., 2005; Clerehan, et al., 2009), by the principal investigator in collaboration with the second author. The procedure is described briefly below. The analysis of each item included counting the number of identified instances and comparing the findings in the old and new ICDs. Instances of uncertainty concerning interpretation, classification and naming were discussed by the authors until consensus was reached.

The seven categories were analysed one at a time, by reading all the 20 ICDs, and extracting and marking the relevant words, sentences or paragraphs directly in the electronic documents or on printed versions. The identified instances were registered into preliminary tables, and/or a summary was written of the findings from each category (not shown in Results). The numbers of identified instances were summarised and entered into the Result tables. Quotes for exemplifications of all the categories were selected.

The analysis of *generic structure* was done by identifying and naming the main themes in the documents. A "theme" was defined according to the examples and findings presented in the studies by Clerehan and colleagues (Clerehan, et al., 2005; Clerehan, et al., 2009). Themes are overall content units (for instance "information about study procedures" or "study background"). A list of the identified themes was compiled for each ICD. The lists also included repetitions of themes and their placement within documents. The analysis of *rhetorical functions* was done by investigating the linguistic and relational function regarding each identified theme (e.g. was the text informing or instructing?). The analysis of the *reader-writer-relationship* was done in two steps. First, actors were identified as visible (explicit) or not visible (implicit); secondly, the ways of addressing and portraying the reader and writer were identified, and additional actors who were neither the reader nor the writer were also identified. The analysis of *technicality of language* was conducted by identifying all words, phrases and sentences in which medical expert terminology or research expert terminology was used, and to determine whether the terminology was explained in lay terms. The analysis of *metadiscourse* was performed by identifying descriptions of the ICDs' purpose and/or function and directions about how to read and interpret the text. The analysis of *headings* was done by identifying the main headings and subheadings and determining the headings' appropriateness by comparing the topic in the headings with the subsequent content. The final item, *visual aspects*, was analysed by counting the number of pages and identifying the graphical elements in the ICDs.

Finally, the readability of the identified and categorised textual characteristics was interpreted as "more readable" or "less readable" based on theoretical premises of reading comprehension that are the basis of the ELF.

Results

I Generic structure of the ICDs

Themes present in the ICDs

The themes, the order of the themes and the rhetorical functions in the new and old ICDs are presented in Table 1. One theme was present in all 20 ICDs: *Information about study procedures*, i.e. practical implications for the patients (examinations, medication, tests, follow-ups, and duration of participation). In the new ICDs, three additional themes were identified in all the documents: *Purpose of the trial*, *Research procedures* (i.e. information about what is being done in the research process by actors other than the patient, such as randomization, data collection, - processing, - analyses, - storage, publication, and confidentiality) and *Contact information* (themes 2–4 in Table 1). In the old ICDs, two additional themes were identified in all ten documents: *Background information* (most often concerning the patient's diagnosis and prognosis) and

information about participant's rights (i.e. voluntary decision, the right to withdraw consent).

The order of the themes

There was a clear lack of consistency regarding the order in which the themes were presented in all the ICDs.

The *invitation/request to participate* is an essential part of a readable ICD since it is directed towards the main goal of the consent process. This theme had a more fixed placement in the new ICDs than in the old ones. In the new ICDs, the request was placed in the beginning of the document or in the main heading. In the old ICDs, the invitation was placed in the beginning of the document in two cases, in the middle of the document in two cases, and at the end of the document in two cases.

One of few examples of a certain degree of fixed order was identified in the introductory paragraphs of the old ICDs, which in nine of the cases consisted of *patient status* and/or *background information*.

The introductory paragraphs in the new ICDs showed no such similarities. The new ICDs opened, for instance, with an invitation to participate, background information, patient status, study procedures, a presentation of the study's name, information about who is responsible for the trial or a request to read carefully and ask questions.

II Rhetorical functions in the ICDs

The rhetorical functions related to each theme in the ICDs are shown in Table 1. The most frequent rhetorical function in the ICDs, both old and new, was *to inform*, i.e. to present facts and implications regarding the reader's (i.e. cancer patient's) diagnosis and treatment, about the clinical trial and the implications of participating. Most of the ICDs in both subsamples consisted almost entirely of the function *to inform*.

