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EMMI REIJULA

INDICATORS OF THERAPEUTIC MISCONCEPTION AND WILLINGNESS TO PARTICIPATE IN CLINICAL DRUG TRIALS:

A survey among patients with epilepsy and Parkinson's disease

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ABSTRACT

Clinical trials are necessary for the development of evidence-based treatment. However, their success depends on patients' willingness to volunteer and the overall process related to trials. Study design, persuasion, and personal experiences all can influence patients' willingness to participate. Epilepsy and Parkinson's disease are prevalent neurological disorders; however, no curative medicines are yet available for either of them, and treatment for both conditions is actively sought. Accordingly, work was carried out to investigate the knowledge of and attitudes toward clinical drug trials of patients with epilepsy and Parkinson's disease, including both patients who had participated in clinical trials and patients who had not. Moreover, factors in willingness to participate and the evaluation of experiences with the informed consent process were studied.

Questionnaires on the views of clinical trials held by patients with epilepsy and Parkinson's disease were developed. These utilised statements that the respondents assessed on a Likert scale ranged from 1 ("strongly disagree") to 5 ("strongly agree"). The questionnaires were mailed to a random sample (n = 1,875) of members of the Finnish Epilepsy Association in 2013 and a random sample (n = 2,000) of members of the Finnish Parkinson Association in 2014. In total, 342 forms (17%) were returned by the patients with epilepsy and 708 (35%) by the patients with Parkinson's disease.

The attitudes of patients with epilepsy and Parkinson's disease toward clinical trials were mostly positive. However, age, education level, and number of medications were significant predictors of failure to understand the nature and purpose of the clinical research. Additionally, correlation was found between therapeutic misconception and respondents' willingness to participate in clinical trials. A significant correlation was also seen between education level and willingness to take part. In addition, patients had difficulties in recognising the concept of randomisation, and 57% of both those who had taken part in a clinical trial and patients who had not indicated a belief that clinical trials are aimed primarily at seeking the best medication for the individual participant. This notwithstanding, 83% of clinical trial participants reported ability to understand the information provided.

There are important gaps in patients' knowledge of methodological issues associated with clinical trials. The oldest subjects, the seriously ill, and people with a low level of education have the greatest information needs. Investigators should be able to recognise vulnerable individuals and pay special attention to the information provided about the purposes and methods of the trial, so as to contribute to high-quality studies. Moreover, recruitment strategies demand further comprehensive development – patients' preconceptions must be considered and discussed with the potential participants.

National Library of Medicine Classification: W 85; QV 771.4; W 20.55.H9; WL 385; WL 359
Medical Subject Headings: Clinical Trials as Topic; Patient Participation; Motivation; Informed Consent; Therapeutic Misconception; Epilepsy; Parkinson Disease; Drug Therapy; Surveys and Questionnaires

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Terapeuttisen väärinymmärryksen indikaattorit ja halukkuus osallistua kliinisiin lääketutkimuksiin: Kysely epilepsiaa ja Parkinsonin tautia sairastaville potilaille
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TIIVISTELMÄ

Kliiniset lääketutkimukset ovat välttämättömiä näyttöön perustuvan hoidon kehittämiseksi. Lääketutkimusten onnistuminen edellyttää halukkaita vapaaehtoisia tutkimukseen osallistuvia potilaita sekä onnistunutta tutkimusprosessia. Tutkimusasetelma, suostuttelu ja henkilökohtaiset kokemukset voivat vaikuttaa potilaiden osallistumishalukkuuteen. Epilepsia ja Parkinsonin tauti ovat yleisiä neurologisia sairauksia. Kuitenkaan nykyisin näihin sairauksiin ei ole saatavilla parantavaa lääkitystä. Uusia lääkehoitoja epilepsiaan ja Parkinsonin tautiin tosin tutkitaan aktiivisesti.

Tämän väitöskirjatyön tarkoituksena oli tutkia, mitä henkilöt, jotka sairastavat epilepsiaa ja Parkinsonin tautia tietävät kliinisistä lääketutkimuksista sekä millaisia asenteita lääketutkimuksiin kohdistuu. Tutkimuksessa oli mukana aikaisemmin lääketutkimuksiin osallistuneita potilaita sekä potilaita, jotka eivät olleet aiemmin osallistuneet lääketutkimuksiin. Lisäksi tutkimuksessa selvitettiin, mitkä tekijät vaikuttavat potilaiden halukkuuteen osallistua lääketutkimuksiin sekä aikaisempia kokemuksia tietoon perustuvasta suostumuksesta.

Tutkimuksessa kehitetyn kyselylomakkeen avulla selvitettiin epilepsiaa ja Parkinsonin tautia sairastavien henkilöiden näkemyksiä lääketutkimuksista. Kyselyt sisälsivät väittämiä, joita vastaajat arvioivat käyttämällä Likert-asteikkoa yhdestä (”täysin eri mieltä”) viiteen (”täysin samaa mieltä”). Kyselylomakkeet lähetettiin, satunnaisotantaa käyttäen, Epilepsialiiton jäsenille (n = 1,875) vuonna 2013 ja Suomen Parkinson-liiton jäsenille (n = 2000) vuonna 2014. Yhteensä epilepsiaa sairastavat henkilöt palauttivat 343 (17%) kyselylomaketta ja Parkinsonin tautia sairastavat henkilöt 708 (35%) lomaketta.

Epilepsiaa ja Parkinsonin tautia sairastavien henkilöiden asenteet kliinisiä lääketutkimuksia kohtaan olivat useimmiten myönteisiä. Kuitenkin ikä, koulutustaso ja lääkkeiden lukumäärä ennustivat, että henkilöillä tulisi olemaan vaikeuksia ymmärtää kliinisen tutkimuksen luonnetta ja tarkoitusta. Tutkimuksissa havaittiin terapeuttisen väärinymmärryksen ja vastaajien osallistumishalukkuuden välillä korrelaatio. Lisäksi koulutustaso ja osallistumishalukkuus korreloivat keskenään. Toisaalta potilailla oli vaikeuksia tunnistaa satunnaistamisen merkitys. Tutkimuksessa havaittiin, että 57% sekä aiemmin lääketutkimuksiin osallistuneista potilaista että potilaista, jotka eivät olleet aiemmin osallistuneet, ilmoittivat, että lääketutkimuksissa ensisijaisesti etsitään parasta lääkettä tutkimukseen osallistuville potilaille. Kuitenkin 83% aikaisemmin lääketutkimukseen osallistuneista potilaista koki, että he olivat ymmärtäneet oikein tutkimuksesta annetun tiedon.

Potilailla on merkittäviä puutteita tiedoissaan liittyen lääketutkimuksien metodologisiin kysymyksiin. Vanhimmilla, matalan koulutuksen saaneilla ja vakavasti sairailla henkilöillä on suurimmat tiedon tarpeet. Tutkijoiden tulisi pystyä tunnistamaan haavoittuvassa asemassa olevat henkilöt ja kiinnittämään erityistä huomiota siihen tietoon, joka koskee tutkimuksen tarkoitusta ja menetelmiä, joita siinä käytetään laadukkaiden tutkimusten edistämiseksi. Lisäksi rekrytointistrategiat vaativat aikaisempaa laajempaa kehitystä: potilaiden lääketutkimuksiin liittyvät ennakkokäsitykset on otettava huomioon ja niistä on tärkeää keskustella rekrytoitavan kanssa.

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Yleinen Suomalainen asiasanasto: kliiniset kokeet; kliininen farmakologia; osallistuminen; asenteet; tiedontarve; tietoon perustuva suostumus; epilepsia; Parkinsonin tauti; lääkehoito; kyselytutkimus

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Kuopio, August 2018

Emmi Reijula

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I Reijula, E., Halkoaho, A., Pietilä, A.-M., Selander, T., Kälviäinen, R., & Keränen, T. Therapeutic misconception correlates with willingness to participate in clinical drug trials among patients with epilepsy – need for better counselling. *Epilepsy & Behavior 48*: 29–34, 2015.

II Reijula, E., Pietilä, A.-M., Halkoaho, A., Selander, T., Martikainen, K., Kälviäinen, R., & Keränen, T. Clinical features of Parkinson's disease patients are associated with therapeutic misconception and willingness to participate in clinical trials. *Trials 18*: 444, 2017.

III Reijula, E., Halkoaho, A., Pietilä, A.-M., Selander, T., Martikainen, K., Kälviäinen, R., & Keränen, T. Comparable indicators of therapeutic misconception between epilepsy or Parkinson's disease patients between those with clinical trial experience and trial non-participants. *Seizure 60:* 61–67, 2018.

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Abbreviations

AED	Antiepileptic drug
CT	Clinical trial / clinical drug trial
FDA	U.S. Food and Drug Administration
FIMEA	Finnish Medicines Agency
GCP	Good clinical practice
ILAE	International League Against Epilepsy
RCT	Randomised controlled trial
REC	Research ethics committee
UNESCO	United Nations Educational, Scientific and Cultural Organization
U.S.	United States of America
USD	United States dollar
TM	Therapeutic misconception
TMis	Therapeutic misestimation
TO	Therapeutic optimism
TUKIJA	National Committee on Medical Research Ethics
WHO	World Health Organization
WMA	World Medical Association

1 Introduction

Clinical trials (CTs) are seen as the gold standard of producing evidence related to the effectiveness of health-care interventions. In addition, development of new medicines involves a long and costly process. Before clinical research can be carried out, the intervention must be tested in pre-clinical studies. After this, clinical trials with drugs are divided into four phases to confirm the efficacy and determine the optimal dose of the drug. Each phase builds on the results of the phase before it. These studies call for patients who have the illness for which the drug is being developed. However, success depends on more than this, including patients' willingness to volunteer and the overall process related to the CT in question. Recruitment problems are reported to be commonplace (Briel et al. 2016); however, some studies indicate that most patients are willing to enrol yet very few are invited to participate (DasMahapatra et al. 2017). In addition, patients may withdraw after recruitment, which poses a risk of compromising the study's validity (Stevens et al. 2013).

CTs are aimed at answering scientific questions: is a specific intervention safer, better tolerated, or more effective than the reference treatment for the given health condition? The protocol to answer this question often involves randomisation, blinding of researchers and participants, restriction on dosing, limits to adjunctive treatments, and additional testing to determine the outcome of an intervention. These procedures differ greatly from clinical care. Indeed, their use in routine medical care might even be unethical, because they limit the tailoring of treatment to individual patients' needs and pose a risk of exposing patients to unnecessary harm. (Christopher et al. 2017).

However, without CTs there would be no new drugs and no evidence-based development of treatments. In principle, a large part of the general population perceives CTs positively. To protect patients, an internationally accepted standard stipulates that participants must give informed consent before enrolment in a trial (Ndebele 2013). It presumes that the subject understands what he or she is committing to and is consenting voluntarily. However, informed consent can be compromised if the patient fails to recognise the differences between research and the standard treatment and also if he or she has a strong expectation of gaining health benefits by participating in the trial (Keranen, Pasternack & Halkoaho 2017). When patients fail to grasp key differences between participating in a CT and receiving ordinary clinical care, they are said to manifest therapeutic misconception (TM) (Appelbaum, Lidz & Grisso 2004). This misconception is an important and prevalent ethics issue connected with consent to clinical trials (Henderson et al. 2007).

Knowledge of and attitudes towards CTs and factors affecting willingness to participate are subject to extensive study among cancer patients. According to a literature review and our research group's clinical experience, patients with neurological disorders, in contrast, have been underrepresented or no data are available for them. While epilepsy and Parkinson's disease (PD) are common neurological disorders worldwide, with both conditions being treated mainly with appropriate medications, currently no curative medicines are available for either. Moreover, significant therapeutic needs remain unmet. These factors can be seen to justify CTs in this context. A thesis project was carried out with the overall aim of describing and analysing knowledge of clinical drug trials and attitudes toward them among patients with epilepsy and PD, including both patients who had participated in CTs and patients who had not. In addition, factors influencing willingness to participate and evaluations of experiences of the informed consent process were studied. Among other things, it was concluded that investigators' recognition of the patients'

information needs and attitudes could greatly enhance recruitment and contribute to high-quality trials.

2 Review of the literature

2.1 CLINICAL TRIALS

Research and investigations of various types have been a part of medicine since the beginning of modern history. The modern development of clinical trials started in the 18th century when James Lind conducted comparative trials and evaluated six treatments for scurvy in 12 patients. In this study, one of the two who were given oranges and lemons made a full recovery. A clinical trial can be defined as a prospective study comparing the effect and value of one or more interventions against a control in human beings (Friedman, Furberg & DeMets 2010). The Finnish Medical Research Act (488/1999) defines clinical drug trials as 'interventional research on persons for the purpose of finding out effects of a medical product in human as well as its absorption, distribution, metabolism or excretion in the human body'. That national legislation uses the term 'clinical trial on medical products'; however, this study refers instead to clinical drug trials or clinical trials, in line with European Union materials (EU 535/2014).

According to the largest database of clinical trials, there were 263,863 open CTs worldwide in January 2018, of which 124,675 alone involved drug or biological research (ClinicalTrials.gov 2018). In the 1990s, Europe held the leading position in the pharmaceutical market. The market has changed since then, though, and 41% of the market was in North America as early as 2012 (Lääketeollisuus 2018). United States (U.S.) development of a new medicine from drug discovery through to Food and Drug Administration (FDA) approval takes at least 10 years and brings an average cost of 2.6 billion United States dollars (USD). In addition, fewer than 12% of the candidate medicines (in 'Phase I') ultimately get approved by the FDA (PhRMA 2015). In 2016, Finnish Medicines Agency FIMEA, the national authority responsible for regulating pharmaceuticals in Finland, received 181 notifications pertaining to the start of a new CT (this number covers phases I–IV, as described below) (Finnish Medicines Agency 2017).

Before CTs are carried out, the experimental drugs must be tested in pre-clinical studies in cells, tissues, and animal models, which typically take 3–5 years on its own. After pre-clinical testing, clinical drug trials can begin. These are commonly divided into four phases (as shown in Figure 1 and discussed below), with the phases designed to respond to different types of clinical questions.

2.1.1 Types of clinical trials

Open trials: In an unblinded or open trial, both the investigator and the research subject are aware of which intervention the participant has been assigned. In this type of trial, placebo control is not used. An open trial setting may be used in such contexts as surgical procedures, comparisons of devices with medical treatment, and changes of lifestyle. (Friedman, Furberg & DeMets 2010).

Blinded trials: In the procedure known as blinding, one or more parties to the trial are kept unaware of the treatment assignments. In a single-blind setting, only the investigator knows which intervention each participant is receiving. Double-blinding is usually used in drug trials. In a double-blind study, neither the study subjects nor the investigators responsible for following the participants, collecting the data, and assessing results should be aware of the intervention assignment. Ideally, a CT should have a double-blind design, so as to avoid potential for problems of biasing during the data-collection phase and assessment. (Friedman, Furberg & DeMets 2010).

Randomised trials: Randomised controlled trials (RCTs) are the foundation for evidence-based medicine. Biasing of CT results can be minimised by designing well-controlled studies, using blinding, and employing procedures that randomise participants to various arms of the study. Randomisation is a process of assigning trial participants to treatment or control groups wherein an element of chance is applied to determine the assignments, for purposes of reducing bias. Randomisation is the preferred method for assigning participants to the various arms of a CT unless another method, such as historical or literature controls, can be justified scientifically and ethically. (Friedman, Furberg & DeMets 2010). Moreover, in some cases there might be a shortage of control groups or the study would require RCTs with extremely large sample sizes and may therefore best be assessed by different type of studies.

Comparative trials: In a comparative study or controlled study, participants are grouped into clusters, with one group of participants receiving the treatment under investigation while one or more control group receives either standard treatment or a **placebo**. Commonly, RCTs feature comparative designs – e.g., use of placebo control (placebos are substances that are inactive for the condition being studied yet appear identical to the investigational treatment. (Friedman, Furberg & DeMets 2010). Use of a placebo can strengthen the rigour of a CT as well as enhance the evaluation of the results (World Health Organization 2002, Lo 2010).

Superiority and equivalence or noninferiority trials: A superiority trial assesses whether the new intervention is better or worse than the control, while an equivalence trial determines whether the new intervention is roughly equal in effect to the control. A noninferiority trial evaluates whether the new intervention is no worse than the control by some margin, delta (δ). (Friedman, Furberg & DeMets 2010).

The series of phases in the development of a novel drug involves the four stages referred to above, where each has its own objectives in establishing the efficacy and safety of the drug.

2.1.2 Phases (I - IV) of clinical trials

Phase-I trials are the first step in the clinical development of new medicines. Primary focus in Phase 1 is on determining the safety profile and recommending an appropriate dosage range for Phase-2 trials. Normally Phase-1 trials are carried out with healthy volunteers or very small patient groups. Researchers should carefully address the information provided to the people recruited for Phase-1 trials and be sure that there is no prior evidence related to safety in humans or other effects on human patients. (Friedman, Furberg & DeMets 2010).

Phase-II trials are preliminary therapeutic studies. These trials are aimed at ascertaining the appropriate dosage range and investigating the safety of the drug, in addition to finding preliminary evidence of its efficacy. Participants are usually selected carefully, with narrow inclusion criteria. (Friedman, Furberg & DeMets 2010).

Patients reflective of the available treatment are often recruited in Phase-2 and Phase-3 studies. In **Phase-III studies**, promising new drugs usually are compared with a standard medical treatment or a placebo drug. These trials are usually randomised, blinded, and controlled. Phase 3 is fundamental to determining whether the drug is safe and effective. On the basis of the results of these trials, a competent regulatory agency (in Finland, FIMEA) can issue marketing authorisation. (Friedman, Furberg & DeMets 2010, Finnish Medicines Agency 2017).

After licensing for marketing, **Phase-IV studies** (post-marketing studies) can be conducted. These trials are conducted principally to study safety and interactions of the medicines in the target patient population. (Friedman, Furberg & DeMets 2010).

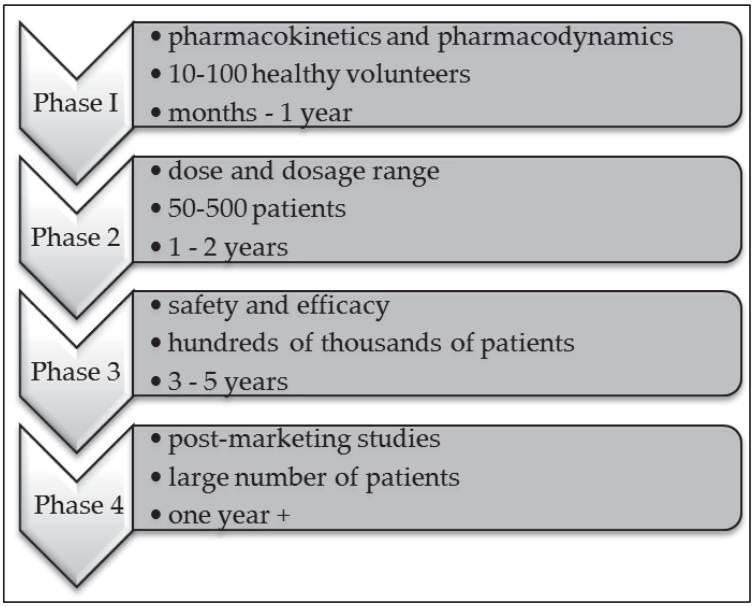

Figure 1. The four phases for clinical trials.

2.1.3 Differences between clinical trials and medical care

Medical care and clinical trials are similar in the underlying set of values; both emphasise beneficence and non-maleficence, integrity and human dignity, and respect for autonomy and justice (Beauchamp, Childress 2013). Clinical medicine aims to provide individual patients with optimal care. In contrast, a CT is committed to answering scientific questions in order to produce generalisable knowledge – the physician-investigators conduct CTs to evaluate experimental treatment in groups of patients, with the ultimate goal of benefiting future patients by improving medical care. (Miller, Rosenstein 2003). At the same time, some patients may gain therapeutic benefits from participating in clinical trials – benefits that could even surpass those of standard medical care (Braunholtz, Edwards & Lilford 2001). Especially on account of this, it is important to stress that RCTs differ significantly from standard care (see Table 1), in, among other things, their purpose, characteristic methods, and justification of risks.

The interventions evaluated in randomised trials are allocated on the basis of chance. In another element noted above, double-blind conditions and placebo controls often are used. For scientific reasons, protocols governing CTs typically restrict flexibility in the dosage of the drugs studied and in the use of concomitant medication. Trials often require drug washout before randomisation – i.e., establishment of a drug-free baseline from which to assess the efficacy of treatment. Research interventions such as blood sampling, imaging, and biopsies are often used to measure trial outcomes. These strictly research-based interventions pose risks to participants that are not offset by medical benefits but that are justified by the potential value of knowledge to be gained from the trial. (Miller, Rosenstein 2003). Moreover, participants in RCTs are insured by the sponsor against claims for any trial-related injuries (World Health Organization 2002).

Table 1. The main differences between a clinical trial and medical care (Miller, Rosenstein 2003, Keränen, Pasternack 2015).

