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HELENA LÄNSIMIES-ANTIKAINEN

Realization of Informed Consent in Health Research

Doctoral dissertation

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Department of Nursing Science
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ABSTRACT

Background: There is a continual need to evaluate and develop the ethical quality of scientific research and to widen knowledge about the ethical aspects of informed consent. Informed consent is ethically and legally required for health research involving human participants. Therefore, there is a need to examine, according to the research participants, how well informed consent has been realized in the research protocol in which they are participating.
Objective: The purpose of this study was to describe, analyze and evaluate the realization of informed consent in lifestyle intervention study from the point of view of voluntary adult participants.
Methods: In the first phase, the questionnaire was created and tested in a pilot study. In the primary study (second phase), the subjects were a random population sample of 1410 men and women aged 57–78 years who are participating in a 4-year randomized controlled intervention trial on the effects of physical exercise and diet on atherosclerosis, endothelial function and cognition in the Kuopio Research Institute of Exercise Medicine. The questionnaire about informed consent was given to all willing participants (n=1324) three months after the randomization. This data were collected over a 23-month period in 2005–2007. The response rate was 91 %. Data on implementation and success in the exercise and diet interventions were evaluated at 12 months by the intervention-group personnel. This evaluation were done in a subpopulation (n=597). The data were analyzed with statistical methods (descriptive statistics and multivariate analyses).
Results: In this study, the key elements of informed consent were defined as information, understanding, competence, voluntariness, and decision-making. The majority of the participants estimated that information given in the exercise and diet intervention study was adequate and in an intelligible form. The competence of the participants was judged to be sufficient. The participants considered that the decision-making had been voluntary, and the majority of them felt that confirmation and verification of informed consent were also carried out well. About half of the participants had achieved good results in the intervention. Nearly half of the participants had added to or improved their own activity in some sector of exercise or diet. Significant associations were found between performance and success in the interventions and participants' knowledge of the purpose of the study.
Conclusions: This thesis adds knowledge about the realization of informed consent in health research from the point of view of voluntary adult research participants. The findings of this thesis indicated the importance of successful informed consent processes at an early stage of trials. This study highlights the need for researchers to analyze critically the quality of information and how it is provided. This is especially important in long-term follow-up studies. Further study efforts should be focuced on understanding potential obstacles faced by research participants knowledge in their understanding of the informed consent process.

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To Aleksi and Annika

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Helena Länsimies-Antikainen

ABBREVIATIONS

CIOMS	Council for International Organizations of Medical Sciences
DR's EXTRA Study	Dose-Responses to Exercise Training. A randomized controlled trial on the effects of regular physical exercise and diet on endothelial function, atherosclerosis and cognition
ETENE	National Advisory Board on Health Care Ethics
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB	Institutional Review Board
RCT	Randomized Controlled Trial
TUKIJA	National Advisory Board on Health Care Ethics Sub-Committee on Medical Research Ethics
UNESCO	United Nations Educational, Scientific and Cultural Organization
WHO	World Health Organization
WMA	World Medical Association

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals I–IV:

I Länsimies-Antikainen H, Pietilä A-M, Laitinen T, Schwab U, Rauramaa R, Länsimies E. 2007. Evaluation of informed consent: a pilot study. *Journal of Advanced Nursing* 59(2), 146–154.

II Länsimies-Antikainen H, Laitinen T, Rauramaa R, Pietilä A-M. 2009. Evaluation of informed consent in health research: a questionnaire survey. *Scandinavian Journal of Caring Sciences*. In press. DOI: 10.1111/j.1471-6712.2008.00684.x. [Published online: Jun 23, 2009]

III Länsimies-Antikainen H, Pietilä A-M, Kiviniemi V, Rauramaa R, Laitinen T. 2009. Evaluation of participant comprehension of information received in an exercise and diet intervention trial: the DR's EXTRA Study. *Gerontology*. In press. DOI: 10.1159/000254484. [Published online: Oct 30, 2009]

IV Länsimies-Antikainen H, Pietilä A-M, Laitinen T, Kiviniemi V, Rauramaa R. Is informed consent related to success in exercise and diet intervention as evaluated at 12 months? DR's EXTRA Study. Submitted.

CONTENTS

1 INTRODUCTION

The ethical acceptability of scientific research, trustworthiness and credibility of results requires that the research should adhere to the principles of good scientific practice. In research being carried out in humans, the main ethical questions are the participant's consent and his/her awareness of possible risks and harm compared with impending benefit. (Tutkimuksen eettinen arviointi Suomessa 2006.) Therefore, research scientists have an obligation to inform those whom they wish to participate in their research of the rights that exist to enhance all aspects of human dignity. For example, protection of identity, privacy, obtaining informed consent and communicating benefit and risk are some of the most important ethical issues that researchers must address. It is self-evident that researchers should commit the same energy and enthusiasm that they display for their scientific endeavours to ethics and scientific integrity. It should be the case that ethics permeates every area of research. In fact, it has been stated that research excellence can only be achieved by getting the ethics right. (Potocnik 2007.)

There is a need in basic and clinical research to develop the knowledge of health and illness (e.g. Federman 2003, Johnston et al. 2006). In addition, clinical research is necessary to establish the safety and effectiveness of specific health and medical products and practices (World Health Organization, WHO 2002). None of these studies would be possible without participation by willing human subjects (Dickert, Emanuel & Grady 2002). Therefore, it is important to motivate people to participate in research projects, since this is the only way to produce a reliable data base about public health (Johnston et al. 2006). Research on 'healthy' voluntary participants needs to be conducted in such a way that the highest ethical standards minimize the risks (Federman 2003, see also Steinbrook 2002). One of the main ethical principles is 'informed consent'.

Informed consent is required for all biomedical and health research involving human participants (e.g. Beauchamp & Childress 2001). Informed consent means that each potential subject must be adequately informed about the study in question; and after

ensuring that the potential subject has understood the information, the researcher should then obtain the subject's freely-given informed consent (World Medical Association, WMA 2004). This entails that the participant must have the formal competence to make the decision in question (Syse 2000). Thus, at the centre of informed consent remains the critical primacy of the right of the patient or participant to understand the given information (Beckerman 2002). Therefore, only persons who are able to freely understand and question, should consent. It does exclude vulnerable persons (i.e. prisoners, mentally-deficient persons, severely-injured patients, very young children). However, to avoid any loss of opportunities for these persons, there should be a legal framework to guarantee their participation (notion of surrogate legal and therapeutic representative). (European Commission 2007.)

In general, the purpose of health research is to improve people's health and well-being. For instance, declining physical activity is associated with a rising burden of global disease (Kinmonth et al. 2008). It is often stated that prevention is better than cure and thus lifestyle interventions are important topics for research. For example, the number of individuals with diabetes is growing at an alarming rate. Prompt intervention by promoting and facilitating improvements in diet, activity levels, and body weight is hoped not only to result in prevention of diabetes, but also to achieve overall improvements in physical and mental health. (Weber & Narayan 2008, cf. Beswick et al. 2008.) However, many efforts to reverse this trend have not been successful (Kinmonth et al. 2008).

Achieving good health can be regarded as a basic human right. The purpose of ethics is to find answers to questions examining good and correct ways to live and act in a world that man shares with others. Ethics helps people make choices and analyzes the grounds for their actions, without giving any ready-made, universally applicable solutions. Concepts of good and bad, for instance, are rather global, but their emphases and interpretations vary according to culture as well as with time. (ETENE 2001a, Pietilä & Länsimies-Antikainen 2008, cf. Lääkärin etiikka 2005.)

In nursing science, ethical questions are an important research topic (Eriksson et al. 2008). Therefore, there has been a recent upswing in interest in the ethics of research. In addition, much has been written about the topic, most of it focusing on the protection of vulnerable participants from harm. (Oberle & Allen 2006). However, more work is needed into nursing ethics (Leino-Kilpi 2004, Spear 2007). Since, the nurse has an advocacy role in patient care and is morally obligated to ensure that patient concerns are heard (Oberle & Allen 2006). More extensive multidisciplinary research on the topic of informed consent is also needed. It has been stated that many ethical questions in health care are much easier to understand if investigated by a multidisciplinary team e.g. consisting of nurse researchers, medical doctors, philosophers, sociologists and lawyers (Leino-Kilpi 2004). This study was performed in a multidisciplinary group which proved the value of this type of approach.

The focus of this thesis is on ethics and the viewpoint is in health sciences. The purpose of this study was to describe, analyze and evaluate the realization of informed consent in health research as expressed by voluntary adult research participants. In this context, voluntary adult participant means that the person has no treatment connections with the research institute or its researchers. Empirical studies from this point of view are still exiguous (e.g. Rabin & Tabak 2006, Spear 2007). This is surprising since many clinical trials are conducted e.g. in Finland and thus many volunteers are needed. In addition, under the Sixth Framework Programme for Research (2002–2006), the European Commission has taken the responsibility of ensuring that e.g. the ethical aspects are taken into account at the earliest possible stage of Community-funded research in the life sciences and biotechnology (European Commission 2008).

In this study, the emphasis was to acquire knowledge of true consent and one starting point for this is to consider the formal requirements related to consent (effective consent). The formal requirement in this study was, for example, the provision of information to research participants (e.g. amount, quality). The significance of formal requirements is to ensure that all possible participants are able to give genuine informed consent. (Mäkelä 2007.) The working hypothesis of this study was that with sufficient and understandable information one can ensure the satisfaction and engagement of the

participants in the research project, while not forgetting safety. As a consequence, one may hope that the participants will remain in the project and as few as possible will drop out. In addition, this commitment can ensure that the aims of the project are achieved and the results are as reliable as possible. The participant obtains a positive experience in which case he or she may be willing to volunteer again in some other project.

The theoretical framework on this thesis is based on current declarations, regulations, guidelines, and legislation. The key elements of informed consent are described from relevant literature and scientific research. The theoretical framework is confirmed with literature review which concentrated on recent empirical scientific research. This study does not further discuss ethics as a philosophical viewpoint or contemplate ethics theories.

2 INFORMED CONSENT IN THE LITERATURE

Informed consent is one of the basic principles of research ethics. We are fortunate that nowadays there are many trust-worthy and excellent open access websites which include details of research ethics (i.e. American Medical Association [http://www.ama-assn.org/ama/pub/category/2512.html], BioethicsWeb [http://www.bioethicsweb.ac.uk], Council for International Organizations of Medical Sciences [http://www.cioms.ch/guidelines_nov_2002_blurb.htm], European Commission [http://ec.europa.eu/research/biosociety/bioethics/bioethics_en.htm], Finnish Medical Association [http://www.laakariliitto.fi/e/ethics/], World Health Organization [http://www.who.int/topics/ethics/en/], World Medical Association [http://www.wma.net/e]. Therefore, the purpose of this chapter is not to review comprehensively the whole wide field of research ethics.

Instead, this chapter considers examples of how 'informed consent' is defined, the background of informed consent, reviewing briefly its history, some declarations and regulations, and also Finnish legislation as well as assessing the basic elements of informed consent. At the end of this chapter, some recent research on the topic of informed consent is reviewed. The same elements are repeated in different definitions, regulations, declarations and legislation. Hence, there is some repetition and overlap in this chapter. However, this highlights the wide consensus of informed consent as an ethical principle.

2.1 Definitions of informed consent

Informed consent means that the patient or study participant is given sufficient and understandable information to enable independent decision-making (Declaration of Helsinki 2008). The philosophical basis of valid consent rests on the principle of patient or participant autonomy. Before one can have valid consent, the physician, researcher etc. must disclose information to the patient or potential participant who is competent

and then the patient or participant should be able to understand the information and make a voluntary decision. (Hope 2005.)

In the dictionary, the word ‘informed’ (adjective) means: 1a) possessing information, b) based on possession of information; 2) knowledgeable about matters of contemporary interest; educated (Longman Group Limited 1984). 3) Instructed; having knowledge of or acquaintance with facts; educated, enlightened, intelligent (Oxford English Dictionary Online 2009). ‘Consent’ (verb intransitive) means: 1) to give assent or approval; agree to; 2) *archaic* to be in agreement in opinion or feeling. ’Consent’ (noun) means: 1) agreement to or approval of what is done or proposed by another; acquiescence; 2) agreement as to action or opinion. (Longman Group Limited 1984.) 3) Voluntary agreement to or acquiescence in what another proposes or desires; compliance, concurrence, permission (Oxford English Dictionary Online 2009).

In the dictionary, the phrase ‘informed consent’ (noun) means: *Law* permission granted in the knowledge of the possible consequences; (Med.) consent to clinical treatment given after all relevant information (especially regarding potential risks and benefits) has been disclosed to the patient or the patient’s guardian; an instance of such consent. (Oxford English Dictionary Online 2009). Table 1 gives some examples of the different definitions of informed consent that have been employed.

Table 1 Some definitions of informed consent

Author/-s	Definition
Fry 1998	Informed consent means that the patient or study subject is given sufficient and understandable information to enable independent decision-making. Informed consent is a process that protects the autonomy of research subjects, protects them from harm, and assists scientists in avoiding fraud and coercion in their role of researcher.
Beauchamp & Childress 2001	An informed consent is an individual's autonomous authorization of a medical intervention or of participation in research. A person must do more than express agreement or comply with a proposal. He or she must authorize something through an act of informed and voluntary consent. An informed consent occurs if and only if a patient or subject, with substantial understanding and in absence of substantial control by others, intentionally authorizes a professional to do something.
Beckerman 2002	Informed consent is a process between physician and patient that must contain an information component and a consent component. The information component refers to the disclosure of information and comprehension of what is disclosed. The consent component refers to a voluntary decision and agreement to undergo a recommended procedure.
ICH – GCP CPMP/ICH/135/95 2002	A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
WMA 2004	Informed consent means that each potential subject must be adequately informed about the study in question; and after ensuring that the potential subject has understood the information, the researcher should then obtain the subject's freely-given informed consent.
Turner 2005	Informed consent is the process by which a potential subject or a legal representative is given explanations about the purpose of the research and the risks, inconveniences, costs, potential benefits, and right to withdraw from the study without repercussions. This must occur prior to obtaining written or verbal consent for enrolment.

In conclusion, informed consent can be defined as follows: Informed consent is a process by which a potential participant is given sufficient and understandable information about the study. After ensuring that the participant has understood this information, the researcher obtains the participant's freely-given written informed consent. This previously described process enable participant's independent decision-making.

2.2 Short history of informed consent

An article by Vollmann and Winau (1996) gives overview of the dark history of informed consent. This treatise exposes the following facts: The Nuremberg code of 1947 is generally regarded as the first document to set out ethical regulations in human experimentations based on informed consent. However, recent research indicates that ethical issues of informed consent in guidelines for human experimentations were recognized as early as the nineteenth century. For example, in 1891, the Prussian minister of the interior issued a directive to all prisons that tuberculin for the treatment of tuberculosis 'must in no case be used against the patient's will'. However, in 1898 Albert Neisser (discoverer of the gonococcus and professor of dermatology and venereology) published clinical trials on serum therapy in patients with syphilis. He had injected cell free serum from patients with syphilis into patients who were admitted for other medical conditions. Most of these patients were prostitutes, who were neither informed about the experiment nor asked for their consent. (Vollmann & Winau 1996.)

Critical press reports and debate in parliament forced the Prussian government to issue the first directive concerned with medical experimentation in humans in 1900. This directive was based on medical and legal scientific reports. Nonetheless, these regulations were not initiated by the medical profession but were issued after critical public discussion and political debate. A clear distinction was made between therapeutic and non-therapeutic research, but regulations were issued only for non-therapeutic research. The regulations were based on the principle of autonomy and represented an early model of informed consent. A 'proper explanation of the possible negative

consequences' of the intervention and 'unambiguous consent' became the mandatory standard. Minors and incompetent subjects were generally excluded from non-therapeutic research, as they could not give valid informed consent. However, these early regulations were not binding in the legal sense and little is known about their actual impact on clinical research. (Vollmann & Winau 1996.)

Most academic physicians at the time supported Neisser. An exception was Albert Moll (a psychiatrist in private practice in Berlin) who collected 600 cases of unethical non-therapeutic research on humans and emphasized the need for informed consent. (Moll 1902, Vollmann & Winau 1996.) In addition, between 1930 and 1945, Japan conducted human experimentation in biological warfare, including physical responses to infection and trauma, and thousands were killed (Beckerman 2002).

Previously, in 1916, the Harvard physician Walter Cannon had recommended to the House of Delegates of the American Medical Association that it should endorse the importance of obtaining patient consent and cooperation in human experimentation. His proposal, however, was not brought up for consideration. One influential physician observed that it would open the way for a discussion of the importance of obtaining the consent of the patient before any investigations were carried out which were not primarily for the welfare of the patient. (Human & Fluss 2001.)

The phenomenon of informed consent was formally defined in the first principle of the Nuremberg Code (Burns & Grove 2001). The Nuremberg Code in 1947 was adopted in response to the human rights atrocities occurring in Nazi concentration camps. The major impetus for increased attention to the issues of informed consent was a series of studies involving unethical actions on the part of researchers toward their participants. These studies involved human rights violations in which participants were neither informed nor had the possibility to refuse participation. (Turner 1998.)

In the Nuremberg war trials, it was revealed that physicians (e.g. Dr. Josef Mengele) conducted abhorrent medical experiments on concentration camp prisoners. This research included human experimentation with germ warfare, freezing individuals to

learn what temperature would kill a person most effectively, and many more horrific trials. The Nuremberg Code, which emerged from the trials, abandoned the earlier paternalistic perspective of medicine and research and replaced it with the centrality of patient self-determination by asserting that for medical research, the voluntary consent of the human subject was necessary under all circumstances. (Beckerman 2002.)

Consequently, since the Nuremberg trials, consent has been at the forefront of biomedical ethics. The term 'informed consent' did not appear until a decade after these trials (held in the late 1940s), and it was not examined in detail until the early 1970s (Beauchamp & Childress 2001). The Nuremberg Code was followed by the Declaration of Helsinki, adopted by the WMA in 1964 (Turner 2005).

2.3 Some regulations of informed consent

Due to the dark history of previous medical research, international declarations and conventions have laid down ethical principles for medical research. They emphasize the autonomy of the research participant, or his or her legal representative, so that he or she can give a free and informed consent prior to the initiation of research. (Halila 2007.) Thus, the notion of voluntary participation in research involving human subjects was enunciated for the first time in the Nuremberg Code. Subsequently, several international declarations sanctioned this concept as being pivotal in research ethics. (European Commission 2007.) Some examples of these declarations are: Declaration of Helsinki by WMA, International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS 1993, last updated in 2002, www.cioms.ch) and Universal Declaration on Bioethics and Human Rights adopted by UNESCO (UNESCO's General Conference on 19 October 2005, www.unesco.org).

All international declarations stipulate that, prior to consent, each participant in a research project should be clearly informed of its goals, its possible adverse events, and the possibility to refuse to enter or to retract his/her consent at any time with no repercussions. Moreover, no inducement should justify the participation in a research.

(European Commission 2007.) In this thesis, some of the declarations or regulations are examined in detail as examples.

Globalisation of research will demand better implementation of international ethical guidelines. This is particularly true in areas like health research. (Potocnic 2007.) The European Commission, for instance, has begun to work more closely also with developing countries to establish high ethical standards for research on a global basis (Watson 2007).

2.3.1 Nuremberg Code

The Nuremberg code (1947, 2007) includes principles such as informed consent and absence of coercion; properly formulated scientific experimentation; and beneficence towards experiment participants. This code includes ten points. The first point is: The voluntary consent of the human subject is absolutely essential. This means that the person involved should have the legal capability to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him/her to make an understanding and enlightened decision.

This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him/her the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his/her health which may possibly result from participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity. (Nuremberg Code 1947, 2007.)

2.3.2 Declaration of Helsinki

The Declaration of Helsinki was adopted by the 18th World Medical Association (WMA) General Assembly at June 1964 in Helsinki, Finland, and has been amended eight times (in 1975, 1983, 1989, 1996, 2000, 2002, 2004 and 2008). The WMA has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance for physicians and other participants in medical research involving human subjects, including research on identifiable human material or identifiable data (Point 1). Although the Declaration was addressed primarily to physicians, the WMA has encouraged other participants in medical research involving human subjects to adopt these principles (Point 2). (Declaration of Helsinki 2008.) In table 2 is presented some more points from the Declaration. These points are directly connected with informed consent.

Table 2 Quotations of Declaration of Helsinki

Relevant portions of Declaration of Helsinki (2008)
Point 24 In medical research involving competent human subjects, each potential participant must be adequately informed about 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 any 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 consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
Point 26 When seeking informed consent for participation in a research study, the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations, the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
Point 27 For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
Point 28 When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
Point 29 Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances, the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
Point 34 The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

2.3.3 Universal Declaration on Bioethics and Human Rights

In October 2005, the General Conference of UNESCO adopted by acclamation the Universal Declaration on Bioethics and Human Rights. It deals with ethical issues arising in medicine, life sciences and associated technologies as applied to human beings. The Declaration is based on the principles it endorses in the rules that govern respect for human dignity, human rights and fundamental freedoms.

This declaration has 15 principles (Article 3 – Article 17). For example, Article 6 discusses consent as follows: "Any preventive, diagnostic and therapeutic medical intervention is only to be carried out with the prior, free and informed consent of the person concerned, based on adequate information. The consent should, where appropriate, be expressed and may be withdrawn by the person concerned at any time and for any reason without disadvantage or prejudice. Scientific research should only be carried out with the prior, free, expressed and informed consent of the person concerned. The information should be adequate, provided in a comprehensible form and should include modalities for withdrawal of consent. Consent may be withdrawn by the person concerned at any time and for any reason without any disadvantages or prejudice." (UNESCO 2005.)

2.3.4 Good Clinical Practice (GCP)

The WHO has developed guidelines for Good Clinical Practice (in 1994) for trials of pharmaceutical products in order to establish globally applicable standards for the conduct of biomedical research on human subjects. The guidelines protect the rights and safety of subjects, including patients, and they ensure that the investigations are directed to the advancement of public health objectives. (Idänpää-Heikkilä 1994.)

In 2002, WHO published 'Handbook for good clinical research practice (GCP): guidance for implementation'. This handbook states that good clinical research practice is a process that incorporates established ethical and scientific quality standards for the

design, conduct, recording and reporting of clinical research involving the participation of human subjects. Compliance with GCP provides public assurance that the rights, safety, and well-being of research subjects are protected and respected, consistent with the principles enunciated in the Declaration of Helsinki and other internationally recognized ethical guidelines, and ensures the integrity of clinical research data.

Informed consent is defined in this guideline as Principle 7: “Freely given informed consent should be obtained from every subject prior to research participation in accordance with national culture(s) and requirements. When a subject is not capable of giving informed consent, the permission of a legally authorized representative should be obtained in accordance with applicable law.” (WHO 2002.)

International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use – Good Clinical Practice (ICH–GCP), in 1996, is also an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of ICH–GCP guidelines is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. The guideline was developed with consideration of the current good clinical practices of the EU, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the WHO. Informed consent is also defined in this guideline (see table 1). (ICH–GCP.)

2.3.5 Finnish Medical Associations code of medical ethics

The Delegate Committee of the Finnish Medical Association has adopted (in May 1988) a code of medical ethics to be observed by physicians in their profession. In its fourth

point it states: “A physician shall not use his (sic) authority to undermine a patient’s right to make decisions concerning himself (sic). Even where the patient cannot convey his (sic) own will, it is incumbent upon the physician to act in the patient’s best interest. If a physician is compelled to make decisions concerning examinations or therapy irrespective of the patient’s will, such decisions shall always be made on medical grounds.” (Finnish Medical Association 2007.)