The second most frequent rhetorical function in the ICDs was *to explain* (including elaborations and exemplifications). Explanations were commonly identified immediately after information. The following excerpt illustrates how explanations were used to clarify a possibly unfamiliar term, "quality of life" (explanation underlined by author): "*The purpose of this questionnaire is to investigate the quality of life among seriously ill people*. *One might say that quality of life has to do with one's own experience of both good and difficult aspects of life"* (41-91). The juxtaposition of *information-explanation* was found both in the old and the new ICDs; however, it was slightly more frequent in the new ones (new ICDs 0–10 examples in each document (median 3 ½), old ICDs 0–4 examples in each document (median 2).

A third rhetorical function present in the ICDs was *to instruct*, mainly giving the reader instructions about what to do in the trial, the participants' responsibilities and how to give consent. Instructions were more frequent in new ICDs than in the old ones (9 new / 4 old).

Instructions in ICDs are written with a specific condition; many of the instructions are only valid *if* the reader consents. The conditions for the instructions might be presented to the reader like this: *If you choose to participate, it is important that you come to the scheduled follow ups* (2007.2125). Several of the instructions in both the old and new ICDs were written without clarifying this condition.

A fourth rhetorical function present in the ICDs was to ask questions (6 new / 7 old) Questions were mainly used for inviting the reader to participate in the trial, for example *Are you willing to help us with an extra blood test and filling in a questionnaire?* (65-87).

III Reader and writer(s) in the ICDs

The analysis showed several similarities concerning the presentation of the writer and reader in the old and the new ICDs. The results are presented in Table 2.

The reader

The reader was addressed in two different ways in the ICDs. Firstly, the reader was addressed personally as "you" in nineteen of the twenty ICDs in the sample, and the pronoun was used frequently throughout most of the documents.

Secondly, the reader was addressed in third person, either as member of a whole group of readers ("*The patients will be divided into two groups")* or as a possible member of a subgroup of the readers ("*Diabetics might have to check the blood sugar more often"*). The two forms of addressing were frequently used within the same document (9 new / 9 old).

Further, the reader was referred to in two different roles: a patient and an eligible trial participant. The reader was a patient when described as a person with a cancer diagnosis who has undergone or is

about to receive treatment: "*You have a form of breast cancer disease which currently is not suitable for surgery or radiation"* (21-87) or "*Request to participate in a study (…) among patients with uterine cancer who receive radiation therapy"* (2007.1024). Three of the old ICDs were initiated with the phrase *Dear patient*. The reader was referred to as an (eligible) trial participant in the actual request to join the trial: *[Y]ou are now being asked if you are willing to participate as a test person* (2006.2144) (5 new / 6 old), and in phrases which showed the reader's choice in the consent process. The most frequent wording for showing the reader's choice was *If you (choose to) participate* (8 new / 3 old).

The writer

The writer was present in the ICDs through the personal pronoun *we*, but to a much lesser degree than *you* to address the reader (52 *we* versus 193 *you* in the new ICDs, 49 *we* versus 76 *you* in the old ones). A clear reference for "we" was often missing. In some of the ICDs, the writer had signed at the end of the document (3 new / 7 old). In three of the old ICDs, the writer signed his name after the closing typical for personal letters "kind regards".

"We" could refer to the researchers in charge of the trial. The responsible researcher/institutions were presented either in the beginning or in the end of the document in 8 new ICDs / 1 old ICD.

The contact information could also give the reader an impression of the writer of the ICD. Detailed contact information was found in eight of the new ICDs and in only one of the old ones.

Through the content of the ICDs, the writer demonstrates his role as an expert who is in possession of a considerable amount of knowledge about the reader, about diseases and treatments, about research, and about the procedures in the actual trial. The writer's expert knowledge is associated with a dual expert role: both a medical expert and a medical investigator.