	Clinical trial	**Medical care**
Aim	1. General benefit: the aim is to answer scientific questions so as to produce generalisable knowledge and benefit future patients	1. Patient personal benefit: the aim is to provide the treatment that is best for the individual patient
Selection of the intervention	a. Study participants are often randomised to the intervention groups	a. The intervention is selected patient-specifically
Execution of the intervention	I. Dosing of the study drug, follow-ups, and medical interventions are tightly bound to the study protocol II. There is the possibility of a placebo III. Potential risks and harm are not necessarily known	I. The treatment method, dosing of the drug, and follow-up are tailored to the individual II. Only effective treatment methods are used III. Potential risks and harms are usually well known
The researcher's or physician's aims and course of action	1. The researcher aims to gather generalisable knowledge 2. There is the possibility of a placebo 3. Researchers cannot affect which intervention group a participant is selected for or randomised to 4. Researchers cannot dictate the dosage of the drug or follow-ups; the protocol determines them	1. The physician applies the best available treatment in order to help each specific patient 2. The physician selects treatment individual-specifically 3. The physician designs the dosage and the follow-ups to suit each individual patient

2.2 ETHICS IN CLINICAL TRIALS

2.2.1 Basic ethics principles

Ethics is a core component of all scientific research, and commitment to principles of sound research ethics is an essential feature in planning and conducting any scientific research (Friedman, Furberg & DeMets 2010). In addition, a researcher's personal commitment to ethics and practical principles for applying research ethics are guided by national and international guidelines and by legislation. In clinical trials, the rights, safety, and dignity and well-being of the study participant should be protected. The best interest of the participant should always take priority over all other interests. The data produced in the study should be reliable and robust. (EU 535/2014). These are the key ethical values guiding all clinical trials at a higher level and in their implementation.

Respect for human dignity is fundamental to clinical trials, and the value of dignity was already recognised in 1948, in the United Nations Universal Declaration of Human Rights. Article 1 underscores that 'all human beings are born free and equal in dignity and rights. They are endowed with reason and conscience and should act towards one another in a spirit of brotherhood'. Also, it is enshrined in the Constitution of Finland (731/1999) that everyone has the right to life, personal liberty, integrity, and security.

The concept of autonomy encompasses liberty, privacy, and self-governance (Beauchamp, Childress 2001). Personal autonomy can be understood as self-rule, without one being controlled by others or being subject to limitations such as deficient understanding. (Varelius 2006). In the field of research ethics, autonomy has been linked to informed consent. The informed consent process has been seen as a key aspect of all scientific research involving human subjects and thus incumbent upon all researchers. The essential content of this process is the provision of the relevant information to a person who is competent to make a decision and who is acting voluntarily. (Ndebele 2013, Tam et al. 2015). Beauchamp and Childress (Beauchamp, Childress 2001) have listed three facets of informed consent: I) threshold elements, consisting of competence and voluntariness; II) information elements, which consist of material information, recommendation of a plan, and understanding; and III) consent elements: decision and authorisation for a selected plan. The main purpose of the informed consent process is to preserve the autonomy of the research participant and avoid harm. Thereby, the informed consent process contributes to both rational decision-making and autonomy. The core idea of voluntariness is that people must not be forced to participate in research. But this is not the only important element: autonomy, voluntariness, and privacy all form an essential part of informed consent. (Beauchamp, Childress 2001).

Privacy can be interpreted as referring to physical, psychological, social, and informational privacy, where the last of these has been linked to confidentiality (Leino-Kilpi et al. 2001). Confidentiality of personal information can be considered a particular case of privacy protection in research (Beauchamp, Childress 2001).

Justice as a principle of ethics can be thought of in terms of fairness and equity. One fundamental question in research is who should receive the benefits arising from research and, on the other hand, who must bear the risks and burdens. According to Beauchamp and Childress (Beauchamp, Childress 2001), the term 'distributive justice' is applicable; it implies that the selection criteria for research participants should always be related to the aim of the research and based on scientific literature.

Beneficence and non-maleficence: The principle 'do no harm' has been seen as essential to medical research since the formulation of the Hippocratic Oath. The principles of beneficence and non-maleficence together impose a moral obligation to maximise benefit and minimise harm caused by research to the participant. Therefore, it is crucial that all research projects be exposed to solid assessment of risk and benefits. (Beauchamp, Childress 2001). This assessment is indispensable in clinical trials. It is unacceptable to prioritise the expected benefits to society over the welfare of an individual research participant. In the evaluation of risk/benefit, all of these elements must be present: risks' identification, estimation, and evaluation. Additionally, the benefits of the research must always be greater than the potential risk to the participant. (Beauchamp, Childress 2001). In CTs, beneficence can be seen as primarily related to promoting the well-being of future patients, while non-maleficence imposes limits on the risks to which research participants are exposed for the benefit of future patients and society. (Miller, Rosenstein 2003).

To assist in application of principles of ethics in practice, Emanuel and colleagues (Emanuel, Wendler & Grady 2000) have proposed certain ethics-related requirements to be followed when one is conducting CTs. Mindful of that fact that, according to researchers, informed consent – seen as fundamental to promoting ethical research – does not necessarily guarantee that research is always ethical, they list seven requirements that together systematically form a coherent framework for evaluating the ethics of a clinical trial (see Figure 2).

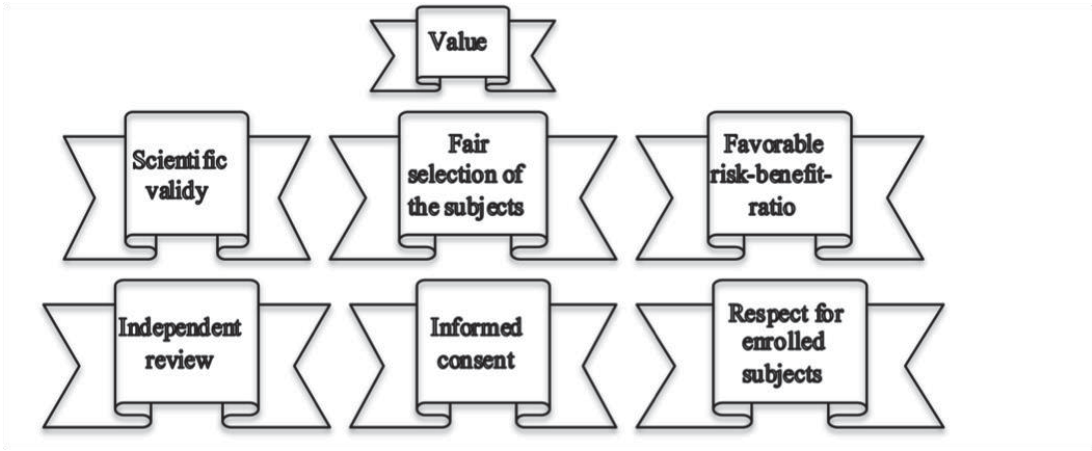

Figure 2. The seven ethical requirements of clinical trials (Emanuel, Wendler & Grady 2000).

2.2.2 Ethics issues in study designs

RCTs commonly include comparative designs. Use of placebos raises some ethical concerns. For instance, participants will not always be given active treatment; they may instead receive a placebo and possibly be harmed thereby. To fulfil requirements of informed consent, the adequate information supplied must include understandable descriptions of the function of placebos and their effects. (Blease, Bishop & Kaptchuk 2017).

The Declaration of Helsinki states that the benefits, risks, burdens, and effectiveness of the new intervention must be studied against the best-proven intervention. Placebos are ethically acceptable under circumstances in which no proven intervention exists or alternative study designs will not produce valid conclusions. Furthermore, compelling and scientifically sound methodological reasons, such as evaluation of the efficiency and trials internal validity, must exist for the use of any intervention less effective than the best proven one in determination of the efficacy or safety of the experimental intervention. Moreover, the additional social value gained by using placebo control must justify the additional risks of using placebo. (World Medical Association 2013, Millum & Grady 2013). However, information about placebos is often incomplete and inaccurate, contributing to participants' misunderstandings (Blease, Bishop & Kaptchuk 2017). A Finnish study of 52 randomised trials revealed that only 35% of disclosure protocols stated a rationale for the use of placebos in the trial. Of these statements, only 23% characterised why placebo use was necessary in the study, and only 12% addressed possible adverse effects of placebos. The study suggests participants need to be better informed of the rationale for the use of placebo. (Keranen et al. 2015). That said, scientists may have justifications for failing to inform patients about placebo effects. One argument is that such disclosures risk sabotaging the methodological integrity of CTs. (Kam-Hansen et al. 2014). Additionally, even if placebo or drug responses may be affected by them, the Declaration of Helsinki makes it clear that informed consent concerns take priority over research methodology (World Medical Association 2013). In addition, there is evidence that placebos have measurable effects on many symptoms – e.g., pain, depression, and fatigue. When patients receive attention from medical professionals for their symptoms and then receive a treatment (even if that treatment is a placebo), the brain can release neurotransmitters and areas of the brain that help to relieve symptoms may be engaged, in a 'placebo effect'. For certainty about the ethicality of the research, it is crucial that participants be aware of the possibility of a placebo. (Blease, Bishop & Kaptchuk 2017).

Similar ethics concerns exist in relation to use of randomisation. However, randomisation is an essential method for reducing bias in clinical trials. Both people asked to participate and those actually taking part in studies seem to poorly comprehend the meaning of randomisation. This is probably due to unclear or complicated description of the method in study information material given to the participants (announcements, handouts, bulletins, and press releases). (Kass, Maman & Atkinson 2005, Locock, Smith 2011a). In a Finnish study, only 23% of volunteers understood the meaning of randomisation and that they had been randomised into treatment groups (Hietanen et al. 2000).

The term 'clinical equipoise', associated with the ethical justification of randomisation, refers to a real uncertainty as to the superiority of research-based and comparative treatment and that the treatments to be compared are basically equal in efficacy (Freedman 1987). If the condition of clinical equipoise is met, the participants shall be not deliberately exposed to a treatment that is inferior to the comparator and, hence, the study is ethically acceptable (Miller, Rosenstein 2003). In addition, randomisation may harm participants if they receive a less effective or riskier intervention (Lo 2010).

2.2.3 Transgression of codes of ethics and the establishment of international guidelines

Research conducted with human subjects has not always been ethically based. During the Second World War, Nazi physicians conducted various types of inhuman and cruel medical research on prisoners, including racial-anthropological research, brain research and neurology experiments, military medical research, and genetic experiments. Additionally, experiments were conducted on children, persons with disabilities, and mentally ill patients. Physicians and medical and biological researchers had central roles in the Holocaust, and they saw killings as an opportunity for research. The killing procedures included poison gas, phenol injections, and calculated use of starvation. Importantly, most of the research was scientifically worthless, poorly planned, and often replicating research results that had already been established through clinical observation. (Emanuel 2011).

The New York Times published an article titled 'Bad Blood: The Tuskegee Syphilis Experiment' in 1981, presenting details of a study the newspaper referred to it as 'the longest nontherapeutic experiment on human beings in medical history' (Jones 1981). The Tuskegee Syphilis Experiment was an American tragedy continuing from 1932 until 1972, in essence a 40-year deathwatch of 400 black men. Only men with advanced cases of syphilis were included in the study, and they all were left untreated. The researchers behind this study were merely eager to learn more about the serious complications the disease inflicts on its victims. When the study began, there was no effective treatment available. However, the participants, many of whom were illiterate and poor, were told that they were receiving treatment for the disease. Within the decade that followed, it was discovered that advanced syphilis could be treated with penicillin. Therefore, in the early 1950s, penicillin became a part of standard treatment for syphilis. In spite of this breakthrough, researchers continued the Tuskegee Syphilis Experiment – which ignored the use of penicillin as a cure for the disease – until 1972. The victims of this study included hundreds of men, their wives and other partners, and their children. (Emanuel 2011).

Unethical research on humans was performed in Finland too in recent history. A professor of neurology was studying treatment for Parkinson's disease. To ensure an adequate number of participants for his study, the researcher 'conserved' patients with whom he had a treatment relationship. Despite the treatment relationship, this physician left patients untreated – even though effective treatment methods were available – for the purpose of recruiting them for future studies. The researcher also neglected his responsibility to explain that the study was placebo-controlled and to explain the meaning of the study to the participants. Another Finnish researcher neglected the obligation of

voluntary participation: in some of his studies, informed consent was not obtained. (Keränen, Pasternack 2015).

These examples, along with several immoral phases and actions in the history of research, stimulated the establishment of international guidelines for ethical research, such as the Nuremberg Code, the above-mentioned Declaration of Helsinki, and Guideline for Good Clinical Practice (see Table 2). In research conducted today, adherence to the ethics principles ensure that research participants are not harmed and that the historical inhumanities cannot recur. While various ethics principles should be borne in mind when clinical trials are planned, the key element is a requirement that participation be voluntary and that the participants know about the risks and purposes of the trials.

Table 2. Relevant international ethics guidelines for clinical trials on human subjects.

Name and publication year	**Internet address**
Nuremberg Code, 1947	https://history.nih.gov/research/downloads/nuremberg.pdf
Declaration of Helsinki, 1964. (latest revision: 2013)	http://www.wma.net/en/30publications/10policies/b3/index.html.pdf?print-media-type&footer-right=[page]/[toPage]
ICH Topic E & (R1) Guideline for Good Clinical Practice, 2002	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf
International Ethical Guidelines for Epidemiological Studies, 2009	https://cioms.ch/wp-content/uploads/2017/01/International_Ethical_Guidelines_LR.pdf
Report of the International Bioethics Committee of UNESCO (IBC) on Consent, 2008	http://unesdoc.unesco.org/images/0017/001781/178124e.pdf
Guide for Research Ethics Committee Members. Steering committee on Bioethics, 2012	http://www.coe.int/t/dg3/healthbioethic/Activities/02_Biomedical_research_en/Guide/Guide_EN.pdf
International Ethical Guidelines for Health-related Research Involving Humans, 2016	https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf

The Nuremberg Code, from 1947, was conceived as the first international set of ethics norms guiding scientific research. Ten norms were established in consequence of the international law under which Nazi doctors were convicted and their studies judged to involve inhuman war crimes. The 10-point statement of rules was designed to protect the rights and welfare of study subjects. The Nuremberg Code emphasises human rights and voluntariness. According to the code, research is to be carried out with human subjects only when there are no other methods available, and the risks are never to exceed the properly determined humanitarian importance of the problem. (Emanuel 2011).

The World Medical Association (WMA) issued the Declaration of Helsinki in 1964 at the 18th General Assembly of the WMA in Helsinki. This document has had great historical impact, but it also became the most influential regulation of research involving human subjects. In 2014, the declaration, which sets forth guidelines for recruitment, informed consent, and balancing the risks and benefits, celebrated its 50th anniversary. This most significant guidance for medical research has undergone several important changes: since 1964, the Declaration of Helsinki has been amended nine times, most recently at the General Assembly in October 2013. The first amendment occurred in Tokyo, in 1975. The first revision brought the single most important addition in terms of the ensuing conduct of medical research. That was the requirement that independent committees be appointed to

review research protocols. In 1996, the Declaration of Helsinki became the first guidance to refer to any specific type of research methods, in terms regarding the placebo-controlled trial. Behind the amendments from 1996 and 2000 was the use of placebo controls in studies of materno-foetal HIV transmission. (Carlson, Boyd & Webb 2004). At the time of the document's 2008 revision, use of placebos was still subject to debate (Siukkosaari 2008). The increase in international clinical trials over the past few decades has contributed to serious debate about the ethics of research conducted in various settings. Most of the debate has centred on issues related to use of placebos and to post-trial access to interventions. (Ndebele 2013).

The 2013 Declaration of Helsinki introduced new formatting to improve readability. It uses 37 bullet points, which are divided into sections: 1) Preamble; 2) General Principles; 3) Risks, Burdens and Benefits; 4) Vulnerable Groups and Individuals; 5) Scientific Requirements and Research Protocols; 6) Research Ethics Committees; 7) Privacy and Confidentiality; 8) Informed Consent; 9) Use of Placebo; 10) Post-Trial Provisions; and 11) Research Registration and Publication and Dissemination of the Results (World Medical Association 2013). The latest version emphasises that access to clinical trials for underrepresented groups needs be increased so that these groups can also benefit from research. Instead of excluding groups (e.g., minority groups, women, and children), researchers need to clarify why these groups have been excluded from research (Ndebele 2013). However, the current guidance for informed consent process poses challenges to recruit participants from vulnerable groups (Kuthning & Hundt 2013). In addition, the latest declaration acknowledges cultural factors linked with informed consent as well as publication of the results and rights to post-trial care. (Ndebele 2013). The use of a placebo is justified in cases in which no proven intervention exists and when, for compelling and scientifically sound methodological reasons, determining the efficacy or safety of an intervention necessitates the use of an intervention less effective than the best proven one, the use of a placebo, or provision of no intervention. The use of placebo control is acceptable also in situations in which those patients receiving any intervention less effective than the best proven one, a placebo, or no intervention will not be subject to additional risks of serious or irreversible harm through not receiving the best proven intervention. (World Medical Association 2013). The principles of the Declaration of Helsinki have become established in Finnish legislation (the Medical Research Act), in EU legislation (Regulation (EU) No 536/2014), in international agreements on human rights, and in the Guideline for Good Clinical Practice (GCP).

GCP refers to an international ethics and scientific-quality standard for designing, conducting, recording, and reporting on trials that involve the participation of human subjects. Compliance with GCP provides public assurance that the rights, safety, and well-being of trial subjects are protected, in a manner consistent with the principles originating in the Declaration of Helsinki, and that the clinical trial data are credible. The guideline document was originally developed in collaboration among the European Union, Japan, the United States, Australia, Canada, the Nordic countries, and the World Health Organization (WHO). The International Conference on Harmonisation – Good Clinical Practice principles are presented in Table 3 (European Medicines Agency 2002).

Table 3. Principles of good clinical practice (European Medicines Agency 2002).

Good Clinical Practice	
1. Clinical trials should be conducted in accordance with ethics principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and the applicable regulatory requirements.	8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective tasks.
2. Before a trial is initiated, the anticipated risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.	9. Freely given informed consent should be obtained from every subject prior to participation in a clinical trial.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.	10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.	11. The confidentiality of records that could identify subjects should be protected, with respect for privacy and confidentiality rules and in accordance with the applicable regulatory requirements.
5. Clinical trials should be scientifically sound and described in a clear, detailed protocol.	12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice. They should be used in accordance with the approved protocol.
6. A trial should be conducted in compliance with the protocol that has received approval or a favourable opinion from an appropriate institutional review board / independent ethics committee.	13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.
7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.	

2.2.4 Regulations

German legal and political philosopher Georg Jellinek (1851–1911) has stated that law determines the minimum state of ethicality and researchers' professional ethicality determines the maximum level. Legislation can be seen as articulating solid moral grounds for research, upon which norms and regulations can be imposed through ethical discussion. (Keränen, Pasternack 2015). In Finland, the fundamental human rights and liberties are enshrined in the Constitution of Finland (731/1999). According to the Constitution, all are equal before the law and no-one shall, without acceptable reason, be treated differently from other persons on grounds of sex, age, origin, language, religion, conviction, opinion, health, disability, or other elements that pertain to his or her person.

Research utilising clinical trials is strictly regulated by Finnish national legislation: the Medical Research Act (488/1999, 295/2004, 794/2010, 143/2015), the Medicines Act (395/1987), rules on clinical trials of medical products (2/2012 regulations from FIMEA), and the Personal Data Act (523/1999). Pre-trail ethics evaluations are regulated in the Medical Research Act, Decree of the Ministry of Social Affairs and Health on Clinical Drug Trials (841/2010), and Medical Research Decree (986/1999). Privacy and confidential handling of personal information are among the matters addressed in the Act on the Status and Rights of Patients (785/1992) (Table 4 provides more details on the content).

The legislation in use will soon change, however, as Finland begins to apply the EU's Clinical Trials Regulation, which came into force in 2014. Moreover, the Personal Data Act is being replaced in May 2018 as the EU's General Data Protection Regulation (2016/679) enters application in Finland.

Table 4. Legislation and regulations relevant for clinical drug trials on human subjects in Finland (www.finlex.fi).

Regulation	ID code	Main content
Constitution of Finland	731/1999	The Constitution guarantees the inviolability of human dignity and the freedom and rights of the individual, alongside promotion of justice in society.
Act on the Status and Rights of Patients	785/1992	Everyone living permanently in Finland, without discrimination, has the right to health care and medical treatment. The treatment must be organised in a way that does not violate the person's human dignity and respects his or her personal convictions and privacy.
Personal Data Act	523/1999	The act regulates processing of personal data, the protection of private life, and other basic rights that safeguard the right to privacy, and it promotes the development of and compliance with good processing practice.
Regulation (EU) No 536/2014 of the European Parliament and of the Council on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC	536/2014	This regulation changed national notification and authorisation procedure for clinical trials on medical products, moving toward a common European authorisation procedure.
Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine	Treaty No.164 24/2010	The treaty preserves human dignity, rights, and freedoms. The convention proceeds from the principle that the interests of the individual persons must come before the interests of science or society.
Medical Research Act	488/1999, 295/2004, 794/2010, 143/2015	This act regulates research involving a person, human embryo, or human foetus for the purpose of increasing knowledge of health; the causes, symptoms, diagnosis, treatment, and prevention of diseases; or the nature of diseases in general.
Medicines Act	395/1987	The act maintains and promotes the safety of drugs. It ensures medicines' proper manufacture and availability.
Biobank Act	688/2012	This act supports research that utilises human biological samples, to promote openness in the use of these samples and ensure the protection of privacy and self-determination in processing of the samples.
Decree of the Ministry of Social Affairs and Health on Clinical Drug Trials	841/2010	The decree lays down provisions for the format of the request for opinion addressed to an ethics committee and for referring requests for opinion to a regional ethics committee.
Medical Research Decree	986/1999	The decree requires a research plan to be submitted for the opinion of the ethics committee of the hospital district in the area in which the person responsible for the research operates and in which most of the research is to be carried out.