The Sixth point discuss patient’s participation in medical research: “Should a physician wish for his (sic) patient to participate in a clinical trial in which the examinations and therapy deviate from the normal procedure for the disease, he (sic) shall obtain the patient’s freely-given consent without pressure, the patient being aware of the trial and of the additional strain and risks involved. Generally accepted declarations and instructions issued by the authorities shall be observed during the trial.” (Finnish Medical Association 2007.)

2.4 Finnish legislation concerning informed consent

Finnish national legislation does take into account research ethics and the protection of individual rights in health care. First, there are several laws and decrees relating to this field. The most important laws concerning informed consent in Finland are: ‘Medical Research Act’ and ‘Act on the Status and Rights of Patients’. It is noteworthy that Finland was the first country to issue an Act on the Status and Rights of Patients in 1992, and one of the first countries to issue an Act on Medical Research in 1999 (Halila 2003). An extensive list and link of laws and decrees can be found, for example, at the local ethical committee website (Kuopio University Hospital > Scientific research > Ethical committee [http://www.psshp.fi/index.asp?tz=-2]).

Second, there are several national ethics commissions in Finland. The National Advisory Board on Research Ethics was first established in 1991. The National Advisory Board on Health Care Ethics was established in 1998, followed by its Sub-Committee on Medical Research Ethics in 1999. This sub-committee acts as a national

research ethics committee and provides opinions about research projects. The National Advisory Board on Research Ethics can promote legislation by making proposals and statements to the ministries and the government. It acts as an expert body on research ethics, promotes discussion, and takes initiatives in advancing research ethics. It also collects and shares information about research ethics. The Board has an advisory role and does not issue legally binding decisions, although while resolving cases of misconduct and fraud in science, the recommendations that the Board makes are highly respected. (Halila 2003.)

The law often represents the lowest level of acceptable behaviour. Therefore, it has been stated that it is important that law and ethics should not totally coalesce, lest ethics vanish altogether and furthermore, clinicians and researchers should surely be striving for higher standards than the bare minimum. (Sokol 2008.)

2.4.1 Medical Research Act

This law (No. 488/1999) applies to medical research carried out on persons, human embryos and human foetuses, unless otherwise provided by legislation. It was enacted on April 1999 (amended No. 294/2004).

Chapter 2, section 6 covers consent of research subjects. In this section it is stated: "Medical research on persons may not be conducted without the research subject's informed consent in writing. Exceptions to this may be made where consent cannot be obtained owing to the urgency of the matter and the patient's state of health and the measure is expected to be of immediate benefit to the patient's health. If the research subject is not able to write, he or she can give the consent orally in the presence of at least one witness who is independent of the research. Research subjects shall have their rights, the purpose and nature of the research and the procedures it involves properly explained to them. The potential risks and harm shall also be properly explained to them. This information shall be given so that research subjects are in a position to give

their informed consent with regard to issues connected with the research that has a bearing on their decision-making."

Furthermore, the Act states that research subjects shall be entitled to withdraw their consent at any point prior to the completion of the research. They shall be informed of this right before the start of the research. Withdrawal of consent and resulting withdrawal from the research shall not involve any negative consequences for the subject.

Chapter 2, section 7 is concerned with research involving persons not able to provide consent: "People who, owing to a mental health disorder, retardation or other similar reason, do not have the capacity to give their consent to research may be research subjects only where it is not possible to obtain the same scientific results using other research subjects and where the risk of harming or distressing the research subject is only very slight. It is a further stipulation that the research should be likely to be of direct benefit to the research subject's health; or the research should be likely to be of special benefit to the health of people in the same age group or with the same state of health."

Section 8 is devoted to research involving minors. The content of section 8 is very similar to section 7. In addition, it states: "Where the minor has reached the age of 15 and, in view of his/her age and maturity and the type of illness and research, is capable of understanding the importance of the research procedure and the research is likely to be confer a benefit on the minor's health, it shall be sufficient for the minor to give his/her informed consent in writing. In such cases, the guardian shall be informed of this. In other cases, minors may be research subjects only where written consent for this has been given by their guardian or legal representative after being provided with the information referred to in section 6. The consent must be in accordance with the minor's supposed will. Where a minor opposes a research or a research measure, the minor's opinion shall be complied with, taking account of his/her age and maturity."

Section 9 is concerned with research involving pregnant women and nursing mothers: 2Pregnant women and nursing mothers may be research subjects only where it is not possible to obtain the same scientific results using other research subjects and the research is likely to be of direct benefit to the health of the woman or the unborn child; or the research is likely to be of benefit to the health of people related to the woman, or to pregnant woman or nursing mothers, or to foetuses, newborn children or unweaned children."

Furthermore, section 10 is devoted to research involving prisoners. It states that prisoners may be research subjects only where the research is likely to be of direct benefit to their own health or the health of people related to them or the health of other prisoners. (Laki lääketieteellisestä tutkimuksesta 1999, Medical Research Act 1999.)

2.4.2 Medical Research Decree

The medical research decree (No. 986/1999) entered into force on November 1999 (amended No. 313/2004). Section 3 is the part of the document related to provision of consent. It states that the document of consent shall include the following: the research subject's name, personal identity code or date of birth, and address; that the information has been given to the research subject and data about the giver of the information; which other sources, information concerning the research subject will be gathered from; whom the information gathered in the context of the research can be delivered to and how the confidentiality of the information is protected; the research subject's voluntary consent; and mention of the right to withdraw the consent without it affecting the research subject's right to receive the care he/she is in need of.

The document of consent shall be dated, and it shall be signed by both the person who gives and the person who receives the consent. A copy of document shall be given to the giver of the consent. If the research subject has given the consent orally because he or she is not able to write, a witness independent of the research shall sign the document of consent. The witness' signature shall be appended with clarification of the name and

contact information. (Asetus lääketieteellisestä tutkimuksesta 1999, Medical Research Decree 1999, Asetus lääketieteellisestä tutkimuksesta annetun asetuksen muuttamisesta 2004.)

2.4.3 Act on the status and rights of patients

This act on the status and rights of patients (No. 785/1992) was issued on August 1992. Chapter 2 defines the rights of patients. The patient's right to be informed is defined in section 5 as follows: "A patient shall be given information about his/her state of health, the significance of the treatment, various alternative forms of treatment and their effects as well as information about other factors related to his/her treatment that are significant when decisions are made on the treatment given to him/her. However, this information shall not be given against the will of the patient or when it is obvious that providing the information would represent a serious hazard to the life or health of the patient. Health care professionals should try to give the information in such a way that the patient can understand it. If the health care professional does not know the language used by the patient or if the patient because of a sensory handicap or speech defect cannot be understood, interpretation should be provided if possible."

Section 6 (chapter 2) defines the patients' right to self-determination. This means that the patient has to be cared with approval. If the patient refuses a certain treatment or measure, he/she has to receive care, as far as possible, some other medically acceptable way to which he/she approves. (Laki potilaan asemasta ja oikeuksista 1992, Act on the status and rights of patients 1992.)

2.5 Key elements of informed consent

In this study, the key elements of informed consent were defined as follows: information, understanding, competence, voluntariness, and decision-making (Beauchamp & Childress 2001, Leino-Kilpi et al. 2002). The basic elements of informed consent are information, understanding and decision-making. Competence is a fundamental factor in the reception and understanding of information and for making an independent and voluntary decision about participation. This definition is based on the early literature (including regulations etc.) and on a pilot study (Original publication I). The key elements are described in various ways in the literature. However, the same elements are repeated. Table 3 presents some different descriptions.

Table 3 Key elements of informed consent

Author/-s	Definition of elements
Beauchamp & Childress 2001	The elements of informed consent are threshold (preconditions), information and consent. Threshold elements are: competence (to understand and decide) and voluntariness (in deciding). Information elements are: disclosure (of material information), recommendation (of a plan) and understanding (of disclosure and recommendation). Consent elements are: decision (in favour of a plan) and authorisation (of the chosen plan).
Beckerman 2002	The informed consent is viable if the person is competent to act, receives thorough disclosure, has an understanding, and is voluntary in his or her consent. For informed consent to be legally recognized, the following steps need to be clearly articulated: Preconditions, which includes competence (to understand and to decide) and voluntariness (in deciding). Information element, which includes disclosure (of risk/benefits), recommendations (plan) and understanding (of information and plan). Consent elements, which include authorization (based on patient autonomy).
Burns & Grove 2001	Informed consent consists of four elements: disclosure of essential information, comprehension, competency and voluntarism.
Leino-Kilpi et al. 2002	Informed consent has three basic dimensions: prerequisites, decision-making activities and the outcomes of decision-making. The prerequisites are information, competence, understanding, willingness, voluntariness and lack of coercion. The consequences of decision-making activities are consent, acceptance or rejection.

Although different definitions of key element of informed consent are presented, there is a consensus that information is the most essential element. Therefore, several institutions have made lists of the topics needed to be mentioned in the informed consent process. For example, according to the European Commission (2007), research participants should be provided with the information presented in table 4 before they participate in a study.

Table 4 Information to be provided to research participants according to the European Commission

List of information
A statement that the study involves research subjects, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
A description of any reasonably foreseeable risks or discomforts to the subject.
A description of any benefits to the subject or to others which may reasonably be expected from the research.
Insurance guarantees provided to participants.
For research involving more than minimal risk, an explanation as to whether there are any treatments or compensation if injury occurs and, if so, what they consist of, or where further information may be obtained.
A disclosure of appropriate procedures in case of incidental findings.
A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.
An explanation of whom to contact at any time for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury to the subject.
A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty.
(European Commission 2007)

International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS 2002) defines the essential information for prospective research subjects with a 26 point list. Some examples of the salient matters on this list are: That the individual is invited to participate in research, the reason for considering the individual suitable for the research, and that participation is voluntary. 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. 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. 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. (CIOMS 2002.)

In addition, the essential information includes: 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. 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. 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. The direct benefits, if any, expected to result to subjects from participating in the research. The expected benefits of the research to the community or to society at large, or contributions to scientific knowledge. And that an ethical review committee has approved or cleared the research protocol. (CIOMS 2002.)

The Ministry of Social Affairs and Health, National Advisory Board on Health Care Ethics (ETENE) sub-committee on Medical Research Ethics (TUKIJA) has devised (2001, updated at April 2009) also a checklist for researchers and members of ethics committees (ETENE 2001b). In this list, the fourth point discusses the information to be given the research subject. This elaborates, for example, that the information to research subjects should include all the essential information on the research that the subjects need to be able to give their informed consent. A good information sheet is short,

matter-of-fact and understandable. The information should be given personally to each research subject both orally and in writing. All research subjects must be provided with an opportunity for asking questions. The written information should include, above all, the following: facts about the research; voluntariness of participation and withdrawal of consent; impacts of participation to research; data protection, costs, remuneration, insurance; treatment after the research.

In addition, the information sheet should be written using easily understandable language, and the research subject should be provided with sufficient time to familiarize him/herself with its contents. Unless the research subjects are clearly restricted to either Finnish or Swedish speaking persons, the information must be available in both languages. If there are persons in the sample who do not understand either of the domestic languages, the information sheet must be available in the language that the research subjects understand well. The standard of language should correspond to the language used by the subject group. For example, there may be a specific information sheet for children or persons suffering from dementia in addition to the possible information to their representatives. (ETENE 2001b.)

2.6 Literature review of recent research

2.6.1 Data retrieval

This literature review is based on a systematic review on MEDLINE (PubMed), Cochrane and Medic databases at January 2009. An extensive number articles concerning informed consent have been published internationally. For example, a search of the Cochrane Library with the phrase "informed consent" resulted without limits: Cochrane reviews 5546, other reviews 9025, clinical trials 549 336, method studies 10 973, technology assessments 7528 and economic evaluations 24 451. Therefore, the review was limited to 1) MEDLINE (PubMed) as follows: a) published in the last 10 years, b) only items with abstracts, c) type of publication: clinical trials, meta-analysis, practice guideline, randomized controlled trial, review, classical article, d) language: English, e) age: all adult: 19+ years. Limit in 2) Cochrane Library was: a) published 2000–2009 and b) keywords. And limit in 3) Medic was: published 2000–2009.

Searches were done with several words and combinations but the final search words in MEDLINE (PubMed) were: "informed consent AND participant", "informed consent AND subject", "informed consent AND intervention study", "informed consent AND health survey, "informed consent AND information", "informed consent AND understanding", "informed consent AND competence", "informed consent AND voluntariness" and "informed consent AND decision-making". The search word in Cochrane was: "informed consent" and in Medic: "informed consent", "tietoon perustuva suostumus" and "tietoinen suostumus".

A search with limits mentioned above, resulted in a MEDLINE (PubMed) total of 502 articles, a Cochrane total of 268 articles and a Medic total of 39 hits. The first selection of articles (n=222) was made by title and the stipulation was that the title contained one or more of the following words: 'informed consent', research or trial or study etc., participant or subject or volunteer etc., information, understanding, competence, voluntariness or decision-making. The second selection was done from abstracts and limited so that the same article was not found from some other database. After deleting

duplications, the number of abstracts was 136. Finally, after reading the abstracts, the remaining amount of printed full text articles was 49. The data retrieval and selection process is presented in detail in table 5.

Table 5 The data retrieval (at January 2009) and selection process

Database	**Words**	**Amount**	**First selection** ***(title)***	**Second selection** ***(abstract + overlapping deleted)***	**Final selection** ***(full text)***
MEDLINE (PubMed)	"ic + participant"	28	12	12	5
	"ic + subject"	41	12	11	2
	"ic + intervention study"	4	0	0	0
	"ic + health survey"	5	1	1	0
	"ic + information"	170	40	34	16
	"ic + understanding"	74	28	11	5
	"ic + competence"	78	24	14	3
	"ic + voluntariness"	5	2	1	0
	"ic + decision-making"	97	28	9	1
	Total	***502***	***147***	***93***	***32***
Cochrane	"ic" at Cochrane reviews	2	1	1	1
	"ic" at Other reviews	5	2	2	2
	"ic" at Clinical trials	252	70	39	14
	"ic" at Method studies	1	1	1	0
	"ic" at Technology assessments	1	0	0	0
	"ic" at Economic evaluations	7	1	0	0
	Total	***268***	***75***	***43***	***17***
Medic	"informed consent, tietoon perustuva suostumus, tietoinen suostumus"	39	0	0	0
	Total	**809**	**222**	**136**	**49**

ic = informed consent

This described data retrieval and selection process excluded results from national literature search of Medic database. However, there have been relevant studies and other reports about informed consent and reviews about research ethics published in this decade in Finland. For example, the above-mentioned national literature search (at January 2009) with phrase 'informed consent' (in English and in Finnish) between years 2000–2009 resulted in 39 search hit. A search of the same database with different combinations of words research and ethics (in Finnish) resulted in 99 hits. However, Välimäki and co-workers (2000) published an overview of academic theses concerning nursing ethics in Finland between the years 1984–1997. There have been 89 theses published in the topic of nursing ethics which accounts for 6.8 % of all published academic nursing theses. Välimäki and co-workers concluded that research on ethics was not common in academic thesis in Finland during that time period. Therefore, the present situation leads to the assumption that interest in ethical topics has increased.

In this context it is a pleasure to mention some examples of recent Finnish doctoral dissertations concerning ethics: Behm (2008) questioned the argument that the moral personality of scientists explains ethical problems in science; in addition, the focus was shifted from individuals to the level of the research environment (*Research norms and norms of the research environment*). Kanerva (2006) analyzed and compared the perceptions of day surgery patients and nurses and doctors about the realization of informed consent in a day surgery patient's care and the perceptions of patients and nurses about a nurse's responsibilities (*Informed consent in a day surgery patient's care – analysis of the realisation of informed consent and a nurse's implication*). Lötjönen (2004) examined the national and international sources of law that are concerned with medical research and addressed the relevance of ethical codes (*Medical research on humans – legal and ethical aspects on encroaching physical integrity in medical research*). Nyrhinen (2007) identified ethical issues in diagnostic genetic testing and described, compared and explained the realization of ethical principles, autonomy, privacy, equality and benefits in diagnostic genetic testing (*Ethics in diagnostic genetic testing*).

In addition, the data retrieval and selection process excluded, for example, articles that dealt with everyday nursing. However, in the final two decades of the 20th century, an explosion of nursing knowledge has guided practice and advanced the health and well-being of individual clients, families, and communities (Hinshaw 2000). In addition, it is noteworthy that the largest group of health care professionals in Europe is represented by nurses (Leino-Kilpi et al. 2002). Nurses are responsible for well-being and quality of life of many people, and therefore their profession requires high standards of technical and ethical competence (Tadd et al. 2006). One notable research from this viewpoint is the project on 'Patient's autonomy, privacy and informed consent in nursing interventions'. This study focused on three different groups (in five European countries): mothers with infants or babies in postnatal wards, surgical patients in hospital wards, and long-term elderly patients in institutions. (Leino-Kilpi et al. 2002, Leino-Kilpi et al. 2003a, Leino-Kilpi et al. 2003b, Schopp et al. 2003, Scott et al. 2003.)

2.6.2 Results of literature review

It has been stated that a great deal of e.g. bioethical literature focuses on the way the individual can be protected in the medical context, for example in relation to research (Nuffield Council of Bioethics 2007). However, the literature review of this thesis reveals that there is a considerable amount of research on the topic of 'informed consent' from the viewpoint of patient and different treatments or therapies (e.g. patient's approval to proposed treatment, patient's selection between alternative treatments or patient's competence to make decisions concerning his/her treatment). There are clearly fewer studies on the topic of informed consent to research. Furthermore, there are even fewer investigations on this same topic but from the point of view of voluntary adult research participants. The literature review of this thesis focused on these two last mentioned groups.

All the reviewed studies are tabulated in detail in Appendix 1. In summary, nearly all (n=45) of the reviewed studies were empirical and only four of them were systematic reviews. These reviews focused on participants' comprehension of informed consent in

clinical trials (Cohn & Larson 2007), measures of decisional capacity for research and treatment (Dunn et al. 2006), effectiveness of leaflets in promoting informed choice in screening (Fox 2006), and effects of different methods of information provision to potential clinical trials participants in informed consent process (Ryan et al. 2008).

In the empirical studies, the main method in use was a questionnaire survey or questionnaire-based interview. The majority of studies used a self-administered questionnaire to assess different components of informed consent. However, some of the studies used a standardized questionnaire. For instance, Hack and co-workers (2007) used the Informed Consent Questionnaire (ICQ), Hietanen and co-workers (2007) used the Quality of Informed Consent (QuIC) questionnaire, and Hutchinson and co-workers (2007) used the Clinical Trial Decision Questionnaire and in addition a self-administered questionnaire. The focus of these three studies was cancer patients. In addition, there were some studies without a specific informed consent questionnaire (e.g. Baker et al. 2000).

The reviewed studies were focused as follows:
Information in: healthy volunteers participating in a phase 3 clinical trial (Fortun et al. 2008), prostate-antigen screening (Gattellari & Ward 2005), clinical trial in breast oncology (Hack et al. 2007), representative cerebral artery infarction patients and representative stroke patients (Hofmeijer et al. 2007), adult outpatients (Kruse et al. 2000) patients on hemodialysis or in a prerenal state (Lynöe, Näsström & Sandlund 2004), cancer patients (Strevel et al. 2007), and colorectal cancer screening for elderly patients (Wolf & Schorling 2000).

Understanding and competence in: participants in a trial of a new drug for hypertension and participants in a trial of an anaesthetic in a sterilisation procedure in women (Bjørn, Rossel & Holm 1999), outpatients (Campbell et al. 2008), cancer patients (Coyne et al. 2003), outpatients with schizophrenia or related psychotic disorders (Dunn et al. 2001, 2002), patients with unstable angina pectoris / non-Q-wave acute myocardial infarction (Kucia & Horowitz 2000), mentally ill prisoners (Moser et al. 2004), volunteers in biomedical research in four clinical research centres (Paris et al.

2007), patients with schizophrenia or depression (Stiles et al. 2001), and voluntary adult participants (Sudore et al. 2006).

Voluntariness in: patients who were scheduled for minor surgery with general anaesthesia (Treschan et al. 2003). ***And decision-making in:*** patients with asthma or stable angina (Baker et al. 2000), older assisted-living residents at a high risk for cognitive impairment (Black et al. 2008), screening for prostate cancer (Davison et al. 1999), colorectal, breast and lung cancer patients (Hutchinson et al. 2007a), participants in a breast cancer prevention trial (Juraskova et al. 2008), women asked to participate to a double-blind randomised drug trial (Lovegrove et al. 2000), genetic testing in women (Mancini et al. 2006), and outpatients referred to the urology surgery (Westberg et al. 2004).

Enhanced informed consent process with different methods: in older inpatients in acute assessment (Adamis et al. 2005), patients with asthma (Dresden & Levitt 2001), primary care clinics outpatients (Dunlop et al. 2007), Down syndrome screening (Hewison et al. 2001), voluntary adult participants (Ishii & Ohashi 2007), voluntary members of the public for screening of type 2 diabetes (Kellar et al. 2008), research subjects from five different randomised clinical trials (Lavori, Wilt & Sugarman 2007), emergency department patients (Marco 2008), patients with Alzheimer disease of mild cognitive impairment (Mittal et al. 2007), and seriously ill patients mental and medical conditions (Wirshing, Sergi & Mintz 2005).

Improvement of design and conduct of randomized trials: in patients from primary care clinics participating in intervention for depression (Dobscha et al. 2005), patients undergoing prostate testing for cancer and treatment (Donovan et al. 2002), and informed consent document developed by Gulf War veterans (Peduzzi et al. 2002). ***And others:*** professional's communication skills in context with cancer patients (Brown et al. 2007, Hietanen et al. 2007), recruitment and retention to trials in injection drug users (Garfein et al. 2007), financial interests in patients with coronary artery disease (Weinfurt et al. 2008a), and patient's perspective of the international cohort study in acute myocardial infarction (Yuval et al. 2000).

2.7 Summary of theoretical background

Informed consent is an essential part of high ethical quality of scientific research with human participants. Informed consent is universally known and recogonized. However, the global clinical research enterprise has become increasingly complex from operational, regulatory, and ethical perspectives (Chanaud 2008). One major challenge is that researcher's must be aware of the large amount of regulations some of which may be confusing, conflicting and difficult to access. The reason for these regulations is the necessity of protecting the individual integrity and privacy of research participants (Lötjönen 2002).

Figure 1 summarizes the theoretical background of this thesis. In the centre is the consent provider who makes the finally decision of participation to research. The aspects to decision-making come from ethics, information provided to and collected from informants. The primary informed consent process is a personal resolution to the posed question: Are you willing to participate in our study?