Sections without visible actors

The analysis of reader-writer relationship revealed that several sections of the ICDs were written without a visible writer, particularly sections concerning study and research procedures, which were often written in passive voice. Through omitting the subject of a sentence, the passive voice gives the impression of being objective. At the same time, it might also hide who is responsible for carrying out the actions mentioned in the document. For instance, in the sentence *"At the beginning of the trial, bone marrow tests will be taken twice as part of regular assessment of the disease"* (2007.94), there is no presentation of who will carry out the bone marrow tests or who will be treated.

Additional actors

The analysis of reader-writer relationship revealed the presence of actors other than patient/participant and physician/investigator. The number of additional actors differed in the old and new ICDs. In the old ICDs, additional actors were a doctor and a nurse (in four ICDs) and one or two approving authorities (ethical review board and the Norwegian Medicines Agency in three ICDs). One old ICD (34-88) referred to a pharmaceutical company and one (66-89) referred to an insurance company. The new ICDs contained several other actors, for instance other approving authorities (The Ministry of Health and Care Services, The Norwegian Directory of Health, The Data Inspectorate, Norwegian Social Science Data Services/The Privacy Ombudsman). Three main categories of actors were identified in the new ICDs: (1) the trial's responsible researchers or instances (a hospital, a university, health authorities, a department, a section, a pharmaceutical company, a study group, and/or named individuals) (2) other individuals involved in the research process, and (3) the trial's sources of finance.

IV Metadiscourse

As shown in Table 3, metadiscourse was identified in three new ICDs and in one old one. However, none of these examples of metadiscourse were used to clarify the main objectives, themes or functions of the ICD.

V Headings

Main headings were identified in every ICD (Table 3). However, the typical main headings differed in the two subsamples. Nine of the main headings in the old ICDs were a variation of *Patient information*, while the majority of the main headings in the new ICDs included the word "request" (7 new ICDs).

Most of the subheadings were thematically appropriate. However, about a fourth of them did not cover all the information presented in the body text that followed. For instance, the subheading *Voluntariness* was used in five new ICDs. The

information following this subheading typically dealt with several aspects concerning participants' rights more than voluntariness, for instance the right to withdraw, the right to get information deleted, and a request to collect information from the participant's journal (2007.846).

A fifth of the subheadings contained terms that were possibly unfamiliar for a patient/lay reader, such as *Biological material* (2007.3217) or terms that were used in a different manner than the reader might be used to, for instance the headings *Public authorities* and *Ethics* which were both used for paragraphs concerning approval of the trial (2007.846, 2006.3217).

VI Technicality of vocabulary

Even though the new ICDs contained more explanations than the old ones, as shown in *Rhetorical functions*, they also contained more examples of expert language without explanations.

Two categories of expert language were identified in the ICDs in this sample: "medical terminology" and "research terminology". The ICDs used for trials of new drugs differed from the other ICDs when it came to using expert terms without explaining them, especially medical terms. In the new drug trial ICDs, 5–22 cases of medical terms, phrases or sentences without explanations were identified, while the number for the other ICDs were 0–10 (median 2). Regarding the use of research terms without explanations, there was a marked difference between old and new ICDs with 1–16 identified cases (median 9 ½) in the new ICDs and 0–3 (median 1 ½) cases in the old ones.

VII Visual aspects

Table 3 shows that the length of the new ICDs was between one and four and a half pages, while none of the old ICDs was longer than one page. The layout in the old ICDs was quite similar, with a main heading and four to six paragraphs without subheadings. There was no use of lists or graphical elements in the old ICDs. Overall, the layout in the new ICDs was also quite homogenous, with only small differences in the use of bold or italics in the headings. Lists were found in only two of the new ICDs (a numbered list in 2007.1890 and lists with both hyphens and bullets in 2006.2144). No illustrations were used in any of the ICDs.