Clinical Trials on Medical Products (Finnish Medicines Agency Administrative Regulation)	2/2012	The regulation deals with issues related to the entire clinical drug trial process. Researchers must deliver notification to the Finnish Medicines Agency about the clinical drug trial.

The most relevant act of law currently addressing CTs in Finland is the Medical Research Act, which states that research conducted under this act has to respect the inviolability of human dignity. The act came into force in 1999, with amendments appearing in 2004 (295/2004), 2010 (729/2010), and 2015 (143/2015). It defines medical research as research involving intervention in the integrity of a person, human embryo, or human foetus for the purpose of increasing knowledge of health; the causes, symptoms, diagnosis, treatment, and prevention of diseases; or the nature of diseases in general.

Furthermore, the Medical Research Act emphasises the participants' personal autonomy and informed consent and considers the position of vulnerable groups. In 2015, an amendment (143/2015) elaborated on the use of personal data after the research subject's withdrawal of consent to participate in research. According to Chapter 2 of the act, which focuses exclusively on clinical trials of medical products, all CTs have to follow good clinical practice. The CT may not start before the ethics committee has delivered an opinion in favour of it and the conditions under which FIMEA has granted it the licence required under the Medicines Act are met.

In addition, the Finnish Medicines Agency administrative regulation on clinical trials of medical products (2/2012) covers commencement, suspension, and ending of a CT; notification to FIMEA pertaining to the CT, along with documents to be appended to that notification; reporting of adverse events and reactions; reporting on the trial's results; and trial documentation and its storage.

Traditionally, legislation and regulations pertaining to research on medical products have been nation-specific. However, changes to legislation are already underway that are aimed at standardising procedures and reducing bureaucracy. The EU Clinical Trials Regulation will change the ethical review process by processing of applications, and a common European portal is to be used to render the licensing procedure more flexible by using a common European portal. (Konttinen, Narhi 2017). However, despite rigorous legislation and ethical guidelines, the quality and ethics of CTs can be compromised. Such situations may include CTs with very selective inclusion criteria. This may result into situation where the subjects under investigation do not represent those with the disorder in the general population.

2.2.5 Ethics review

In general, there are two instruments to protect human subjects in clinical trials: the study must have undergone a process of ethics review by an ethical review board, and voluntary informed consent must be obtained from the research subjects prior to their participation (Medical Research Act 488/1999). Research ethics committees (RECs) have existed since the 1960s in several countries. However, their importance has increased over the years (Hemminki, Virtanen & Regushevskaya 2015). Affected by the Helsinki Declaration, the first RECs in Finland were established in early 1970s in prominent hospitals and in the 90s in every hospital district (Keränen, Pasternack 2015). Moreover, reviews by RECs have been regulated since 1999 by means of a medical research law and associated decrees, specifying in detail an REC's mandate and tasks (Hemminki, Virtanen & Regushevskaya 2015). In addition, an appropriate ethical review process takes into account everyday standards of morality and the shared moral values of the relevant society (Siipi 2017). In 2007, Finland's medical RECs handled 106 international drug trial protocols and 156 domestic ones (Hemminki, Virtanen & Regushevskaya 2015).

Finland's National Committee on Medical Research Ethics (TUKIJA) is responsible for issuing opinions on the ethics of clinical trials of medical products that are to be run in Finland. However, TUKIJA may delegate the task to a regional ethics committee. The members of TUKIJA and also the members of the regional ethics committees include experts in pharmaceutical research, genetics and medical genetics, epidemiology, clinical trials, law, and ethics. Also present at every meeting are laypersons who represent the interests of the research subjects. Under the Medical Research Act, the REC has to take into account the issues presented in Figure 3 in particular.

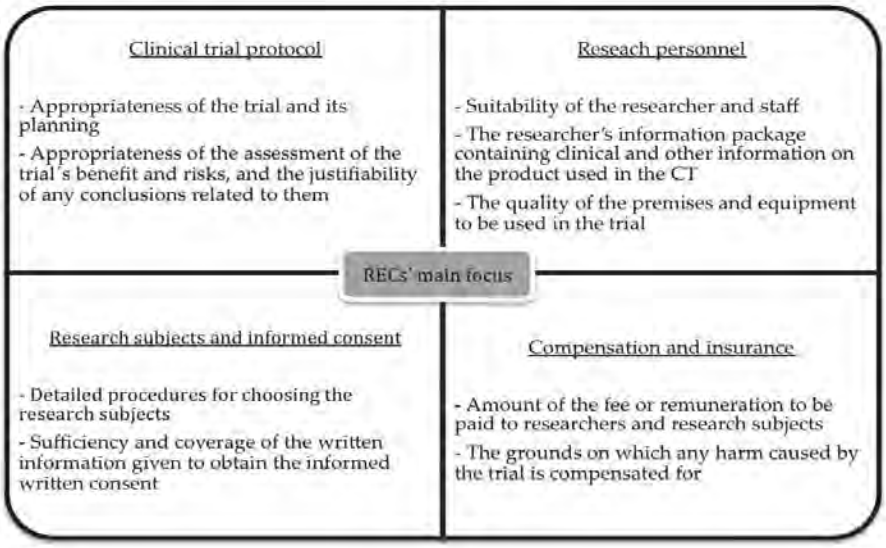

Figure 3. The most relevant factors in REC evaluation related the clinical drug trials.

2.3 PARTICIPATION IN CLINICAL TRIALS

Clinical drug trials always require an adequate number of research subjects with the specific condition of the disease under study. However, recruiting potential study participants in great enough numbers has often proved challenging or even unfeasible. Problems with recruiting appropriate patients are the most common reason for discontinuing a trial (Briel et al. 2016).

2.3.1 General opinions and knowledge

On a general level, most members of the population know what a clinical trial means and perceive them either in positive terms or positively but with reservationsedly positively. (Madsen, Holm & Riis 1999, Comis et al. 2003, Ohmann, Deimling 2004). Patients consider CTs important and view their own involvement too as essential. Most patients indicate that the developments of new therapies for their illness are necessary. (Henrard, Speybroeck & Hermans 2015). Both number of years of education and level of cognitive functioning are correlated with comprehension of key study information (Ravina et al. 2010). High education seems to increase participants' general knowledge of the issues related to CTs, among them policies for protection of study participants, the purpose of informed consent forms, and randomisation (Kaplan et al. 2015). Ciurtin and colleagues (Ciurtin et al. 2015) are among those reporting such results: patients with higher levels of education had

significantly greater knowledge of CTs than those with less education and also expressed more willingness to take part in research. Lack of understanding of research principles was found to be correlated with lack of willingness to participate in CTs. Among patients with haemophilia, 70% reported having some knowledge of the principles of clinical research, but only 30% understood the phases of CTs (Henrard, Speybroeck & Hermans 2015).

2.3.2 Motivation and expectations related to participation

According to recent research, most patients with cancer would be willing to participate in CTs (Kaplan et al. 2015, Igwe et al. 2016). However, according to some studies, only 25–36% of those who completed the relevant questionnaires have been personally willing to participate (Madsen, Holm & Riis 1999, Comis et al. 2003, Ohmann, Deimling 2004). A hope for personal health benefits is a significant factor in signing up for a study, especially if the person in question suffers from a life threatening or otherwise serious disease (Kass, Maman & Atkinson 2005, Wendler et al. 2008, Locock, Smith 2011a). According to previous research, the factor most strongly driving participation was patients' understanding and accurate knowledge of the study (Henrard, Speybroeck & Hermans 2015, Al-Tannir, El-Bakri & Abu-Shaheen 2016). Helping society and advancing medical knowledge were among other reasons cited by patients for participating in CTs, as was receiving medical care (Al-Tannir, El-Bakri & Abu-Shaheen 2016).

In the findings of Valadas and colleagues (Valadas et al. 2011) the main reasons to participate in CTs among patients with PD were to help advance science (63.7%), to gain access to better treatment (56%), and to help others (51.6%). Another relevant factor is that most patients would like to discuss the decision with their physician and family members before deciding about participation (Henrard, Speybroeck & Hermans 2015, Al-Tannir, El-Bakri & Abu-Shaheen 2016). In addition, patients are much more likely to enrol in a CT if their personal physician is engaged as an investigator for the study (Sherber, Powe & Braunstein 2009). Patients suffering from a life-threatening condition have cited routine health checks as the main benefit of being involved in trials (Ssali, Poland & Seeley 2015). It seems that willingness to participate may be directly correlated with education level (Henrard, Speybroeck & Hermans 2015). Tailored education materials have been cited as an important element for increasing willingness to participate in CTs. In a study conducted by Igwe and colleagues (Igwe et al. 2016), more than half of the patients agreed to participate in CTs that required additional education.

Most patients consider participation in CTs to be an opportunity and to provide access to health services (Locock, Smith 2011a, Townsend, Cox 2013). However, a third have reported that participating in a CT would cause anxiety or be incompatible with their personal/professional life (Henrard, Speybroeck & Hermans 2015). According to recent literature, demotivating factors with regard to participation include fear of risks due to participation and fear of the unknown. Additionally, medical factors can reduce motivation to participate (Al-Tannir, El-Bakri & Abu-Shaheen 2016). Patients may be concerned about time demands: the frequency of required clinic visits, the duration of the study, and the amount of time needed for travel to and from clinic visits. Furthermore, it may be challenging to meet the needs of all patients, since some potential study participants prefer to get more check-ups (Carroll et al. 2012). Yet another factor is the trial information, which can be off-putting or complex, and the information presented may be otherwise inadequate for decision-making (Locock, Smith 2011a). Furthermore, suspicions surrounding the source of funding for the trial can contribute to not taking part (Locock, Smith 2011a). Finally, the study design (use of a placebo, randomisation of the participants, etc.) can affect patients' willingness to participate (Valadas et al. 2011, Moorcraft et al. 2016) (see Table 5).

Table 5. Factors affecting whether or not one participates in a clinical trial.

Promoting participation	Hindering participation
Altruistic motives	Concerns about the adverse effects
Personal health benefits	Worries about the concept of randomisation and use of a placebo
Increased physician surveillance	The time demands of the CT
Recommendation by one's physician	Travelling to and from study appointments
Appropriate knowledge of CTs	Concerns about forgoing treatment
The possibly of receiving the current medication	Lack of knowledge of CTs
Compensation	Lack of family support

At the same time, clinical demographic factors can influence the decision on whether to participate in a CT. Age, gender, education level, and ethnicity have been found to have an effect. Among cancer patients, younger people are less likely to participate in CTs, as are female patients (Jenkins et al. 2013). In contrast, in studies involving patients with Parkinson's disease, being older, male, or less educated has been associated with poor recruitment (Picillo et al. 2015).

2.3.3 Informed consent

Participation in clinical trials always requires the subject's voluntary (written) consent, based on subject's knowledge of the study. The information provided must be accurate, complete, and understandable. Researchers have an ethical obligation to verify the participant's understanding of the investigational nature of the study. However, informed consent is more than a signature on a document. To provide informed consent, one must be accurately informed about the purpose, methods, risks, the benefits, and alternatives to the research; understand this information and its bearing on his or her clinical situation; and make a voluntary and un-coerced decision on whether to participate in the study. (Beauchamp, Childress 2001).

A study conducted with PD patients revealed that 90% of the patients felt that they had understood the informed consent materials and 89.9% found the consent form simple to read and understand. Nearly all patients understood that they would be entering a CT, but one of them did not, and 46% were not aware that they could withdraw at any time. (Valadas et al. 2011). In another study conducted with patients with PD, 42.3% of the participants incorrectly endorsed the statement that participating in the study was part of the 'usual treatment' for their PD (Ravina et al. 2010). While the patients were satisfied with the quality of the informed consent materials (Valadas et al. 2011) the need exists for an improved informed consent process (de Melo-Martin, Hellmers & Henchcliffe 2015). Hence, researchers should focus on the patient's cognitive function, emotional state and ability to receive extensive information. Moreover, e.g. cognitively impaired patients are considered to be vulnerable, which places challenges to fulfil informed consent. (Keränen, Pasternack 2015).

The quality of the consent given in clinical research is determined by the extent to which participants understand the process of informed consent (Sreenivasan 2003). According to recent meta-analysis, around 75% of subjects understood the nature of the study, their right to refuse to participate, their right to withdraw at any time, and the direct benefits of participation. However, participants have difficulties in understanding particular components of informed consent, such as randomisation and the use of a placebo. They understood the benefits of participating in a study but were less aware of the uncertainty of

these benefits coming to pass. A participant's understanding depends, to a certain degree, on literacy and also on the duration of the informed consent process and the explanation skills of the researchers. Although there have been many attempts to improve the quality of informed consent, significant advances have not been made in 30 years. (Tam et al. 2015). Information provided to the participants has increased. However, this hasn´t necessarily improved their comprehension, but rather resulted in extended consent documents. One factor may be that, even if informed consent procedures and other ethics-related components (RECs approval and Helsinki Declaration principles) must be addressed in manuscripts submitted for publication, even high-impact journals often fail to enforce this requirement (Trung et al. 2017). That said, the scientific community has identified this challenge and others related to informed consent, and innovative approaches have recently been presented (Vickers et al. 2017, Kim, Flory & Relton 2017).

2.3.4 Therapeutic misconception

A person can give voluntary consent only when the decision is based on adequate, relevant information and comprehension. Therefore, a subject who misunderstands the aim of the study and believes that the aim of the trial is to benefit him or her personally cannot give voluntary autonomous consent. (Beauchamp, Childress 2001). This phenomenon, referred to as therapeutic misconception, was first defined by Paul Appelbaum with his colleagues in 1982 (Appelbaum, Roth & Lidz 1982). They described a situation in which a study participant conflates research with treatment. This may lead to subjects misunderstanding the purpose of research, failing to understand that the research procedures are not personalised for them, and having false beliefs about the risks and benefits of participation. (Appelbaum, Lidz & Grisso 2004). More than three decades later, there is still no consistent definition for this phenomenon (Henderson et al. 2007, Kim et al. 2015). Consensus exists that study participants should understand that research has scientific goals, but there are differences in scholars' views of what they should understand about therapeutic goals in clinical research (Henderson et al. 2007) and whether the phenomenon can be reliably investigated in a hypothetical setting (Kim et al. 2016, Appelbaum 2016).

Appelbaum and colleagues (Appelbaum et al. 2012) constructed a validated measurement for recognising and determining the prevalence of TM. The three main elements of TM addressed are uncertainly about the ultimate goal of clinical research and the perception that treatment is individually selected and participation brings personal health benefit to the participant. These authors studied 220 patients and found from interviews that TM was present in 50.5% of the cases, and 55% when the validated measurement tool was used. There are several other studies in which the prevalence of TM and risk factors for it have been investigated (Appelbaum, Lidz & Grisso 2004, Kim et al. 2009, Mansour et al. 2015, Lidz et al. 2015). These characteristics can be divided into participant characteristics and study-level characteristics (Appelbaum, Lidz & Grisso 2004). More advanced age, lower levels of education, and severe illness have been found to be associated with increased risk of TM in several studies (Appelbaum, Lidz & Grisso 2004, Durand-Zaleski et al. 2008). Worse self-reported health and functional status is also associated with increased risk (Appelbaum, Lidz & Grisso 2004) and so is the patient having an acute life-threatening condition (Durand-Zaleski et al. 2008). Perhaps the two potential sources of TM discussed most often are study participants' motivation by direct personal benefit (Henderson et al. 2006) and the involvement of their own doctors as researchers (Miller, Rosenstein & DeRenzo 1998). While a participant's own doctor acting as researcher for the CT has been strongly associated with increased risk of TM, Kim and colleagues did not observe this association (Kim et al. 2015).

Misunderstanding the treatment significance of the research affects not only study participants. Even investigators and ethics committee members may assess the significance of the research incorrectly from the perspective of the study participant (Henderson et al.

2007, Dresser 2002). According to an American study, more than half of the health-care professionals participating in clinical studies thought that possible health benefits to the participant are an essential factor in the recruitment (Lidz et al. 2009).

2.3.5 Concepts closely related to therapeutic misconception

In addition, it has been suggested that measurement problems may occur and that TM studies err by, for example, misconstruing 'therapeutic desire' for TM (Kim et al. 2009). Language is a complex phenomenon, and that might be the one explanation behind several related notions used alongside that of TM (Lyons 2016). Table 6 summarises related concepts and also phenomena often studied together with TM.

Table 6. Concepts related to therapeutic misconception.

Concept	Description of the phenomenon	References
Therapeutic desire	Even if individuals tend to process information in terms of their desire for therapeutic benefit, this does not mean that they do not understand the scientific purpose of the CT.	Kim et al. (Kim et al. 2009)
Therapeutic misestimation	Participants misestimate the likelihood of benefit and/or risk.	Pentz et al. (Pentz et al. 2012)
Therapeutic optimisim	The person has a future-oriented emotional state, which manifests itself in a desire for a particular health-care outcome.	Horng & Grady (Horng, Grady 2003) Chou et al. (Chou, O'Rourke 2012) Hallowell et al. (Hallowell et al. 2016) Jansen et al. (Jansen et al. 2016a)
Therapeutic misunderstanding	Participants (I) conflate the goals and nature of research and treatment because of a mistaken belief that there will be personal care, failure to apprehend the purposes of research, or misunderstanding of the research methods (therapeutic misconception); (II) appraise the risks and benefits of research participation unrealistically because of either a misattribution of therapeutic intent or a different conceptualisation of probabilistic information (therapeutic misestimation); or (III) understand both I and II but remain unduly hopeful or excessively optimistic about the outcomes for them (therapeutic optimism).	Horng & Grady (Horng, Grady 2003) Chou et al. (Chou, O'Rourke 2012)
Dispositional optimisim	There is 'the generalised positive expectancy that one will experience good outcomes'. People with high dispositional optimism generally tend to accentuate the positive and downplay the negative.	Jansen (Jansen 2011) Jansen et al. (Jansen et al. 2016a)
Unrealistic optimisim	A bias occurs when the subject believes that he or she is more likely to gain benefits and/or is less likely to experience harm than similar others who are subject to the same intervention.	Jansen et al. (Jansen et al. 2017)

Pentz and colleagues (Pentz et al. 2012) studied the associations among TM, therapeutic misestimation (TMis), and therapeutic optimism (TO) with Phase-1 cancer patients. In their results, 94% of the patients misestimated risk and benefit. In addition, most of the misestimations were overestimations of benefit. Moreover, 14% of the respondents estimated that their personal risk was zero. Therapeutic optimists accounted for 41% of these patients. In addition, TM was widespread in this study population.

Therapeutic misunderstanding consists of elements linked to TM, TMis, and TO. Chou and O'Rourke (Chou, O'Rourke 2012) developed the Therapeutic Misunderstanding Scale, which is intended to serve as a screening instrument for clinicians' more thorough assessment of informed participant consent. In this tool, the TM factor is composed of items related to purposes of clinical-trial-based research, individualised treatment, and uncertainty surrounding treatment benefits. Items for the TMis factor addressed the various benefits of participation in research, from quality of life to curing illness. The instrument's TO factor was composed of items measuring situational optimism and unrealistic hope.

Dispositional optimism and unrealistic optimism are both reported on in the latest studies conducted with patients with cancer (Jansen et al. 2016a, Jansen et al. 2017, Jansen et al. 2016b, Jansen et al. 2018). Persons exhibiting dispositional optimism seem to have high expectations of personal therapeutic benefit; however, dispositional optimism is not associated with TM (Jansen et al. 2016a). In contrast, unrealistic optimism has been positively correlated with TM and failures to appreciate research-related information (Jansen et al. 2016b). In a study by Jansen and colleagues (Jansen et al. 2017), patients who declined to participate in a CT exhibited less TM and unrealistic optimism in comparison to people who accepted participation. However, TM was reported to be high in both groups. In addition, therapeutic misconception does appears to be a factor that explains expectations of therapeutic benefit even when subjects do not report unrealistically optimistic assessments of the likelihood of personal benefit. If subjects mistakenly think that by participating in a CT one will get the best treatment, they may overestimate the probability of them benefiting from participation, even if they are not themselves optimistically biased (Jansen et al. 2017).

2.3.6 Experiences of trial participation

The overall picture of participation in CTs has been found to seen as positive by various patients groups (Locock, Smith 2011a, Bevan et al. 1993), including patients with a neurodegenerative disorder (Ravina et al. 2010, Valadas et al. 2011). In addition, many patients have seen participation as an opportunity or even a right and sought out participation opportunities (Locock, Smith 2011b). Moreover, according to Valadas et al. (Valadas et al. 2011), 67.4% of those who have participated in a CT would be willing to be part of another trial.

Patients appreciate the attention given to them and believe that their participation is important for the advancement of science (Locock, Smith 2011b). Most trial participants have participated in CTs out of a motivation to improve their own treatment (Locock, Smith 2011b), they enrolled to help others, or they took part because the doctor asked them (Bevan et al. 1993).