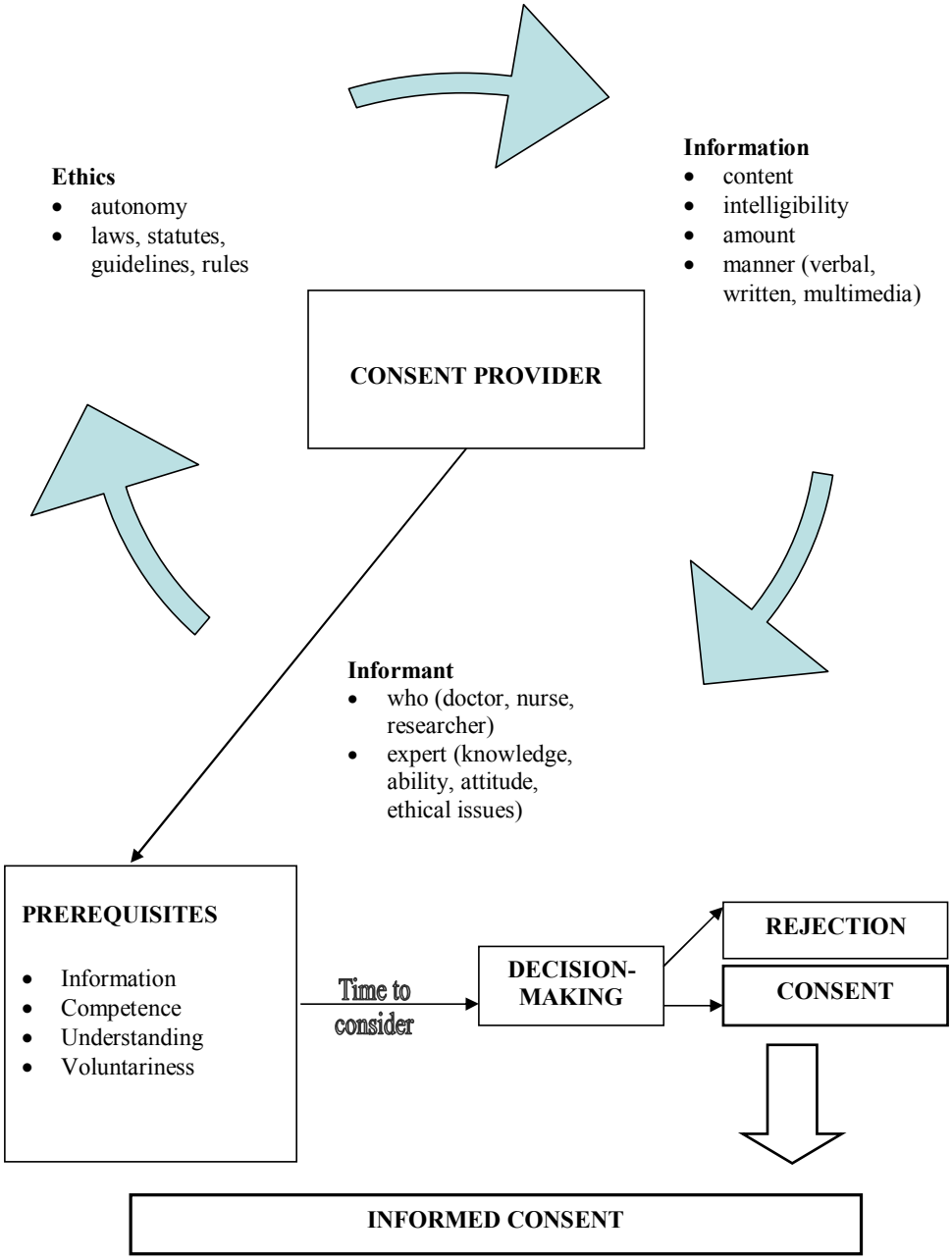

Figure 1 Theoretical background of informed consent (adapted from Beauchamp & Childress 2001; Leino-Kilpi et al. 2002)

3 AIM OF THE STUDY

The aim of this study was to add empirical knowledge about informed consent in health research. The purpose of the present thesis was to describe, analyze and evaluate the realization of informed consent in health research as expressed by voluntary adult research participants. This thesis had two phases: the pilot study and the primary informed consent study; though the emphasis on phase 2.

Phase 1 ***The Pilot Study*** (Original publication I)
The purpose of this stage was to develop a questionnaire designed to evaluate informed consent in health research and to test it in a pilot study.

Individualized research questions at Phase 1 were:

1 How informed consent is realized in a clinical research project?
2 Is the created questionnaire (interview schedule) a useful tool for monitoring the quality of the informed consent process?

Phase 2 ***Informed Consent Study*** (Original publications II–IV)
The purpose of this primary stage was to describe, analyze and evaluate the realization of informed consent in a population-based exercise and diet intervention study.

Individualized research questions at Phase 2 were:

1 How the key elements of informed consent (information, understanding, competence, voluntariness and decision-making) are realized in an exercise and diet intervention study?
2 What factors are associated with the participant's comprehension of information received in the exercise and diet intervention study? Supplementary question: Is understanding related to long-term continuation in the intervention trial?
3 Is informed consent related to success in the exercise and diet intervention as evaluated at 12 months?

4 METHODS

4.1 Study populations and data collections

The Pilot Study (Phase 1)

The study population consisted of subjects (N=32) who participated in a clinical research project evaluating the effects of betaine on cardiovascular risk factors in high risk subjects with the metabolic syndrome. This 'Betaine' Study was arranged in the Department of Clinical Nutrition, University of Kuopio. The participants, aged 36–66 years, had impaired fasting glucose or impaired glucose tolerance or type 2 diabetes and at least two of the following: blood pressure $\geq$ 140/90 mmHg, serum triglyceride concentration $\geq$1.7 mmol/l and/or HDL-cholesterol <0.9 mmol/l, waist-to-hip ratio >0.90 in men and >0.85 in women and/or BMI >30kg/m², microalbuminuria. The kidney, liver and thyroid functions of the participants had to be normal.

The data of the Pilot Study were collected by interview between May and June 2004 in the Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital. Before the interviews, the participants received oral information, an information letter and a request to return a form containing their contact details in the return envelope. Of the 32 persons invited, a total of 26 (16 male and 10 female) took part. Those who did not return the contact details form were not approached again.

The Informed Consent Study (Phase 2)

The study population at this primary stage consisted of subjects who are participating in a randomized controlled intervention trial on the effects of regular physical exercise and diet arranged by the Kuopio Research Institute of Exercise Medicine (*DR's EXTRA: Dose-Responses to Exercise Training. A randomized controlled trial on the effects of regular physical exercise and diet on endothelial function, atherosclerosis and cognition)*. In 2002, a representative 15 % sample (N=3000) of 55- to 74-year-old men and women living in the city of Kuopio (in eastern Finland) were invited to participate in an exercise and diet intervention study. Of the participants initially invited, 2062

expressed an interest in participating and 1410 subjects participated in all four baseline examinations between April 2005 and November 2006.

The main exclusion criteria at entrance were conditions that would prevent safe engagement in the prescribed exercise training, malignant diseases as well as other conditions preventing potential participants from co-operating, as judged by the research physicians. The participants were randomized into six intervention groups: 1) Reference, 2) Aerobic Exercise, 3) Resistance Exercise, 4) Diet, 5) Aerobic Exercise and Diet, 6) Resistance Exercise and Diet. These interventions are intended to continue for four years. The formation of the study population of the DR's EXTRA Study is presented in figure 2.

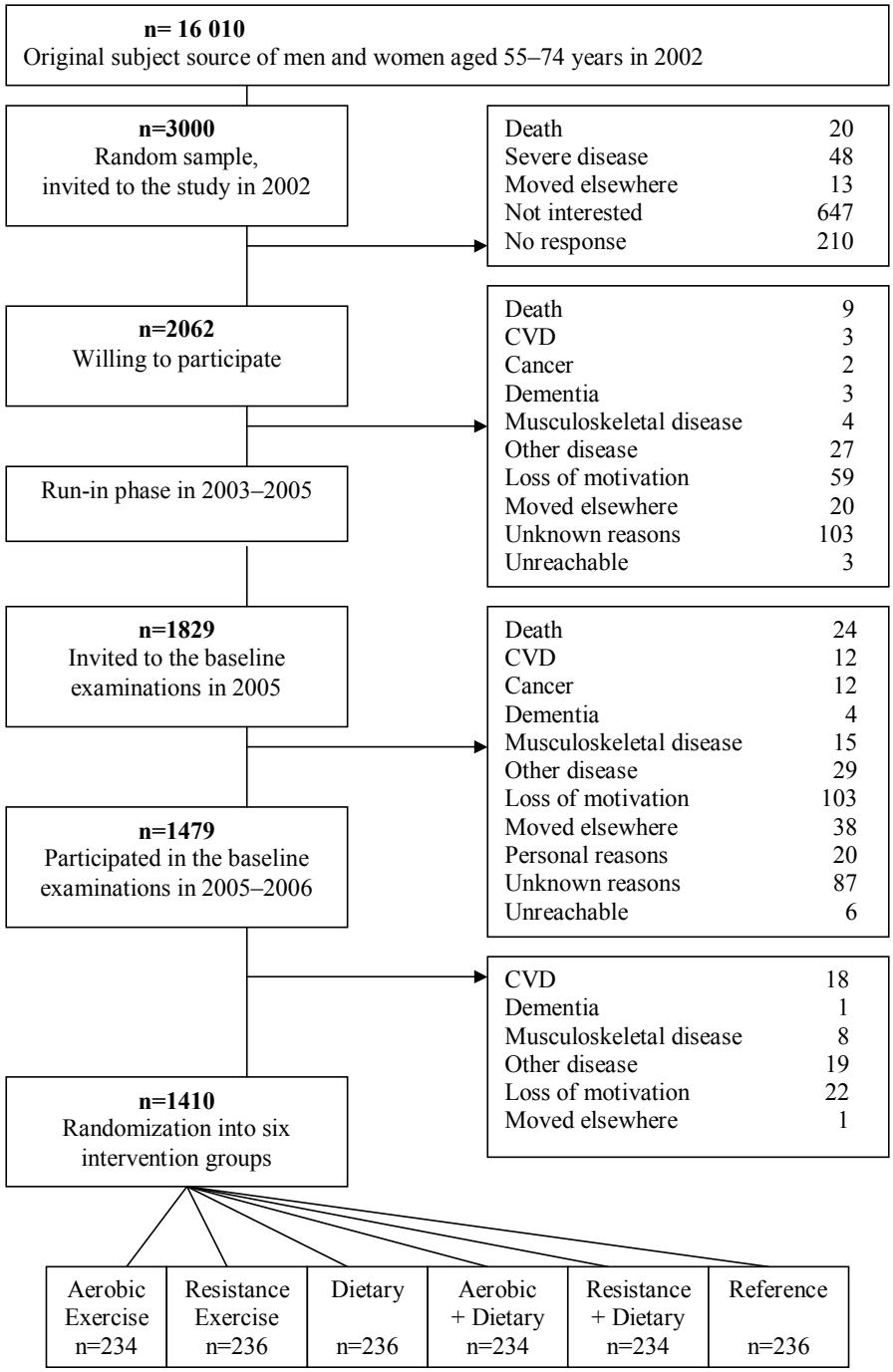

Figure 2 Formation of study population in DR's EXTRA Study (Hassinen 2008, Komulainen 2008)

The interventions protocol in the DR's EXTRA Study is as follows: Participants in the ***Reference group*** have been given general public health advice on regular physical activity for a minimum of 30 minutes of moderate exercise on most days of the week causing an exercise energy expenditure (EEE) of 750–1000 kcal (3.1–4.2 MJ) per week. Each exercise group started the intervention with a four-week aerobic exercise period to accustom the individuals to physical exercise.

Participants in the ***Aerobic Exercise group*** have been prescribed an individualized training program at an intensity corresponding to ventilatory aerobic threshold (at 55–65 % of the maximum level). The main exercise models are walking, skiing, jogging-running, pole walking, biking and swimming. In addition, the participants in this group have been further divided randomly into two subgroups (stratified by age and gender) after 6 months intervention: EEE of 1000–1500 (4.2–6.3 MJ) or more than 1500 kcal/week, by varying the exercise frequency and duration. The training frequency has been gradually increased during the following 5–11 months to either two or four sessions per week. Training intensity has been monitored either by a personal heart rate recorder or by artery palpation. (Rauramaa et al. 2004, Haskell et al. 2007, Nelson et al. 2007.)

Resistance Exercise group have been given a training program according to the guidelines of the American Heart Association (AHA) and American College of Sports Medicine (ACSM). After the baseline strength measurement, the subjects participated in supervised, individually prescribed progressive strength training for 6–12 months (from 40–50 % to 70–80 % of 1 repetition maximum (RM)) twice a week for all the major muscle groups (12 exercises, 12 repetitions, 2–3 sets; e.g. 60/70/80 % for muscle hypertrophy). One third of the total volume of training included leg extensor with light loads only (40–50 % of 1 RM) but executed all repetitions as explosively as possible (rapid muscle actions) in order to stimulate the neural control of muscle contraction. The duration of each training session has been from 45 to 60 minutes, plus 5 minutes aerobic warm-up, and 10 minutes muscle stretching. Participants were supplied with a personal smart card, with details of the training program and which kept a record of all exercises. In addition, the participants in this group have been given the general public

health advice on aerobic exercise. (Rauramaa et al. 2004, Haskell et al. 2007, Nelson et al. 2007.)

Participants in the ***Diet group*** have been given personal dietary counselling on a low fat, high fibre diet enriched with omega-3 fatty acids (max 30 E% from fat), and the general public health advice on aerobic exercise. The participant in the ***Combined Diet and Exercise groups*** have followed aerobic (EEE 1000–1500 kcal/week) or resistance exercise (2 exercise sessions per week), respectively, and been given personal dietary counselling.

The data of the Informed Consent Study were collected between August 2005 and June 2007 using a semi-structured questionnaire (Appendix 3). During the three-month intervention visit of DR's EXTRA Study at Kuopio Research Institute of Exercise Medicine, the questionnaire was given to all able and willing participants (n=1324) who were still involved in the study. The participants received oral information and an information letter (Appendix 2) with a return envelope during this intervention visit. The participants were given two weeks time to return the questionnaire. Persons who did not answer the first time were not reminded. The response rate was 91 % (n=1200). Five questionnaires were rejected due to insufficient answers, and thus the total number of accepted questionnaires was 1195. Formation of study population for Informed Consent Study is presented in figure 3.

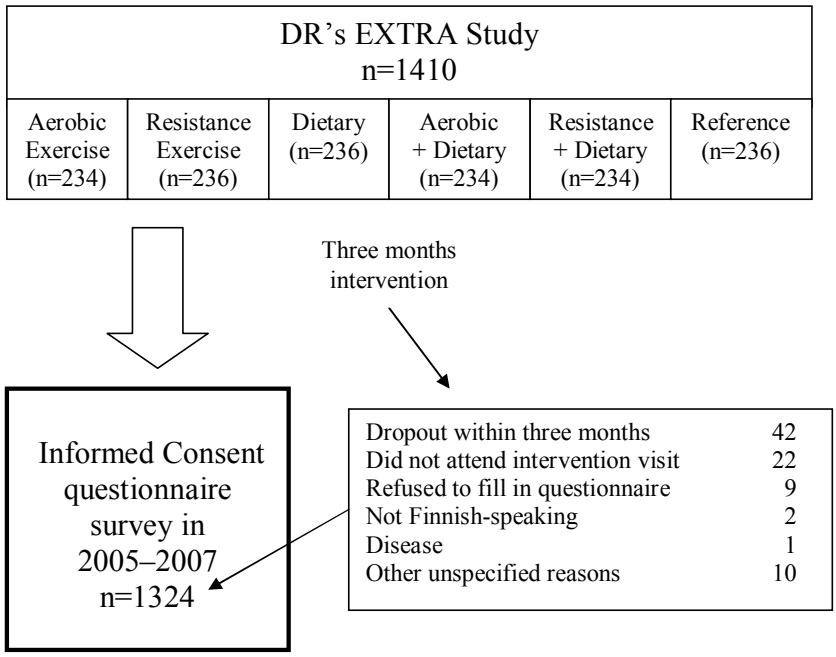

Figure 3 Formation of study population in Informed Consent Study

The data on success in DR's EXTRA Study after 12 months intervention were measured by the intervention-group personnel. The participants (n=597) included here are a subpopulation of the whole randomized sample. This subgroup consists of three intervention groups: Aerobic Exercise, Resistance Exercise and Diet. In addition, participants' long-term continuation in the DR's EXTRA STUDY was evaluated two years after the randomization.

4.2 Questionnaire

This study used a new questionnaire for assessing informed consent in health research. The development of the questionnaire was based on international declarations and guidelines of research ethics (e.g. Declaration of Helsinki, ICH–GCP Guidelines for Clinical Trials), on national legislation, codes and guidelines of ethics (e.g. Medical Research Act, Finnish Medical Associations code of medical ethics, Guidelines of ETENE and TUKIJA), on relevant literature (e.g. Beauchamp & Childress 2001, Leino-Kilpi et al. 2002) and on a pilot study (Original publication I). In the Pilot Study the questionnaire was used and designated as interview schedule. The development process of the questionnaire is depicted in figure 4.

The Pilot Study resulted in only minor adaptations to the questionnaire: Two questions were deleted and two were added. The deleted questions dealt with the starting point and ending of the exercise and diet intervention study. The added questions dealt with confirmation of received information and confirmation of understanding the information. A few questions were relocated to improve the inner coherence of the questionnaire. The Likert-scale was simplified from 7-point to 5-point (e.g. Burns & Grove 2001). Taking into account the method of data collection (a questionnaire survey study) the verbal presentation of all questions was carefully considered and clarified. The improved questionnaire was tested preliminarily (June 2005) by five persons who had been participants in a life-style intervention study organized by Kuopio University Hospital (*Lifestyle intervention in patients with obstructive sleep apnoea*).

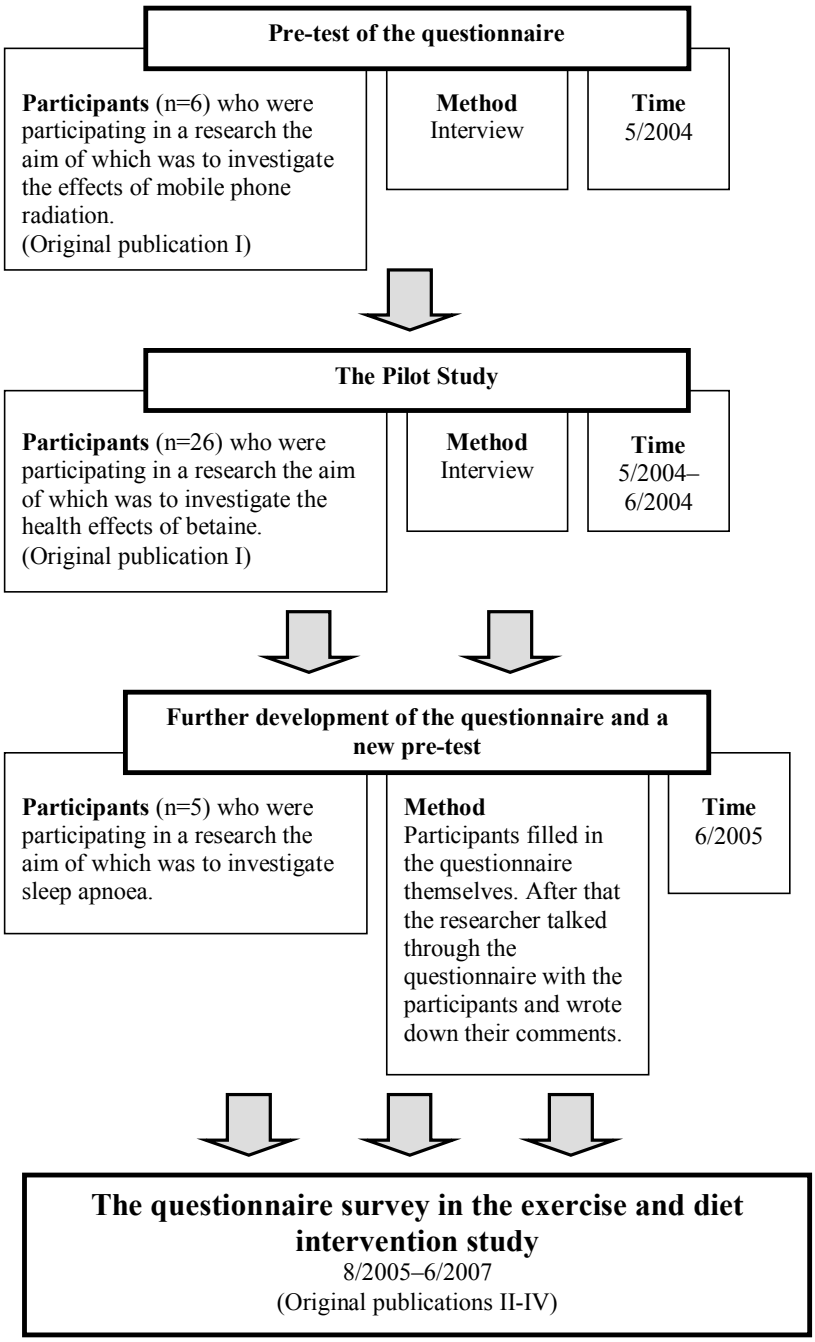

Figure 4 Development of the questionnaire

The questionnaire included 44 questions: 1) background information (14 questions), 2) information, understanding and competence (16 questions), 3) voluntariness and decision-making (14 questions). The questionnaire contained multiple-choice questions, yes/no questions, short specifying open questions and a scale of 1–5 (Likert-scale). On this scale, 5 was the most positive choice (example: completely enough, I understood completely, significant possibility to exert influence) and number 1 was the most negative (example: I received no information, I did not understand at all, no possibility to influence). The structure and content of the questionnaire are described in Original publication II (see Table 1) and the whole questionnaire is shown in Appendix 3.

4.3 Data analysis

In the Pilot Study, the statistical analyses were performed using SPSS for Windows (SPSS Inc., Chicago, version 11.5). The following steps were taken in the data analysis phase: First, the 7-point Likert scale answers were turned into three categories: poor (1–2), moderate (3–5), good (6–7). The explanation for this classification is that this modification makes the data analyses more reliable when the amount of participants is small. Second, frequencies and percentages were calculated on categorical and numerical discrete data.

In the Informed Consent Study, all statistical analyses were performed using SPSS for Windows (SPSS Inc., Chicago, version 14.0, 2005). The main aim of the statistical analysis was to use the information gained from a sample of individuals to make inferences about the relevant population (Altman 1999).

At individualized research question number one (*How the basic elements of informed consent are being realized in exercise and diet intervention study?*) the statistical methods were descriptive. The following steps were taken in the data analysis phase: First, the answers to the 5-point Likert scale were turned into three categories: poor (1–2), moderate (3) and good (4–5). The explanation for this modification is that this classification is used in Phase 1, individualized research question one. In addition, clear

minority of the participants had chosen answer alternatives two or four. Second, to describe the data, frequencies and percentages were calculated. Third, differences between categorical variables (sex, age, education) were tested using cross-tabulations and chi-square tests. A p-value less than 0.05 was considered to be statistically significant. This means that if the p-value was small, the null hypothesis was rejected as implausible. When p-value was >0.05 it was taken to indicate that insufficient information was available to discount the null hypothesis. (Campbell & Machin 1993.)

With respect to individualized research question number two (*What factors are associated to participant's comprehension of information received in the exercise and diet intervention study?*) the understanding of the received information was measured by the respondents' answers to three questions: 1) What is your opinion of the intelligibility of information given in the exercise and diet intervention study? 2) What is the purpose of the exercise and diet intervention study? 3) What is your opinion of the sufficiency of the confirmation by research personnel that you have understood the information given in the exercise and diet intervention study?

The following steps were taken in the data analysis phase: First, the answers to the 5-point Likert scale were turned into two categories: poor to moderate (1–3) and good (4–5). The explanation for this classification is that also those participants who chose the moderate choice were not unambiguously satisfied with the information given. Second, frequencies and percentages were calculated to describe the data. Third, in order to examine the associations of the response variables and potential predictors, univariate analyses were performed. Fourthly, backward-directed stepwise multiple logistic regression models were used to identify correlates of variables concerning participants' understanding of the information received. P-values less than 0.05 were considered statistically significant. In addition, the participants' long-term continuation in the intervention trial with relation to the above-mentioned three questions was evaluated two years after the randomization. The lists of variables used in research question two and their classifications are presented in detail in Original publication III (see Table 1).