Discussion

The aim of the present study was to evaluate goal-oriented readability of ICDs by identifying textual parameters that contribute to the text's readability, and to compare readability in old and new ICDs. While the analysis indicated that the new ICDs were in some ways more readable than the old ICDs, the analysis did not show a clear tendency towards increased or decreased readability in newer ICDs. Different textual characteristics contributing to increased readability were identified in both old and new ICDs, such as a clearer relationship between reader and writer in the old ones and a clearer presentation of the overall aim of the document in the new ones. Similarly, characteristics contributing to decreased readability were also found in both subsamples, such as much information about disease and treatment in the old ones (at the expense of research information) and many actors presented in the new ones.

Readability is not an unambiguous concept

Several textual aspects may contribute to a readable document. These aspects must be appropriate for the specific situation and the specific participants and their goals for a document to be readable. This implies that the most relevant textual aspects for enhancing readability in one situation may not be the most relevant in another.

In this study, we used the Evaluative Linguistic Framework (ELF) to investigate the textual aspects that might create readability in the ICDs. One aspect considered to be of relevance for readability is that the reader can recognise a genre in part by recognising the set of themes presented in an order that is typical for that genre (Clerehan & Buchbinder, 2006; Clerehan, et al., 2005; Clerehan, et al., 2009). However, the main results of the analysis of ICDs showed that few themes could be identified as obligatory across the ICDs, and the ordering of the themes was inconsistent. It should be noted that the ELF was developed for the study of drug information leaflets. The assumptions about genre and theme recognition might not be as relevant for ICDs as for the drug information leaflets, since the reader of an ICD is not likely to have read an ICD previously, and therefore is not likely to have developed any generic expectations.

Consequently, readability of ICDs is more dependent on a logical order of information in order to assist the reader in comprehending a genre that is unfamiliar. In order to guide the reader, the writer needs to consider which topics

might be most appropriate to place in the beginning, the middle, and in the end of the document. The information written in the beginning of a document is a basis for the reader's interpretation of the rest of the information (Nystrand, 1986). Thus, a readable ICD would present information about the overall purpose of the document in the introduction. The new ICDs were more readable in this respect since a crucial function of ICDs – the request to the reader about participation – was placed in the beginning of most of the documents. Presenting the contact information in the end might also contribute to increased readability, since it gives the reader an impression of who is the sender of the document and also is a relevant address for where to get answers to questions that might arise after having read the ICDs. While the sender was present in the end of most ICDs in both subsamples, only the new ones included complete contact information.

Research-oriented new ICDs

When comparing the old and new ICDs, we found several textual characteristics that made the new ICDs more oriented towards research as the main topic. This should contribute to increasing readability, since the overall goal of ICDs is to ask the reader to participate in research and to explain the implications of being a research participant compared to being a regular patient.

One of the textual characteristics that contributed to research-orientation in the new ICDs was the typical main heading: "Request your participation in…". The request to participate was placed in the beginning of the document, and gave a clear picture of who is responsible for the trial (for instance through detailed contact information).

In contrast, the old ICDs were more oriented towards the reader's diagnosis and treatment. This was obvious in the typical main heading in the old ICDs: "Patient information". Furthermore, the introductions in the old ICDs typically presented background knowledge or information about diagnosis and treatment. For the author of an ICD, initiating a document with background information might be familiar, since it typically comprises the first part of other genres in the research community, such as research articles and protocols. However, it might not necessarily be an appropriate introduction in ICDs, which have a patient audience, since it might indicate that the ICD first and foremost is oriented towards the reader's disease and treatment instead of a document concerning research, including a request for the reader to participate in that research (even if information about diagnosis and treatment is probably considered as very relevant and important for most patients (Sand, Berger, Loge, Grønberg, & Kaasa, 2008)).

Complex cast of characters in ICDs

The interaction between the actors was complex in both subsamples. The reader, the writer and the interaction between them were often not clearly presented. The reader was addressed both personally and as a member of groups, while the writer was presented as a general "we" or missing completely.

Moreover, both the reader and writer of ICDs were ascribed dual roles: the reader as patient and participant, and the writer as physician and investigator. This ambiguity might hinder the reader from getting a clear picture of his own and others' roles related to the ICD. Uncertainty or confusion about who is going to perform what, and what role(s) the reader actually has could reduce the ICDs' readability. In an ICD, it should be made clear that the reader must first make a decision regarding participation, and then is to sign the consent form in a correct manner if he wishes to take part. In consenting, the reader may be subject to various precautions and commitments related to his role as participant. All of these actions need to be clearly presented to the reader.