Ravina and colleagues (Ravina et al. 2010) examined the relationship of comprehension of the key study information with compliance and satisfaction with study procedures. They discovered that there was no correlation between comprehension and compliance. Over 90% of the participants were satisfied with their overall experience and stated that they had received all the information they wanted. However, approximately 5% indicated that they did feel pressure to enter or remain in the CT. An interesting finding from their study was that even if patients were satisfied, they often conflated research and their usual treatment. Similar results have been obtained in other studies, conducted with various patient groups (Locock, Smith 2011b).

Hopes for personal benefit have seemed important for people with a life-threatening illness – people with cancer can feel even 'cheated' if getting assigned to the control group (Locock, Smith 2011a). During a trial, patients may worry about side-effects, starting to take a new tablet, lack of potential benefit to themselves, and stopping the previous treatment, and they report these as the worst features of CTs (Bevan et al. 1993).

2.4 DEFINITIONS AND EPIDEMIOLOGIES OF EPILEPSY AND PARKINSON'S DISEASE

2.4.1 Epilepsy

Epilepsy is a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this. Classification as epilepsy requires the occurrence of at least one unprovoked epileptic seizure. Epilepsy is best described as a variety of disorders reflecting an underlying brain dysfunction that may result from any of many, quite different causes. An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. (Fisher 2017).

Epileptic seizures are diverse in their presentation, pathophysiology, syndromic relationship, prevalence, and triggering factors. The signs and symptoms may include stereotypical alteration of consciousness; behaviour; emotion; and motor, sensory, or autonomic functions. The International League Against Epilepsy (ILAE) Commission on Classification and Terminology groups epileptic seizures into three main types: focal, generalised, and unknown. (Fisher et al. 2017). Furthermore, there are four identified types of epilepsies: focal, generalised, combined generalised, and focal and unknown (Scheffer et al. 2017).

According to the relevant ILAE report, there are six groups of causes of epilepsy: 1) genetic epilepsies are a direct result of one or more known/presumed genetic defect in which seizures are the core symptom of the disorder, 2) among structural causes are structural lesions that may be either acquired or of genetic origin, 3) infectious ones result from a known infection, 4) a metabolic epilepsy results from a metabolic disorder, 5) an immune epilepsy is a direct result of an immune disorder, and 3) cases of an unknown cause of epilepsy involve the nature of the underlying defect not yet having been identified. The epilepsy syndrome is a complex of clinical features, signs, and symptoms that together characterise a distinctive, recognisable clinical disorder. In adults, the most common epilepsy syndrome is temporal lobe epilepsy. (Scheffer et al. 2017).

Epilepsies constitute one of the most common chronic neurological diseases worldwide. According to the World Health Organization, around 50 million people in the world have epilepsy and an estimated 2.4 million new cases arise yearly. Epilepsy accounts for 0.5% of the global burden of diseases, according to a metric that combines years of life lost because of premature mortality and time spent in states of less than full health (World Health Organization).

Epilepsy affects people of all ages. In the Nordic countries, the incidence curve for epilepsy is double-humped, with a peak early in life and a new increase for the oldest age groups (Syvertsen, Koht & Nakken 2015). According to a systematic review, the age-specific prevalence of active epilepsy among European children and adolescents ranges from 4.5 to 5.0 per 1,000; among adults is six per 1,000; and among the elderly is estimated at seven per 1,000 (Forsgren et al. 2005). In studies conducted in the Nordic countries and Estonia, the prevalence of active epilepsy among adults has been found to vary between 5.3 and 6.3 per 1,000 (Keranen, Riekkinen & Sillanpaa 1989, Forsgren 1992, Oun, Haldre & Magi 2003).

Most patients with epilepsy are able to work, study, and take care of their daily activities normally. However, approximately 25% of the patients are not seizure-free and their ability

to function is compromised. Additionally, in some studies 40–60% of the patients have reported being hindered by cognitive problems, with memory problems being especially prevalent. (Kälviäinen et al. 2016).

2.4.2 Parkinson's disease

Parkinson's disease is the most common and complex neurological disorder wherein progressive death of dopaminergic neurones leads to a movement disorder with numerous non-motor symptoms. James Parkinson made the first detailed description of PD almost two centuries ago, but the conceptualisation of the disease continues to evolve. In addition, its aetiology is still unknown, although research indicates that this disease develops from a complicated interplay of genetics and environment. (Kalia, Lang 2015).

The diagnosis is made on the basis of clinical criteria. Parkinson's disease presents with four cardinal motor manifestations: tremor at rest, muscular rigidity, bradykinesia (or slowing of movement), and postural instability. However, a wide variety of dysfunctions are connected with it, extending well beyond these classic motor disabilities associated with the disease. (Kalia, Lang 2015).

Among the non-motor symptoms are olfactory dysfunction, cognitive impairment, psychiatric symptoms, sleep disorders, autonomic dysfunction, pain, and fatigue. These symptoms are commonplace in early Parkinson's disease and are associated with reduced health-related quality of life. (Kalia, Lang 2015, Aarsland et al. 1999). Most patients with PD suffer from selective cognitive impairments, including difficulties with attention, concentration, problem-solving, set-shifting, and memory. The prevalence of cognitive impairment in PD has been estimated to be around 55%. (Janvin et al. 2003).

PD is an age-related disease, being rare before the age of 50. Indeed, age is the single most consistent risk factor at population level. With the increasing age of the general population, the prevalence of PD is only going to rise. The incidence of the disease rises steeply with age, from 17.4 in 100,000 person-years between 50 and 59 years of age to 93.1 in 100,000 person-years between ages 70 and 79, with a lifetime risk of developing the disease of 1.5%. (Bower et al. 1999, de Rijk et al. 1995, Kempster, Hurwitz & Lees 2007). The age-adjusted prevalence of PD in the Finnish population is about 166 per 100,000 members of the general population, and the total age-adjusted incidence is 14.9 per 100,000. There are about 10,000 PD patients in Finland. (Kuopio et al. 1999).

The mean age of symptom onset found in eight individual studies was 60 to 65 years, though it was above 65 years in a review of five studies (Twelves, Perkins & Counsell 2003). Sex is another pertinent factor: men are more likely to develop PD than women (Kuopio et al. 1999), with the male-to-female ratio being approximately 3:2 (Kalia, Lang 2015).

PD's effects on patients' life vary greatly. However, PD is a chronic and progressive disease, in which consequence the quality of life of patients with PD cannot remain unaltered. In a Finnish study, women with the disease reported lower quality of life than men did. It should be stressed that PD affects physical and social functioning, not just cognition. Still, despite the difficulties involved in living with chronic illness, some individuals appear to adapt to their condition well. (Kuopio et al. 2000).

2.4.3 Antiepileptic drugs and medications for Parkinson's disease

The goal with antiepileptic treatment is to achieve long-term seizure control without significant adverse effects. The first-line treatment for epilepsy is antiepileptic medication, which can be used either in monotherapy or later in refractory patients also as polytherapy. Among the commonly used first-line agents for epileptic seizures are carbamazepine, oxcarbazepine, levetiracetam, and valproic acid. (Käypä hoito -suositus 2014). Irrespective of an increase in the number of antiepileptic drugs (AEDs) available, some of the patients with epilepsy continue to have seizures (Brodie et al. 2012). Therefore, also other treatment

modalities – such as epilepsy surgery, neurostimulation, and a ketogenic diet – are needed. In the last 10–15 years, researchers have been able to gather knowledge on the basic mechanism of epilepsy, on the basis of which new AEDs have become available. (Kälviäinen et al. 2016).

Since PD is an incurable progressive disease, the choice of treatment is intended to substantially improve quality of life and functional capacity, either increasing the amount of dopamine in the brain or inhibiting its breakdown. The management of PD can be subdivided into three categories: protective or preventive treatment, symptomatic treatment with dopaminergic or non-dopaminergic therapy, and treatment of non-motor symptoms. (Gardian, Vecsei 2010). The dose and combination of drugs are set individually, since many factors should be considered, among them the patient's age; the symptoms and their severity; cognitive, behavioural, and psychiatric status; and medical comorbidities (Pahwa, Lyons 2014).

No medication has been shown to stop or significantly slow the progression of the disease. There are several types of drugs available for reducing motor symptoms of PD. The most effective of them is levodopa. However, long-term use of levodopa leads to motor complications in many cases. (Gardian, Vecsei 2010). Other frequently used medications are carbidopa, dopamine agonists, and MAO-B inhibitors. Further research is needed for identifying new treatment options, with more consistent benefits and fewer adverse events, including motor complications. (Pahwa, Lyons 2014).

Though diverse treatment options are available for the management of epilepsy and for Parkinson's disease, major therapeutic needs are still unmet, and this justifies conducting CTs. A major goal in Parkinson's disease research is the development of disease-modifying drugs that slow or stop the underlying neurodegenerative process (Kalia, Lang 2015), while epilepsy researchers strive to develop drug treatment that brings long-term seizure-freedom. New AEDs are often studied with patients who are refractory to the treatments already available. In addition, studies of new AEDs and medications for PD alike frequently involve newly diagnosed, relatively young patients receiving monotherapy. There is a particular gap in terms of clinical drug trials with elderly patients who have epilepsy (Keränen 2007). Both conditions are under active research worldwide. However, patients' vulnerability to misconceptions related to CTs are underrepresented.

3 Aims of the study

The general aim behind the thesis was to assess knowledge of and attitudes towards clinical drug trials among patients with two common neurological diseases (epilepsy and Parkinson's disease), including both patients who had participated in CTs and those who had not.

The specific aims were:

1. To assess knowledge and attitudes related to clinical drug trials.

2. To study factors influencing willingness to participate in clinical drug trials.

3. To evaluate experiences of the informed consent process in clinical drug trials.

4 Therapeutic misconception correlates with willingness to participate in clinical drug trials among patients with epilepsy; need for better counseling

4.1 INTRODUCTION

In the last 20 years, more than a dozen new antiepileptic drugs (AEDs) have become internationally approved. Typically, new AEDs are initially studied in clinical trials (CTs) in patients who have seizures that are refractory to available antiepileptic drugs. These trials raise important ethical concerns due to the fact that patients with severe epilepsy may be exposed to placebo and undue morbidity, especially because they may also be good candidates for epilepsy surgery (Perucca 2012). Clinical trials involving newly diagnosed patients, on the other hand, usually include an established AED as an active comparator, but these studies may still fail to yield answers to important questions (Glauser et al. 2013).

In principle, a large part of the general population is aware of what CTs mean, and these trials are viewed positively overall [(Madsen et al. 2000, Ohmann, Deimling 2004, Burns et al. 2013). However, surveys have reported that only 25–36% of the population is personally willing to participate in a CT (Ohmann, Deimling 2004, Madsen, Holm & Riis 1999, Comis et al. 2003). Several of the common methods applied in CTs, including randomisation, blinding, and the use of placebo, differ greatly from the practices of standard medical care. Patients asked to participate in CTs often have difficulties in understanding the meaning and purposes of these methods (Hietanen et al. 2000, Locock, Smith 2011b). Furthermore, CT participants may fail to appreciate fundamental differences between research protocols and standard care: They may not understand that the primary purpose of a clinical trial is to produce generalisable knowledge regardless of whether the subjects in the trial may benefit from the intervention (Appelbaum, Lidz & Grisso 2004, Henderson et al. 2007). This phenomenon, called therapeutic misconception, is relatively common and may lead to overestimation of benefits, underestimation of the risk of harm, and/or underappreciation of alternatives to participation in CTs (Appelbaum, Lidz & Grisso 2004, Henderson et al. 2007).

Lack of adequate knowledge may have a negative impact on participation in CTs. On the other hand, unrealistic expectations of the personal health benefits associated with a CT may lead to disappointment and distrust in CTs among study participants. To avoid these pitfalls, the investigators and other stakeholders associated with CTs should obtain information about patients' knowledge and views of CTs. In the study reported upon here, we sought to assess knowledge of CTs and attitudes toward them in patients with epilepsy. Furthermore, we attempted to evaluate the association of various demographic and clinical factors with the subjects' attitudes to CTs and willingness to participate in them.

4.2 METHODS

4.2.1 The study sample

Subjects with epilepsy who were at least 18 years old and who were members of the Finnish Epilepsy Association (FEA), the Finnish chapter of the International Bureau for Epilepsy, were the target population of the study. Questionnaires and other materials were sent to a random sample (n = 1875) of FEA members (out of the total membership of 7500)

in 2013. The list of subjects to whom the material was to be sent was generated by the FEA via selection of every fourth person on the membership list. While most members of the FEA are patients with epilepsy and their relatives, some health-care professionals, too, are members, so the research information sheet and covering letter requested answers from only adults (age ≥ 18 years) suffering from epilepsy who were able to give responses independently. The questionnaire forms were returned anonymously.

In total, 342 questionnaires were returned, for a response rate of 18%. However, 17 of the questionnaires returned were rejected from the analysis because of inadequate information (i.e., an empty form or only a few answers). Therefore, the final number of questionnaires accepted for inclusion was 325 (17% of the total sample).

4.2.2 The study design and data collection

For the purposes of the study, a questionnaire to be self-administered by the patients was developed. This questionnaire, which was based on our previous research (Halkoaho 2012) and the available literature (Madsen, Holm & Riis 1999, Chou, O'Rourke 2012, Jenkinson et al. 2005), had two parts. The first part covered data on demographic and socioeconomic issues, along with clinical aspects of epilepsy and its treatment. The second part formed the actual survey instrument, which featured 45 statements. These items covered factors previously identified as reflecting knowledge of and attitudes toward CTs (30 statements), willingness to participate in CTs (seven statements), and experiences of participation in CTs (13 statements), with the last of these elements to be the subject of another paper. The subjects responded to the statements by using a five-option Likert scale. The options for the statements were 'strongly disagree' (1), 'disagree' (2), 'cannot say' (3), 'agree' (4), and 'strongly agree' (5).

From the statements in the questionnaire, four factors were constructed: sense of control over the epilepsy (six items) was covered by statements describing experiences with epilepsy and its drug treatment, for example; knowledge of CTs (11 items) was addressed with statements on awareness of basic principles and procedures of CTs; the factor called 'willingness' (nine items) was examined via statements on elements promoting willingness to participate in CTs; and therapeutic misconception (eight items) was addressed through items for measuring how patients understood the differences between the purposes of CTs and standard care and how expectations of personal health benefits would affect decision-making (see Table 7).

Table 7. Descriptions of statements and factors.

Factor	Statements	Alpha
F1: Sense of control over the epilepsy	- I have enough information about epilepsy - I am satisfied with the efficacy of my antiepileptic drugs - Seizures don't cause me worry - My epilepsy medication will not cause any harm - The frequency of seizures is not a fundamental factor determining my quality of life - Adverse effects don't diminish my quality of life	0.76
F2: Knowledge of CTs	- I know what a CT means - Each new drug has been studied with patients before it becomes available via pharmacies - CTs are always assessed beforehand by a research ethics committee - Participation in a CT is always voluntary - A potential CT participant signs a consent document before taking part in the research - The research participant may at any point terminate his or her participation in the CT - A clinical trial may include procedures differing from ordinary treatment - Clinical trials are mostly funded by a medical corporation - The essential goal of clinical treatments is to find better medication for future patients - Different treatment procedures can be assigned randomly in clinical trials (for example, by flipping a coin or other randomisation)	0.60
F3: Willingness	- I would like to receive as much information as possible about the trial and the new drug before I make a decision about participation in a CT - I would participate in a CT only if the treating physician also is the investigator - I would not participate in a CT if I did not receive enough information about the CT and the investigational drug - I would participate in a CT if that guaranteed me new and improved medication - I would participate in a CT only if I were not satisfied with my current medication - I would participate only in a CT in which all participants are given an effective agent - I will not participate in clinical trials if a possibility of receiving placebo medication exists - I would not participate in a CT if it included a significant risk of severe adverse effects - I would participate only in a CT in which at least one of the drugs being compared has been shown to be effective	0.60
F4: Therapeutic misconception	- I would like to participate in CTs in order to determine the continuation of my current treatment relationship - I would like to participate in a CT because then I would receive more thorough monitoring relative to standard treatment - Usually clinical trials are aimed primarily at seeking the best medication for the research participants - In CTs, all participants always receive a new effective agent - In CTs, the physician conducting the research is aware of whether the participant is receiving a new drug, a placebo (which does not include an effective agent), or an older AED - In CTs, the physician conducting the research may choose which drug the participant receives - The patient participating in the research may often choose which drug he or she receives - I would participate in a CT only because it would guarantee me the best possible treatment	0.73

4.2.3 Statistical analysis

The data were analysed by means of the SPSS Statistics 19.0 statistical analysis software. The background information was characterized in terms of frequency and percentage distributions. The scale for responses to the statements (the abovementioned 1–5 range) was adjusted to 0–100 (1 = 0 to 5 = 100) for clearer presentation of the results.

Cronbach's alpha was used for assessment of reliability with respect to the factors. Factor scores were formed via calculation of the means for the statements. The dependence relationship between factors was assessed via Spearman's correlation. A sample size of 300 respondents was estimated to be sufficient for the purposes of the study (MacCallum et al. 1999).

The association of selected demographic and clinical variables (age, gender, education level, work ability, age at onset of epilepsy, seizure frequency, and number of AEDs) with the four factors was analysed via multiple linear regression. Statistical significance was achieved at $p < 0.05$. Section 3 focuses on adjusted p-values from linear regression analysis. The assumptions of linear regression were visually checked through assessment of the residuals.

4.2.4 Ethics considerations

A favorable opinion of the study was obtained in advance from the Research Ethics Committee of the University of Eastern Finland, and permission to carry it out was granted by the Executive Board of the Finnish Epilepsy Association. To ensure the privacy of the participants in the study, it was FEA staff who sent the questionnaires to the participants. The investigators did not have access to the study population's personal data. All responses to the questionnaire were given anonymously.

4.3 RESULTS

The 325 questionnaires included in the analysis represented a preponderance of women over men, and more than half of the subjects were at least 50 years old. Half of the patient population had been seizure free or had no more than 1–2 seizures per year, and close to 50% of the participating patients were on one AED (see Table 8).

Table 8. Demographic and clinical data of the study subjects.

Variable		**n**	**%**
Age band (years)	18–29	27	8.5
	30–39	52	16.4
	40–49	54	17
	50–59	81	25.6
	≥60	103	32.5
Gender	Female	211	65.1
	Male	113	34.9
Education	Basic education	84	25.9
	Vocational training	165	50.9
	Academic degree	75	23.1
Work ability	Able to work	130	44.8
	On sick leave	7	2.4
	Retired	153	52.8
Age at onset of epilepsy (years)	0–9	59	18.7
	10–18	47	14.9
	19–29	56	17.8
	≥30	153	48.6
Seizure frequency	Seizure-free for at least one year	103	33.2
	1–2 per year	71	22.9
	3–6 per year	41	13.2
	6–11 per year	43	13.9
	1 or more per month	52	16.8
Antiepileptic medication	1 drug	154	48.7
	2 drugs	90	28.5
	3 drugs	42	13.3
	4 or more	30	9.5

4.3.1 Attitudes to CTs and knowledge of the procedures of clinical trials

In general, patients with epilepsy held positive attitudes toward clinical trials (as indicated in Fig. 4). Furthermore, the subjects strongly favored that the results of the trials were published and that the trial participants were informed about the results.

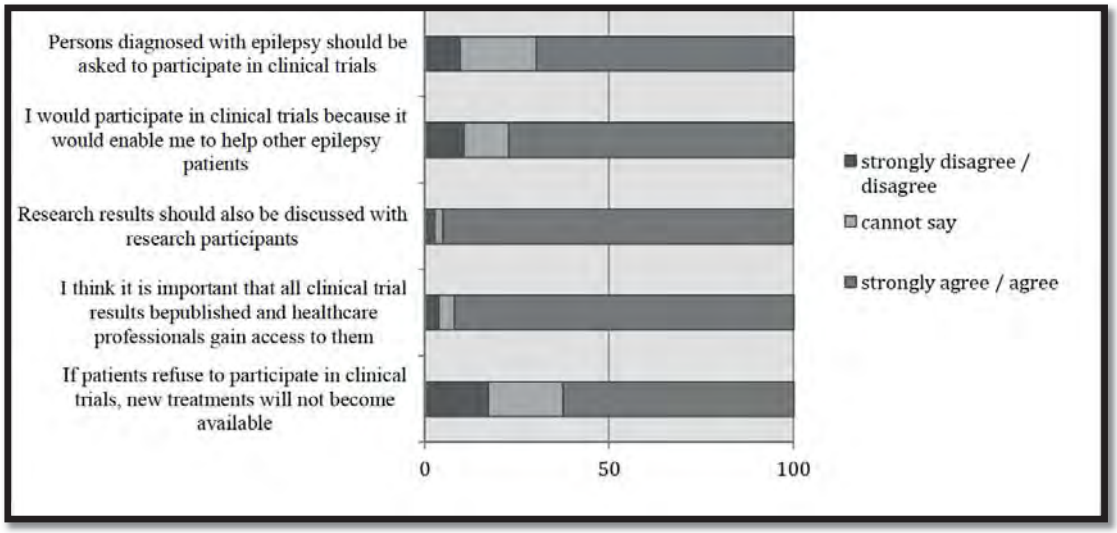

Figure 4. Attitudes of the patients with epilepsy toward clinical trials.