The multiple regressions examined the simultaneous relationship between one dependent variable and a number of independent variables (Campbell & Machin 1993). In general, a regression model is a statistical model for describing the relationship between one or more explanatory variables and the response (dependent) variable. The purpose of statistical modelling is to fit the best model from a medical or epidemiological point of view that describes this relationship. A simple linear regression model describes how much a continuous quantitative response variable depends on the explanatory variable. In the multiple regression model, a linear combination of several explanatory variables is included. (Everitt & Palmer 2005.)

Finally, with respect to individualized research question three (*Is informed consent related to success in exercise and diet intervention as evaluated at 12 months?*) the success of intervention was measured through evaluation by the intervention-group personnel via the following two questions: 1) How intervention has been implemented in the exercise and diet intervention study after 12 month intervention? 2) Have the participants been successful in the exercise and diet intervention study after 12 month intervention as measured by changes in their activities concerning exercise or diet?

Three intervention groups were taken into account in this data analysis (Aerobic Exercise, Resistance Exercise, and Diet) and with the three other groups omitted. The reason for this decision was that in Reference group the participants did not receive any intervention and in combined groups (Aerobic Exercise and Diet, Resistance Exercise and Diet) two intervention-group personnel evaluated separately the participant's success with respect to the different aspects of the intervention. In addition, the data analysis was restricted to those participants who responded to the Informed Consent questionnaire.

The following steps were taken in the data analysis phase: First, the answers to the 5-point Likert scale were turned into two categories: poor to moderate (1–3) and good (4–5). Second, frequencies and percentages were calculated to describe the data. Third, univariate analyses were calculated between every examined variable. The multivariate analyses utilized those variables which had a p-value ≤ 0.1 in the univariate analyses.

Fourthly, stepwise multivariate analyses (Ordinal Regression) were used to identify correlates of variables concerning realization and success. Multivariate ordinal regression model were used to identify significant predictors of outcome these being set at $p<0.05$. The list of variables used and their classifications are presented in detail in Original publication IV (see Table 1).

The questionnaire included also short supplementary open questions. The idea was that these answers would provide a more in-depth understanding of the quantitative data (cf. Malterud 2001). The content analysis was used to collate, synthesize and refine this qualitative data. The words in the open questions were classified into a few categories chosen according to their theoretical importance. This technique provides a systematic means of measuring the frequency, order or intensity of occurrence of words, phrases or sentences (Burns & Grove 2001).

4.4 Ethical considerations

All of these studies (the Betaine Study, the Pilot Study, the DR's EXTRA Study and the Informed Consent Study) were approved by the Research Ethics Committee of the Hospital District of Northern Savo (permit numbers: 98/2003, 66/2004, 105/2002, 99/2005). This thesis was performed by adhering to good scientific practice. The main principle in research involving humans is primacy of the research participant. This means that participant's benefit and welfare should be placed ahead of any benefit to society or science. All participants had to be voluntary and they had to give their informed consent to research in question. (Declaration of Helsinki 2008.) Therefore, written informed consent was obtained. Participants were given a copy of the consent form and they were told that they could withdraw at any phase. In the Betaine and Pilot Study the informed consent was asked separately. The DR's EXTRA Study and Informed Consent Study used a common informed consent form.

Before obtaining the written consent, the research participants were given written and verbal information and also time to consider. Those who did not display any interest

were not reminded or persuaded. The research participants did not obtain any compensation for their participation. The data were coded and treated confidentially (Henkilötietolaki 1999, Personal Data Act 1999, European Commission 2007). This coding system means that personal details can still be identified by specific requests and safeguards (European Commission 2007).

5 RESULTS

5.1 Evaluation of the questionnaire

The results of the Pilot Study are presented in detail in Original publication I. In this context, only the result of the development of the questionnaire is shortly described. According to the results of the Pilot Study, the initial questionnaire appeared to be suitable in its present form. The assessment by the respondents was that the questionnaire used was mainly clear and in an intelligible form. The strength of the questionnaire was that there were not too many number of questions (44 questions), harmony of classifications used and similarity of statements.

There were, however, two questions in which the respondents required verbal help almost every time. Both questions were concerned to more common opinions, whereas other questions were related to experiences gained in the Betaine Study. Special attention was paid to these two questions when further developing the questionnaire and devising written instructions on how it was to be filled in. Although the data collection method in the Pilot Study was interview, this phase 1 confirmed that it is possible to investigate informed consent by means of a questionnaire.

5.2 Results of the Informed Consent Study

The results of the Informed Consent Study are presented in a similar manner as in the original publications. The results are reported by individualized research questions. The total number of accepted questionnaires in the Informed Consent Study was 1195. The respondents (586 male and 609 female) ranged in age from 57 to 78 years (66 ± 5 years). Background information is presented in detail in Original publication II (see Table 2).

5.2.1 Realization of the key elements of informed consent

Information Most respondents (86 %) reported that they had so far received complete enough or sufficient information about the exercise and diet intervention study (DR's EXTRA). There were no statistically significant associations between sex, age or education and opinions about the amount of information given. However, some participants (3 %) reported that they had not received information at all or that the information about the study was completely insufficient. In addition, the majority of the respondents (66 %) considered that the research personnel had confirmed satisfactorily that the participant had received sufficient information. About one in five of the respondents (19 %) felt that this matter had been taken into account moderately well. However, 15 % reported that confirmation of the received information was completely insufficient or insufficient.

In addition, there was interest in elucidating what the participants felt was sufficient information. Therefore specific questions were asked concerning the information. Most respondents (74 %) knew the people responsible for the research and nearly all (98 %) who had wished had been able to contact the researcher when necessary. Nearly half of respondents (46%) reported that they had been sufficiently informed about why they had been chosen as subjects in the study. On the other hand, 34 % of the respondents reported that they did not know this reason. About half of all respondents (54 %) considered that they had been sufficiently informed of the possible negative effects of the study. However, 31 % of the respondents felt that they had received no information or completely insufficient information about the possible negative effects. Almost all respondents (95 %) were aware of their right to withdraw from the study at any point though only 6 % had actually considered withdrawing. The reasons why participants had considered withdrawing from the DR's EXTRA are presented in detail in figure 5.

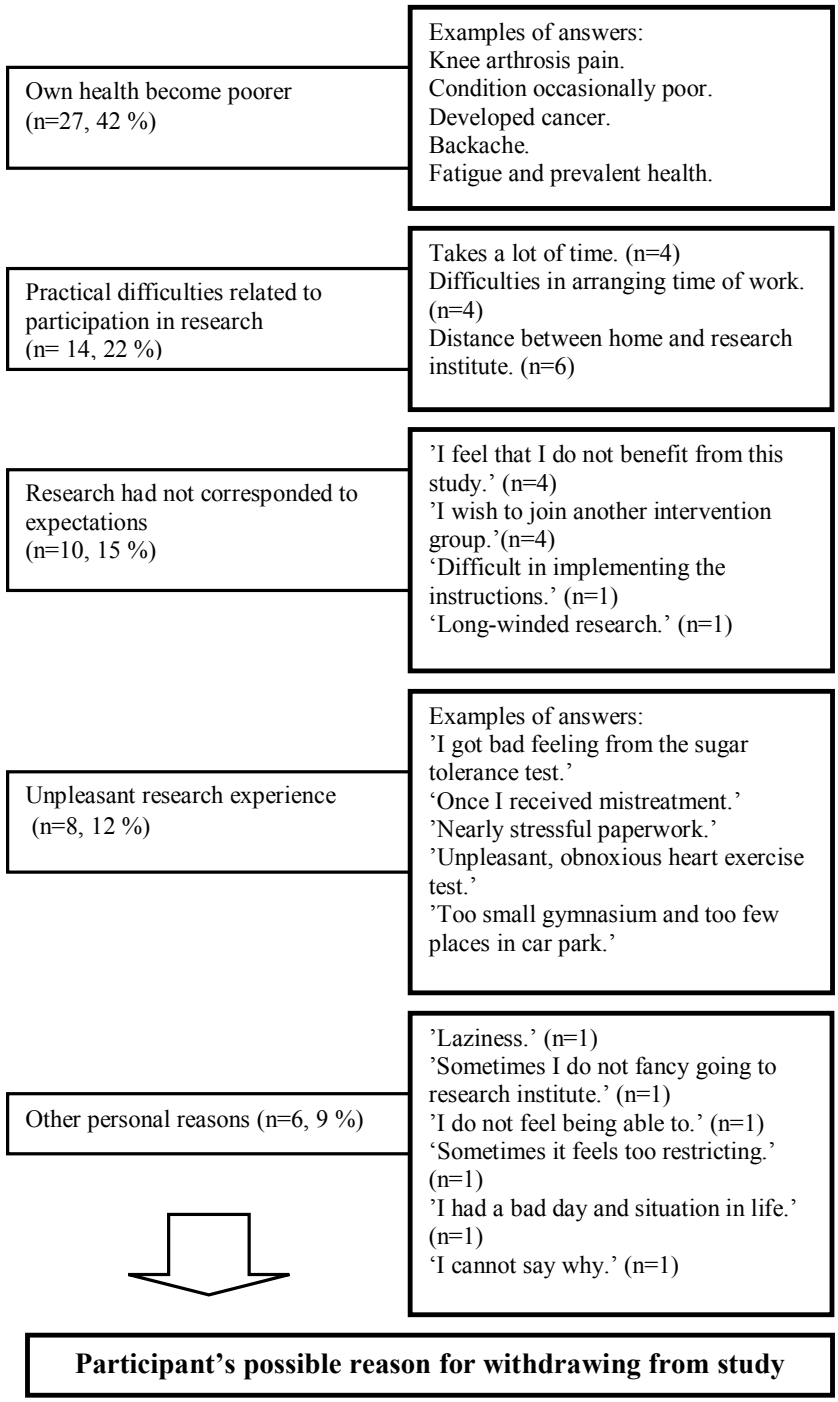

Figure 5 Reason why participants had considered withdrawing

Nearly half of the respondents (49 %) did not know how the DR's EXTRA Study had been funded and whether it was sponsored. On the other hand, 35 % of the respondents believed they knew these facts. Most of respondents (68 %) were unaware of the intention of reporting or publishing the results. Only 12 % of the respondents believed that they knew the financial connections of the researchers to the DR's EXTRA Study. Most of respondents (75 %) did not know this. Almost all of the respondents (96 %) knew that they would not receive any financial compensation for participating. A few (3 %) answered that they did not know whether they would receive any financial compensation and very few (<1 %) reported that they would obtain some compensation.

In addition, some respondents (1 %) had written comments related to this issue. For example, some stated that they wished to have compensation for travel expenses (n=4) or recompense for their trouble (n=2). On the other hand, some wrote that they receive recompense them for their trouble, e.g. free examinations with a medical certificate, use of a gymnasium and guidance (n=5), improvement in their own condition and health (n=3) and possibility to participate during work hours (n=1).

At the end of this section, the respondents were asked whether they needed more information. Most of them (81 %) reported that they had received enough information. There was no statistically significant association between sex or age and the need to obtain more information. However, there was a statistically significant association between education and the requirement for additional information ($p<0.001$), so that the higher the education of the respondent, the more information he/she required.

Understanding and Competence Almost all respondents (89 %) reported they had received information in an intelligible form. Again, there were no statistically significant associations between sex, age or education and opinions about intelligibility of the information given. The majority of the respondents (66 %) considered that the research personnel had confirmed satisfactorily that the participant had understood the information received. A fifth of the respondents (19 %) reported that this matter had been taken into account moderately well. Again, it is noteworthy that 14 % of the

subjects reported that confirmation of understanding the information given was either completely insufficient or insufficient.

The respondents' ability to understand was also evaluated in an open question concerning the purpose of the DR's EXTRA Study. These replies confirmed the impression that the information had been understood appropriately by a majority of the study population. Most of the respondents (82 %) answered correctly. Only 5 % of the replies indicated that the respondent had not understood the purpose, and 2 % answered that they did not know or remember the purpose of the study. In addition, 11 % of the questionnaires lacked an answer to this question.

Voluntariness Almost all respondents (99 %) reported that they had participated in the DR's EXTRA Study of their own free will and without coercion. Three respondents felt that they had been coerced into participating. Only one of these told why he/she felt that way. In his/her answer this respondent said that the adviser of the intervention group had made him/her continue.

Half of the respondents (50 %) reported, however, that it was their responsibility to participate. For example, these were: obligation to one's own health (29 %), helping other people now and in the future (29 %), willingness to assist in research (18 %), positive attitude toward participating in projects like this (6 %), promising means commitment to the project (5 %), important aim of the project (4 %), belonging to the group selected for this project (3 %) and also some individual feelings of responsibility. The associations between responsibility to participate and sex ($p<0.001$), age ($p<0.001$) and education ($p=0.001$) were statistically significant, so that men, older people and the less educated felt more responsibility to participate.

Decision-making Willingness to participate in research projects was greatly influenced by desire to help other people (69 %), chance to obtain help for one's own disease (75 %) and an opportunity to participate in treatment and/or examinations (82 %). On the other hand, the factors that did not or only slightly influenced willingness to participate were: willingness to please research personnel (10 %), fear of annoying the hospital

personnel (3 %), and whether family or friends or many of their colleagues at work have participated in the same research projects (6 %). According to the respondents, the illness of a loved one led to divided opinions in relationship to the factors influencing participation (great influence 42 %, no influence 39 %).

Furthermore, the participants were asked what different people could have influenced their decision to participate in research projects. According to a majority of the respondents, only the researcher (doctor) (77 %), research nurse (67 %) and research personnel (55 %) were the people who are able to influence their decision-making concerning participation. These results are reported in detail in Original publication II (see Table 4).

Almost all respondents (99 %) reported that the period of consideration before the decision to participate in the DR's EXTRA Study was sufficient. Most respondents (64 %) had decided to participate immediately, and the second most common period of time for consideration was from one day to a week (19 %). The other respondents had thought about participation for either less than a day (10 %) or more than a week (5 %). There were also respondents who did not remember how long they thought about participation (2 %). It is noteworthy that 13 % of the respondents did not answer this question or answered so that it could not be classified. Most of the respondents (74 %) had not discussed the research project with people other than the researcher before giving their consent. It was, however, common that conversations took place between respondents and their spouses (64 %). Other individuals who may have been consulted were children, relatives, friends, acquaintances in the same project participating, other doctor or nurse, workmate or employer.

Most of the respondents (69 %) remembered having given written consent before the examinations began. Nearly a fifth of the respondents (17 %) remembered that they had given written consent after they had started the project. Seven percent remembered having given consent orally, and five percent believed that they had started without providing any specific consent. Two percent did not remember or had no concept of how their consent had been confirmed.

5.2.2 Factors associated with participant's comprehension of information received

Multivariable analyses were conducted on this second research questions. The Original publication III presents the results of the logistic regression models in detail: estimates of the Odds Ratios (OR), their 95 % confidence intervals and the p-values of the most predictive variables selected by the stepwise procedure (see Tables 3–5).

There were statistically significant associations between opinions about the intelligibility of the information given and 1) education ($p=0.01$), 2) adequacy of time for the first visit in the DR's EXTRA Study ($p=0.01$), 3) adequacy of received information at the DR's EXTRA Study ($p<0.001$), and 4) sufficient confirmation by the research personnel of the participant's understanding of the information given at the intervention ($p<0.001$). Participants who were highly educated were most satisfied with the intelligibility of the given information. Participants who were most content with the time used for the first visit, or with the received information, or with the confirmation by the research personnel that the participant had understood the information given at the DR's EXTRA Study were also most satisfied with the intelligibility of the information provided. These results are presented in detail in Original publication III (see Table 3).

In addition, there were statistically significant associations between knowledge of the purpose of the DR's EXTRA Study and 1) education ($p<0.001$), 2) health ($p=0.01$), 3) satisfaction about intelligibility of the information given ($p=0.03$), and 4) adequacy of confirmation by the research personnel of the participants' understanding of the information given at the DR's EXTRA study ($p=0.03$). Better educated participants and those who felt themselves to be healthier were most aware of the purpose of the study. In addition, participants who were most content with the intelligibility of the information given, or with the research personnel confirmation of participant understanding the information given at the DR's EXTRA were also most aware of the purpose of the study. These results are presented in detail also in Original publication III (see Table 4).

Furthermore, there were statistically significant associations between opinions about the adequacy of the confirmation by the research personnel that the participant had understood the information given and 1) adequacy of received information during the intervention study in question ($p<0.001$), and 2) adequacy of the confirmation by the research personnel that the participant had received enough information during the DR's EXTRA Study ($p<0.001$). Participants who were most content with the received information or with the confirmation by the research personnel that he/she had received sufficient information at the DR's EXTRA Study were also most satisfied with that the research personnel had confirmed that they had understood the information given. Again, these results are presented in detail in Original publication III (see Table 5).

There were no statistically significant associations between participants' long-term continuation and their understanding of the trial. In addition, no significant associations were found between long-term continuation and sex, age or education. However, there was a statistical association ($p < 0.001$) between opinion of one's own health and continued participation in the intervention evaluated after two years. Participant who felt themselves to be healthier were more likely to continue involvement in the DR's EXTRA Study.

5.2.3 Participants success in exercise and diet interventions after 12 months

In this last stage three intervention groups were analysed (Aerobic Exercise, Resistance Exercise, and Diet). This subpopulation consisted of 597 participants. The Original publication IV presents the results of the ordinal regression model in detail: p-values from all steps, and p-values, estimates, and standard errors of the most predictive variables selected by the stepwise procedure of the ordinal regression model (see Tables 2–3).

The age of this subpopulation (293 male and 304 female) ranged from 57 to 78 years (mean 67 years, SD 5 years). The majority of the participants (75 %) were married or in cohabitation without marriage. Participant's education level was categorized as follows:

37 % of participants had vocational school or course background, 26 % had college-level training, 22 % of participant's had no professional training, and 16 % had academic degree education. The clear majority of the participants (87 %) were retired and the rest (13 %) were working either full-time or part-time. A minority of the participant's (37 %) had earlier participated in some research project. Above half of participant's (56 %) had the opinion that their health was moderate and 37 % felt that their health was good. Only 4 % reported that their health was remarkably good, 3 % poor and less than 1 % felt that their health was remarkably poor.

Approximately half of participants (54 %) had attained a good result in aerobic exercise, resistance exercise, or diet interventions. About third of participants (35 %) had achieved a moderate result and a minority of participants (12 %) had a poor result. There were statistically significant associations only between realization of interventions and participants knowledge of the purpose of the DR's EXTRA Study ($p<0.001$). Participants who were most aware or had understood the purpose of the study had also attained better results at their intervention evaluated after 12 month. The results are presented in detail in Original publication IV (see Table 2).

Nearly half of participants (47 %) had added or improved some personal activity in some sector of exercise or diet. Almost fifth of participants (18 %) had added or improved some personal activity in many sectors of exercise or diet. One third of the participants (33 %) experienced no changes in their activities concerning either exercise or diet and only a few participants (1 %) reduced or worsened their activities. There were statistically significant associations between success in interventions and 1) working status ($p=0.02$), and 2) participants' knowledge of the purpose of the DR's EXTRA Study ($p=0.04$). Participants who were still in working life or who were most aware or had understood the purpose of the study had also succeeded better in the intervention when this was evaluated after 12 months. These results are also presented in detail in Original publication IV (see Table 3).

5.3 Summary of the main findings

To summarize the main findings, according to a majority of the participants, the key elements of informed consent (information, understanding, competence, voluntariness, and decision-making) were well realized in the exercise and diet intervention study in question. This means that the majority of the participants believed that information given was adequate and had been presented in an intelligible form. The competence of the participants was judged to be sufficient. The participants considered that their decision-making had been voluntary, and the majority felt that confirmation and verification of informed consent were also carried out well. These results are in agreement with the results of the Pilot Study. In addition, compared to background variables, higher education and satisfaction with one's own health were statistically significantly associated with adequate comprehension of the provided information.

About half of the participants had achieved good results in the intervention after one year. Nearly half of the participants had added to or improved their own activity in some sector of exercise or diet. Significant associations were found between performance and success in the interventions and participants' knowledge of the purpose of the study, and between success in interventions and working status. Furthermore, participants who felt themselves to be healthy were more likely still to be participating in the intervention after two years.

6 DISCUSSION

The goal of this thesis was to analyze how well informed consent could be achieved in population-based health research from the point of view of voluntary adult research participants. This chapter discusses the key elements of informed consent and ways of enhancing the informed consent process by comparing the results of this thesis with earlier studies. In addition, this chapter evaluates the validity, reliability and study limitations of this thesis.

6.1 Discussion of the key elements

6.1.1 Information

The majority of the participants estimated that information given on the exercise and diet intervention study was sufficient and had been presented in an intelligible form. The participants had received both written and verbal information. Written information was mailed to potential participants at the very beginning; and when the participant started the baseline study, written information was given again to ensure that it had been received. In addition, the participants received personal counselling after they had been randomized into the intervention groups. All participants received the same information until they started in their intervention groups.

The quality of the informed consent or assent process is directly related to the quality of the information provided (Koren et al. 2003, cf. Kaptchuk et al. 2006). The general population appears to have only a limited knowledge of clinical trials. Therefore it is necessary to provide potential research participants with adequate information. (Campbell et al. 2008.) In addition, numerous anthropological studies have pointed out that participants are rarely able to recall what they have agreed after signing an informed consent form (European Commission 2007).

There are still many unanswered questions about the ideal informed consent process, the best way to appropriately inform potential research subjects of risks and benefits in a way that will improve their understanding and retention of information presented (Marco 2008). Thus, the critical part of the process is how to inform (how we deal with 'informed consent'). For instance, despite efforts to improve informed consent, clinical trial accrual continues to be poor, and this may be related to the lack of sufficient informational support for patients. (Hack et al. 2007.) Therefore, providing information e.g. both orally and writing and providing sufficient time for consideration was stated to improve the informed consent also in a group of severely ill elderly patients (Lynöe, Näsström & Sandlund 2004).

The literature describes many different strategies which may enhance participant's receipt of information. For example, one study examined the benefit of providing a clinical trials information handbook on patient knowledge, perceptions, and likelihood of participation, and indicated that those participants who read the clinical information handbook scored 80 % higher on an assessment of knowledge about clinical trials than the participants who did not read the handbook. That study also demonstrated that it is important to consider re-educating the research participant about clinical trials if more than two months have passed between reading the handbook and providing consent for a trial. Therefore, it was postulated that the use of an educational handbook to supplement informed consent about a specific trial may provide truly informed consent. (Campbell et al. 2008.)

In another study, patient information leaflets were found to be a useful tool also for the surgeon to improve the recall of the information given to the patient, in order to facilitate informed consent (Ashraff et al. 2006). The preparation of a genetic consultations booklet for cancer patients led to an increase in satisfaction with the information provided, and to a decrease in the level of decisional conflict due to lack of information. Even the increase of knowledge was marginal, the provision of the booklet was found to encourage the patients to undergo the tests. (Mancini et al. 2006.)

However, in everyday practice, evidence-based leaflets were not effective in promoting informed choice in women using maternity services (O'Cathain et al. 2002). The same conclusion was made in a literature review of the effectiveness of leaflets in promoting informed choice in screening programmes. Therefore, it has been stated that screening programmes should not rely on routine provision of information to ensure that prospective users can make informed choices about participation. Even in cases where such information has been specifically designed to promote informed choice, there is little evidence that it actually achieves its goal. Therefore, the most effective way to achieve informed choice in screening programmes is still unclear. (Fox 2006.)

The European Commission (2007) proposed the following strategies: participation of a linguist for preparing the informed consent, interviews conducted among the participants to ensure that they understand the issues at stake in the research project, and presentation of the research project using information technologies (video, Powerpoint, theatre play, etc.). Several research groups have examined the use of information technology, for instance, an educational videotape can represent a useful tool for informing the general public about the nature of cohort studies and these kinds of videotapes may increase probable participation (Ishii & Ohashi 2007).