Another aspect that may hinder the readability is the number of other actors present in the ICDs that the reader is expected to interact with, for example physicians, nurses, researchers, pharmaceutical companies and authorities. The number of actors presented in ICDs has increased from the end of the 1980s to 2006–2007. This implies more relationships that the reader has to contend with. The readability could be increased by limiting the number of actors and by clarifying the interaction between them.

The interaction between reader and writer in ICDs is further challenged because the actual first readers of ICDs are not the eligible trial participants, but members of ethical review boards that assess whether the mandatory information is present in the ICD before the eligible participants receive the document as the second reader. The author thus attempts to write appropriately for both audiences. Some of the details given in the ICDs appear to be addressed to the ethical review board, rather than the patient, for example the details concerning who is involved in data processing, the acts that regulate processing and storage of the data, sources of finance and all the

approving authorities. In a previous study of subjects' evaluation of ICDs, we found that lung cancer patients eligible for a clinical trial were most interested in practical information concerning which hospital they would go to for treatment, who was going to perform the blood tests, and who they might contact if they had questions (Sand, et al., 2008). The readability of ICD can be improved if the information is more clearly directed towards the main reader: the eligible trial participant.

Some study limitations need to be addressed. Even if the ELF is developed for studies of text quality in written patient information and is a broad framework, it does not cover all aspects that might influence readability. During the analysis, additional aspects within the predefined items were identified and included into the results. Moreover, a potentially vast amount of aspects beyond the text would influence readability, for instance health condition, cognitive status, age, and psychological state. Still, the linguistic approach in this study highlights several factors relevant for an ICD's readability beyond the level of traditional readability indexes and a framework with predefined items was considered a strength in a qualitative readability analysis.

Conclusions

To summarize, the readability of an ICD might increase if the text is (1) oriented towards *research* as the main topic, (2) oriented towards the *eligible trial participant as the main reader* and (3) presents the actors clearly, including who will perform which actions subsequent to the reading of the ICD.

The old ICDs appeared accessible since their length was one page or shorter and they resembled personal letters both in appearance and in the communication between a reader and a sender. However, their content was less to the point than the new ICDs. The old ICDs were not sufficiently oriented towards asking the reader to participate in research and explaining the alternatives and actions related to the research. During the 20-year period the ICDs in the present study represents, the regulations regarding the content have increased, and the length and complexity of the documents have increased accordingly (Berger, et al., 2009Berger, et al., 2009). However, ICDs' readability has not been unambiguously negatively affected by this development. Textually, the new ICDs are more logically organized and more thematically adequate according to the goal of the communication in the informed consent process: To ask the patient to participate in research, to show him his alternatives and help him make his voluntary decisions.

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Table 1 Themes and rhetorical functions in the new and old informed consent documents (ICDs). In the first column the identified themes are listed, while the two next columns show the number of ICDs that included the theme. The fourth and fifth columns show the rhetorical functions identified related to each theme in the ICDs. The most frequent function is presented first in each table cell. In the Examples column, the signs of explanations are underlined in some of the cases.

Themes	**Number (new ICDs)**	**Number (old ICDs)**	**Rhetorical functions new ICDs**	**Rhetorical functions old ICDs**	**Examples**
1. Study procedures	10	10	Inform Instruct Ask	Inform Explain Instruct	"Velcade is given as intravenous injections lasting a few seconds, while dexametason is given as tablets" (2007.94) "You have to take the study medication for 7 days"(2007.846) "In addition, blood tests will be taken in order to learn in detail how the drug works" (18-90) " (…) we ask you and one of your parents to fill out some questionnaires" (2006.2610) "For most items just mark with a ring or an x for the alternative that best describes your situation" (41-91)
2. Purpose of the trial	10	7	Inform	Inform	"The purpose of the trial is to investigate what leads to the best control of the disease and the fewest side effects (…)" (2007.2125) "[we investigate] whether a special test could be useful for detecting and follow-up of cancer" (65-87)
3. Research procedures	10	7	Inform Explain	Inform Explain	"All the answers will of course be made anonymous (…) " (2006.2610) "All the information related to the test will be treated with ordinary confidentiality…" (66-89) "so that individuals wont be recognized" (2006.2610) "(…) such that half of the patients will be treated with tablets and the rest with a combination