The association of selected demographic and clinical variables with the four factors is shown in Table 9. The factor 'sense of control over the epilepsy' was statistically significantly associated with the subjects' age at the onset of epilepsy, seizure frequency, and the number of AEDs. The 'knowledge of CTs' factor showed a statistically significant association with ability to work and with age at onset of epilepsy. When the association between the variables and the factor labeled 'willingness' was assessed, statistically significant correlation was found with the participants' education level, work ability, and number of AEDs. Finally, evaluation of the relationship between the individual independent variables and the factor 'therapeutic misconception' revealed that education level and the number of AEDs were statistically significant predictors (see Table 9)

Table 9. The association of selected demographic and clinical variables with the four factors as analysed via multiple linear regression. Mean score and standard deviation for each demographic and clinical variable and factor, where with factor 1, scores close to 100 indicate a full sense of control over the epilepsy; with factor 2, scores near 100 mean complete knowledge of CTs; with factor 3, scores close to 100 indicate commitment to participating in order to achieve health benefits; and factor 4 scores near 100 indicates serious therapeutic misconception.

Variables	F1: Sense of control over the epilepsy				F2: Knowledge of CTs				F3: Willingness				F4: Therapeutic misconception			
	Mean score	SD	*p*-value	Adjusted *p*-value	Mean score	SD	*p*-value	Adjusted *p*-value	Mean score	SD	*p*-value	Adjusted *p*-value	Mean score	SD	*p*-value	Adjusted *p*-value
Age band (years)			0.422	0.323			0.211	0.391			0.659	0.812			**0.001**	0.084
18–29	58.5	24.2			74.5	13.8			69.7	14.4			49.4	18.1		
30–39	53.5	25.8			74.8	11.6			66.1	11.8			42.5	19.4		
40–49	60.0	23.2			71.9	12.7			66.1	13.3			48.8	19.0		
50–59	61.2	26.5			73.9	13.6			67.8	19.8			53.8	20.8		
60 or over	60.6	21.4			70.4	13.6			69.2	15.9			56.3	19.9		
Gender			0.108	0.406			0.383	0.477			0.518	0.077			0.59	0.461
Female	58.2	23.8			73.0	13.4			68.1	15.1			50.1	20.4		
Male	62.7	24.2			71.7	12.9			66.9	17.5			54.5	19.5		
Education			0.911	0.796			**0.001**	0.091			**0.040**	**0.010***			**<0.001**	**0.001***
Basic education	58.7	23.0			69.4	12.7			69.6	15.9			59.0	17.5		
Vocational training	59.9	24.6			72.5	12.8			68.6	15.4			51.8	20.3		
Academic degree	60.1	23.4			76.8	13.2			63.7	15.5			43.1	19.7		
Work ability			**0.020**	0.199			**<0.00**	**0.037***			0.086	**0.035***			**<0.001**	0.433
Able to work	63.4	23.9			75.9	11.6			66.8	13.1			45.8	19.8		
On sick leave (*n* = 7)	44.1	31.8			79.8	12.8			56.0	20.2			58.0	25.9		
Retired	57.3	23.3			69.9	13.7			68.8	17.7			56.0	19.5		
Age at onset of epilepsy			0.301	**0.012***			**0.001**	**0.006***			0.872	0.212			0.726	0.298
0–9	64.3	25.6			72.9	12.8			67.4	16.4			51.0	19.3		
10–18	57.7	22.0			66.2	13.9			66.9	15.5			51.7	17.3		
19–29	61.4	22.8			72.5	13.1			66.9	17.1			49.1	19.1		
30 or over	57.8	24.4			73.1	12.1			68.5	15.5			52.6	21.6		
Seizure frequency			**<0.001**	**<0.001**			0.542	0.923			0.754	0.813			0.14	0.21
At least one year without	69.6	20.9			73.8	11.7			66.8	14.3			46.8	19.2		
1–2 per year	57.3	21.1			73.5	12.4			66.6	16.7			49.8	23.1		
3–6 per year	55.6	26.8			69.7	15.7			70.2	17.4			56.4	19.6		
6–11 per year	61.7	25.7			72.7	12.9			66.4	17.8			54.4	19.0		
1 or more per month	42.5	21.2			73.4	13.8			68.2	15.2			56.6	19.1		

Antiepileptic medication (AED)			**<0.001**	**0.009***			**0.028**	0.505			**0.003**	**0.007***			**<0.001**	**0.001***
1 drug	65.2	22.1			73.7	13.3			64.6	14.5			46.0	20.6		
2 drugs	54.1	25.0			73.6	12.3			71.3	15.3			54.5	19.0		
3 drugs	57.0	25.6			70.3	10.9			71.9	19.2			58.4	18.6		
4 or more	51.4	22.6			66.6	17.1			66.6	15.6			60.5	17.3		

*Statistically significant adjusted *p*-value <0.05.

4.3.2 Correlations between factors

A statistically significant positive correlation was observed between the 'willingness' and 'therapeutic misconception' factors ($r = 0.405$, $p < 0.001$) (see Fig. 5).

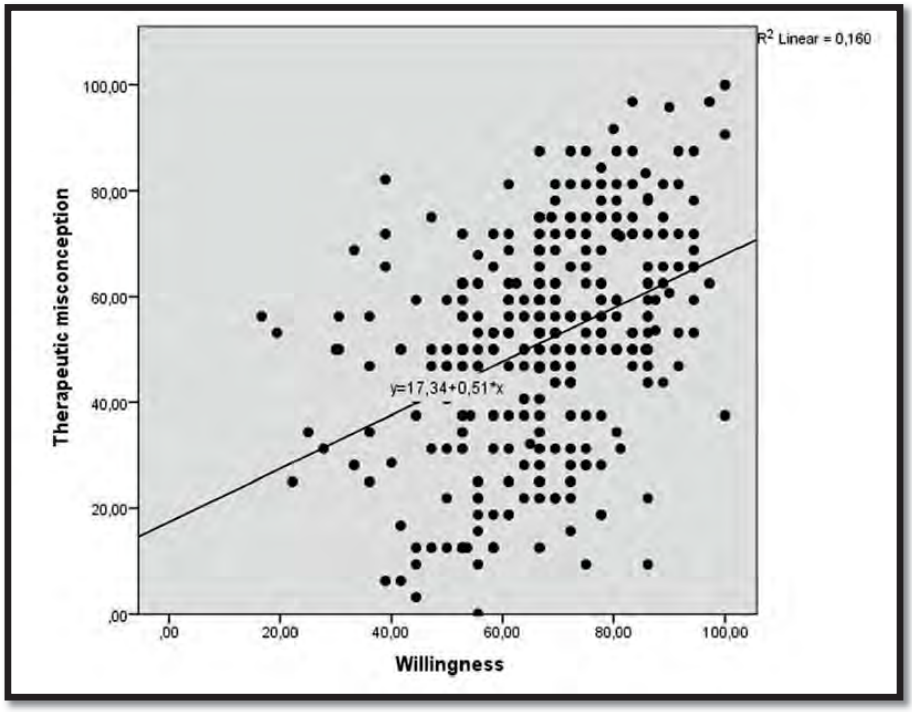

Figure 5. The correlation between willingness to participate in CTs and therapeutic misconception.

The 'sense of control over the epilepsy' factor showed a negative correlation with 'willingness' ($r = -0.125$, $p = 0.025$) and 'therapeutic misconception' ($r = -0.121$, $p = 0.030$). Furthermore, a weak negative correlation was observed between the factors representing knowledge of clinical trials and therapeutic misconception ($r = -0.113$, $p = 0.042$).

There was no correlation between the sense of control over the subject's epilepsy and the 'knowledge of CTs' factor ($r = -0.013$, $p = 0.811$). Neither did the 'knowledge of CTs' factor and the 'willingness' factor exhibit mutual correlation ($r = 0.053$, $p = 0.344$).

4.4 DISCUSSION

To the best of our knowledge, our study was the first to assess how CTs are perceived by patients with epilepsy. The study identified several factors that are related to knowledge of CTs. We also found that therapeutic misconception is an important issue to consider in recruitment of patients for CTs.

In general, attitudes toward CTs were positive among patients with epilepsy. This finding is consistent with studies in the general population and performed with patients with cancer (Ohmann, Deimling 2004, Burns et al. 2013, Ellis et al. 1999, Trauth et al. 2000, Madsen et al. 2000). It is interesting, however, that positive opinions do not automatically mean high interest in participating in CTs (Ohmann, Deimling 2004, Burns et al. 2013). In parallel study with findings among people with other disorders, patients with epilepsy were interested in personally receiving information on the research results and also supported the publication of results (Locock, Smith 2011b, Sood et al. 2009). According to Ellis et al. (Ellis et al. 1999), publication of results may encourage people to take part in future trials. In addition, studies with patients with cancer have indicated that the lack of information about the results can push attitudes toward being negative to future trials. Therefore, briefing the participants on the CT's results should be an integral part of the research process (Madsen et al. 2000).

Proper understanding of the purposes and procedures of CTs is a prerequisite for informed consent to participate. Previous studies have reported that patients and the general public have difficulties in understanding many methodological elements of CTs, such as randomisation, blinding, and the use of placebo (Miller et al. 2011). Our results suggest that patients with a lower level of education and those who are retired have less knowledge of CTs. This should be taken into account by investigators when they recruit patients for CTs. Another noteworthy finding in our study was that fuller knowledge of CTs was associated with a lower degree of therapeutic misconception. Clinicians and investigators should consider methods for the development of material to increase awareness of CTs, as should pharmaceutical companies. For example, computer-based applications could be used for these purposes (Kass et al. 2009, Taylor et al. 2012).

Among patients with epilepsy, willingness to participate in CTs is closely related to expectations of personal health benefits, especially in retired subjects and those with a lower education level. As a whole, however, patients with epilepsy also considered altruistic reasons to be strong motivating factors for participation. In earlier literature, expected personal health benefits have been seen as a strong motivator to take part in clinical trials (Kim et al. 2015a) especially if the participant's condition is severe (Locock, Smith 2011b, Kass, Maman & Atkinson 2005, Valadas et al. 2011, Kwon et al. 2012). Our data suggest that better knowledge of epilepsy and higher satisfaction with one's current treatment is associated with lower willingness to participate in CTs.

Our study is consistent with previous literature in its findings that therapeutic misconception is a common phenomenon and that it should be considered in the recruitment of patients to be CT subjects (Appelbaum, Lidz & Grisso 2004, Appelbaum et al. 2012, Durand-Zaleski et al. 2008). The prevalence of therapeutic misconception of some extent has been found to be in the 55–74% range among CT participants (Appelbaum, Lidz & Grisso 2004, Appelbaum et al. 2012, Durand-Zaleski et al. 2008, Dunn et al. 2006, Wazaify, Khalil & Silverman 2009). The results of our study strongly support earlier research results in that selected patient groups appear to be at particular risk of therapeutic misconception (Appelbaum, Lidz & Grisso 2004). For investigators and other stakeholders of CTs, it is worthwhile to recognize that patients on multiple AEDs — i.e., patients often included in phase II and III CTs — in addition to subjects with less education, are at higher risk for therapeutic misconception. A logical and important finding in our study is that willingness to participate in CTs is correlated with the degree of therapeutic misconception. This phenomenon can be a double-edged sword. Persons who experience therapeutic

misconception and are recruited to take part in a CT may possess false expectations about the CT. This could lead to disappointment and withdrawal from the study and also lead to an enhanced placebo effect in some patients. Better perceived knowledge was associated with lower risk of therapeutic misconception.

The study has some limitations. Firstly, the response rate (17%) was quite modest. In the interest of privacy, the list of study subjects was generated by the FEA, and the survey forms were returned anonymously. Therefore, the authors were unable to contact those who did not respond in the survey. For this reason, it is not possible to evaluate whether the respondents differ from those who did not respond. However, the clinical and demographic characteristics of the respondents, such as the age at onset of epilepsy, their age range, seizure status, and AED treatment pattern, seem to represent adult populations with epilepsy well (Forsgren et al. 2005, Keranen, Riekkinen & Sillanpaa 1989). Furthermore, the number of respondents (n = 325) did represent a sample size sufficient for factor analyses. However, more than half of our respondents were female. In general, females may be more active in responding to questionnaires. In conclusion, we believe that our findings are generalisable to adult populations with epilepsy. A second issue to consider is the questionnaire, which has not been validated with patients who have epilepsy. However, it was developed in accordance with studies that measured knowledge of and attitudes to CTs on the part of the general public and outpatients with medical disorders.

4.5 CONCLUSIONS AND IMPLICATIONS OF THE RESEARCH

Our analysis shows that attitudes of patients with epilepsy to CTs are positive and that they consider the trials important. Patients with refractory illness or a low level of education are the most vulnerable to therapeutic misconception. Expected personal health benefits are a factor strongly influencing willingness to participate in CTs. During recruitment, special attention should be paid to the information supplied about the purposes and methods of the trial, in order to reduce the risk of therapeutic misconception in patients with epilepsy who are asked to participate.

5 Clinical features of Parkinson's disease patients are associated with therapeutic misconception and willingness to participate in clinical trials

5.1 BACKGROUND

Parkinson's disease (PD) is a neurodegenerative disorder with progressive deterioration of motor, autonomic, and neuropsychiatric functions. While important advances have been made in symptomatic therapy for PD, many unmet needs remain – e.g., for disease modification and treatment of motor complications and non-motor symptoms in advanced PD (Katzenschlager 2014). Clinical trials (CTs) are essential for ascertaining the effectiveness and safety of new drugs and medical devices. According to published surveys, a large part of the general population has positive attitudes toward CTs; however, only 25–36% of people are personally willing to participate in a CT (Ohmann, Deimling 2004, Chu et al. 2015, Comis et al. 2003, Madsen, Holm & Riis 1999). The main motivations for patients' participation in CTs are to gain personal health benefits, help other patients, and advance science (Chu et al. 2015, Madsen, Holm & Riis 1999, McCann, Campbell & Entwistle 2010). Similar motivating factors have been identified specifically in selected groups of patients with PD (Valadas et al. 2011, Goetz et al. 2003, Finder et al. 2012).

Strong motivation for participation in a CT stemming from expected personal health benefits may lead to some challenges. If potential study participants do not understand that the primary purpose of CTs is to produce generalisable knowledge, regardless of whether the research subject may benefit from the trial intervention, they may suffer from therapeutic misconception (TM). Unrealistic expectations as to the personal health benefits associated with a CT may lead to disappointment and distrust in CTs among participants. Adequate knowledge of CTs, on the other hand, may increase willingness to participate and improve recruitment (Ohmann, Deimling 2004, Mathur et al. 2015). Consequently, it is important for clinical investigators and other stakeholders associated with CTs to obtain information about patients' knowledge and views of CTs.

The aim of the study described here was to assess knowledge of, and attitudes toward, CTs among a random sample of patients with PD who were members of the Finnish Parkinson Association (FPA). Furthermore, we attempted to evaluate the association of various demographic and clinical factors with the subjects' attitudes to CTs and willingness to participate in them.

5.2 METHODS

5.2.1 The study sample

The target population of the study consisted of subjects with PD who were members of the national patient organization the FPA. Questionnaires and other materials were sent to a random sample of FPA members ($n = 2000$, from a total membership of 8000) in 2014. The list of subjects to whom the material was to be sent was generated by the FPA via selection of every fourth person on the membership list. While most members of the FPA are patients with PD, relatives of PD patients, health-care professionals, and other supporters are also included. The cover letter and the Study Information Sheet requested responses only from subjects with PD who were able to complete their responses to the study material

independently. The study was conducted in compliance with the Declaration of Helsinki, and a favorable opinion of the study was obtained from the Research Ethics Committee of the University of Eastern Finland.

In total, 708 questionnaires were returned. However, 27 of the forms returned were dismissed from analysis because of inadequate information (i.e., a blank form or only a few answers). Therefore, the final number of questionnaires accepted for analysis was 681 (34% of the full sample).

5.2.2 The study design and data collection

For the purposes of the study, a questionnaire to be self-administered by the patients was developed. This questionnaire, which was based on our previous research (Reijula et al. 2015, Halkoaho 2012), the available academic literature (Chou, O'Rourke 2012, Jenkinson et al. 2005), and pilot testing by a group of patients with PD ($n = 12$), had two parts. The first part covered demographic and socioeconomic issues, along with clinical aspects of PD and its treatment. The second part formed the actual survey instrument, which featured 50 statements. These items covered areas such as knowledge of, and attitudes toward, CTs; factors associated with willingness to participate in CTs; and experiences of participation in CTs, which will be the subject of another paper. The subjects responded to the statements by using a five-option Likert scale. The options for the statements were "strongly disagree" (1), "disagree" (2), "cannot say" (3), "agree" (4), and "strongly agree" (5).

From the statements in the questionnaire, three factors were constructed: "Knowledge of CTs" (nine items) was addressed with statements on awareness of basic principles and procedures of CTs, the factor called "Willingness" (with five items) was examined via statements on elements promoting willingness to participate in CTs, and "Therapeutic misconception" (12 items) was addressed through items for measuring how patients understood the differences between the purposes of CTs and standard care and how expectations of personal health benefits would affect decision-making (see Table 10).

Table 10. Descriptions of the statements and factors.

Factors	Statements	Alpha
F1: Knowledge of CTs	- I know what a CT means - Each new drug has been studied with patients before it becomes available via pharmacies - CTs are always assessed beforehand by a research ethics committee - Participation in a CT is always voluntary - A potential CT participant signs a consent document before taking part in the research - The research participant may at any point terminate his or her participation in the CT - A clinical trial may include procedures differing from ordinary treatment - Clinical trials are mostly funded by a pharmaceutical corporation - The essential goal of clinical treatments is to find better medication for future patients	0.60
F2: Willingness	- New PD medications are usually studied in comparative trials (an old drug is compared to a new substance or a placebo); I would like to participate in this kind of CT - I would participate in a CT if I did not receive enough information about the CT and the investigational drug - I would participate in a CT even if because of that I would need to go to a doctor's office much more often than in ordinary care - I would participate in a CT in which there were a possibility of receiving a placebo (placebos do not contain any active ingredient) - I would participate in clinical trials because it would enable me to help other patients with Parkinson's disease	0.62
F3: Therapeutic misconception	- Usually CTs are aimed primarily at seeking the best medication for the research participants - I would participate in a CT only if the treating physician also is the investigator - I would like to participate in CTs in order to determine the continuation of my current treatment relationship - I would like to participate in a CT because then I would receive more thorough monitoring relative to standard treatment – usually clinical trials are aimed primarily at seeking the best medication for the research participants - I would participate in a CT if that guaranteed me new and improved medication - I would participate in a CT only if I were not satisfied with my current medication - In CTs, all participants always receive a new effective agent - In CTs, the physician conducting the research is aware of whether the participant is receiving a new drug, a placebo (which does not include an effective agent), or an older Parkinson's disease medication - In CTs, the physician conducting the research may choose which drug the participant receives - The patient participating in the research may often choose which drug he or she receives - I would participate in a CT, because then I would receive the best treatment for me - I would participate only in a CT in which at least one of the drugs being compared has been shown to be effective	0.79

"CT" = clinical trial.

5.2.3 Statistical analysis

The data were analysed by means of IBM SPSS Statistics for Windows, Version 21.0 software. The background information (presented in Table 13) and selected statements were characterized in terms of frequency and percentage distributions (Tables 11 and 12). The scale for responses to the statements (the aforementioned 1–5 range) was adjusted to 0–100 (1 = 0 to 5 = 100) for clearer presentation of the results (Table 13).

Factor scores were formed via calculation of the means for the various statements. Cronbach's alphas were used for assessment of reliability with respect to the factors. The linear relationships between the three factors were assessed via Spearman's correlation. Factor scores were presented as means and standard deviations in Table 13. The association of selected demographic and clinical variables (age, gender, education level, ability to work, duration of PD, number of PD medications, and other chronic disease(s)) with the three factors was analysed via multiple linear regression. Coefficients of regression model were also presented to measure difference to reference category (see Table 13). The assumptions of linear regression were visually checked through assessment of the residuals. The relationship between factors and clinical variables was assessed via Spearman's correlation.

Statistical significance was achieved at $p < 0.05$. To identify the key items for the "Therapeutic misconception" factor, Spearman's correlation was used (for all correlations with $p < 0.001$) (Table 14).

5.3 RESULTS

5.3.1 General attitudes and willingness to participate

In the main, patients with PD held positive attitudes toward clinical trials. Participants strongly favored the publishing of trial results and informing the trial participants about the results. Nearly 90% indicated that they would participate in CTs to help other patients with PD, but 36% stated that they would refuse if there were a possibility of receiving a placebo (see Table 11).

Table 11. Attitudes toward clinical trials and study participation.

Statements	Agreement		"cannot say"		Disagreement	
	n	%	*n*	%	*n*	%
Persons diagnosed with PD should be asked to participate in CTs	559	83	81	12	32	5
If patients refuse to participate in CTs, new treatments will not become available	417	63	140	21	108	16
Research results should be discussed with research participants	634	95	17	3	13	2
I think it is important that all clinical trials' results be published and health-care professionals gain access to them	620	93	29	4	19	3
I would like to receive as much information as possible about the trial and the new drug before I make a decision about participation in a CT	561	83	57	9	54	8
New PD medications are usually studied in comparative trials (an old drug is compared to a new substance or a placebo); I would like to participate in this kind of CT	336	50	177	26	157	23
I would participate in clinical trials because it would enable me to help other patients with Parkinson's disease	567	86	64	10	32	5
I would participate in a CT in which there is a possibility of receiving a placebo (placebos do not contain any active ingredient)	274	42	145	22	238	36
I would participate in a CT if it involved a significant risk of severe adverse effects (adverse effects that could lead to prolongation of hospitalization or cause permanent disability)	34	10	100	15	492	75

The agreement and disagreement categories were formed by combining the "agree" and "strongly agree" responses and the "disagree" and "strongly disagree" responses, respectively. "CT" = clinical trial.