In addition, the use of computer-based visualization increased the satisfaction and knowledge of patients and its presentation did not require significantly more time than the standard paper-based conversation (Enzenhofer et al. 2004). The knowledge of prenatal testing can also be increased by using a video, at least in principle. Moreover, this can be done without making women more anxious, or more worried about fetal abnormalities. (Hewison et al. 2001.) In one other study, the use of audiovisual patient information was a useful addition to the consent process for randomized cancer trials in terms of improving patient knowledge and understanding before decision making. It appeared to reduce anxiety at this time point and was found to be an acceptable medium for patients. The use of audiovisual patient information was not shown to have any effect on refusal rates to randomized cancer trials. (Hutchison et al. 2007.)

However, the evidence of a review was that the value of audio-visual interventions for people considering participation in clinical trials was mixed with respect an individual's awareness of the trial they are considering entering, and/or the health condition the trial is designed to address; one study showed improved retention of knowledge amongst intervention recipients. The intervention may also have small positive effects on the quality of information disclosed, and may increase willingness to participate in the short-term; however again the evidence is weak. There were no data about several primary outcomes, including harm. In the absence of clear results, it has been recommended that researchers should continue to explore innovative methods of providing information to potential trial participants. (Ryan et al. 2008.)

One further strategy to improve the provision of information is to use different types of consent forms. In one study, the research group compared a standard, industry-designed consent form and a modified, shortened version of the same form to determine which would allow the patient with a history of asthma to retain more information in the immediate post consent period. They concluded that patients retained more information from the shortened version. (Dresden & Levitt 2001.) Another research group concluded also that shorter information sheet with a test and feedback session should be evaluated so that informed consent would become valid informed consent (Fortun et al. 2008).

A recent literature search did not identify any previous publications addressing the direct impact of the type of consent required, and potential research subjects' participation. The length and type of informed consent required affected potential research subject participation in a survey research design. Participants who were asked to sign a detailed written informed consent document had a lower rate of participation compared to those asked either orally or with a brief written consent form. (Marco 2008.)

If one wishes to ensure that clinical research subjects are participating as well-informed and willing partners it is crucial to have a better understanding of how literacy might impact on comprehension of the information provided and how to best to address this

issue (Raich, Plomer & Coyne 2001). For example, patients welcome evidence-based information and are able to utilize it to make an informed choice e.g. about prostate-specific-antigen screening. Concerns that evidence-based information may induce anxiety or 'fear' about prostate cancer or would be perceived as biased against screening appeared to be unwarranted. (Gattellari & Ward 2005, cf. Chan et al. 2003.) When elderly patients were provided with a balanced discussion of the benefits, burdens, and uncertainties of colorectal cancer screening this information did influence their perception of screening effectiveness, but had no impact on their preference for undergoing screening. This negative result does not diminish the importance of involving elderly patients in decisions, but does suggest that factors other than information must be more important in determining their interest in participating in screening programmes. (Wolf & Schorling 2000.)

Although the majority of our participants felt that the information received was sufficient, there were issues about which many of them felt they had insufficient information. These were: selection criteria of the participants, possible benefits, and negative effects, funding and reporting. It is noteworthy that these facts were provided in the written information. In addition, the respondents wrote in open questions that they needed more information about general matters related to this particular intervention study and whether they would have access to their own results. An earlier study found also that many participants were interested in receiving individual results rather than a summary of the entire trial (Dixon-Woods et al. 2006, cf. MacNeil & Fernandez 2006).

According to the European Commission's detailed guidance for ethics committees, written information should be provided to subjects concerning any financial or other ties to a sponsor, institutional affiliations of the investigators, and the name and address of sponsors or sources of funding (European Commission 2004). Although disclosure of investigators' financial interests in research does not substantially affect willingness to participate, potential research participants do attach some importance to this information, for example, they are more troubled by equity interests than by per capita payments intended to cover the costs of research. (Weinfurt et al. 2008b.) The results of this thesis showed that about half of the respondents considered that receiving

information on funding is important, almost third considered this information to be of moderate importance, and nearly one third answered that this matter was not at all important to the research participant.

In general, according to our findings, a higher educational level is related to a need for more information. Nonetheless, we may ask the question of whether highly educated persons are really those who need more information or whether they are used to receiving extensive information on topics affecting them personally. A particular challenge in the informed consent process for clinical trials is to assess the beliefs of those patients or participants, who have already made their decision about whether or not to take part in the trial, before receiving any information or discussion about it. They are often unwilling to even consider the information, an issue that is difficult to assess in any research study. (Hutchison, Cowan & Paul 2007.)

In summary, perhaps nothing is changing more dramatically in health care than the increased volume and influence of information. Patients and potential participants face a growing need for assistance in knowledge management and for access to professionals who are qualified this task. (Woolf et al. 2005.) It has been claimed that more research is needed on what participants in clinical investigations want and need to know, and how to convey this information in a format and in an environment that is conducive to individualized decision-making (Raich, Plomer & Coyne 2001).

6.1.2 Understanding

The findings of this thesis support the proposal that the participants had understood most of the information given in the exercise and diet intervention study. Nonetheless, it is difficult to assess how well the participants have comprehended the information (e.g. Sreenivasan 2003). For example, a signature on an informed consent document does not guarantee that the individual has understood or appreciated what it means to be a research subject in a clinical trial (Schwartz & Appelbaum 2008). Virtually every bioethics text includes material on informed consent in general and more specifically on

the ethics of human experimentation. However, both empirical reseach and bioethics analyses tend to focus on the philosophical principles of autonomy and doing no harm, rather than on the difficult practical problems of how to ensure comprehension and how to assess voluntariness (Higgins & Daly 2002).

Information sheets for clinical research are becoming increasingly complex but the extent to which they are understood is uncertain (Fortun et al. 2008). It has been stated that for many patients or participants, issues of health care literacy, the language used in the process, and the peoples' ability to comprehend what is being presented, can lead to a misperception of the true nature of research trials. (Naarden & Cissik 2006). Therefore, there appears to be a clear need for empirical testing of methods and instruments capable of increasing the participant's intake and uptake of relevant information (Rabin & Tabak 2006).

The literature describes different ways to improve understanding. These efforts are somewhat similar to those intended to improve the dissemination of information. For example, in order to enable comprehension and facilitate informed choices, the written information about the research should be easy for the potential participants to read (Coyne et al. 2003, Paasche-Orlow, Taylor & Brancati 2003, Franck & Winter 2004). It has been shown that readability cannot be improved by adding lengthy explanations to a consent form because this may undermine participants' understanding of the research in which they are being asked to take part (Shalowitz & Wendler 2006). In addition, the European Commission (2007) recommends interviews conducted with the participants to ensure that they have understood the issues at stake in the research project.

Techniques for improving subjects' understanding of the research include giving a copy of the informed consent form to the subject, viewing a videotape of the research procedure, and calling subjects after they have signed the consent so that they can ask questions or express concerns (Turner 2005). Using of a modified consent approach (improving the readability and design of the consent form, reading the consent form to participants in their native language, and using an iterative, teach-to-goal strategy), has also been considered to improve the quality of informed consent also in lower literacy

and minority status populations. One study showed that complete comprehension of consent information could be achieved for 98 % of participants who engaged in this improved consent process, including those with literacy and language barriers. (Sudore et al. 2006.)

The readability and comprehensibility of a standard information leaflet can be also improved by professional linguistic revision of the leaflet (Bjørn, Rossel & Holm 1999). One ideal solution is to couple information with high-quality decision counselling to help patients or participants understand the potential risks, benefits, and uncertainties of clinical options etc. (Woolf et al. 2005). Given adequate support, research participants can be helped to understand sufficiently well in order to enable them to give valid consent. This support has been shown to improve understanding also in rare disease research. (Parker et al. 2004.)

Many researchers agree that the use of informational videos may enhance the informed consent process for clinical research (e.g. McLaughlin, Brindley & Crowther 2002, Koren et al. 2003). However, a systematic review proved that above mentioned procedures do not consistently improve research participants' understanding. Instead, face-to-face interactions, especially extended discussion interventions, may improve understanding more effectively. But even if an informational video does not improve understanding, at least all research participants in a study are exposed to the required information. (Flory & Emanuel 2004.)

Another review came to the same conclusion that no method proved to be perfect in terms of improving comprehension (Paris et al. 2007). For instance, two recent strategies for improving the comprehension of research consent disclosures (graphically enhanced consent form and meditation of the consent process by a third-party facilitator) may not be effective. However, the understanding of consent disclosures may be improved, at least in the short term, by providing iterative feedback to those potential research participants who appear to be experiencing some initial difficulties with comprehension. (Stiles et al. 2001.) In addition, extended discussion interventions

seemed to be more effective than, for example, enhanced consent forms or multimedia (Paris et al. 2007).

Even though the focus in this thesis is on volunteer adult research participants, the viewpoint of patients cannot be overlooked. It has been reported that the actual understanding of the clinical trial information by patients is rarely optimal (Hietanen et al. 2007, cf. Denberg, Wong & Beattie 2005). In addition, there are currently no formal practice guidelines from professional societies for the assessment of a patient's capacity to consent to treatment (Appelbaum 2007). Little is known also about patient characteristics associated with comprehension at consent information, and whether modifications to the consent process could promote understanding (Sudore et al. 2006).

Physicians have a duty to offer to their patients, of all ages, the opportunity to take part in clinical trials and to ensure that research is appropriately designed and conducted. However, special consideration should be given to ensure that patient consent is fully informed and freely given. (Bayer & Fish 2003.) For example, participants in early-phase clinical trials have reported high expectations of benefiting from their participation. There is concern that many participants may misunderstand the trials to which they have consented. Patients who express high expectations may not do so as evidence of understanding but rather as a way of registering optimism. (Weinfurt et al. 2008a.) Therefore, the issues surrounding informed consent include readability of the consent, educational level of participants, relationships with health care providers, therapeutic misconceptions, and the severity of the illness (Steinke 2004).

Fortunately, there have been studies focusing on ways to improve patient understanding. For example, one research group tested the effect of an easy-to-read informed consent statement with participants in a cancer treatment trial. Patients in the intervention group demonstrated significantly lower consent anxiety and higher satisfaction compared with patients in the control arm. Patient comprehension and state anxiety were not affected by the intervention. The study indicates that easy-to-read informed consent statements are associated with reduced patient consent anxiety and increased satisfaction with the informed consent document, but not with improved patient comprehension. It has been

recommended that clinical trial informed consent statements should be modified to be easier to read without omitting critical information. Patient anxiety and satisfaction can be affected by the consent document. (Coyne et al. 2003.) In addition, the effects of social support on comprehension and recall of consent form information in a study of Parkinson disease patients and their caregivers showed that social support played a significant role in enhancing comprehension and recall of consent form information (Ford et al. 2008).

One study examined patients with psychotic disorders to clarify whether it would be possible to improve understanding of research consent with this group of patients. The participants were randomized to receive a routine consent or enhanced consent procedure. Those who received an enhanced consent procedure displayed better comprehension than those who received the routine consent procedure. Among the patients, comprehension test scores correlated with level of education and cognitive performance. The normal comparison subjects also seem to have benefited from the enhanced consent procedure. The authors concluded that when a concerted effort was made to impart crucial consent information, even older patients with chronic psychotic disorders displayed improved post consent understanding. (Dunn et al. 2001, 2002.) Elderly patients, in general, may encounter greater more difficulties comprehending consent information and thus it is recommended that particular attention should be paid to compensating for communication and sensory deficits, improving readability of information sheets and consent forms as well as considering the use of innovative consent procedures. (Bayer & Fish 2003.)

Some more examples are given; one research group evaluated the feasibility, acceptability, and preliminary efficacy of two enhanced consent procedures provided to patients with Alzheimer disease or mild cognitive impairment. The patients were randomly assigned to an enhanced written consent procedure or a slideshow presentation. The results showed that verbal re-explanation was associated with improved understanding in both conditions. The level of understanding did not significantly differ between the two consent groups, but the time needed for viewing the slideshow presentation was less than that for an enhanced written consent procedure.

Nonetheless, enhanced consent procedures seem to be a feasible and useful way for obtaining consent in patients with mild cognitive impairment or mild Alzheimer disease. (Mittal et al. 2007.) In addition, a decision aid booklet was noted to help women in deciding about whether or not they would participate in a breast cancer trial. The booklet was found to add to their understanding over and above the participant information sheet and was not anxiety provoking. (Juraskova et al. 2008.)

Even though proper attention was paid in adhering to accepted ethical and legal standards, it was noted that patient in a trial in acute myocardial infarction comprehension was incomplete or even totally lacking in a considerable number of subjects (Yuval et al. 2000). In addition, at present there is little information about whether cardiac patients' understand what is meant when they are asked to volunteer in a clinical trial for drugs to treat unstable angina pectoris/non-Q-wave acute myocardial infarction. One study explored prevalence, pattern, and determinants of patient comprehension for investigations in this area and reported that significant determinants of poor initial score were female sex, limited education, and the presence of pain during the consent process. Young age was the only determinant of improvement with repeat assessment. Thus initial understanding of the research protocols for trials in patients with unstable angina pectoris or non-Q-wave acute myocardial infarction was imperfect, especially with respect to the risk associated with participation. These workers recommend that consent procedures (including information sheets) be brief, concise, and designed to highlight potential benefits and risks, and differentiating between standard and experimental modes of therapy. (Kucia & Horowitz 2000.)

In summary, it is critical that efforts should be made to increase subject understanding in current biomedical and health research. The provision of written information to volunteers is one of the ways to address this issue. In most studies performed in healthy volunteers, the written information is provided at the screening visit, at the same time as the oral explanation. However, the written information is kept by the subject and questions may arise before the randomization process. By that time, the subjects are expected to have assimilated the information. (Paris et al. 2007.) In the exercise and diet intervention study, written information was sent to the potential participants' homes and

handed them when they attended the screening visit when it was supplemented with verbal instructions (see page 73).

The findings of this thesis indicated that the research participants' comprehension of the information received was adequate in 82 % of the whole study population. In addition, higher education and satisfaction with personal health were statistically significantly associated with adequate comprehension of received information. However, if one considers the incorrect answers, 5 % of the population had not understand the purpose of the study in question, 2 % did not know or remember the purpose of the study in which they were participating and 11 % gave no response to a question concerning the purpose of the exercise and diet intervention study.

Understanding is a complex process based on both intelligibility of the text and the subject's ability to assimilate this information. Its assessment is complex and requires validated questionnaires. Many factors can influence subject comprehension; one earlier study showed that a medical or paramedical professional background as well as a high school level was associated with increased comprehension. This same study showed also that there is a significant interaction between the type of informed consent document and gender with women having an increased comprehension score at baseline compared with men. (Paris et al. 2007.)

In addition, lower literacy and minority status have been shown to be associated with requiring more time to achieve complete comprehension of the consent process (Sudore et al. 2006). Furthermore, lower educational level, mental illness, and perhaps advanced age have been claimed to be associated with decreased understanding (Flory & Emanuel 2004). However, data of this thesis do not support these assumptions. For example, there were no statistically significant associations between age, education or health care professional background and opinions about intelligibility of the information given.

Despite increasing regulatory scrutiny, deficiencies still exist in participant comprehension of the research in which they are being asked to participate, as well as differences in how comprehension is measured and assessed. An integrative review of

the literature indicated that no single intervention was identified as being consistently successful for improving participant comprehension, though it does seem that a successful consent process should at a minimum include various communication modes and is likely to require one-to-one interaction with an individual who is knowledgeable about the study. (Cohn & Larson 2007.) One interesting finding in the literature is that there is a correlation between the respondents' own assessment of the comprehensibility of the form, and their actual comprehension. This indicates that it may be useful simply to ask whether or not a prospective research subject has found the information leaflet easy or difficult to understand. (Bjørn, Rossel & Holm 1999.) In this thesis the participants were asked to give their own assessment of the comprehension of how understandable they felt the information had been.

6.1.3 Competence

We estimated whether the participants in the exercise and diet intervention study were competent to make a decision about participation and to understand what is included and required. However, it has been claimed that there is no gold standard by which to determine adequate decisional capacity (Dunn et al. 2002). In addition, it is difficult to determine what the word "competence" actually means. According to the literature review, very few of the empirical studies, for example, in the field of intensive and critical care nursing offered any definitions or descriptions of the concept of competence. (Ääri, Suominen & Leino-Kilpi 2008.)

In general, it is not possible to obtain informed consent if the person is very young, severely ill, mentally impaired, demented or unconscious, or even frail or confused. People often cannot give informed consent to their own emergency treatment. (O'Neill 2003.) Emergency medicine research also requires the enrolment of subject with varying decision-making capacities, including capable adults, adults incapacitated by illness or injury, and children (McRae & Weijer 2008). Mental inability to make decisions on treatment is common in people admitted to psychiatric wards from the community though this assumption has been questioned (Owen et al. 2008). For

example, in one study a high percentage of particular vulnerable, mentally ill prisoners showed adequate decisional capacity to consent to participation in research. Therefore, it has been recommended that ethicists must continue to study and weigh the potential vulnerability of special groups e.g. prisoners since it has been claimed that they have become an overprotected population. (Moser et al. 2004, cf. Fisher et al 2006.)

It has stated that with today's complex research protocols and increasingly sophisticated and sometimes risky treatment options, when combined with an aging population at risk of having cognitive impairment and therefore impaired decisional capacity, there is an undeniable need for reliable and valid capacity assessment methods (Dunn et al. 2006). In a study concerning assisted living residents, it was noted that the need to assess decisional capacity of all potential research participants who are members of a population at high risk for cognitive impairment. The results of this study also emphasize the importance of identifying an appropriate surrogate decision maker to participate in the consent process for research focused on dementia or psychiatric disorders and to provide proxy informed consent if needed. (Black et al. 2008.)

However, it is possible that by implementing best ethical practice including a formal assessment of capacity to consent to a research project in an acute medical ward may have resulted in a considerable reduction in the numbers of subjects willing to participate in a study. Also, patients who enter a research study after a formal test of capacity may be unrepresentative of all patients who might be recruited into a research study. In other words, the process of the formal assessment may itself reduce the consent rate. (Adamis et al. 2005.)

Research involving healthy volunteers is less likely to cause ethical concerns. Since these research participants are not ill and, more specifically, do not have a condition with the potential to compromise decision-making capacity, there is no reason to question their ability to provide informed consent. (Miller 2003.) It has stated that the biggest thief of autonomy is sickness (Cassell 2005). In summary, the argument that the participants in the exercise and diet intervention study were competent to make a decision about participation is reinforced by previous publications. The participants

were adult volunteers without any treatment association to the Kuopio Research Institute of Exercise Medicine. We have no ethical reason to question their ability or competence to provide consent.

6.1.4 Voluntariness

Voluntarism refers to the capacity to make a choice freely and in the absence of coercion (Roberts 2002). Our participants considered that they participated in the exercise and diet intervention study of their own free will and without coercion. However, a minority of the participants (5 %) were not aware of their right to withdraw from the intervention study at any time. The right to withdraw from the study at any time might include passive withdrawal, such as the participant not returning study materials. In such a case, the researcher must then carefully decide when to cease follow-up procedures (Steinke 2004). In this Informed Consent Study, no questionnaire was sent to those participants who failed to show up for his/her guidance visit or to any participant who refused to fill in the questionnaire. A related issue that is not as well understood or studied is the collection and reporting data from potential participants who refuse to take part when approached for consent. One argument is that researchers are obligated to respect patient autonomy and confidentiality by refraining from collecting data from patients who withhold permission. (Higgins & Daly 2002.)

Research ethics committees and institutional review bodies increasingly stipulate that investigators refrain from repeated contact with potential participants, unless these patients actively signal willingness to consider participation (the so called ‘opt-in’ approach). However, recruiting unbiased patient samples with high response rates is vital for the scientific rigour of many types of medical research. The traditional means of participant recruitment assumes that patients are potentially willing to participate, and non-response to an initial approach can be followed up with a further communication (the so called ‘opt-out’ approach). One research group showed that the opt-in approach resulted in lower response rates and a biased sample. Therefore, they concluded that the

opt-out approach should be the default recruitment strategy for studies with low risk to participants. (Junghans et al. 2005.)

Another study (Baker et al. 2000) suggested that researchers should seek consent also if data are to be collected from patient's records, and allowances should be made for the likely magnitude of refusal in calculating sample sizes. It has been stated that if researchers are to retain the trust of patients, individual consent should always be sought first before collecting data from records. The only exception should be when a research ethics committee has waived the requirement to seek consent for pressing and justifiable reasons. Willison and co-workers (2003) concluded the same.

The results of a study concerning neurological emergency treatment trial did suggest that it may be difficult to obtain truly informed consent even in a relatively simple and straightforward trial. However, this study also showed that even in a study involving a clinical situation perceived as life threatening, asking permission for study inclusion is generally considered as acceptable. (Hofmeijer et al. 2007.) From elsewhere, a study quantifying the influence of risk and discomfort or pain on patients' willingness to participate in clinical studies reported that the consent process protected patients, although not for the anticipated reason. Understanding was poor, but patients who failed to understand the risks or discomforts rarely consented to participate and those patients who felt pressured did not consent. Consequently, relatively few patients unknowingly agreed to participate in risky or painful studies. In contrast, patients who understood the risks involved were twice as likely to consent. In addition, many patients have been shown to be willing to participate in risky or painful studies, apparently for altruistic reasons. (Treschan et al. 2003.) It has been claimed that a balance between 'opt-in' 'opt-out' approaches can perhaps be achieved by giving a limited amount of accurate and relevant information and providing user friendly ways as well as easy ways of rescinding consent once given (O'Neill 2003).

In conclusion, a major determinant of willingness to participate appears to be an individual's trust in medical research and researchers (Weinfurt et al. 2008b). In addition, one finding from this thesis is that 'helping other people' is an important factor

contributing to willingness to participate in a research project. Earlier studies have come to the same conclusion. For instance, when asked the positive reasons for joining a trial in women with a high familial risk of breast cancer, 40 % of women on the trial cited 'helping future generations' (Lovegrove et al. 2000).

6.1.5 Decision-making

In our exercise and diet intervention study the participants estimated that the decision-making concerning participation had been voluntary. In addition, the participants considered that sufficient time given for considering participation. It has been emphasized that potential participants need time to read the information in peace and think about it before discussing it again with the researchers. Thus, if nobody refuses to take part in a study, one may speculate whether participation entirely has been voluntary. For example, recruitment may have been too persuasive or refusal made too difficult. (Vähäkangas 2004.) One study concerning genetic testing showed that providing adequate time to consider whether or not to be tested and giving more support to patients after testing could also be considered to promote the rights of patients (Nyrhinen et al. 2009). Therefore, it has been recommended that patients and potential participants should be encouraged to take enough time to understand all available options in order that they may make informed decisions (Yoder 2006).

According to the majority of the respondents, the researcher (doctor), research nurse and research personnel were persons who are able to affect their decision-making concerning participation. When asked what factors had affected their participation, one important opinion was that there was a moral duty for people to volunteer: willingness to help other people and advancement of knowledge. This result is similar to the results of Russell and co-workers (2000). In addition, other reasons have been given e.g. a prisoner stated that participating was a way to avoid boredom, others liked to meet someone new, or wished to appear to be cooperative in hopes of being treated better, and helping society (Moser et al. 2004).