					of tablets and interferon" (40-90)
4. Contact information	10	5	Inform	Inform	"If you have any questions, they may be directed to the doctor in charge of treatment" (2007.558) "If you have further questions, you may consult Dr (…) or nurse (…)" (61-88)
5. Background	9	10	Inform Explain	Inform Explain	" Lymphoma in the brain is a rare kind of cancer and has proven to be more difficult to treat than other kinds of lymphoma" (2007.3217) "To illuminate the psychological aspects of a serious disease is a highly neglected area in research" (41-91) "In such investigations one needs a large and varied normal material of blood tests from healthy people for comparison" (65-87)
6. Participants' rights	9	10	Inform Instruct Explain	Inform	"Participation in this trial is completely voluntary (2007.1024) "You can, as a patient, choose to interrupt this mentioned treatment at any time, if you want to" (70-88) "If you do not want to participate in the trial or want to withdraw, you will be offered the treatment that is considered standard treatment. <u>This would usually imply</u> the similar treatment as the one described above, or an additional radiation therapy" (2006.3217)
7. How to give consent	8	2	Instruct Ask Inform	 Ask	"If you want to participate in the study, you sign the attached consent form and return it to the doctor in charge of treatment" (2007.1024) "If you are willing to let the sample be labelled with your name (…), we ask you to state this" (65-87) "If you want to consent we ask you to sign the attached consent form" (2007.1890) "If you consent to participation in the trial, this implies that you consent to let biological material be included in a biobank" (2006.3217)

8. Approval of the trial	8	3	Inform	Inform	"The study has been reviewed and recommended by the Privacy Ombudsman for Research (…)" (2006.2179)
9. Invitation to participate	7	6	Ask Invite Ask		"We wish to ask you if you want to participate in a scientific study (…)" (2007.94) "We would like you to participate in the testing of a new type of hormonal treatment" (18-90) "Are you willing to help us with an extra blood sample and to fill out a questionnaire? (65-87)
10. Access to other information	6	0	Ask Inform		"We ask for your permission to use information from your journal when this is necessary" (2007.1890) "Participation in the trial implies that journal information has to be collected" (2006.3217)
11. Financing	6	1	Inform	Inform	"You will not be paid to participate in the trial" (2007.94)
12. Possible advantages	5	4	Inform	Inform	"Even though participation does not lead to any direct advantages for you, you contribute to increased knowledge about the disease (…)" (2006.2144) "A lot of results show that hormonal treatment as adjuvant treatment to surgery is of importance for preventing or delaying relapse" (61-88)
13. Who is responsible for the trial	5	1	Inform	Inform	"The investigation is conducted in collaboration with the clinic for children and adolescents (…)" (2006.2610) "In cooperation between MRI centre and Cancer department at [hospital] we are investigating (…)" (65-87)
14. Patient status	5	6	Inform	Inform	"You use analgesics for pain" (2007.846) "You have learned to know that your breast cancer is developing" (18-90)
15. Side effects	5	8	Inform	Inform	"All medication may cause side effects" (2007.94) "Interferon causes quite a few side effects which resemble the symptoms of flu" (40-90)