5.3.2 Knowledge of the issues related to clinical trials

Overall, the respondents were well aware of general aspects of CTs, such as voluntary participation, written consent, and the right to withdraw from a CT. However, several issues related to trial methods (e.g., randomisation and the possibility of the investigator or

the participant choosing the trial treatment) were correctly recognized by only a minority (Table 12).

Table 12. General knowledge of clinical trials.

Statements	Right		Wrong	
	n	%	*n*	%
I know what a CT means	331	50	329	50
Each new drug has been studied in patients before it becomes available via pharmacies	482	72	188	28
CTs are always assessed beforehand by a research ethics committee	312	47	349	53
Participation in a CT is always voluntary	623	93	45	7
A potential CT participant signs a consent document before taking part in the research	560	83	112	17
The research participant may at any point stop his or her participation in the CT	518	77	152	23
A CT may include procedures different from standard care	303	46	360	54
Clinical trials are mostly funded by a pharmaceutical corporation	424	64	241	36
The essential goal of CTs is to find better treatment for future patients	633	94	37	6
*Clinical trials are usually aimed primarily at seeking the best medication for the research participants	145	22	523	78
*In CTs, all participants always receive a new effective agent	298	45	732	55
Different treatment procedures can be assigned randomly in CTs (for example, by flipping a coin or via other methods of randomisation)	236	36	427	64
*In CTs, the physician conducting the research is aware of whether the participant is receiving a new drug, a placebo (which does not include an effective agent), or standard PD medication	112	21	523	79
*In CTs, the physician conducting the research may choose which drug the participant receives	193	29	474	71
*Often, the patient participating in the research may choose which drug he or she receives	401	60	265	40

The "Right" category encompasses the "agree" and "strongly agree" responses; the "Wrong" category is a combination of "disagree," "strongly disagree," and "cannot say." For starred (incorrect) items, the "Right" category was composed of "disagree" and "strongly disagree" responses and the "Wrong" category covered "agree," "strongly agree," and "cannot say." CT clinical trial

5.3.3 Mean values and dependences of clinical features of Parkinson's disease with the "Knowledge of CTs," "Willingness," and "Therapeutic misconception" factors

"Knowledge of CTs" was statistically significantly associated with education and work ability. "Willingness" showed a statistically significant association with gender. "Therapeutic misconception" was positively associated with higher age, lower education, and lower number of PD medications (Table 13).

"Knowledge of CTs" showed relatively small but significant positive correlation with education ($r = 0.177$, $p < 0.001$) and negative correlation with age ($r = -0.098$, $p = 0.011$). Positive correlation was found between "Willingness" and education ($r = 0.088$, $p = 0.024$). There was a negative medium size correlation of "Therapeutic misconception" with

education ($r = -0.26$, $p < 0.001$) and with the number of PD medications ($r = -0.100$, $p = 0.010$). On the other hand, positive correlation was observed between "Therapeutic misconception" and age ($r = 0.195$, $p < 0.001$).

Table 13. The association of selected demographic and clinical variables with the three factors as analysed via multiple linear regression mean score and standard deviation (SD) for each demographic and clinical variable and factor, where with factor 1, scores near 100 mean complete knowledge of clinical trials (CTs); with factor 2, scores close to 100 indicate commitment to participating; and factor 3 indicates high therapeutic misconception (* = statistically significant p value < 0.05)

Variables		F1: Knowledge of CTs				F2: Willingness				F3: Therapeutic misconception			
		Mean score	SD	β-coef.	*p*-value	Mean score	SD	β-coef.	*p*-value	Mean score	SD	β-coef.	*p*-value
Age band (years)	***n***				0.092				0.552				**0.004***
≤59 (ref.)	67	79.3	10.5			60.3	21.9			48.4	18.0		
60–69	278	78.0	11.8	-1.5	0.381	61.9	19.7	-2.1	0.472	53.1	17.1	4.4	0.076
70–79	261	76.4	12.2	-2.5	0.147	59.5	20.8	-0.2	0.946	56.4	18.4	6.5	0.011
≥80	65	74.3	10.5	-5.2	0.021	59.7	19.3	-0.7	0.868	61.4	15.3	11.4	**0.001***
Gender					0.556				**<0.001***				0.187
Female (ref.)	298	77.1	11.8			57.2	19.8			54.4	18.7		
Male	374	77.0	12.4	0.5	0.556	63.2	20.6	6	**<0.001***	54.9	17.3	1.8	0.19
Education					**<0.001***				0.111				**<0.001***
Basic education (ref.)	199	73.7	12.5			57.4	20.1			59.4	18.5		
Vocational training	338	77.8	11.7	3.2	**0.003***	61.6	20.9	3.3	0.083	55.2	16.6	-3.5	**0.027***
Academic degree	132	79.9	11.4	6.1	**<0.001***	62.6	19.4	4.5	0.058	45.7	17.3	-12.9	**<0.001***
Work ability					**0.015***				0.477				0.866
Able to work (ref.)	26	77.9	12.0			58.7	22.3			50.3	20.1		
On sick leave	10	71.3	11.4	-9.9	**0.04***	53.9	11.4	-9.5	0.261	49.6	18.3	3.8	0.594
Retired	635	77.1	12.3	2.2	0.396	60.6	20.5	-0.5	0.907	54.9	17.8	-1.2	0.761
Duration of Parkinson's disease					0.419				0.733				0.168
0–4 years (ref.)	221	77.6	11.8			60.0	20.1			54.2	17.0		
5–9 years	238	76.5	11.7	-1.2	0.304	61.5	19.4	1.2	0.547	56.0	18.3	2.0	0.253
≥10 years	202	77.9	11.8	0.2	0.902	60.2	21.7	-0.2	0.928	53.3	18.3	-1.1	0.531
Parkinson's disease medication					0.600				0.502				**0.022***
1 drug (ref.)	118	75.0	13.1			57.4	19.7			59.3	18.7		
2 drugs	202	77.2	10.9	1.4	0.319	60.5	21.4	1.5	0.538	54.8	17.4	-4.7	**0.023***
3 or more drugs	346	77.6	12.4	0.8	0.571	61.4	20.0	2.8	0.251	53.0	17.7	-5.5	**0.007***
Other chronic disease(s)					0.285				0.860				0.168
Yes	428	78.0	11.5	-1	0.285	60.9	20.3	0.3	0.86	55.0	16.8	-2.0	0.168
No (ref.)	249	76.5	12.4			60.3	20.5			54.4	18.5		

5.3.4 Correlations between three factors

A minor but statistically significant positive correlation was found between the "Willingness" and "Therapeutic misconception" factors ($r = 0.158$, $p < 0.001$). "Knowledge of CTs" and "Willingness" exhibited positive correlation ($r = 0.212$, $p < 0.001$). Correlation was not observed between "Knowledge of CTs" and "Therapeutic misconception" ($r = 0.015$, $p = 0.706$).

5.3.5 Driving statements of therapeutic misconception

Coefficients of correlation between component statements for the "Therapeutic misconception" factor and the factor score ranged from 0.437 to 0.703, being highly significant ($p < 0.001$) for all statements (see Table 14).

Table 14. Spearman correlation coefficients of individual statements and the score for the "Therapeutic misconception" factor.

Statement	***r***
Usually CTs are aimed primarily at seeking the best medication for the research participants	0.703
I would participate in CTs, because then I would receive the best treatment for me	0.673
I would like to participate in CTs in order to determine the continuation of my current treatment relationship	0.643
In CTs, all participants always receive a new effective agent	0.638
In CTs, the physician conducting the research may choose which drug the participant receives	0.564
Often, the patient participating in the research may choose which drug he or she receives	0.540
I would participate only in a CT in which at least one of the drugs being compared has been shown to be effective	0.525
I would participate in a CT only if the treating physician also is the investigator	0.485
I would participate in a CT if that guaranteed me new and improved medication	0.476
I would like to participate in a CT because then I would receive more thorough monitoring relative to standard treatment	0.469
I would participate in a CT only if I were not satisfied with my current medication	0.468
In CTs, the physician conducting the research is aware of whether the participant is receiving a new drug, a placebo (which does not include an effective agent), or an older Parkinson's disease medication	0.437

"CT" = clinical trial.

5.4 DISCUSSION

To date, there have been few studies reporting on attitudes toward, and experiences of, participation in CTs among patients with PD (Valadas et al. 2011, Goetz et al. 2003, Finder et al. 2012, Mathur et al. 2015, Ravina et al. 2010), though some have been carried out among patients with very advanced PD on participation in trials involving sham surgery (Kim et al. 2015a, Kim et al. 2012). To the best of our knowledge, ours is the first large-scale survey to assess how CTs are perceived by a random sample of patients with PD. Our study identified several clinical characteristics that are related to knowledge of, and willingness to participate in, CTs and revealed elements of how TM is associated with these issues.

Patients with PD had positive attitudes toward CTs, as is the case also with the general population (Burns et al. 2013, Madsen, Holm & Riis 1999), patients e.g., with epilepsy (Reijula et al. 2015), and cancer (Ellis et al. 1999, Madsen et al. 2000). Furthermore, more than 80% of the subjects in our study stated that patients with PD should be asked to participate in CTs. An important message for those who commission and conduct CTs is that the patients with PD were strongly in favor of the publication of the research results and indicated also that they were interested in learning the results themselves.

A large majority of the patients in our study were well aware of basic ethical issues and participant's rights associated with CTs such as voluntary participation, informed consent, and the right to withdraw from a CT. Over 90% of the respondents supported the statement that the essential goal of CTs is to benefit future patients. However, at odds with that view is the fact that nearly 80% of the subjects thought that CTs are aimed primarily at seeking the best treatment for the participants. A similar observation has been made in another study with a different kind of PD population (Kim et al. 2015a). Patients may think that the combination of gathering scientific knowledge together with benefiting an individual study participant formulates the ultimate goal of the study. Clearly, understanding the purposes of CTs is complex, and, as Kim et al. (Kim et al. 2015a) conclude, the issue is impossible to resolve fully with closed-ended items.

Overall, various methodological issues of CTs, such as randomisation and the investigator physician's ability to be aware of, or choose, the participant's treatment, were correctly recognized by just 21–26% of the subjects. It is also important to note that nearly half of the respondents thought that all participants in CTs will receive effective study treatment. Furthermore, fewer than half of the subjects knew that CTs may include procedures deviating from standard care. In a group of PD patients who had all participated in CTs, 42% of the subjects thought that the study was part of the standard treatment (Ravina et al. 2010). Thus, subjects with PD share with other patient groups many difficulties in understanding the meaning and purposes of CT methods (Burns et al. 2013, Locock, Smith 2011a, Hietanen et al. 2000). Our data further suggest that subjects with a low level of education and who are older in age are especially likely to have gaps in their knowledge of the principles of CTs. Indeed, a report on a survey of patients with PD who had participated in CTs (Ravina et al. 2010) observed that less educated subjects had poorer comprehension of the study information. Our findings and those of previous research (Hietanen et al. 2000) highlight significant information needs of patients in relation to essential elements of informed consent for a CT.

With statements on issues such as information needs, study design, possible adverse effects, and altruistic interests, we explored some aspects of willingness to take part in CTs. As observed previously in patients with PD (Valadas et al. 2011, Goetz et al. 2003, Finder et al. 2012), altruism and contributing to science were also important factors in motivation to take part in CTs in this study. Study design, especially the use of placebos, and the high risk of adverse effects were negative motivating factors, as has been observed with other patient groups (Welton et al. 1999, Agoritsas, Deom & Perneger 2011), among them patients with PD specifically (Valadas et al. 2011, Mathur et al. 2015). A study of patients with PD who

had taken part in a CT found that the subjects retained positive impressions of participation in placebo-controlled trials although they had wished to receive active treatment instead of a placebo (Goetz et al. 2003). Among our subjects, a higher level of education seemed linked to greater willingness to participate in CTs. An encouraging finding was that willingness to participate in CTs was positively correlated with knowledge of CTs.

The term TM was originally introduced almost 35 years ago by Applelbaum et al. – and still there remains uncertainty and disagreements regarding how it is defined and measured (Appelbaum 2016, Kim et al. 2016). The key point of TM is the mistaken belief that the purpose of CT is to benefit potential study subjects individually, as opposed to its real goal which is to gather scientific knowledge. This raises a number of specific problems – the validity of (informed) consent as well as overestimation of benefits, under-estimation of the risk of harm, and/or under-appreciation of alternatives to participation in CTs (Appelbaum, Lidz & Grisso 2004, Henderson et al. 2007). However, TM is not coherently constructed, and several terms related to TM (e.g., therapeutic optimism, therapeutic misestimation, unrealistic optimism or expected therapeutic benefit) have been proposed (Hallowell et al. 2016, Sulmasy et al. 2010, Jansen 2011, Lyons 2016). TM is considered to be common among participants of CTs (Appelbaum, Lidz & Grisso 2004, Durand-Zaleski et al. 2008, Lidz et al. 2004, Mansour et al. 2015) but this conclusion has been recently challenged (Kim et al. 2015b, Kim et al. 2016). One issue in the assessment of TM has been that no universally accepted operational definitions or metrics for the phenomenon have been available or that it is the term argue for by scientists (Henderson et al. 2007, Lyons 2016). However, a scale for the identification of TM among study subjects has recently been developed (Appelbaum et al. 2012). Our survey instrument included several items in parallel with that scale. Usually, issues related to TM are assessed in patients who have already been recruited to take part in CTs. Our data suggest that patients with PD, as potential study participants, have important preconceptions of CTs. Expectation of therapeutic benefits increases their willingness to participate in CTs. These expectations may place them at risk of TM, especially the older patients and those with a lower level of education, as observed previously (Appelbaum, Lidz & Grisso 2004, Reijula et al. 2015). A possibly unexpected finding was that, in comparison with patients prescribed a higher number of PD medications, those with fewer drugs and, presumably, less severe PD, stated stronger indicators of TM. It might be that subjects who used more PD drugs and had more advanced disease had less expectation of therapeutic gains associated with CTs, or they may have gained fuller knowledge of their disease and hence shown realistic expectations of treatments overall. Our results suggest that level of general knowledge of CTs is not associated with degree of TM. However, poor understanding of specific methodological issues of CTs, as discussed above, may expose patients to misunderstanding of the main goals of research. Taken together, our findings suggest that patients' preconceptions of CTs may lead to TM if adequate information is not given to, or appreciated by, the patients during the consent process. We agree with Lyons (Lyons 2016) that what really matters is the relationship and the discussion between the potential study participant and their physician/investigator before the patient can meaningfully consent in a study. We suggest that researchers should first enquire about patient preconceptions considering the CTs and then provide tailored information to the patient.

All of the statements linked to the "Therapeutic misconception" factor showed statistically significant correlation with the level of that factor. The highest scores were observed for statements pertaining to expected personal health benefits to participants, such as CTs offering new, or the best, medication and treatment, and continuation of the current health-care relationship. However, overall, most of the other statements receiving high scores had to do with issues related to personal benefit. Previous studies conducted both among the public at large and with various patient populations, PD patients among them, have shown that expectations of personal health benefits are the main factor behind participation in CTs (Kim et al. 2015a, Valadas et al. 2011, Madsen, Holm & Riis 1999,

Finder et al. 2012, Chu et al. 2012). In our study, the possibility of one's own physician being the site investigator was associated with willingness to take part, but Kim et al. (Kim et al. 2015a) did not find such an association. However, the study population in the latter study differed greatly from ours: the subjects were participants or subjects to be enrolled in a surgical trial. Therapeutic motivation in the case of participants in CTs may result from optimism that is not related to misunderstanding of the study information (Jansen 2011); however, our study revealed that patients with PD do show deficiencies in their understanding of the purposes of CTs and the key methodological issues thereof.

Our study has some limitations. Firstly, the response rate (35%, after exclusion 34%) was quite modest. However, the number of survey forms ($n = 681$) accepted for the analyses was sufficient for statistical evaluations. The members of the FPA include about 50% of the Finnish patients with PD. These patients might be more than averagely motivated and interested in CTs and in their own condition. This issue needs to be taken into account since it can give a slightly more positive impression of the results. Our study population showed male predominance (see Table 13), as is also commonplace in many epidemiological studies (Marttila, Rinne 1979, Kuopio et al. 1999, Van Den Eeden et al. 2003, Havulinna et al. 2008). Two thirds of the respondents had suffered from PD for at least 5 years, but patients aged at least 80 years accounted for only about 10% of the study subjects. Thus, the oldest PD patients seemed under-represented (de Rijk et al. 1997), an effect that may be due to their inability to complete the questionnaire themselves, arising from motor or cognitive deficits. A second issue to consider is the questionnaire which was developed for a study among patients with epilepsy (Reijula et al. 2015) and then modified in light of the feedback from those patients, and also after pilot testing with patients diagnosed with PD. However, the questionnaire was not validated statistically or against in-depth interviews of the subjects. Assessing TM by means of questionnaires is challenging, because the items intended for measuring TM may not be understood as intended (Kim et al. 2015b).

5.5 CONCLUSIONS

In conclusion, the results of this study suggest that attitudes toward CTs are mostly positive among patients with PD. However, there is a need for greater awareness of the purposes and methods of CTs. Older age and lower level of education are most strongly associated with TM. Recruiters should take patients' preconceptions into account and strive to improve communication between them. Investigators should verify that the patients understand the meaning of randomisation and – if relevant for the study at hand – the justification for using a placebo. Increasing patients' comprehensive knowledge related to CTs may improve not only quality of consent – but also increase willingness to participate in general.

6 Comparable indicators of therapeutic misconception between epilepsy or Parkinson's disease patients between those with clinical trial experience and trial non-participants

6.1 INTRODUCTION

Clinical trials (CTs) are necessary for the development and approval of new medical therapies. A sufficient number of potentially enrolling study participants is a critical component of high CT quality. Attitudes toward CTs are positive among the general public and in various patient groups alike (Valadas et al. 2011, Locock, Smith 2011a, Bevan et al. 1993), yet recruitment of suitable patients may be challenging (Treweek et al. 2010, Picillo et al. 2015). Altruism and a desire to contribute to science are major motivating factors for participation in CTs among patients with various disorders (Durand-Zaleski et al. 2008, Locock, Smith 2011a). However, expectations of personal health benefits and of research providing access to health-care services are reported to be equally important factors driving participation in CTs (Valadas et al. 2011, Locock, Smith 2011a, Townsend, Cox 2013). Patients seem to appreciate the attention paid to them during the course of CTs, and most of them have high expectations of the therapeutic effects of the study medication (Madsen et al. 2000, Valadas et al. 2011, Bevan et al. 1993).

Before entering a CT, potential participants are required to give written informed consent for respecting their autonomy and protecting them from exploitation [9]. It can be challenging to fulfil the various elements of informed consent. The purpose and the method of CTs often differ greatly from those in standard medical treatment; for instance, CTs may include randomisation of the subjects, blinding of the participant and the investigator, and the use of placebo. Patients often have difficulties in understanding these issues (Valadas et al. 2011, Tam et al. 2015). The concept of therapeutic misconception (TM) refers to a situation wherein CT participants fail to recognise the differences between clinical research and standard medical care and, hence, the requirements for informed consent are not met (Appelbaum, Lidz & Grisso 2004, Appelbaum 2002). A recent systematic review concluded that the proportion of CT participants who actually understand the individual components of informed consent ranges from 52% to 76% (Tam et al. 2015).

Epilepsy and Parkinson's disease (PD) are neurological disorders under active clinical research. In recent years, attitudes toward CTs, motivation for participation, and understanding of study information by selected groups of patients with epilepsy or PD have been reported (Valadas et al. 2011, Goetz et al. 2003, Finder et al. 2012, Ravina et al. 2010, Kim et al. 2012, Canvin, Jacoby 2006, de Melo-Martin, Hellmers & Henchcliffe 2015). One challenge with disorders such as epilepsy and PD is that those invited to participate in a CT may include cognitively challenged subjects. Thus, comprehension of the study information can be compromised (Ravina et al. 2010, de Melo-Martin, Hellmers & Henchcliffe 2015). Indeed, in one study, 42% of patients who had participated in a CT stated after enrolling in the 12-month trial that participation in the study was a part of the usual treatment for their disease (Ravina et al. 2010). These findings also highlight the importance of written informed consent.

We have previously assessed knowledge of and attitudes toward CTs in two large populations of patients with epilepsy (Reijula et al. 2015) or PD (Reijula et al. 2017). Both patient groups included subjects who had participated in CTs. The aim of the study was to

compare knowledge of and attitudes toward CTs, alongside issues related to TM, between members of the two populations: patients who had taken part in a CT and those who had not. Furthermore, we examined issues affecting willingness to participate in clinical drug trials and how CT participants had experienced the process related to informed consent.

6.2 METHODS

6.2.1 The study sample

The subjects in the study were a random sample of members of patient organisations who have epilepsy (n=1,875, from a membership base of 7,500) or PD (n=2,000, from a total association membership of 8,000). The patient organisations were the Finnish Epilepsy Association (FEA), which is the Finnish chapter of the International Bureau for Epilepsy, and the Finnish Parkinson Association (FPA). The lists of patients to whom the material was to be sent were generated by the FEA and FPA via randomisation in which every fourth person on the member list was selected. The study information sheet and covering letter, sent to the subjects identified, requested a response from only adults with a diagnosis of epilepsy or PD who were able to give responses independently. A breakdown of the data-gathering process applied in the study is shown in Figure 6. In total, 1,050 questionnaires were returned, for a response rate of 27%.