These findings can be generalized when voluntary research participants are investigated. However in clinical research, the situation is quite different. Emotions, such as hope and desperation, frequently motivate people to participate in a clinical trial. For example, it has been reported the despair can predispose patients and their families to make decisions based on unrealistic hopes (Chen, Miller & Rosenstein 2003). Expectations of being treated as 'a special patient' in a trial are important in convincing subjects to participate (Madsen et al. 2000).

In another report, it was stated that if the patient is in a critical clinical condition and there is an absence of a patient representative at the critical time period then it may be difficult and sometimes impossible to receive informed consent before the beginning of the trial. However, not requesting consent before a trial is also contradictory. (Halila 2007.) Despite this fact, an earlier study revealed that an appreciable proportion of patients undergoing surgery for acute abdominal conditions were aware that they retained the ability to give informed consent for surgery. Nonetheless, informed consent prior to urgent surgery is perceived to be less comprehensive than for elective procedures. (Kay & Siriwardena 2001.) In addition, one challenging group is participants and their parents in paediatric clinical research (Chappuy et al. 2006).

The use of financial compensation as a recruitment tool in medical research continues to be debated on ethical grounds (Dunn & Gordon 2005). Various methods have been used to compensate research participants, and these can influence participation. Researchers must carefully determine what compensation, if any, is provided and the amount of compensation, and develop strategies to avoid possible coercion (Steinke 2004). One systematic review of the literature revealed that financial rewards were important motivator among normal healthy volunteers in their decision to participate in clinical trials (Tishler & Bartholomae 2002). In Finland, the law prohibits researchers from paying compensation to research participants. However, the participants can be compensated for the use of their time, travelling expenses, loss of earnings and other inconveniences (cf. Dickert, Emanuel & Grady 2002).

An amount of money that is not excessive and is calculated on the basis of time or contribution may, rather than constituting an inappropriate inducement, be an indication to the participant about how much time their contribution to the research may entail (Grady 2001). Even though there are no financial rewards many people are willing to participate in research projects, fortunately. Some earlier studies have come to the same conclusion. For example, in the work of Russel and co-workers, the majority of the respondents were opposed to payment of research subjects, regardless of whether the subjects were healthy volunteers or patients (Russell, Moralejo & Burgess 2000).

In the exercise and diet intervention study most participants felt that informed consent had been confirmed and verified well. The participants had given their written consent for participation. In the literature there is considerable discussion about the actual implications of the written consent form. For example, discussion about the fact that institutions and professionals increasingly view informed consent as some kind of protection against accusations, litigation and compensation claims. Hence, informed consent has become "the modern clinical ritual of trust". (O'Neill 2003.) On the other hand, there is the opinion that the informed consent form is only a stand-in for the process of informed consent itself and that greater attention should be paid to the professional-participant interaction in the process of informed consent in research with less reliance placed on the signed consent form as evidence of adequate informed consent (Kahn & Mastroianni 2001). It has been claimed that for informed consent to be adequate, then it should represent a systematic educational process rather than a mere ethical form or procedure (Matsui, Kita & Ueshima 2005).

There have been discussions also about waiving informed consent, for example, in the quality-improvement studies. It has proven that it is often impossible to obtain informed consent from patients enrolled in quality-improvement research programs because interventions must routinely be adopted for entire hospitals or hospital units. Therefore, it has been stated that it is justifiable from an ethical and a regulatory perspective to waive informed consent for low-risk research when soliciting consent is not practicable and consent would not provide any meaningful protection to the subjects. (Miller & Emanuel 2008.) My opinion is still that written consent is essential and in addition,

informed consent should be a process which continues through the whole research project. However, the concerns posed above are valid.

In summary, it has been claimed that informed choice is a complex concept that depends on more than knowledge alone (Kellar et al. 2008). Nonetheless, the discussion about the decision-making process still revolves around the topic of adequate information. For example, the use of educational DVD increased cancer patient knowledge and satisfaction regarding participation in phase I clinical trials and enhanced the decision-making process (Strevel et al. 2007). Furthermore, providing men with information about screening for prostate cancer enabled them to assume a more active role in decision-making with their family physician, and this resulted in a lower level of anxiety and decisional conflicts. In other words, providing the participants with information enables them to make informed screening decisions with their physicians. (Davison et al. 1999.) In addition, to improve decision-making, the research team should not only ensure full disclosure, but determine that the information has been understood and assimilated (Rabin & Tabak 2006). In this thesis, the majority of participants were satisfied with information they received. Therefore, it is concluded that decision-making was based on a voluntary informed choice.

6.2 Enhancing the informed consent process

The literature review as well as the discussion of this thesis indicated how much effort has been expended on enhancing the informed consent process. However, even though there is widespread agreement on the importance of informed consent in clinical research, uncertainty remains about the adequacy of current consent procedures and documentation. Many studies have failed to provide evidence that they have adhered to effective informed consent procedures. For example, Guarino and co-workers (2006) concluded that making the consent document more consumer-friendly did not lead to either benefit or harm in understanding, satisfaction, or study refusal and adherence rates. However, they demonstrated that embedding consent studies in a clinical trial is

feasible and can address important questions about informed consent without disrupting the primary study.

One aspect of enhancing the informed consent process is the effectiveness of ethical review. The European Union directive provides a workable recommendation for an effective ethical review. Despite European legislation to harmonize procedures for ethical approval, it has claimed that the rules and regulations need to be better standardized and implemented in order to improve harmonization, especially in multicenter trials. It has also noted that obtaining approval for multinational studies is still complex and time consuming. (Schnitzbauer et al. 2009.) There are also concerns that legislation on privacy may unduly bias observational studies using medical records. Therefore, ethical review boards need to give thoughtful decisions on whether the need for mandatory consent is necessary. (Kho et al. 2009.) However, these kinds of studies are outside the scope of this thesis.

The Declaration of Helsinki and the WMA's International Code of Ethics contain the crucial statement that a physician's or investigator's conscience and ethical duty must transcend national laws. Thus simply being compliant with national laws that respect basic human rights and ethical norms is a necessity, but is not in itself a sufficient standard. However, the Food and Drug Administration (FDA) of the United States (US) has ruled that clinical trials performed outside the US no longer have to conform to the Declaration of Helsinki if used to support applications for registration of products in the US. (Goodyear et al. 2009.) This is one signal that reforms are needed (cf. Fost & Levine 2007).

The crucial ethical challenge is to balance risks and benefits in the context of the needs and capacities of individual research subjects. Thus, it is important that the Institutional Review Board (IRB) system must become evidence-based and not rely on unproven assumptions. In addition, the contexts of medical practice and of research changed so dramatically in the last quarter of the twentieth century. Over and above IRB's uniform rules about informed consent, there are many still outstanding issues, including coercion, explaining randomization and alternative treatments to subjects, the role of

physicians as investigators, and informed consent for special populations that have not been standardized to any great extent at the institutional level. Relative little attention has been given to whether there should be a special type of consent process for longer-term studies. In particular, if there is a long maintenance schedule (e.g. 2–3 years in duration) and consideration could be given to asking the subject for consent again at the end of each year of the maintenance phase. (Frank, Novic & Kupfer 2003.)

The large-scale randomized trial by Lavori and co-workers (2007) demonstrated that it is possible to design and conduct randomized studies of innovations in the informed consent, in the context of real clinical studies, without interfering with the parent studies, and at a modest cost. That study underlined the need to evaluate rigorously (with validated experimental methods) any suggested changes to the informed consent process that may be advanced by those interested in ensuring the valid informed consent of participants. They also recommended that it might be useful to examine the current consent processes that have grown by accretion of plausible but untested procedures and requirements. For example, an anonymous telephone interview immediately after the consent process, conducted by an independent interviewer not affiliated with the parent study is more likely obtain an unbiased assessment of the consent process than a face-to-face interview by a study team member. Despite belief to the contrary, a standardized quality assurance tool, for instance, did not enhance informed consent in actual clinical trials. (Lavori, Wilt & Sugarman 2007.)

One should not overlook the educational aspects when attempting to improve the informed consent process (e.g. Fletcher et al. 2007, Khalil et al. 2007). For example, it has been reported that a short communication skills course for physicians and nurses engaged in a clinical trial about disclosing patient information improved the quality of informed consent and patient satisfaction and therefore, it may be advantageous to include this kind of training in the clinical trial planning process (Hietanen et al. 2007). In addition, surgical trainees' knowledge of informed consent for bedside procedures has been shown to be enhanced by an educational program. The training programme did improve their knowledge but not the practice of obtaining consent. Thus, it was concluded that providing instructions about the consent process concomitantly with

technical training may increase awareness and success in obtaining informed consent for bedside procedures. (Steinemann et al. 2006.) However, when the impact of a communication skills training workshop targeting specific doctor behaviours during a cancer clinical trial consultation were evaluated, no differences were obtained between the pre- and post-training groups. Nonetheless, a short training programme did achieve limited success in improving the oncologist's communication skills in gaining informed consent. (Brown et al. 2007.)

In summary, more research is needed to rigorously evaluate proposed methods to enhance informed consent prior to any widespread adoption (Lavori, Wilt & Sugarman 2007). In addition, discussion about the ethical issues involved between different interested parties is essential. Discussion allows for the weighing of different arguments and makes it possible to form balanced and reasoned decisions. The citizens in Finland are becoming increasingly aware of their rights. A vigorous on-going debate is needed in order to make health care more ethically acceptable, particularly in today's world where there is absolute no good or evil, but most often a compromise between these two polarities. (Halila 2003.)

6.3 Validity and reliability

Validity is a complex idea that is important to the researcher and to those who read the study report and consider using the findings in their practice. Validity represents a major foundation for making decisions about which findings are useful for patient care. (Burns & Grove 2001.) The validity of this thesis can be viewed in terms of its external validity. External validity is concerned with the extent to which the study findings can be generalized beyond the sample used in the study. The significance of the study depends on the number of types of people and situations to which the findings can be applied. (Burns & Grove 2001, McDowell 2006.) The DR's EXTRA Study is a randomized controlled intervention trial in which a representative 15 % sample of the population was invited to participate as the target population. Therefore, the results of this study can apply probably to older people, at least in Finland.

It has been discussed about whether participation in a randomized controlled trial (RCT) increases a participant's (especially patients) risk of a bad outcome, or that the results of RCT's are not applicable to usual clinical practice. However, a systematic review concluded that participants in the RCTs had similar outcomes to comparable patients who received the same or similar treatment outside the trial. Therefore, it seems that the results of RCTs are applicable to comparable patients, for example, those receiving usual clinical practice. (Vist et al. 2005.)

The internal validity of this thesis can be considered by selection. That topic addresses the process by which subjects are chosen to take part in a study and how subjects are grouped within a study. For example, people assigned to the control group could be different in some important way from people allocated to the experimental group. This difference in selection could cause the two groups to react differently to the treatment. (Burns & Grove 2001, McDowell 2006.) Again, the DR's EXTRA study is a population-based intervention trial and the participants were randomized into six intervention groups. This procedure avoided the possibility of allowing the participants to select the intervention group they would have preferred.

In this Informed Consent Study the sample size was large (n=1329) which added to the validity of the research. Since the validity of the statistical evaluation decreases if statistical power is low. A low statistical power increases the probability of concluding that there is no significant difference between samples when actually there is a difference (Type II error). A Type II error is most likely to occur when the sample size is small. (Burns & Grove 2001, McDowell 2006.)

In this thesis, content-related validity evidence was obtained from the literature, content experts, and representatives of the relevant populations. Content validity is the extent to which the method of measurement includes all the major elements relevant to the construct being measured (Campbell & Machin 1993, Burns & Grove 2001, Everitt & Palmer 2005, McDowell 2006). The content of the questionnaire was based on the relevant literature about informed consent. The questionnaire was developed

collaboratively through critical discussion within a multidisciplinary expert group. To improve the validity and reliability of the questionnaire, a pilot study was conducted; and subsequently a new pre-test (with written instructions) was evaluated with five people chosen to simulate the actual participants. In addition, a representative 15 % sample of the target population was invited to participate in the DR's EXTRA Study.

If one wishes to obtain reliable results then it is essential to employ an appropriate research design (Altman 1999). The reliability of a measure denotes the consistency of measures obtained in the use of a particular instrument. For example, if the same measurement scale is administered to the same individuals at two different times, the measurement is reliable if the individuals' responses to the items remain the same (assuming that nothing has occurred to change their responses). (Burns & Grove 2001, Everitt & Palmer 2005, McDowell 2006.) One limitation of this thesis is that measure of the reliability was not pre-arranged.

To ensure the validity and reliability of data analyses, a statistical expert was used as a consultant. Statistics can contribute to good research by pointing to the optimum way to analyze the results (Campbell & Machin 1993). In addition, the variables used in logistic regression model (individualized research question two) were also classified into three classes: poor (1-2), moderate (3) and good (4-5). The intention was to check if this classification would change the results. There was only a difference between the two and three classes division in one comparison: the purpose of the study and confirming of understanding. This correlation showed statistically significant association when two classes were used ($p=0.03$), but not when the results were subdivided into three classes ($p=0.09$). This difference was considered insignificant in our estimation of the overall validity of the results of the study.

One significant factor is the high response rate (91 %) of this Informed Consent Study which increases both the validity and reliability of this research. The participants received the questionnaire, written instructions and verbal directions personally during the three-month intervention visit. This gave them an opportunity to pose any questions at the same time, which probably contributed to the high response rate. The response

rate to questionnaires is generally lower than that with other forms of self-reporting, particularly if the questionnaires are mailed out. If the response rate is lower than 50%, the representativeness of the sample must seriously be questioned. (Burns & Grove 2001.)

6.4 Study Limitations

This thesis has several limitations. First, the main limitation of the Informed Consent Study was that the questionnaire is new and has not been used by other research groups. However, this questionnaire has a sound foundation on recent legislation, regulations and literature. In the 21st century, the research ethics guidelines have been overhauled and are now better defined. Therefore, there was a need to create a questionnaire which would take into account recent literature concentrating on voluntary research participants who have no treatment connections with the research institute or researchers. In addition, many of standardized questionnaires for evaluating the quality of informed consent are either focused on or have been developed for the hospital/patient context. For example, the QuIC (Quality of Informed Consent questionnaire by Joffe and co-workers) was developed and pre-tested in a population of cancer clinical trial participants and, therefore, its wording is cancer-specific. The authors emphasize that differences between cancer and non-cancer clinical trials means that the QuIC should not be used in a non-cancer setting until it is verified as being valid. (Joffe et al. 2001a, 2001b, Barrett 2005, Hietanen et al. 2007.)

Due to the novelty of this Informed Consent questionnaire, it was developed and tested very carefully. This process is described in detail in pages 56–58. It should be taken into account that this questionnaire was developed, pre-tested and used in a population of 'healthy' adult volunteers. Nonetheless, since there may be differences between volunteers and patient in clinical trials we recommend that our questionnaire should be re-tested before further use.

Second, this questionnaire does not address in sufficient depth several aspects of understanding and competence. However, evidence from this thesis is that it is extremely difficult to evaluate how much a participant really understands the information he/she received, and whether the participant is competent to comprehend its meaning.

Third, this study does not provide information on how to define the optimal point of time to conduct an interview or inquiry for investigation of informed consent. According to the findings, this questionnaire was appropriate, at least over the short term, for the research in question. The data were collected after three months of participation in the exercise and diet intervention study. The opinion was that after a few months, the participants will have a better idea about the intervention study than immediately after randomization. On the other hand, the period of time was so short that the recall of the participants was still strong. However, when the participants were asked where they obtained first information about the exercise and diet intervention study, over 30 % did not remember this correctly. For example, a fifth of the respondents remembered that they had seen an announcement, some of respondents thought that they had been invited through a previous study, a few remembered that they had first obtained information from a friend. In actual fact, the participants had each received an invitation through the post telling them about the exercise and diet intervention study. The period between sending the letter and the baseline survey was, on average, two years.

7 CONCLUSIONS

This thesis adds empirical knowledge about obtaining informed consent in health research from the point of view of volunteer adult research participants. In addition, this thesis reveals that it is possible to examine and measure the extent of realization of informed consent by means of a questionnaire. On the grounds of this study it can be estimate that the exercise and diet intervention study (DR's EXTRA Study) was conducted with and adhered to high ethical standards with respect to the informed consent process.

Based on the results of this thesis, implementation and success in intervention are linked to whether subjects receive a sufficient amount of information which they are able to comprehend and in this way can provide truly informed consent. However, this thesis highlights objectively how difficult it is to disseminate information even to voluntary adult participants. Therefore, this study identifies the need for all health-related researchers to critically analyze the quality and manner in the way that information is provided. This is especially important in long-term follow-up studies. Based on the results of this thesis, special efforts should be made with participants with lower educational levels or subjective feelings of impaired health.

One further aim is that all members of the research and study group view informed consent as a continuous process to be considered through the whole duration of the project. In addition, further study efforts should be focuced on improving the ways that potential research participants are made aware and ensuring that they have understood the informed consent process for example by studying how participants' understanding of the research process could be improved. One important question is: 'How can we be sure that research participants really understand the information they receive?' Although, 100 % comprehension is probably unachievable, it should nonetheless be the goal.

Recommendations based on this thesis:

1 In all studies, a random sample of participants should be given a questionnaire which is concerned with informed consent. This kind of enquiry will provide important information about the participants' true knowledge and satisfaction concerning the research project in which they are participating.

2 The standard should be adopted that every research participant is asked to describe in their own words the purpose of the study in which they are participating. This will ensure that they have an adequate grasp and understanding of the information provided.

3 The results of this thesis showed that those subjects who felt themselves to be healthier were more likely still to be participating in the intervention study at the 2-year intervention. Therefore, it is not enough to inquire about possible medical information of the participants. It is important to simply ask how the participants view their own health.

Fortunately, people are still willing to participate in scientific research – for this scientists should be thankful. This apparently originates from people's trust in science, research and researchers. However, this trust should not and cannot be taken for granted. We can maintain people's confidence in science only if all professionals honour a commitment to ethical principles, such as those enshrined in the principal of 'Informed Consent'.

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APPENDICES

Appendix 1

Literature review

Author(s)	Purpose, Sample, Method and Main findings and conclusions
Adamis, Martin, Treloar, et al. (2005) UK	**Purpose:** To investigate whether different methods of obtaining informed consent affected recruitment to a study of delirium in older, medically ill hospital inpatients. **Sample:** All patients (n=130) 70 years or older admitted to the unit between Nov 2000 and Jan 2001 for acute assessment, directly from home or other wards if this was within three days of admission to hospital. **Method:** Randomized into two groups: a) a formal test of capacity, followed by either a request for consent or an attempt at obtaining assent from a proxy (n=57, mean age 83.4 years, SD 6.1, men 47.4 %), or b) a combined informal capacity/consent process (n=73, mean age 83.8 years, SD 6.8, men 41.1 %). **Main finding and conclusions:** Using the formal method of assessing capacity and obtaining consent excluded more patients overall and also led to fewer people with case note delirium being recruited. Thus, a stringent assessment of capacity may exclude patients with delirium from studies, thus rendering findings less generalizable and predispose to sample bias.
Baker, Shiels, Stevenson, et al. (2000) UK	**Purpose:** To investigate what proportion of patients refuse consent to data collection from their records for research purpose. **Sample:** n=3429, age: 16 or above. Random samples of patients with either asthma or stabile angina in 81 volunteer practices. **Method:** Questionnaires that included a request for consent to collect data from the patient's clinical records was sent to randomized patients. **Main finding and conclusions:** There were no significant differences between patients who consented and those who did not for mean age, sex, severity of symptoms or satisfaction with care. Researchers should seek consent if data are to be collected from patient's records, and allowances should be made for the likely magnitude of refusal in calculating sample sizes.
Bjørn, Rossel, Holm. (1999) Denmark	**Purpose:** To study whether linguistic analysis and changes in information leaflets can improve readability and understanding. **Sample:** Two different groups (n=235): a) testing of a new drug for hypertension (n=135, mean age 74 years, median range 62-92, male 34) , b) the effect of a new local anaesthetic in connection with the sterilisation of women (n=100, mean age 35, 25-45). **Method:** Two information leaflets concerning trials of drugs for conditions/diseases which are commonly known were modified, and the original was tested against the revised version. **Main finding and conclusions:** The perception of the readability and comprehensibility of a standard information leaflet can be improved by professional linguistic revision of the leaflet.

Author(s)	Purpose, Sample, Method and Main findings and conclusions
Black, Brandt, Rabins, et al. (2008) USA	**Purpose:** To identify factors associated with providing either informed consent or assent for research in individuals at high risk for cognitive impairment. **Sample:** A stratified random sample of 198 assisted living residents (mean age 85.7 years, SD 8.25, male 21 %) participated in the study from 22 assisted living facilities. **Method:** Residents' consent or assent status was documented as providing informed consent, written assent, or verbal assent/no objection. **Main finding and conclusions:** Residents were more likely to provide written assent or verbal assent/no objection than informed consent at enrolment. The relatively small proportion of participants who could provide informed consent highlights the importance of assessing decisional capacity for research in a high-risk population and identifying an appropriate surrogate decision maker to provide proxy consent if needed.
Brown, Butow, Boyle, et al. (2007) Australia	**Purpose:** To evaluate the impact of a communication skills training workshop targeting specific doctor behaviours during a cancer clinical trial consultation. **Sample:** Oncologists (n=10, mean age 42.7 years, range 35-40, male 6) and their adult cancer patient (n=90, mean age 55 years, range 33-84, male 32 %) who where eligible for a Phase II or Phase III clinical trial. **Method:** Informed consent consultations were audiotaped before (n=59) and after (n=31) training. **Main finding and conclusions:** There were no differences between the pre- and post-training groups. Thus, this short training programme demonstrated limited success in improving the oncologist's communication skills when gaining informed consent.
Campbell, Raisch, Sather, et al. (2008) Mexico	**Purpose:** To study the impact of a clinical trials information handbook on patient knowledge, perceptions, and likelihood of participation. **Sample:** Randomized controlled trial from the outpatient clinic waiting areas (18 years or older). The control group (n=62) and the intervention group (n=84). **Method:** Intervention group read the information handbook then immediately answered a questionnaire. The control group completed the questionnaire without reading the handbook. In addition, retained knowledge was assessed between 6 and 12 weeks through follow-up phone interviews to subgroup of intervention group participants. **Main finding and conclusions:** The participants who read a clinical information handbook scored 80 % higher on an assessment of knowledge about clinical trials than participants who did not read the handbook. Use of an educational handbook to supplement informed consent of a specific trial may provide truly informed consent.

Author(s)	Purpose, Sample, Method and Main findings and conclusions
Cohn, Larson (2007) USA	**Purpose:** To critically analyze studies published within the past decade about participants' comprehension of informed consent in clinical research and to identify promising intervention strategies. **Design:** Integrative review of literature. **Method:** Studies published between Jan 1996 and Jan 2007. **Main finding and conclusions:** Of the 980 studies identified, 23 met the inclusion criteria. Interventions tested included simplified written consent documents, multimedia approaches, and the use of a trained professional to assist in the consent process. Collectively, no single intervention strategy was consistently associated with improved comprehension.
Coyne, Xu, Raich, et al. (2003) USA	**Purpose:** To test the effect of an easy-to-read informed consent statement with participants in a cancer treatment trial. **Sample:** Randomized controlled trial in 44 institutions. Total of 207 patients participated either in the control group (n=129, mean age 53 years, male 9.3 %) or in the intervention group (n=78, mean age 53 years, male 7.7 %). **Method:** Telephone interviews (approximately 1 to 2 weeks later) were conducted to assess study outcomes. **Main finding and conclusions:** This study indicates that easy-to-read informed consent statements are associated with reduced patient consent anxiety, an increased satisfaction with the informed consent document, but not with improved patient comprehension.
Davison, Kirk, Degner, et al. (1999) Canada	**Purpose:** To determine if providing men with information about screening for prostate cancer would enable them to assume a more active role in decision-making with their family physician, and lower level of anxiety and decisional conflicts. **Sample:** Men (n=100) recruited from one family medical clinic. Randomized in intervention (n=50, mean age 60.7 years, 8.6) and control (n=50, mean age 63.6 years, SD 8.0) groups. **Method:** Men in intervention group were asked what they knew about screening for prostate cancer. They were then provided with both verbal and written information. Men were encouraged to discuss screening issues with their family physician and participate in making a screening decision. **Main finding and conclusions:** Men who received the information prior to the periodic health examination (PHE) assumed a significantly more active role in making a screening decision, and had lower levels of decisional conflict post PHE. The groups did not differ with regard to levels of state anxiety. Providing men with information enables them to make informed screening decisions with their family physicians.