			Instruct Explain		"If you get a fever, you should see a doctor" (2007.846) "(…) the side effects are the same as for other chemotherapy, that is, risk of anemia, increased bleeding tendency and infections (…)" (2006.3217)
16. Possible disadvantages	5	2	Inform	Inform	"The disadvantages for participation could be possible side effects (…) and that you have to come to the outpatient clinic to get your Velcade injections" (2007.94) "No considerable discomfort by ingestion of the contrast medium has been registered" (34-88)
17. Participants' responsibilities	5	2	Instruct	Instruct	"At each visit: Tell how you are feeling and report any side effects (…)" (2006.2144) "If you register any unusual symptoms you must rapport this to the doctor" (21-87)
18. Inclusion/exclusion criteria	5	1	Inform	Inform Instruct	"Only people over 18 (adults) can participate in this trial" (2007.558) "You cannot be using an antihypertensive" (4-92)
19. Reasons to leave the trial	2	0	Inform		"If you choose to participate in the project, you may be taken out of the project later on even if you have not asked to withdraw" (2006.3217)

Table 2: The reader and writer in the ICDs

The reader:

- "You" (in all 20 ICDs)
- Group addressing (9 new ICDs / 9 old ICDs)
- Typically presented as a patient or as a potential trial participant

The writer:

- "We" (in all 20 ICDs). A reference for "We" is often missing.
- Typically presented as a medical expert and/or a researcher (both = someone with considerable knowledge about the reader)

Relationship between the reader and writer:

- The writer gives the reader a lot of information (based on knowledge)
- The writer gives the reader tasks, responsibilities, instructions and also recommendations and advices

Table 3: Metadiscourse, headings, expert terminology and format in the old and new ICDs

	New ICDs	**Old ICDs**
Metadiscourse	Used in 3 ICDs - To present the name of the project (2006-3217, 2006-2610) - A request to the reader concerning reading the document carefully and ask questions (2006-2144)	Used in 1 ICD - To present the content of the document
Headings	Main headings present in all ICDs - Seven main heading included "enquiry/invitation", three "patient information" Subheadings used in eight of the ICDs (2-12 subheadings in each ICD) - A total of 61 subheadings in the sample - 13 subheadings (21 %) were explicitly linked to the trial ("Purpose of the study" or "Side effects and possible risk by participating in the study") - 16 subheadings (26 %) did not cover the subsequent content - 12 subheadings (20%) contained terms that might be unfamiliar for readers	Main headings in all ICDs - Nine of the headings: "patient information" / "information to the patient" / "information (to the patient) concerning [kind of study]" - One heading: A direct question concerning participation ("Are you willing to help us in cancer research?"), including direct addressing of the reader ("Blood donors at [name of hospital]" (65-87) - In addition "Dear patient" followed the main heading in four ICDs No use of subheadings
Expert terminology without explanations[1]	Medical terms: Large variety in the amount of medical terms without explanations - Drug trial ICDs: 5-22 (median 10) medical terms not explained (*changes in the number of blood cells, active drug, bone marrow smear, transfusion, the treatments are combined with adrenal cortex hormone*)	Medical terms without explanations: - Nine ICDs contained 0-5 examples (the last ICD contained 10), for instance: *to separate stomach/intestines from the adjacent tissue and organs in the MR-pictures*, *distant metastases*, *tissue sample* or *decalcification* - Research terminology without explanations: 0-3 examples, for

[1] Not only "medical language", but also "research language". For instance is terms like confidentiality seldom explained in the ICDs

	- Not drug trial ICDs: 0-6 (median 2) medical terms not explained Some variety in research terminology without explanations - Drug trial ICDs: 9-14 (median 11), for instance *complete control of the trial and the results, confidential, Norwegian Social Science Data Service, outstanding accounts among the persons involved in the project and public authorities, private companies or individuals* - Not drug trial ICDs: 1-16 (median 5)	instance *confidential, statistical presentations* and *The Norwegian Medicines Agency*
Format	Length 1-4,5 pages 2 ICDs one page	No more than one page in any of the ICDs

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95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

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104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.
109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

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110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANCER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.

133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
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160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.

162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT

192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.

217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA

244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

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248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
263. Eszter Vanky: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN PREGNANCY
264. Hild Fjærtoft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

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269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE
271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT

272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT
273. Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS
275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
278. Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION
279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS
280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281. Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION
282. Idar Kirkeby-Garstad: CLINICAL PHYSIOLOGY OF EARLY MOBILIZATION AFTER CARDIAC SURGERY
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