The study was conducted in compliance with the Declaration of Helsinki, and a favourable opinion of the study was obtained from the Research Ethics Committee of the University of Eastern Finland. The study was approved also by the Executive Board of the FEA and of the FPA. Moreover, the FEA and FPA staff sent the study questionnaires to the participants in order to ensure their privacy. The investigators did not have access to the study population's personal data, and the responses to the questionnaire were given anonymously.

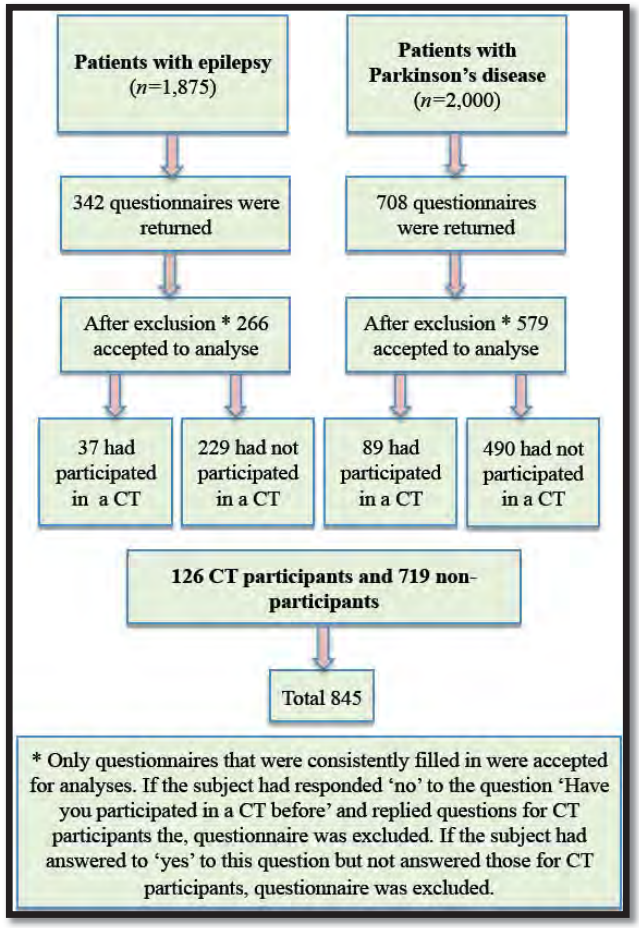

Figure 6. An outline of the process of data-collection.

6.2.2 The data

The data for the study were obtained via a questionnaire developed for the purposes of our previous studies (Reijula et al. 2015, Halkoaho 2012). In brief, the questionnaire, which was to be self administered by the patients, was grounded in previous literature (Jenkinson et al. 2005, Chou, O'Rourke 2012) and pilot testing among patients with PD (n=12). The first part of the questionnaire covered data on demographic and socio-economic matters, along with clinical aspects of epilepsy or PD and its treatment. The second part formed the actual survey instrument, which featured 50 items addressing elements such as knowledge of and attitudes toward CTs, factors associated with willingness to participate in CTs, and experiences of the informed consent process. The subjects responded to each item's statement by using a five-option Likert scale, where the options were 'strongly disagree' (1), 'disagree' (2), 'cannot say' (3), 'agree' (4), and 'strongly agree' (5).

6.2.3 Statistical analysis

The data were analysed by means of the SPSS Statistics 21.0 statistical analysis software. The background information was characterised in terms of frequency and percentage distributions. Frequencies, means, and standard deviations (SDs) were used to describe the CT participants' and non-participants' attitudes and knowledge of CTs, motivation for participation / potential participation, and expectations of personal health benefits. For clearer presentation of the results, agreement and disagreement categories were formed by combining the 'agree' and 'strongly agree' responses and the 'disagree' and 'strongly

disagree' responses, respectively. Pearson's chi-squared test was used to determine differences in clinical variables between CT participants and non-participants. A non-parametric Mann–Whitney U test was used to determine differences between CT participants and non-participants for the statements. Results were considered statistically significant at $p<0.05$.

6.3 RESULTS

In all, 126 (15%) of the respondents had participated in a CT (they are referred to below as CT participants), and the remaining 719 (85%) had not (hereinafter they are denoted as non-participants). Significant differences were not observed between CT participants and non-participants in age band (p=0.510), gender (p=0.168), or education (p=0.342) (see Table 15).

Table 15. Demographic and clinical variables for the clinical trial participants and non-participants.

Variable		participants		non-participants	
		n	**%**	***n***	**%**
Patient group	Parkinson's disease	86	70	490	68
	Epilepsy	37	30	229	32
Age band (years)	under 50	15	13	108	15
	50–59	15	13	105	15
	60–69	42	35	263	37
	70 or above	48	40	237	33
Gender	Female	55	46	374	52
	Male	66	54	342	48
Education	Basic education	36	30	186	26
	Vocational training	64	53	364	51
	Academic degree	21	17	165	23

6.3.1 General attitudes and willingness to participate among CT participants and non-participants

In general, both CT participants and non-participants held positive attitudes toward CTs (see Table 16). Over 80% in both groups indicated that they would participate in CTs to help other patients with epilepsy or PD. The use of placebo control and risk of severe adverse effects were associated with decreased willingness to participate in a CT in both groups. A significant difference was observed between CT participants and non-participants in willingness to participate in a comparative trial.

Table 16. Attitudes to clinical trials and study participation among CT participants and non-participants.

Statement	Mean	SD	*p*-value	Disagree		Cannot say		Agree	
				f	%	*f*	%	*f*	%
Persons diagnosed with PD or epilepsy should be asked to participate in CTs[1].									
Participants	4.20	1.03	0.341	11	**9**	12	**10**	99	**81**
Non-participants	4.15	0.96		43	**6**	109	**15**	562	**79**
If patients refuse to participate in CTs, new treatments will not become available.									
Participants	3.83	1.27	0.094	23	**19**	17	**14**	81	**67**
Non-participants	3.67	1.22		118	**17**	150	**21**	438	**62**
Research results should be discussed with research participants.									
Participants	4.74	0.63	0.365	3	**3**	3	**3**	115	**94**
Non-participants	4.79	0.58		10	**1**	15	**2**	683	**97**
I think it is important that all clinical trials' results be published and health-care professionals gain access to them.									
Participants	4.61	0.86	0.271	4	**4**	6	**5**	112	**91**
Non-participants	4.72	0.68		16	**2**	23	**3**	670	**95**
I would like to receive as much information as possible about the trial and the new drug before I make a decision about participation in a CT.									
Participants	4.29	1	0.135	8	**7**	9	**7**	104	**86**
Non-participants	4.37	1.01		53	**7**	55	**8**	605	**85**
New [PD/AED] medications are usually studied in comparative trials (an old drug is compared to a new substance or a placebo); I would like to participate in this kind of CT.									
Participants	3.59	1.35	**0.001**	26	**22**	24	**20**	71	**58**
Non-participants	3.17	1.36		202	**28**	214	**30**	295	**42**
I would participate in clinical trials because it would enable me to help other patients with [Parkinson's disease / epilepsy].									
Participants	4.34	1.05	0.102	9	**7**	10	**8**	102	**85**
Non-participants	4.24	1		47	**7**	73	**10**	581	**83**
I would participate in a CT in which there is a possibility of receiving a placebo (placebos do not contain any active ingredient).									
Participants	2.93	1.52	0.917	47	**39**	26	**21**	48	**40**
Non-participants	2.95	1.48		273	**39**	149	**22**	272	**39**
I would participate in a CT if it involved a significant risk of severe adverse effects (adverse effects that could lead to prolongation of hospitalisation or cause permanent disability).									
Participants	1.78	1.29	0.493	90	**75**	13	**11**	17	**14**
Non-participants	1.65	1.12		554	**80**	85	**12**	58	**8**

[1] CT = clinical trial

6.3.2 Knowledge of the issues related to clinical trials among participants and non-participants

Overall, the respondents were well aware of general aspects of CTs, such as the voluntary nature of participation and informed consent (see Table 17). However, a lower proportion of non-participants than CT participants were aware of the right to withdraw from a CT. Fewer than half of the subjects in each group recognised the possibility of random allocation of treatment in CTs.

Table 17. General knowledge of clinical trials among clinical trial participants and non-participants.

Statement	Mean	SD	*p*-value	Disagree		Cannot say		Agree	
				f	%	*f*	%	*f*	%
I know what a CT[1] means.									
Participants	3.71	1.25	**0.001**	23	**19**	20	**17**	75	**64**
Non-participants	3.28	1.32		192	**27**	155	**22**	363	**51**
Each new drug has been studied in patients before it becomes available via pharmacies.									
Participants	4.39	0.97	**0.001**	7	**6**	15	**12**	99	**82**
Non-participants	4.06	1.06		52	**7**	171	**24**	492	**69**
CTs are always assessed beforehand by a research ethics committee.									
Participants	3.78	1.02	0.176	5	**4**	50	**42**	63	**54**
Non-participants	3.68	0.97		29	**4**	361	**51**	315	**45**
Participation in a CT is always voluntary									
Participants	4.74	0.69	0.908	2	**2**	5	**4**	115	**94**
Non-participants	4.73	0.68		10	**2**	45	**6**	656	**92**
A potential CT participant signs a consent document before taking part in the research.									
Participants	4.54	0.98	0.328	7	**6**	10	**8**	106	**86**
Non-participants	4.5	0.92		24	**3**	97	**14**	592	**83**
The research participant may at any point terminate his or her participation in the CT.									
Participants	4.52	0.92	**<0.001**	5	**4**	12	**10**	104	**86**
Non-participants	4.17	1.08		53	**7**	149	**21**	510	**72**
A CT may include procedures different from standard care.									
Participants	3.52	1.19	0.424	19	**15**	40	**33**	63	**55**
Non-participants	3.49	1.01		70	**10**	319	**45**	315	**45**
Clinical trials are mostly funded by a pharmaceutical corporation.									
Participants	4.09	1.06	**0.018**	6	**5**	30	**25**	86	**70**
Non-participants	3.89	1.01		42	**6**	234	**33**	432	**61**
The essential goal of CTs is to find better treatment for future patients.									
Participants	4.61	0.76	0.747	3	**3**	8	**7**	111	**91**
Non-participants	4.66	0.79		18	**3**	18	**2**	672	**95**
Different treatment procedures can be assigned randomly in CTs (for example, by flipping a coin or via other methods of randomisation).									
Participants	3.17	1.51	0.326	37	**31**	32	**26**	52	**43**
Non-participants	3.06	1.27		191	**27**	277	**39**	240	**34**

[1] CT = clinical trial

6.3.3 Respondents' therapeutic expectations toward CTs

There were no significant differences in responses between CT participants and non-participants with respect to expectations of personal health benefits except that a higher proportion of non-participants than CT participants thought that a CT physician is aware of whether the participant is receiving a new drug vs. a placebo. Almost 60% of the respondents in both groups failed to recognise that CTs are not aimed primarily at seeking the best medication for the research participants (see Table 18).

Table 18. Issues related to expectations of personal health benefits for participation in clinical trials among CT participants and non-participants.

Statement	Mean	SD	*p*-value	Disagree		Cannot say		Agree	
				f	%	*f*	%	*f*	%
Usually CTs are aimed primarily at seeking the best medication for the research participants.									
Participants	3.49	1.5	0.875	34	**28**	18	**15**	70	**57**
Non-participants	3.56	1.5		171	**24**	134	**19**	402	**57**
I would participate in CTs, because then I would receive the best treatment for me.									
Participants	3.64	1.42	0.61	28	**23**	15	**12**	78	**65**
Non-participants	3.62	1.32		160	**23**	117	**17**	423	**60**
I would like to participate in CTs in order to determine the continuation of my current treatment relationship.									
Participants	2.97	1.44	0.443	44	**36**	27	**22**	50	**42**
Non-participants	2.78	1.38		259	**37**	207	**29**	241	**34**
In CTs, all participants always receive a new effective agent.									
Participants	2.57	1.46	0.56	55	**45**	31	**25**	36	**30**
Non-participants	2.48	1.27		333	**47**	241	**34**	135	**19**
In CTs, the physician conducting the research may choose which drug the participant receives.									
Participants	2.88	1.5	0.094	46	**38**	27	**22**	49	**40**
Non-participants	3.15	1.32		196	**28**	227	**32**	286	**40**
Often, the patient participating in the research may choose which drug he or she receives.									
Participants	2.02	1.26	0.663	80	**66**	22	**18**	19	**16**
Non-participants	2.04	1.15		434	**61**	202	**29**	71	**10**
I would participate only in a CT in which at least one of the drugs being compared has been shown to be effective.									
Participants	3.12	1.41	0.342	38	**32**	29	**24**	53	**44**
Non-participants	3.27	1.28		178	**26**	191	**27**	323	**47**
I would participate in a CT only if the treating physician also is the investigator.									
Participants	3.16	1.43	0.36	43	**35**	23	**19**	56	**46**
Non-participants	3.04	1.37		259	**36**	161	**23**	292	**41**
I would participate in a CT if that guaranteed me new and improved medication.									
Participants	4.08	1.2	0.843	15	**12**	12	**10**	93	**78**
Non-participants	4.09	1.15		74	**11**	94	**13**	538	**76**
I would like to participate in a CT because then I would receive more thorough monitoring relative to standard treatment.									
Participants	3.59	1.42	0.436	29	**24**	13	**11**	80	**65**
Non-participants	3.55	1.3		142	**20**	157	**22**	407	**58**

I would participate in a CT only if I were not satisfied with my current medication.									
Participants	2.76	1.51	0.763	56	**46**	19	**16**	46	**38**
Non-participants	2.7	1.36		332	**48**	124	**21**	215	**31**
In CTs, the physician conducting the research is aware of whether the participant is receiving a new drug, a placebo (which does not include an effective agent), or standard PD/AED medication.									
Participants	3.16	1.48	**0.027**	38	**32**	27	**22**	56	**46**
Non-participants	3.49	1.36		136	**19**	235	**33**	338	**48**

[1] CT = clinical trial

6.3.4 Views about the informed consent process

Overall, the informed consent process was perceived mainly positively by the 126 respondents who had participated in a CT. In total, 80% of them stated that they were able to concentrate on the information about the trial, and just over 80% indicated that they had understood this information. Of the full group of respondents, 85% agreed that they had been given enough time for the decision-making. Clinical trial participants trusted that their personal data were handled confidentially. However, nearly 80% agreed that consent ought to be asked for again if the data are to be used in an additional study (see Figure 7).

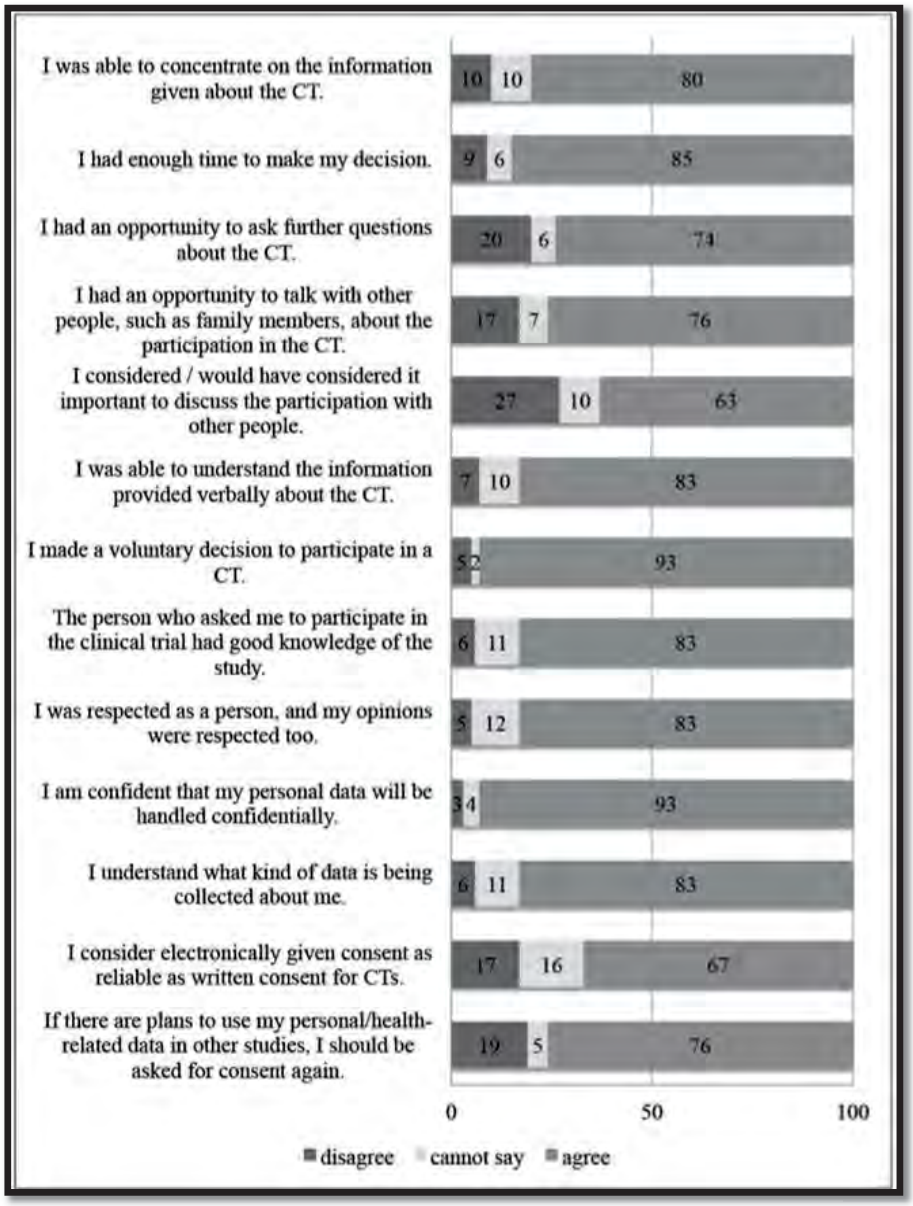

Figure 7. The CT participants' views on the informed consent process, presented by percentage.

6.4 DISCUSSION

Several works reporting on attitudes toward and experiences of participation in CTs among patients with PD or epilepsy have been published (Valadas et al. 2011, Canvin, Jacoby 2006, Ravina et al. 2010, de Melo-Martin, Hellmers & Henchcliffe 2015, Goetz et al. 2003, Finder et al. 2012, Kim et al. 2012). To the best of our knowledge, however, ours is the first large-scale survey to assess how a random sample of CT participants and non-participants among patients with PD or epilepsy perceive CTs and to gauge the differences between the two groups.

Attitudes toward CTs were nearly identical between those who had participated in a CT and those who had not, and they were mainly positive. Also, most respondents concluded that patients should be asked to participate in CTs for the development of new therapies. In both the CT participant and non-participant group, interest in taking part in placebo-controlled trials was rather low, as was that in trials with a risk of severe adverse effects. Prior work has identified both issues as significant barriers to participation in CTs (Valadas et al. 2011, Bevan et al. 1993, Sood et al. 2009, Mathur et al. 2015, Agoritsas, Deom & Perneger 2011).

There were statistically significant differences in knowledge of general issues related to CTs between CT participants and non-participants in areas such as the overall concept of CTs, the necessity of CTs for the approval of new drugs, the right to withdraw from a CT, and the sponsoring of CTs (see Table 17). These findings suggest that information given to CT participants prior to and during the trials had increased their knowledge and understanding of participants' rights and their awareness that trials must be done before a drug can enter the market. It is encouraging to note that both groups were well aware of the voluntary nature of participation and the need for informed consent in CTs. However, only approximately 40% of the CT participants, a proportion similar to that among non-participants, were aware that trials might include procedures different from those used in standard medical care, such as randomisation. Between 40% and 50% of the subjects in both groups held the fundamentally erroneous opinion that the investigator is able to choose the study treatment for the participant or at least is aware of the given treatment.

More than 90% of both the CT participants and non-participants recognised that the essential goal for CTs is to find better treatment for future patients. However, almost 60% of the subjects in both of the groups also indicated that CTs are aimed primarily at finding the best treatment for the trial participant. Furthermore, 60–65% of the subjects in both groups stated that they would participate in a CT because they would receive the best treatment for them and that participation would offer them better monitoring of their health problem than standard treatment does. Expectations of personal health benefits are a major motivating factor in participation in research, as previously found in patients with PD, epilepsy, and other disorders (Valadas et al. 2011, Canvin, Jacoby 2006, Finder et al. 2012, Kim et al. 2012, Bevan et al. 1993, Locock, Smith 2011a). In general, participation in research is considered a means of access to health services (Locock, Smith 2011a, Townsend, Cox 2013). Strong motives linked to personal benefits are considered a risk factor for TM. Therapeutic misconception may lead to overestimation of benefits, underestimation of the risk of harm, and/or under-appreciation of alternatives to participation in CTs (Appelbaum, Lidz & Grisso 2004, Henderson et al. 2007).