Author(s)	Purpose, Sample, Method and Main findings and conclusions
Dobscha, Corson, Solodky, et al. (2005) USA	**Purpose:** To describe the effects of using videoconferencing on participant enrolment, research measure administration and responses, study retention, and satisfaction. **Sample:** Patients from primary care clinics who were recruited for a randomized clinical trial of a care management intervention for depression (n=400). This article discusses a subgroup (n=31) who were interviewed using videoconference. **Method:** Initial interview or interview using videoconferencing and mail survey regarding the interview. **Main finding and conclusions:** There were no significant problems with the process of interviewing and obtaining informed consent by videoconference. No differences were observed between depression scores of videoconference and in-person participants, and there was no significant difference in the 6-month rate of loss to follow-up in the randomized trial. In conclusion, videoconference allows patients in rural and remote locations to participate in psychiatric research and expands sources of recruitment for research projects.
Donovan, Mills, Smith, et al. (2002) UK	**Purpose:** To improve design and conduct of randomized trials by embedding them in qualitative research. **Sample:** Controversal ProtecT (prostate testing for cancer and treatment) trial embedding within qualitative research. Men aged 50-59. **Method:** In-depth interviews explored interpretation of study information. Audiotape recordings of recruitment appointments. Findings were used to determine changes to content and presentation of information. **Main finding and conclusions:** Changes in the content and delivery of study information increased recruitment rates from 40% to 70%. The embedding of randomized controlled trials in qualitative research may enable even the most difficult evaluative questions to be tackled and could have substantial impacts on recruitment to apparently routine trials.
Dresden, Levitt. (2001) USA	**Purpose:** To compare a standard, industry consent form (IF) and a modified, shortened version of the same form (MF) which allows the patient to retain more information in the immediate post consent period. **Sample:** 100 patients with a history of asthma were randomized to IF (n=50) and MF (n=50) groups. Mean age 39.4 years (SD 12.1), male 48 %. **Method:** After reading the consent form, the patients were given a post consent test to determine how much information was retained. **Main finding and conclusions:** Compared with an industry consent form, a shortened version allowed patients to retain more information in the immediate post consent period.

Author(s)	Purpose, Sample, Method and Main findings and conclusions
Dunlop, Graham, Leroy, et al. (2007) USA	**Purpose:** To examine the impact of infusion of Health Insurance Portability and Accountability Act (HIPAA) authorization on the willingness to participate in a clinical research study and explore reasons for nonparticipation. **Sample:** 384 African American outpatients at 4 metropolitan primary care clinics. **Method:** Interviewees were randomly assigned to undergo informed consent alone (control group, n=192) or informed consent with HIPAA authorisation (HIPAA group, n=192). They were asked whether they would participate and reasons for their decisions. **Main finding and conclusions:** A smaller proportion of interviewees in the HIPAA group were willing to enrol in the study. In conclusion, the infusion of HIPAA authorization within the informed consent process may adversely affect the willingness of African American to participate in clinical research and may raise concerns about privacy, understanding the forms, and mistrust or fear of research.
Dunn, Lindamer, Palmer, et al. (2002) USA	**Purpose:** To improve understanding of research consent in patients with psychotic disorders. **Sample:** 80 outpatients with schizophrenia or related psychotic disorders and 19 normal comparison subjects, ranging in age from 40 to 80. **Method:** Participants were randomized to receive a routine consent (41 patients, 10 comparison subjects) or enhanced consent (39 patients, 9 comparison subjects) procedure. A comprehension test was administered after the consent procedure. **Main finding and conclusions:** Those who received enhanced consent procedure (EC) had better comprehension than those who received routine consent procedure (RC). EC patients did not differ significantly from RC normal comparison subjects in their post-test scores. Among the patients, comprehension test scores correlated with level of education and cognitive performance. Normal comparison subjects also seem to have benefited from the EC procedure.
Dunn, Lindamer, Palmer, et al. (2001) USA	**Purpose:** To examine whether a novel consent procedure improve the comprehension of consent for older patients with psychosis. **Sample:** 80 outpatients with schizophrenia or related psychotic disorders and 19 normal comparison subjects, ranging in age from 40 to 80. **Method:** Participants were randomized to receive a routine consent (41 patients, 10 comparison subjects) or enhanced consent (39 patients, 9 comparison subjects) procedure. A comprehension test was administered after the consent procedure. **Main finding and conclusions:** A significantly greater proportion of patients who received the enhanced consent procedure scored 100 % on first and second trials of the post-test, compared to those receiving the routine procedure. In conclusion, the enhanced consent method improved comprehension of information relevant for consent in older patients with psychosis.

Author(s)	Purpose, Sample, Method and Main findings and conclusions
Dunn, Nowrangi, Palmer, et al. (2006) USA	**Purpose:** To critically review existing measures of decisional capacity for research and treatment. **Sample:** 23 decisional capacity assessment instruments. **Method:** Articles from 1980 to 2004 describing structured assessments of adults' capacity to consent to clinical treatment or research protocols. **Main finding and conclusions:** 10 instruments focused on consent in research protocols, 15 on consent to treatment and 2 were used in both contexts. The instruments focused mostly on the understanding component of decisional capacity. Those who work in the field of capacity assessment need to develop consensus on the appropriate definitions and standards for measuring each domain.
Fortun, West, Chalkley, et al. (2008) UK	**Purpose:** To assess recall by healthy volunteers of key facts in a patient information sheet in a phase 3 clinical trial. **Sample:** Healthy volunteers (n=82) participating in a capsule endoscopy study. **Method:** A 13 page written information sheet were given and allowed to ask questions. After participants indicated being ready to give consent they were asked to complete a questionnaire covering the identity and adverse effects of trial treatments and of the procedure, the duration of the trial and value of the inconvenience allowance. **Main finding and conclusions:** A comprehensive information sheet resulted in limited recall of trial risks. Shorter information sheet with a test and feedback session should be trialed so that informed consent becomes valid informed consent.
Fox (2006) UK	**Purpose:** Review studies of the effectiveness of leaflets in promoting informed choice in screening. **Sample:** 9 studies from 264 identified articles. **Method:** A critical literature review. **Main finding and conclusions:** Most studies demonstrated that providing written information increased knowledge, but evidence that this promoted informed choice was poor. In conclusion, the most effective way for screening programmes to achieve informed choice is unclear.
Garfein, Swartzen-druber, Ouellet, et al. (2007) USA	**Purpose:** Explore methods to recruit and retain a cohort of young-adult injection drug users for the research of HIV/HCV (hepatitis C virus) prevention trial. **Sample:** New injection drug users (IDU) who were HIV and HCV antibody negative at baseline (n=857, mean age 23.8 years, male 69 %). **Method:** Interview at baseline and follow-up assessment at 3 and 6 months post-intervention. **Main finding and conclusions:** Recruitment and retention of young-adult IDUs for complex intervention trials is complicated, yet feasible.

Author(s)	Purpose, Sample, Method and Main findings and conclusions
Gattellari, Ward. (2005) Ausralia	**Purpose:** To compare the impact of 3 information resources about prostate-specific-antigen (PSA) screening: a leaflet, a video and an evidence-based booklet. **Sample:** 421 men (aged between 50 and 70) recruited from the community. **Method:** 140 received a leaflet, 141 a video and 140 an evidence-based booklet. Computer-assisted telephone pre-test and post-test surveys. **Main finding and conclusions:** Men in all three groups demonstrated significant increases in knowledge scores from pre to post-test. Scores were significantly higher among those who had received evidence-based booklet compared with men who received the leaflet or video.
Hack, Whelan, Olivotto, et al. (2007) Canada	**Purpose:** To compare two audiotape formats for the delivery of information relevant to informed consent to participate in a clinical trial in breast oncology. **Sample:** 69 women with newly diagnosed breast cancer and 21 oncologists from 5 Canadian cancer centres. **Method:** Patients were randomized to three groups: standardize audiotape, consultation audiotape or both audiotapes. Patients received their audiotapes immediately following the clinical trial consultation. **Main finding and conclusions:** There were no differences in clinical trial knowledge or perception of being informed across the intervention groups. Patients tended to prefer receiving an audiotape of their own consultation over a standardized audiotape. The majority of oncologists considered the audiotape intervention feasible.
Hewison, Cuckle, Baillie, et al. (2001) UK	**Purpose:** To assess the effect of a Down syndrome screening video on test uptake, knowledge and psychological stress. **Sample:** 2000 women referred for antenatal care. **Method:** Women were allocated to two equal groups: one to be sent a video to their home, before their hospital booking visit (n=993), and a control group (n=1007). A subset of 1200 women was selected to be posted at 17-19 weeks' gestation a questionnaire to assess the psychological endpoints. **Main finding and conclusions:** The video had no effect on the screening uptake rate. Knowledge of screening was increased in the video group with a statistically significant difference. There were no significant differences between the groups in specific worries about abnormalities in the baby, and general anxiety. In conclusion, a video can increase knowledge without affecting the uptake of the test, or psychological stress.

Author(s)	Purpose, Sample, Method and Main findings and conclusions
Hietanen, Aro, Holli, et al. (2007) Finland	**Purpose:** To investigate whether a short course in communication skills for physicians would improve the quality of informed consent in a randomized clinical adjuvant trial on breast cancer. **Sample:** Patients participating in a breast cancer trial (n=288): intervention group (n=149, mean age 50.6) and control group (n=139, mean age 50.2). **Method:** Physicians and research nurses attended a one-day communication skills course. The quality of informed consent was evaluated by addressing a standardized questionnaire to trial patients at involving hospitals. **Main finding and conclusions:** The patients of the intervention group were significantly more satisfied with the information received and the time given to make their decision. They also understood the main aim of the study better and recalled more often that the physician had also offered other therapeutic options. In conclusion, a short communication skills course for the trial physicians and nurses improved the quality of informed consent and patient satisfaction in the trial.
Hofmeijer, Amelink, Hertog, et al. (2007) Netherlands	**Purpose:** To study differences in recall of information and in appreciation of the informed consent procedure between representatives included in two controlled trials testing treatment strategy. **Sample:** Representatives in the Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial (HAMLET) (n=28) and representatives of patients participating in the randomized trial of Paracetamol In Stroke (PAIS) (n=30). **Method:** Recall of trial details and appreciation of the informed consent procedure were interviewed, one year after study inclusion, using a questionnaire and compared between the two groups. **Main finding and conclusions:** HAMLET representatives remembered statistically significantly more trial details. With respect to appreciation of the informed consent procedure, there were no differences between the groups. In conclusion, recall of trial details is lower in a trial in which less vital issues are at stake.
Hutchison, Cowan, McMahon, et al. (2007) UK	**Purpose:** To determine the effect of an audiovisual patient information (AVPI) intervention on refusal rates to randomized cancer trials, knowledge and anxiety, and to investigate patients' perceptions of the AVPI. **Sample:** 173 colorectal, breast or lung cancer patients were randomized to receive either the AVPI in addition to the standard trial-specific written information (n=86, male 23.3 %), or the written information alone (n=87, male 23 %). **Method:** Data were collected by questionnaire at hospital visit of patients' general medical care. **Main finding and conclusions:** The AVPI had no effect on refusal rates to the randomized cancer trials. It did have a positive effect on levels of knowledge about clinical trails. It also reduced anxiety. In addition, the AVPI was perceived by patients to be a useful adjunct to the informed consent process.

Author(s)	Purpose, Sample, Method and Main findings and conclusions
Ishii, Ohashi. (2007) Japan	**Purpose:** To examine whether an educational videotape might change peoples' attitudes toward participating in future cohort studies. **Sample:** The participants (n=255) were recruited at a health promotion festival (n=139), a nursery care study class (n=54), an elderly class (n=53), and individuals who had not attended a health check-up for more than 10 years (n=9). **Method:** All participants were randomized into a control group and an intervention group (a videotape), and were asked to fill out a questionnaire. **Main finding and conclusions:** The educational videotape intervention showed a statistically significant positive attitude to future participation. In conclusion, the videotape provided to be a useful tool for informing the general public about the nature of cohort studies and to increasing probable participation.
Juraskova, Butow, Lopez, et al. (2008) Australia	**Purpose:** To pilot a decision aid (DA) booklet for a high priority breast cancer prevention trial (IBIS-II DCIS). **Sample:** 31 women participating in the IBIS-I breast cancer prevention trial. **Method:** Participants read the information sheet and the DA booklet, completed a standardized questionnaire and provided feedback on the DA via a semi-structured phone interview. **Main finding and conclusions:** Women found the DA helpful in deciding about trial participation, reporting that it aided their understanding over and above the approved information sheet and was not anxiety provoking.
Kellar, Sutton, Griffin, et al. (2008) UK	**Purpose:** To evaluate an innovative invitation to increase informed choice in relation to screening for type 2 diabetes. **Sample:** Volunteer members of the public (n=417) aged between 40 and 69 years, with no previous diagnosis of diabetes. **Method:** Participants were randomized to receive one of two hypothetical invitations for screening for type 2 diabetes: traditional invitation (n=139, male 50.4%) and informed choice invitation (n=278, male 45.3 %). Informed choice was assessed immediately after the invitation (n=417, male 47 %) and 2 weeks later using a questionnaire (n=407). **Main finding and conclusions:** Compared with the traditional invitation, the informed choice invitation resulted in a significantly higher proportion of informed choice. This increase reflected increased type 2 diabetes screening-related knowledge but not increased attitude-intention congruence.

Author(s)	Purpose, Sample, Method and Main findings and conclusions
Kruse, Kjaergard, Krogsgaard, et al. (2000) Denmark	**Purpose:** To examine how three types of written information influence outpatients' knowledge about and attitude toward research and randomized clinical trials (RCTs). **Sample:** 415 outpatients 18 years or over. **Method:** The patients were randomized to the following groups: control (n=89, mean age 48 years, SD 18, male 32), leaflet (n=94, mean age 50 years, SD 20, male 38), brochure (n=96, mean age 46 years, SD 19, male 39), or booklet (n=90, mean age 45 years, SD 19, male 38). These formats differed in length, reading ease, and reader appeal. Data were collected by structured questionnaires at entry and 2 weeks after intervention. **Main finding and conclusions:** Written information about general aspects of RCTs improved knowledge about and attitude towards RCTs. Elaborate information rather than brief information was more effective.
Kucia, Horowitz. (2000) Australia	**Purpose:** To explore patients' understanding of clinical trials in unstable angina pectoris (UAP) / non-Q-wave acute myocardial infarction (NQAMI) **Sample:** 20 patients, mean age 66.7 years, SD 10.5, male 60 %. **Method:** Subjects were interviewed twice with the same questionnaire: at 10 (+/-4) and 24 (+/-3) hours after randomization to index clinical trial. **Main finding and conclusions:** Significant determinants of poor initial score were female sex, limited education, and presence of pain during the consent process; young age was the only determinant of improvement on repeat assessment.
Lavori, Wilt, Sugarman. (2007) USA	**Purpose:** Test the cumulative effect of a quality assurance questionnaire intended to enhance awareness in the person obtaining informed consent on the quality of the informed consent in clinical trials. **Sample:** 836 research subjects from five participating randomized clinical trials: HOST (n=11, mean age 73 years, SD 8.2, male 100 %), RadArt (n=45, mean age 62 years, SD 8.8, male 100%), SELECT (n=297, mean age 60 years, SD 6.7, male 100 %), ThlNRS (n=373, mean age 67 years, SD 10.3, male 98 %), and WPTSD (n=110, mean age 44 years, SD 9.1, female 100 %). **Method:** Either uses a new quality assurance questionnaire after each informed consent encounter or the standard process of obtaining informed consent. The quality of informed consent was evaluated using independent telephone interviews. **Main finding and conclusions:** The quality assurance questionnaire does not provide an appreciable effect on the quality of informed consent. In conclusion, despite prior beliefs, a standardized quality assurance tool does not enhance informed consent in actual clinical trials. Future research is needed to rigorously evaluate proposed methods to enhance informed consent prior to widespread introduction.

Author(s)	Purpose, Sample, Method and Main findings and conclusions
Lovegrove, Rumsey, Harcourt, et al. (2000) UK	**Purpose:** To identify measurable differences between women who elect to join a placebo-controlled, double-blind randomized trial of the drug tamoxifen and women who elect not to join. **Sample:** 106 participants (women not on the trial: n=53, mean age 45.8 years, SD 9.9 and women on the trial: n=53, mean age 51 years, SD 8.1). **Method:** Questionnaires covering demographic details, health locus of control, perception of risk and adequacy of medical communication. **Main finding and conclusions:** Only half of the sample elected to join. The significant findings were that the women who elected not to join the trial were younger and aware of significantly more lifestyle factors that predispose to the development of breast cancer.
Lynöe, Näsström, Sandlund. (2004) Sweden	**Purpose:** To elucidate the quality of information provided to patients who participated in a clinical trial of a lipid-lowering remedy. **Sample:** Patients (n=44) on hemodialysis or in a prerenal state (34 males, mean age 67.8 years, range 39-82, and 10 females, mean age 67.3 years, range 44-82) who had included in the clinical study over a 1-year period. **Method:** Questionnaire concerning different aspects of the information provided. **Main finding and conclusions:** Compared to younger patients, elderly patients tended to be informed about the trial only orally and were also inclined to let the doctor decide whether or not they should participate. In conclusion, providing information both orally and writing and providing sufficient time for consideration may improve the informed consent process for severely ill patients.
Mancini, Noguès Adenis, et al. (2006) France	**Purpose:** To assess the impact of a standardized patient information booklet on decisions women make about genetic testing. **Sample:** The control group (n=263, mean age 49.1 years, SD 10.8) and the experimental group (n=297, mean age 50.3 years , SD 11.2). **Method:** Questionnaire completed at home within one month. **Main finding and conclusions:** The booklet led to an increase in satisfaction with the information provided, and to a decrease in the level of decisional conflict due to lack of information. The increase of knowledge was marginal. The booklet was found to strengthen patients' decision to undergo the tests.

Author(s)	Purpose, Sample, Method and Main findings and conclusions
Marco. (2008) USA	**Purpose:** To measure potential research subjects' participation in a survey research design, based on level and type of informed consent required before enrolment. **Sample:** 300 eligible Emergency Department participants (mean age 40 years, range 18-83, male 39%) were randomized to one of three groups: verbal consent (n=100), limited written consent (n=100), and detailed written consent with signature (n=100). **Method:** Patient satisfaction survey. **Main finding and conclusions:** Participants who were asked to sign a detailed written informed consent document had a lower rate of participation compared to those with verbal or limited written consent.
Mittal, Palmer, Dunn, et al. (2007) USA	**Purpose:** To evaluate the feasibility, acceptability, and preliminary efficacy of two enhanced consent procedures provided to patients with Alzheimer disease (AD) or mild cognitive impairment (MCI). **Sample:** 35 consecutively referred patients with possible or probable mild AD (n=19) or MCI (n=16). The mean age was 75.6 (SD 7.8) years, male 57.1%. **Method:** Patients randomly assigned to an enhanced written consent procedure or slideshow presentation (PowerPoint) were assessed with the MacArthur Competence Assessment Tool for Clinical Research. **Main finding and conclusions:** Verbal reexplanation was associated with improved understanding in both conditions. Level of understanding did not significantly differ between the two consent groups, but administration time for slideshow presentation was less than that for an enhanced written consent procedure. In conclusion, enhanced consent procedures are feasible and useful for consent to research among patients with mild cognitive impairment or mild Alzheimer disease.
Moser, Arndt, Kanz, et al. (2004) USA	**Purpose:** To assess decisional capacity and susceptibility to coercion in prison research subjects. **Sample:** Subjects were 30 mentally ill prisoners in a medium-security facility (mean age 31.9 years, SD 9.84, men 26, mean education 12.1, SD 1.84) and 30 healthy controls recruited advertisement and word of mouth (26 men, 4 women, mean age 30.0 years, SD 11.46, mean education 12.7 years, SD 0.94). **Method:** The groups were compared on ability to provide informed consent to a hypothetical drug trial, susceptibility to possible coercion, neuropsychological functioning, and psychiatric symptoms. Used assessment tools: The MacArthur Competence Assessment Tool for Clinical research and self developed questionnaire: the Iowa Coercion Questionnaire. **Main finding and conclusions:** A very high percentage of these prisoners demonstrated adequate capacity to consent to research. Prisoners performed in a quantitative measure of decisional capacity significantly worse scores. Regarding possible coercion, prisoners' main reason for participating in research included avoiding boredom, meeting someone new, appearing cooperative in hopes of being treated better, and helping society. In conclusion, ethicists will need to consider the possibility that prisoners have become an overprotected population.

Author(s)	Purpose, Sample, Method and Main findings and conclusions
Paris, Chaves, Cornu, et al. (2007) France	**Purpose:** To identify whether a working group, a systematic improvement in lexico-syntactic readability or their association can improve the comprehension of the written information given to volunteers in biomedical research. **Sample:** Subjects (n=200) in four clinical research centres (ages from 18 to 45 years) were randomized to one of four groups: unchanged informed consent form (n=50, mean age 27.4 years, SD 7.5, male 26), informed consent form with systematic lexico-syntactic readability (n=50, mean age 28.2 years, SD 8.3, male 17), informed consent form modified by a working group (n=50, mean age 26.5 years , SD 7.4, male 23), and informed consent form modified by the working group followed by systematic lexico-syntactic improvement (n=50, mean age 26.4 years, SD 6.6, male 19). **Method:** Volunteers read the informed consent form and answered orally what they had understood with own words (answers were recorded). Then they completed a questionnaire. About 5 weeks later, they were sent the same questionnaire again. **Main finding and conclusions:** Improving the informed consent document in phase I biomedical research leads to better comprehension, whether the method used is systematic lexico-syntactic improvement or a review by a working group.
Peduzzi, Guarino, Donta, et al. (2002) USA	**Purpose:** To compare the utility of an informed consent document developed by a focus group of Gulf War veterans (focus group-developed) to an informed consent document developed by the standard process involving the study investigators (investigator-developed). Design paper. **Sample:** Focus group: five Gulf War veterans. **Method:** Veterans convened at the coordinating centre and developed a consent document during three sessions. The focus group used the investigator-developed consent document as a 'starting point' and then modified it by consensus agreement. **Main finding and conclusions:** Veterans were willing to participate in this process and believed that their input could make a difference in the design of informed consent documents in future trials.

Author(s)	Purpose, Sample, Method and Main findings and conclusions
Ryan, Prictor, McLaughlin, et al. (2008) Australia	**Purpose:** To assess the effects of providing audio-visual information alone, or in conjunction with standard forms of information provision, to potential clinical trial participants in the informed consent process, in terms of their satisfaction, understanding and recall of information about the study, level of anxiety and their decision whether or not to participate. **Method:** Review. Selection criteria: randomized and quasi-randomized controlled trials comparing audio-visual information alone, or in conjunction with standard forms of information provision, with standard forms of information provision alone, in the informed consent process for clinical trials. Trials involved individuals or their guardians asked to participate in a real clinical study. **Main finding and conclusions:** Four trials involving data from 511 people. Studies were set in the USA and Canada. Their quality was mixed and results should be interpreted with caution. In conclusion, the value of audio-visual interventions for people considering participating in clinical trials remains unclear.
Stiles, Poythress, Hall, et al. (2001) USA	**Purpose:** To evaluate alternative procedures for improving the understanding of research consent disclosures by person who have mental illness. **Sample:** 241 participants aged 18 years or older: persons with schizophrenia (n=79, male 69 %), persons with depression (n=82, male 61 %), and a healthy control group (n=80, male 61 %). **Method:** The participants were guided through an informed consent process in which two factors were manipulated. One was the structure of the disclosure form; either a typical disclosure form involving standard dense text was used, or a graphically enhanced form was used. The other was interpersonal process: the presence or absence of a third-party facilitator, with iterative feedback given to participants for whom a facilitator was not present. Assessed with the recall tests. **Main finding and conclusions:** Neither the graphically enhanced consent disclosure form nor presence of a third-party facilitator was associated with improved understanding. The use of iterative feedback was associated with improvement in comprehension scores in all groups.
Strevel, Newman, Pond, et al. (2007) Canada	**Purpose:** To assess an educational DVD's impact on knowledge and satisfaction in cancer patients newly referred to a phase I clinic. **Sample:** 49 patients (mean age 56.3 years, SD 12.1, male 30) and 8 physicians at a single institution. **Method:** Patients were randomly to view an educational DVD (n=22) which explained phase I trials or a placebo DVD (n=27). Patients completed a questionnaire assessing knowledge of phase I studies and satisfaction with the DVD. The blinded interviewing physician rated the patient's understanding of phase I trials. **Main finding and conclusions:** An educational DVD increased patient knowledge and satisfaction regarding participation in phase I clinical trials.

Author(s)	Purpose, Sample, Method and Main findings and conclusions
Sudore, Landefelt, Williams, et al. (2006) USA	**Purpose:** To describe a modified research consent process, and determine whether literacy and demographic characteristics are associated with understanding consent information. **Sample:** 204 ethnically diverse subjects (male 96, female 108), mean aged 61 years and 40 % had limited literacy. Exclusion criteria: if they had dementia, were deaf, delirious, or not well enough to complete the interview. **Method:** A modified consent process: consent form read to participants, combined with 7 comprehension questions and targeted education, repeated until comprehension achieved. **Main finding and conclusions:** 28 % of subjects answered all comprehension questions correctly on the first pass. Lower literacy and minority status were associated with requiring more passes through the consent process.
Treschan, Scheck, Kober, et al. (2003) Austria	**Purpose:** To evaluate the influence of protocol risk or discomfort and pain on patients' willingness to participate in clinical trials. **Sample:** Patients (n=148) who were scheduled to undergo minor surgery with general anaesthesia. **Method:** Presented one of three sham protocol: no risk of pain (Control, n=47, mean age 47, +/- 13 years, men 55 %), pain but no risk (Pain, n=51, mean age 51, +/- 16 years, men 41 %), or risk but no pain (Risk, n=50, mean age 49, +/- 15 years, men 38 %). Patients were debriefed at the end of the interview. **Main finding and conclusions:** Understanding was poor, but patients who failed to understand the risks or discomforts rarely consented. Patients who felt pressured did not consent. Relatively few patients unknowingly agreed to participate in risky or painful studies. In contrast, patients who understand the risks involved were twice as likely to consent. Thus, patients are willing to participate in risky or painful studies, apparently for altruistic reasons.
Weinfurt, Hall, Friedman, et al. (2008) UK	**Purpose:** To examine the effects of the disclosure of financial interests in a research consent process with patients recruited as they might have been for an actual clinical trial. **Sample:** 470 adults diagnosed with coronary artery disease. **Method:** A telephone survey were participants randomly assigned to receive a simulated informed consent document: per capita payments to the research institution (n=160, mean age 66.7 years, SD 11.5, male 116), equity ownership by the investigator (n=169, mean age 66.8 years, SD 10.4, male 130) or no disclosure (n=141, mean age 67.1 years, SD 11.6, male 101). **Main finding and conclusions:** Although disclosure of investigators' financial interests in research does not substantially affect willingness to participate, potential research participants attach some importance to this information, and they are more troubled by equity interests than by per capita payments that cover the costs of research. A far grater determinant of willingness to participate appears to be people's trust in medical research and researchers.

Author(s)	Purpose, Sample, Method and Main findings and conclusions
Westberg, Duchek, Sandlund, et al. (2004) Sweden	**Purpose:** To study whether or not the provision of written information in advance might influence patients' inclination to participate in the clinical education of medical students at a urology surgery. **Sample:** 42 outpatients referred to the urology surgery. **Method:** Participants were randomly allocated either to receive information in advance (n=19, mean age 60.3 years, male 16) or not (n=23, mean age 60.4 years, male 19). The doctors/teachers nor the students knew in advance to which group a certain patient had been allocated. At the end of visit the patients were asked to complete a questionnaire. **Main finding and conclusions:** The provision of information in advance does not negatively influence patients' inclination to participate in the clinical training of medical students.
Wirshing, Sergi, Mintz. (2005) USA	**Purpose:** To evaluate a brief educational video designed to enhance the informed consent process for people with serious mental and medical illnesses who are considering participating in treatment research. **Sample:** 83 participants: Schizophrenia patients (mean age 37.2 years ,SD 13.9, men 82 %), medical patients without self-reported comorbid psychiatric illness (mean age 59.1 years, SD 12.9, men 82 %) and university undergraduates without obvious medical, cognitive, or psychiatric problems (mean age 21.4 years, SD 7.2, men 40 %) **Method:** Participants were randomly assigned to view either a highly structured instructional videotape about the consent process in treatment research or a control videotape that presented only general information about bioethical issues in human research. Knowledge about informed consent was measured by questionnaire before and after viewing. **Main finding and conclusions:** The videotape was an effective teaching tool across diverse population, ranging from individuals with severe chronic mental illness to university students.
Wolf, Schorling. (2000) USA	**Purpose:** To assess the impact of informed consent on elderly patients' colorectal cancer (CRC) screening preferences. **Sample:** 399 elderly patients visiting their primary care provider for routine office visit. **Method:** Patients were randomized to receive a scripted control message briefly describing CRC screening method (n=133, mean age 75 years, SD 6, male 38 %), informational intervention described CRC mortality risk reduction in relative terms (n=130, mean age 74 years, SD 6, male 37 %), or informational intervention described CRC mortality risk reduction in absolute terms (n=136, mean age 74 years, SD 6, male 35 %) **Main finding and conclusions:** Provision of information had no impact on patients' preferences for screening.

Author(s)	Purpose, Sample, Method and Main findings and conclusions
Yuval, Halon, Merdler, et al. (2000) Israel	**Purpose:** To examine the perspective of the Israeli patient cohort who participated in the Fourth International Study of Infarct Survival (ISIS-4), a randomized trial acute myocardial infarction. **Sample:** 150 participants. **Method:** A patient questionnaire was mailed. Main outcome measures included patient perception of consent procedures, comprehension of the study, subjective reaction to participating in the trial, and interest in present and future trials. **Main finding and conclusions:** Despite proper attention to accepted ethical and legal standards, perceived patient comprehension in this trial in acute myocardial infarction was incompetence or lacking in a considerable number of subjects. Much progress must be made toward the goal of true informed consent in clinical trials.

Appendix 2

Information letter to participants

Kuopion liikuntalääketieteen tutkimuslaitos
30.06.2005/hla

TIEDOTE TUTKITTAVALLE

ARVOISA VASTAANOTTAJA

Olette mukana Kuopion liikuntalääketieteen tutkimuslaitoksen liikunta- ja ruokavaliotutkimuksessa (DR's EXTRA). Pyrimme toteuttamaan tutkimusprojektit mahdollisimman hyvin ja tästä syystä haluamme selvittää kuinka tutkimukseen liittyvistä asioista tiedottaminen, ohjaus sekä käytännön järjestelyt ovat toteutuneet Teidän kohdallanne. Näitä asioita selvitämme kyselylomakkeella. Tämä osatutkimus toteutetaan Kuopion liikuntalääketieteen tutkimuslaitoksen, Kuopion yliopiston hoitotieteen laitoksen ja Kuopion yliopistollisen sairaalan kliinisen fysiologian osaston yhteistyöprojektina.

Pyydän Teitä täyttämään oheisen kyselylomakkeen ja palauttamaan sen mukana olevassa kuoressa Kuopion liikuntalääketieteen tutkimus-laitokselle. Postimaksu on maksettu puolestanne. Toivon Teidän vastaavan kahden (2) viikon kuluessa lomakkeen saannista lukien.

Kaikki vastaukset käsitellään nimettöminä ja luottamuksellisesti. Teidän osallistuminen on vapaaehtoista ja kieltäytyminen ei vaikuta Teidän mahdollisuuksiin jatkossa osallistua erilaisiin tutkimushankkeisiin.

Yhteistyöstä kiittäen,

Helena Länsimies-Antikainen

Terveystieteiden maisteri / sairaanhoitaja, tutkija
Kuopion liikuntalääketieteen tutkimuslaitos
Haapaniementie 16, 70100 Kuopio

Appendix 3

Questionnare

OHJEET VASTAAJALLE

Tämän kyselylomakkeen kysymykset koskevat suurimmalta osin nyt meneillään olevaa liikunta- ja ruokavaliotutkimusta (DR’s EXTRA). Liittäkää vastauksenne tähän kyseiseen tutkimukseen, ellei kysymyksessä toisin mainita. Kyselylomake jaetaan jokaiselle tutkimushenkilölle kolmen kuukauden käynnillä.

Lukekaa jokainen kysymys huolellisesti ennen vastaamista. Kysymyksiin vastataan ympyröimällä sopiva vaihtoehto tai kirjoittamalla kysytty tieto sitä varten varattuun tilaan. Jos joudutte korjaamaan jotain vastaustanne, vetäkää virheellinen merkintä yli. Kirjallisissa kysymyksissä kirjoittakaa tarvittaessa sekin, jos Teillä ei ole kysymykseen mielipidettä.

Vastausaikaa Teillä on kaksi (2) viikkoa lomakkeen saannista lukien. Mikäli koette johonkin kysymykseen vastaamisen vaikeaksi, voitte kysyä neuvoa soittamalla Kuopion liikuntalääketieteen tutkimuslaitokselle (puhelin: 017- 288 44 77 tai 288 44 22 / Helena Länsimies-Antikainen).

Täyttöpäivämäärä _____ / _____ 200___

I OSA: TAUSTATIEDOT

1. Sukupuoli

1 Mies
2 Nainen

2. Ikä (vuosina): _____

3. Siviilisääty

1 Avioliitto tai avioliittoa vastaava (avoliitto)
2 Naimaton
3 Eronnut tai asumusero
4 Leski

4. Asuinalue

1 Kaupungissa keskustassa tai muussa taajamassa
2 Kaupungissa keskustan tai taajaman ulkopuolella
3 Maaseudulla kirkonkylässä, asutuskeskuksessa tai muussa taajamassa
4 Maaseudulla kirkonkylän, asutuskeskuksen tai taajaman ulkopuolella

5. Ammattikoulutus

1 Ei ammattikoulutusta
2 Ammattikoulutason tutkinto tai ammattikurssi
3 Opistotasoinen ammatillinen tutkinto (myös amk)
4 Yliopistotasoinen tutkinto
5 Muu, mikä _____

6. Työtilanne

1 Työssä
2 Työtön
3 Eläkkeellä
4 Sairauslomalla
5 Päätoiminen opiskelija
6 Kotiäiti tai –isä
7 Muu, mikä _____

7. Millaiseksi koette terveydentilanne tällä hetkellä?

1 Erittäin huonoksi
2 Huonoksi
3 Kohtuulliseksi
4 Hyväksi
5 Erittäin hyväksi

8. Oletteko itse tai onko joku perheenjäsenenne terveydenhuoltoalan ammattilainen?

1 Olen itse
2 Perheenjäseneni on, kuka _____
3 En ole, eikä perheenjäseneni ole

9. Oletteko ennen DR's EXTRA tutkimusprojektia osallistunut tutkimushenkilönä tutkimusprojektiin?

1 Kyllä
9.1.a. Kuinka monta kertaa (älkää laskeko DR's EXTRA tutkimusprojektia mukaan)? _____
9.1.b. Milloin DR'S EXTRAa edellinen tutkimusprojekti loppui Teidän osaltanne? _____ (kk/vuosi)
2 En

II OSA: TUTKIMUKSEEN SUOSTUMISEN EDELLYTYKSIÄ

10. Mistä/keneltä saitte tiedon DR's EXTRA tutkimusprojektista ensimmäisen kerran?
Valitkaa vain yksi vaihtoehto.

1 Lehti-ilmoituksesta
2 Työpaikalta tiedotteesta (esim. ilmoitustaululta)
3 Työtoverilta
4 Sukulaiselta / omaiselta
5 Tuttavalta
6 Harrastuksen kautta
7 Tutkimuslaitoksen henkilökuntaan kuuluvan yhteydenotosta
8 Edellisen tutkimusprojektin kautta
9 Sairaalasta hoitajalta / lääkäriltä (ympyröikää kumpi kyseisistä henkilöistä)
10 Työterveydenhuollosta terveydenhoitajalta / lääkäriltä (ympyröikää kumpi kyseisistä henkilöistä)
11 Muualta, mistä _____

11. Kenen Kuopion liikuntalääketieteen tutkimuslaitoksen ammattihenkilön kanssa keskustelitte DR's EXTRA tutkimusprojektista ensimmäisen kerran?

1 Lääkärin
2 Hoitajan
3 Sihteerin / toimistotyöntekijän
4 Muun, kenen _____

12. Millä tavoin kävitte ensimmäisen kerran keskustelua edellisessä kysymyksessä mainitun henkilön kanssa?

1 Puhelimessa
2 Henkilökohtaisella tapaamisella
3 Muuten, miten _____

13. Ovatko Teillä tiedossa DR's EXTRA tutkimusprojektin vastuuhenkilöt?

1 Kyllä
2 Ei

14. Oletteko saanut tarvittaessa yhteyden DR's EXTRA tutkimusprojektin yhdyshenkilöön tai henkilökuntaan?

1 Kyllä
2 En
3 Minulla ei tähän mennessä ole ollut tarvetta ottaa yhteyttä

15. Kuka on tähän mennessä huolehtinut DR's EXTRA tutkimusprojektissa ajanvaraukset, yhteydenotot ym. käytännön asiat?

1 Lääkäri
2 Hoitaja
3 Sihteeri / toimistotyöntekijä
4 Muu, kuka _____
5 Ei kukaan tietty, vaan aina eri henkilö

Seuraavasta kysymyksestä eteenpäin aina lomakkeen loppuun asti on joukossa kysymyksiä, joissa pyydetään arvioimaan eri asioita asteikolla 1–5. 1=huonoin vaihtoehto ja 5=paras vaihtoehto. Ympyröikää kunkin kysymyksen kohdalla vain yksi Teille sopivimmalta tuntuva vaihtoehto.

16. Mitä mieltä olette DR's EXTRA tutkimusprojektin ensimmäisellä varsinaisella tutkimuskäynnillä Teille varatusta ajasta?

Täysin riittämätön 1 2 3 4 5 Täysin riittävä

17. Mitä mieltä olette tähän mennessä DR's EXTRA tutkimusprojektista annetun tiedon määrästä?

En ole saanut tietoa lainkaan 1 2 3 4 5 Olen saanut täysin riittävästi tietoa

18. Mitä mieltä olette saamanne tiedon ymmärrettävyydestä?

En ole ymmärtänyt lainkaan 1 2 3 4 5 Olen ymmärtänyt täysin

19. Kuvailkaa omin sanoin, mikä on DR's EXTRA tutkimusprojektin tarkoitus.

_____

_____

_____

20. Kuinka paljon olette saanut tietoa perusteista, miksi Teidät valittiin tutkimushenkilöksi DR's EXTRA tutkimusprojektiin?

En ole saanut tietoa lainkaan 1 2 3 4 5 Olen saanut täysin riittävästi tietoa

21. Kuinka paljon olette saanut tietoa DR's EXTRA tutkimusprojektiin mahdollisesti liittyvistä haitoista?

En ole saanut tietoa lainkaan 1 2 3 4 5 Olen saanut täysin riittävästi tietoa

22. Onko Teillä tiedossa oikeutenne keskeyttää tutkimus missä vaiheessa tahansa?

1 Kyllä
2 Ei

23. Oletteko tähän mennessä harkinnut DR's EXTRA tutkimusprojektin keskeyttämistä?

1 Kyllä, miksi _____
2 En

24. Kuinka paljon olette saanut tietoa DR's EXTRA tutkimusprojektin rahoituksesta ja mahdollisista "sponsoreista"?

En ole saanut tietoa lainkaan 1 2 3 4 5 Olen saanut täysin riittävästi tietoa

25. Kuinka paljon olette saanut tietoa tutkijoiden taloudellisista sidoksista DR's EXTRA tutkimusprojektiin?

En ole saanut tietoa lainkaan 1 2 3 4 5 Olen saanut täysin riittävästi tietoa

Seuraava kysymys (26) koskee mielipidettänne tutkimusprojektien rahoitukseen liittyvästä tiedottamisesta, eikä koske vain DR's EXTRA tutkimusprojektia.

26. Kuinka tärkeänä koette tutkimusprojektin rahoitusta koskevan tiedon saamisen?

En lainkaan tärkeänä 1 2 3 4 5 Erittäin tärkeänä

27. Onko Teillä tietoa kuinka DR's EXTRA tutkimusprojektista saadut tulokset on suunniteltu raportoitavan ja julkaistavan?

1 Kyllä
2 Ei

28. Olisitteko tarvinnut DR's EXTRA tutkimusprojektiin liittyen joistakin asioista enemmän tietoa?

1 Kyllä, mistä asioista _____

2 En

III OSA: TUTKIMUSPROJEKTIIN OSALLISTUMISTA KOSKEVA PÄÄTÖKSENTEKO

Seuraavat kaksi kysymystä (29–30) koskevat mielipidettänne eri tutkimusprojekteista, eivätkä tarkoita vain meneillään olevaa DR's EXTRAa. Mikäli Te ette ole aikaisemmin ollut tutkimushenkilönä, vastatkaa DR's EXTRA tutkimusprojektin perusteella. Teillä ei tarvitse olla omakohtaista kokemusta jokaisesta kysyttävästä asiasta, vaan niin sanottu mielikuva riittää. Täyttäkää jokainen kysyttävä kohta (1–9).

29. Kuinka paljon seuraavat asiat voivat mielestänne vaikuttaa haluun osallistua tutkimusprojekteihin?

Asteikko on samanlainen kuin aikaisemmissa kysymyksissä eli
1=Kyseinen asia ei mielestäni vaikututa lainkaan haluun osallistua
5=Kyseinen asia vaikuttaa mielestäni erittäin suuresti haluun osallistua.

1	Halu auttaa muita	1	2	3	4	5
2	Apua omaan sairauteen	1	2	3	4	5
3	Läheisen henkilön sairaus	1	2	3	4	5
4	Mahdollisuus päästä hoitoon/tutkimuksiin	1	2	3	4	5
5	Halu miellyttää tutkimushenkilöstöä	1	2	3	4	5
6	Pelko sairaalan henkilökunnan suuttumisesta	1	2	3	4	5
7	Muut läheiset ovat osallistuneet	1	2	3	4	5
8	Työpaikalla moni on osallistunut	1	2	3	4	5
9	Muu vaikuttava asia, mikä					
	_____	1	2	3	4	5

30. Ympyröikää henkilöt, jotka voivat mielestänne vaikuttaa tutkimusprojekteihin osallistumista koskevaan päätöksentekoon. Voitte valita useamman vaihtoehdon.

1 Tutkijalääkäri
2 Tutkimushoitaja
3 Muu tutkimusprojektiin kuuluva henkilö (esim. ravitsemusterapeutti)
4 Lääkäri (muu kuin tutkimusprojektissa toimiva)
5 Hoitaja (muu kuin tutkimusprojektissa toimiva)
6 Osastonsihteeri / toimistotyöntekijä
7 Omainen
8 Tuttava
9 Muu vaikuttava henkilö, kuka _____

31. Oliko Teille mahdollisuus rauhassa harkita osallistumista DR's EXTRA tutkimusprojektiin?

1 Kyllä
2 Ei

32. Kuinka kauan harkitsitte osallistumistanne?

_____

33. Millaiseksi koitte DR's EXTRA tutkimusprojektiin osallistumista koskevan harkinta-ajan riittävyyden?

En saanut harkinta-aikaa lainkaan 1 2 3 4 5 Sain täysin riittävästi aikaa

34. Keskustelitteko kenenkään ulkopuolisen (= ei tutkimuslaitoksen henkilökuntaan kuuluvan) henkilön kanssa DR's EXTRA tutkimusprojektista ennen suostumustanne?

1 Kyllä, kenen _____
2 En

35. Koetteko osallistuvanne DR's EXTRA tutkimusprojektiin vapaasta tahdosta ja ilman painostusta?

1 Kyllä
2 En, miksi _____

36. Tunnetteko velvollisuudeksenne osallistua DR's EXTRA tutkimusprojektiin?

1 Kyllä, miksi _____
2 En

37. Kuinka tutkimushenkilöstö varmisti tutkimuksen alussa, että olitte saanut riittävästi tietoa DR's EXTRA tutkimusprojektiin liittyen?

Tiedonsaantia ei varmistettu lainkaan 1 2 3 4 5 Täysin riittävästi

38. Kuinka tutkimushenkilöstö varmisti tutkimuksen alussa, että olitte ymmärtänyt DR's EXTRA tutkimusprojektista saamanne tiedon?

Ymmärtämistä ei varmistettu lainkaan 1 2 3 4 5 Täysin riittävästi

39. Suostumuksen antaminen DR's EXTRA tutkimusprojektiin.

1 Annoin suostumuksen suullisesti.
2 Annoin suostumuksen kirjallisesti ennakkoon.
3 Annoin suostumuksen kirjallisesti tutkimushenkilöstöön kuuluvan todistamana ensimmäisellä tapaamisella ennen tutkimusten alkua ja sain itselleni kopion, jossa on myös vastaanottajan allekirjoitus.
4 Annoin suostumuksen kirjallisesti tutkimusten jo käynnistyttyä.
5 Minulta ei kysytty varsinaisesti suostumusta, vaan saapumiseni tapaamiseen katsottiin ikään kuin myöntymiseksi.
6 Muuten, miten _____

40. Saatteko korvausta osallistumisestanne DR's EXTRA tutkimusprojektiin?

1 Kyllä
2 En
3 En tiedä

Mikäli vastasitte edelliseen kysymykseen (40) kyllä, vastatkaa myös kysymyksiin 41–44.

41. Mitä ja kuinka paljon saatte korvauksena? (esimerkiksi matkakulukorvaus, korvaus menetetystä työajasta, selvät rahakorvaukset, mainostuotteet jne.)

_____
_____
_____

42. Mikäli saatte korvausta, niin tiedättekö kuka on maksaja?

1 Kyllä
2 En

43. Mikäli saatte korvausta, niin tiesittekö siitä ennen kuin olitte tehneet DR's EXTRA tutkimusprojektiin osallistumista koskevan päätöksen?

1 Kyllä
2 En

44. Mikäli vastasitte edelliseen kysymykseen (43) kyllä, niin vaikuttiko tieto korvauksesta päätökseenne osallistua DR's EXTRA tutkimusprojektiin?

1 Kyllä, miten _____
2 Ei

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