A higher proportion of CT participants than of non-participants in our study indicated that they would take part in a CT only if their own physician were the investigator; however, this difference was not statistically significant. Also, continuation of the physician–patient relationship was slightly more important as a motivating factor in the CT participants group. Furthermore, it has been suggested that having one's personal doctor as the investigator may blur the line between standard treatment and research, leading to a risk of TM (Levine 1992, Miller, Rosenstein & DeRenzo 1998).

A critical issue that arises is how TM may affect the informed consent process; i.e., is consent valid when the study participant holds false beliefs (Appelbaum 2002). Evaluation of TM is a complicated task, and there is still disagreement about its definition and how to measure it (Kim et al. 2016, Appelbaum 2016). The possibility and prevalence of TM usually are assessed in patients recruited to CTs; however, patients potentially eligible for CTs may have preconceptions of the benefits and the methods related to CTs before actual recruitment for a trial. These preconceptions, which may vary with individual-specific health problems, might, in turn, predispose them to TM.

Our study and previous research have shown that patients who have participated in CTs express a high degree of satisfaction with the informed consent process as a whole and also with the information they received. In previous studies, most of the PD patients taking part reported that they understood the key components of the informed consent process. (Valadas et al. 2011, Ravina et al. 2010). To our knowledge, no such data are available for patients with epilepsy. About 20% of our CT participant respondents, however, indicated that they would have wanted an opportunity to ask more about the trial. Moreover, about 20% felt that they did not understand the information given or that their opinion was not respected. Over 80% of our respondents considered the person who recruited them for the CT to have had proper knowledge of the trial and stated that they had been given enough time to make the decision. Generally, patients seemed to be satisfied with the time given for the decision (Bevan et al. 1993). Participants' understanding depends, in addition to their competence, on the duration of the informed consent process and on the explanation skills of the researchers (Tam et al. 2015). As for future trials, three quarters of our CT participant subjects concluded that new consent should be sought if the CT data are to be used for other research purposes. This issue has been given attention globally and remains under debate (Vandenbroucke, Olsen 2013, Dove, Townend & Knoppers 2014).

Our study has some limitations. Firstly, the response rate (27%) was quite modest. However, the number of survey forms (n=845) proved to be sufficient for statistical evaluations. Also, the subjects in the study represented a random sample of members of the FEA or FPA, and the age and sex distribution of the subjects corresponded well to those of the general patient populations for the disorders in question. In the interest of privacy, the list of study subjects was generated by the FEA and FPA, and the survey forms were returned anonymously. Therefore, the authors were unable to contact those who did not respond. Furthermore, we were not able to confirm the diagnoses of respondents. However, in Finland a diagnosis of epilepsy and PD always requires assessment by either a neurologist or, in the case of elderly subjects, a geriatrician. An issue to consider is the questionnaire, which was developed for a study among patients with epilepsy (Reijula et al. 2015) and then modified in light of the feedback from those patients and also after pilot testing with PD patients. However, the questionnaire was not validated statistically or against in-depth interviews of the subjects. When the attitudes, knowledge, and views of those subjects who had participated in CTs are considered, it should be taken into account that we have no information on the time between participation and the questionnaire or on what kind of CT the subjects had taken part in. These issues may introduce a risk of recall bias.

6.5 CONCLUSIONS

Although most respondents in our study agreed that patients with epilepsy or PD should be asked to take part in CTs, only 15% of the subjects had actually participated in such trials. This gulf between willingness to participate in CTs and recruitment of enough patients in practice, which manifests well-recognised problems, could be minimised by improving knowledge and understanding of CTs and also by a more thorough communication between patients and those conducting the research (Mathur et al. 2015). Our finding that subjects who had taken part in CTs showed only slightly better knowledge of the general issues related to CTs than did those who had not participated highlights the need for better understanding. Additionally, the two groups displayed comparable false assumptions related to the goals and methods of CTs – a feature that is associated with TM. It is essential for CT participants to understand that the purpose of research is to generate generalisable knowledge and not necessarily to guarantee personal therapeutic benefit (Sacristan et al. 2016). Although the CT participants in our study were satisfied with the informed consent process, our results raise questions as to whether these subjects fully understood the ultimate goal of the clinical research and whether the informed consent was valid. These issues have both ethics-linked and practical implications for clinical investigators.

7 General discussion

Several studies have been carried out for identifying attitudes and experiences of participation in CTs among patients with PD or epilepsy (Valadas et al. 2011, Canvin, Jacoby 2006, Ravina et al. 2010, de Melo-Martin, Hellmers & Henchcliffe 2015, Goetz et al. 2003, Finder et al. 2012, Kim et al. 2012). However, the present work is the first large-scale survey to assess how CTs are perceived by random samples of patients with epilepsy and Parkinson's disease. In addition, to the author's knowledge, this is the first study performed with epilepsy or PD patients that compares perceptions of CTs between CT participants and non-participants. Moreover, the study has identified several clinical characteristics related to knowledge of and willingness to participate in CTs and has revealed aspects of how therapeutic misconception is associated with these issues. In addition, the thesis project investigated CT participants' experiences of the informed consent process.

An important finding from this research is that most of the patients seemed to conflate research with treatment on some level. In addition, an encouraging finding emerged in that most respondents agreed that patients with epilepsy or PD should be asked to participate in CTs, since it is generally known that recruitment problems are widespread. Those who had participated in a CT were satisfied with the informed consent process in most respects. Still, there was evidence that they did not fully understand the differences between medical care and clinical research. The study identified several clinical factors, old age and lower levels of education among them, that were associated with an increased risk of therapeutic misconception.

This chapter focuses on the key empirical results reported from our own research studies. In this chapter, the work for 'Therapeutic misconception correlates with willingness to participate in clinical drug trials among patients with epilepsy; need for better counseling is referred to as Study I, that for 'Clinical features of Parkinson's disease patients are associated with therapeutic misconception and willingness to participate in clinical trials' is denoted as Study II, and 'Comparable indicators of therapeutic misconception between epilepsy or Parkinson's disease patients between those with clinical trial experience and trial non-participants' is denoted as Study III.

7.1 PATIENTS SHARE POSITIVE ATTITUDES TOWARD CLINICAL TRIALS

In general, the Finnish population have viewed research in a positive light in prior work (Tieteen tiedotus ry). Strong similar indications were observed in this study. This was especially evident for patients with PD, who in Study II indicated nearly unanimously that persons should be asked to participate in CTs – only 5% disagreed. Moreover, patients with epilepsy and PD considered it very important that research results be discussed with research participants (found in studies I, II, and III). In addition to the researcher being ethically obliged to discuss research results with the participants (World Medical Association 2013), doing so can enhance recruitment and increase willingness to participate in trials in the future (Locock, Smith 2011b). Also, patients feel that discussion of the trial results is a matter of respect for their contribution (Locock, Smith 2011b).

In data from this thesis, over 70% of the patients – both those who had been CT participants and those who had not – agreed that patients with these conditions should be asked to participate in CTs. Still, of 845 patients, only 126 had participated before. One fundamental requirement for good ethics is that all patients who meet the inclusion criteria have the same opportunity to be recruited. From previous research and our results, the

question remains of whether there is some kind of pre-selection by the stakeholders in CTs that may lead to not asking eligible patients to participate. In addition, potential trial participants share the view that this gatekeeper role of health professionals is problematic (Locock, Smith 2011b). The data from this thesis do not reveal whether there are patients who have been asked to participate but declined. Moreover, more research needs to be carried out with epilepsy and PD patients who have chosen not to take part in CTs, to explore their perspective.

Respondents in the thesis project were in favour of publishing results, which also gives health-care professionals access to the results. According to the Helsinki Declaration, researchers have a duty to make the results of their research publicly available. In addition, open-access publishing has become more popular in recent years. This may support better and more equal access to research results. Transparency, improved availability, and fuller utilisation of the results are, in addition, central objectives in current science policy (Opetus- ja kulttuuriministeriö 2014).

7.2 KNOWLEDGE AND OTHER FACTORS AFFECTING WILLINGNESS TO PARTICIPATE IN CLINICAL TRIALS

As has been noted in the literature, patients with epilepsy (Study I) and PD (Study II), along with CT participants and non-participants (Study III), have shown strongly altruistic motives. However, the results of the work reported upon here are consistent also with the finding from previous research that one major factor in participation is the desire for personal health benefits (Valadas et al. 2011, Locock, Smith 2011b). In Study I, with epilepsy patients, the factor labelled as willingness was assessed mostly with statements that capture a person's willingness to gain personal benefit from the CT. Being of retirement age, having less education, and using multiple medications all were associated with increased willingness to participate and the patient's wish to benefit from taking part.

The results were different for patients with PD. In their data, the factor referred to as willingness referred to patients' general level of willingness to participate – without an association with personal benefits. In addition, higher levels of education were associated with better knowledge and with willingness to participate.

A distressing observation was made with regard to willingness to participate and therapeutic misconception: studies 1 and 2 indicate that TM seems to increase a patient's willingness to participate. Furthermore, some researchers may worry that participants might be unwilling to enrol in a study if TM were dispelled (Miller, Brody 2003). In addition, the latest research suggests that unrealistic optimism may raise the likelihood of deciding to participate (Jansen et al. 2017). Another conclusion is that additional research is needed to investigate whether unrealistic optimism is present for patient groups other than those with cancer.

An additional finding is that interest in taking part in placebo-controlled trials was rather low, much as has been seen in trials with a risk of severe adverse effects (studies I, II, and III). Nonetheless, augmenting materials that address issues related to study design might increase a patient's interest in signing up, as the literature suggests. Furthermore, respondents stated that they would have liked to receive as much information as possible about the trial and the intervention being tested before making the decision about participation.

7.3 THE RISKS OF THERAPEUTIC MISCONCEPTION

The literature review suggests that this thesis is unique in presenting TM-related results from the Nordic region. Research on the subject has been performed mainly in the U.S.

(Kim et al. 2016, Appelbaum et al. 2012, Lidz et al. 2015), although some studies have been implemented in the Middle East or Africa lately (Mansour et al. 2015) as well as in Europe (Durand-Zaleski et al. 2008).

TM can be characterised in any of three ways: an incorrect belief that treatment will be personalised for the participant, failure to recognise that promoting scientific knowledge is the primary purpose, and unrealistic expectations of personal benefit from participation that are rooted in a misunderstanding of the research methods (Christopher et al. 2017). Results presented in this thesis indicate that patients with epilepsy and PD display all of these features, and that they are present in both CT participants and non-participants. Studies conducted within the last decade (Appelbaum, Lidz & Grisso 2004), including very recent research indeed, suggest that TM is widespread among study participants (Christopher et al. 2017, Pentz et al. 2012). Traditionally TM has been discovered in patients who have participated in CTs (Appelbaum, Lidz & Grisso 2004); however, the latest studies have shown that patients may exhibit TM more broadly also in invented trial situations (Kim et al. 2016, Christopher et al. 2017).The clinical risk factors for TM identified in the thesis are old age, lower level of education, and severe illness, as noted also in previous work.

Results presented in this thesis support various earlier findings and provide a new angle on the phenomena in that it seems that patients' preconceptions of CTs can create a risk factor for TM (as seen in studies I, II, and III). People who experience therapeutic misconception and are recruited to take part in a CT may hold false expectations about the CT. Other issues aside, this can lead to disappointment and withdrawal from the study, also resulting in an enhanced placebo effect. In fact, improving disclosure practices related to placebo effects in CTs could help to reduce therapeutic misconceptions among study participants (Blease, Bishop & Kaptchuk 2017). Showing encouraging results, Christopher and colleagues (Christopher et al. 2017) were able to reduce TM in a hypothetical setting among patients similar to those who would be recruited for CTs, using an intervention specially designed for this purpose. Their study tested whether augmenting the traditional informed consent process with an educational intervention designed to help participants reframe the elements of a CT. According to them, TM arises in part from individuals' tendency to view trial participation in a personal clinical frame – i.e., with regard to their individual-specific illness and treatment needs.

The intervention was designed to address this issue. In their study, conducted with 154 participants, TM was reduced significantly in the scientific reframing group as compared to the control group. A further encouraging result is that the reduction in TM did not cause a statistically significant change in willingness to enrol in CTs. (Christopher et al. 2017).

7.4 NEED FOR IMPROVED RECRUITMENT STRATEGIES

The problems connected with understanding trials and information related to them are well understood, and considerable effort has been invested in attempting to address them. However, challenges in obtaining truly informed consent may actually grow, as more complicated research settings and procedures become available (de Melo-Martin, Hellmers & Henchcliffe 2015, Tenhunen, Turpeinen & Kurki 2017). Furthermore, it is worrisome that, while participants in the research reported upon here (Study III) felt reasonably well informed, their answers did not fully support this. This finding is consistent with previous work (Locock, Smith 2011b).

What can be done in response? According to Kenyon et al. (Kenyon, Dixon-Woods 2004) a 'one size fits all' approach is unlikely to meet the highly varied needs and preferences. Even with the best possible leaflet design and staff training, it is unrealistic to aim for

perfect understanding by every individual. This is not to say that improvements are impossible, however. Results presented in this thesis suggest that research personnel should take patients' preconceptions related to CTs into account and strive to improve communication between patients and research staff. The researcher should ascertain patients' level of knowledge towards CT and clarify basic principles related to it in plain language. In addition, increasing patients' knowledge related to CTs in a holistic manner may improve not only quality of consent (reducing the risk of TM, etc.) but also willingness to participate in general.

To summarise the implications of the thesis in combination with previously published literature, Figure 8 presents a practical framework for improving the recruitment strategies applied by recruiters and other stakeholders working with clinical drug trials. There are several steps that must be taken for ensuring a high-quality process with respect to both participants and the trial itself.

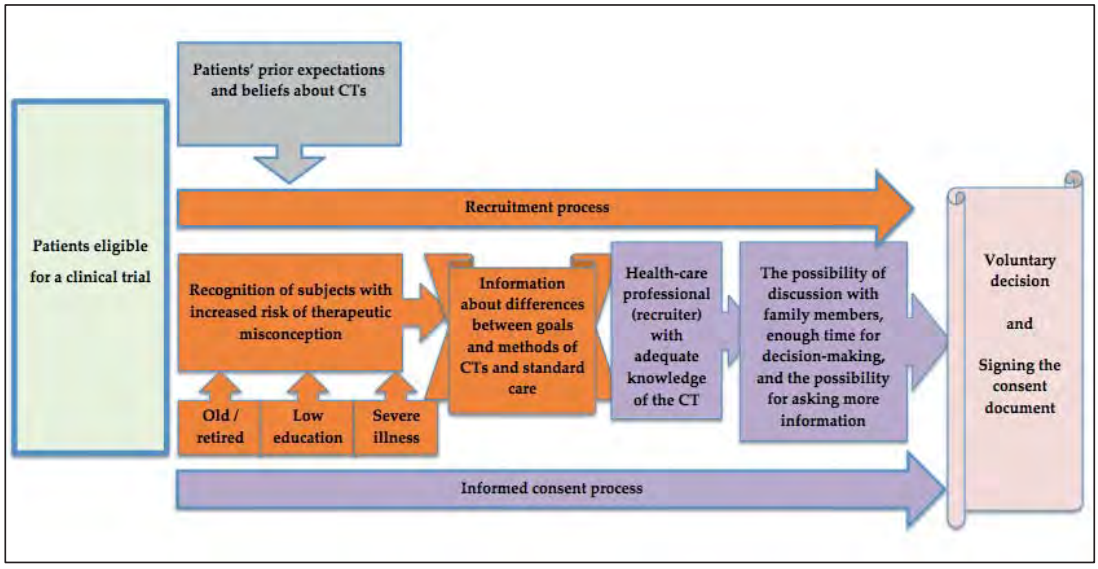

Figure 8. A practical framework for recruiters.

Potential study subjects may have significant preconceptions surrounding CTs, and expecting therapeutic benefits can increase their willingness to participate. This expectation may place them at risk of TM, with this being especially true for older patients, those with a lower education level, and people with severe illness. It is particularly important that research personnel not put themselves in a gatekeeping position, since all suitable patients should have equal possibilities for being recruited. Researchers have to admit that they are aware of selection biases and explicit deviations during the recruitment process, so this clearly needs to be borne in mind (Lidz et al. 2009).

As described above, the efforts of Christopher and colleagues (Christopher et al. 2017) managed to reduce TM through a scientific reframing intervention focused on providing education related to the rationale behind CTs and the specific differences between research and clinical care. This intervention design is worth considering in more detail. It is divided into five content areas. Firstly, the materials stress that the purpose of the CT-based research is to assess whether the experimental intervention is more effective than the standard (control) treatment and that the reason for the researchers' interest in carrying out the study is their unawareness as to whether the experimental treatment is better than the current standard of care. Secondly, randomisation is described. This description covers both the logic behind randomisation (i.e., minimising the risk of selection bias in

assignment to the different arms of the study) and the researcher's incapacity to affect the assignment. In the third content area, limitations on dosage and adjunctive medications are addressed, along with why such limits are important for the validity of the study. Fourthly, an explanation is given of the blinding of the participant and the physician as to which medication the participant is getting and of how that will protect the study design from expectation bias. Finally, the materials discuss all of the foregoing elements as being implemented only to improve the scientific design and thereby assure that the results of the study are valid, not to improve the care of the people enrolled in the study. The scientific reframing information was provided by means of a 12-minute computerised slideshow, with professional narration accompanying slides containing text and animation (Christopher et al. 2017). Pictures and animation used alongside spoken information can support understanding and learning among neurological patients (Halkoaho et al. 2018).

With new interventions of this type, a real possibility exists to improve the quality and validity of the informed consent process and recruitment. In addition, for strengthening a patient's autonomy, physicians should describe the current care for the disease in detail and also inform the patient about the treatment options available (Keranen, Pasternack & Halkoaho 2017). Most patients seek opportunities to discuss treatment options with members of their family, and they appreciate having an opportunity to ask more questions after this.

Once patients have made their voluntary decision, signing of the consent document takes place. In addition, results presented in this thesis suggest that patients would be willing to use electronic provision of consent. Furthermore, interest in digitalisation of the consent process has grown globally. Already, in the United States, the FDA has approved electronic consent wherein that consent has all the elements of informed consent including that potential participants have had enough time for their decision-making (Halkoaho et al. 2018).

Another important finding is related to respondents' conclusion that consent should be sought anew if the CT data are to be used for other research purposes (Study III). At the same time, patients seemed to trust that the data collected are going to be handled confidentially. However, findability, accessibility, interoperability, and reusability of research data are under active development in the science community. This may lead to situations in which a research participant's confidential information is threatened and must be borne in mind.

It is an encouraging message that patients who have found their participation in a CT satisfying are more willing to participate in a proposed CT than are people with no experience of participation. Developing high-quality processes in which every step has been taken carefully guarantees that there will be patients willing to participate in the future. On the other hand, disappointment in one's CT experience can lead to refusal in the future. Another negative factor is that patients who want to take part in clinical trials may find it difficult to access information about their availability, at least in the UK (Locock, Smith 2011b). Further research is needed for determining whether challenges of the latter type exist in Finland. While respondents in the thesis were eager to be recruited, only 15% had participated before. This raises questions as to whether patients have easy access to information on available trials.

7.5 LIMITATIONS

A few limitations to the work reported upon here should be noted. Firstly, the response rate was low. However, the number of survey forms returned did prove to be sufficient for statistical evaluations and for answering the research questions. In addition, the respondents were representative of the members of the FEA or FPA, and the age and sex

distribution of the subjects corresponded well to those of the general patient population for the disorder in question.

In the interest of privacy, the list of study subjects was generated by the patient organisations, and the survey forms were returned anonymously. Patients who are members of a patient organisation might be more than averagely motivated and interested in CTs and the relevant medical condition. This issue could lead to a slightly more positive impression of the results. Another issue to consider is the questionnaire itself, which was developed for a study among patients with epilepsy (Study I) and then modified in light of the feedback from those patients, and also after pilot testing with patients diagnosed with PD. The questionnaire was not validated statistically or against in-depth interviews of subjects. Furthermore, assessing statements used in questionnaire items is challenging: some items may not be understood as intended and therefore could cause bias.

8 Conclusions

1. Attitudes of patients with epilepsy and PD toward CTs are positive, and they see participation in clinical trials as indispensable to new treatments becoming available.

2. While most participants in our study agreed that patients should be asked to participate in CTs, only a minority of them had actually been asked to do so. It was found also that the discrepancy between willingness to participate and recruitment figures could be minimised by improving knowledge of CTs and the communication between patients and researchers.

3. New treatment methods are often studied among patients with a high risk of TM and impaired comprehension of general procedures associated with CTs. The oldest subjects, those with a low level of education, and the severely ill have the greatest information needs. Investigators should be able to recognise vulnerable individuals and pay special attention to the information provided about the purposes and methods of the trial, in order to contribute to high-quality studies.

4. Recruitment strategies demand further comprehensive development. Patients' preconceptions must be considered and discussed with each potential participant.

5. More accessible information on trials' availability should be developed.

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EMMI REIJULA

Clinical trials are essential for the development of treatments for future patients. However, recruitment problems are common and patients' willingness to participate varies. The aim of this study was to assess knowledge of and attitudes towards clinical drug trials among patients with epilepsy and Parkinson's disease, including patients who had participated in CTs and those who had not. Currently, no curative medicines are available for either of the patient groups. Moreover, both conditions are under active research. According to this study, therapeutic misconception was relatively common, meaning they failed to identify differences between clinical trials and clinical care. Recognition of patients' information needs and attitudes could enhance recruitment and contribute to the quality and ethicality of the trials.

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