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Cooperation between Investigators and CROs

Investigators' Experiences in Clinical Trials in Finland

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Drug development is a long-lasting, complex, expensive and highly regulated process. International ethical and scientific quality standard "Good Clinical Practice" (GCP) defines roles and responsibilities of sponsors and investigators conducting clinical trials. Sponsor may transfer trial-related duties and functions to Contract Research Organizations (CROs). Outsourcing clinical trials to CROs has been growing trend since 1980s and outsourcing is estimated to continue in the future. Cooperation between sponsors and CROs is followed in yearly surveys, but there are only few studies about cooperation between investigators and CROs.

The purpose of this qualitative research is to increase knowledge about cooperation between Investigators and CROs. Aim is to describe how investigators are experiencing cooperation with CROs by finding out what kind of positive and negative experiences investigators have in cooperation between investigators and CROs. Data was collected from in-depth interviews of six physicians who had over five year experience in the field of clinical trials and had experience in cooperation with CROs. Data was analyzed by using conventional content analysis.

Results showed that investigators had positive experiences especially in cooperation with trial monitor (CRA). Positive experiences were related to situations where CRA was working together with trial site personnel, CRA was qualified and CRA was working in business-like manner. Negative experiences related to cooperation with CRA were related to situations where CRA´s working methods were not satisfactory and site was left alone with increased workload. Investigators also reported experiences that were related to CRO´s position and operational environment. Experiences were related to situations where CRO was using sites to get profit, CRO-sponsor contract caused difficulties, CRO´s working methods were not satisfactory and how operational environment influences in cooperation.

Results of this research increase knowledge about cooperation in clinical trial field. Results help to identify development needs in cooperation between investigators and CROs and these can be used to improve procedures related to investigator – CRO cooperation.

Keywords	Cooperation, clinical trial, investigator, contract research organization

Contents

1 Introduction

Drug development is a long-lasting, complex, expensive and highly regulated process. It takes approximately 10 years from finding a suitable compound to the market authorization of a new drug (Alkio 2012:13). During those years pharmaceutical company needs to conduct clinical trials to provide substantial evidence of drug's safety, effectiveness and efficacy. Clinical trials that involve participation of human subjects are conducted according to international ethical and scientific quality standard "Good Clinical Practice" (GCP) guideline (Azoulay - Repenning - Zuckerman 2010: 474). Principles of GCP are implemented in EU legislation in EU directives 2001/20/EC and 2005/28/EC and in Finnish legislation in Medical Research Act 488/1999 and in Finnish Medicine Agency (Fimea) Administrative Regulation "Clinical Trials on Medical Products" 2/2012.

Good Clinical Practice defines roles and responsibilities of two important actors in clinical trials; sponsor's and investigator's. According to GCP (1996) "A sponsor may transfer any or all sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor". Due to expensiveness of a long clinical trial phase in drug development, pharmaceutical companies have been seeking for lower costs and higher effectiveness. From the mid-1980s clinical research outsourcing has increased meaning that pharmaceutical companies (sponsors) have transferred increasing amount of their trial-related duties to contract research organizations (CROs) (Azoulay et al 2010: 474). According to Petryna (2011) CROs are the biggest and most profitable sector in clinical trial industry.

The other vital party in putting clinical trials in practice is the investigator. As stated in GCP (1996) the investigator is responsible of conducting the clinical trial at the trial site. The sponsor is responsible for selecting investigators and monitoring that trial is conducted in compliance with approved protocol, good clinical practice and local regulations. The activities contracted out to CROs from the start of the trend of outsourcing have been recruiting, coordinating, monitoring and supervising the investigators. (Azoulay et al 2010: 474; Petryna 2011: 954)

Finland has a long tradition and good reputation as an interesting country for pharmaceutical companies to conduct clinical trials. However, the number of clinical trials and the number of participants in clinical trials in Finland are decreasing. Lack of resources in healthcare has decreased the opportunities for doctors to participate in clinical trials as investigators. Participating in drug development has also wider effects: via participation doctors familiarize themselves with new therapies and novel medicine, patients are able to get new therapies and research offers also incomes and work to other competent people (for example study nurses) in hospitals, universities and companies (Pharma Industry Finland 2014c). Ministries in Finland have also set a goal for growing by 2.5 times by 2020 in pharmaceutical and health technology sector (Työ- ja elinkeinoministeriö 2014, 1).

There has been research about relationship and cooperation between sponsors and CROs. Many publications indicate that co-operation is often complicated and both parties have been dissatisfied with partnerships. Cooperation between sponsor and investigator is also important for successful clinical trial, but this partnership has not been studied. Because the most of the pharmaceutical companies have outsourced sponsor's activities which are done at the clinical trial site and in collaboration with investigators, it is important to find out how investigators are experiencing this "third party" partnership.

Purpose of this Master's Thesis is to find out how investigators in Finland are experiencing cooperation with contract research organizations in a field of clinical trials. Aim is to find out what kind of positive and negative experiences investigators have in cooperation with CROs. Results may help in identifying development needs in CRO operations and in cooperation between investigators and CROs.

2 Theoretical Background

2.1 Clinical Trial

Developing a new drug to the markets is an intensive, expensive and long-lasting process. Only one of 10000 product ideas is approved on the markets and research process takes 10-15 years. Estimated cost of the whole research and development pro-

cess is approximately 1,1 Milliard Euros. In drug development the focus is on individualized treatments and only one out of ten medicines makes profit which covers costs of the development process. (Alkio, 2012: 13-14.) Figure 1 describes the drug development process from the start to the end. In this thesis the focus is on clinical trial phase in which drugs are tested on human trial subjects.

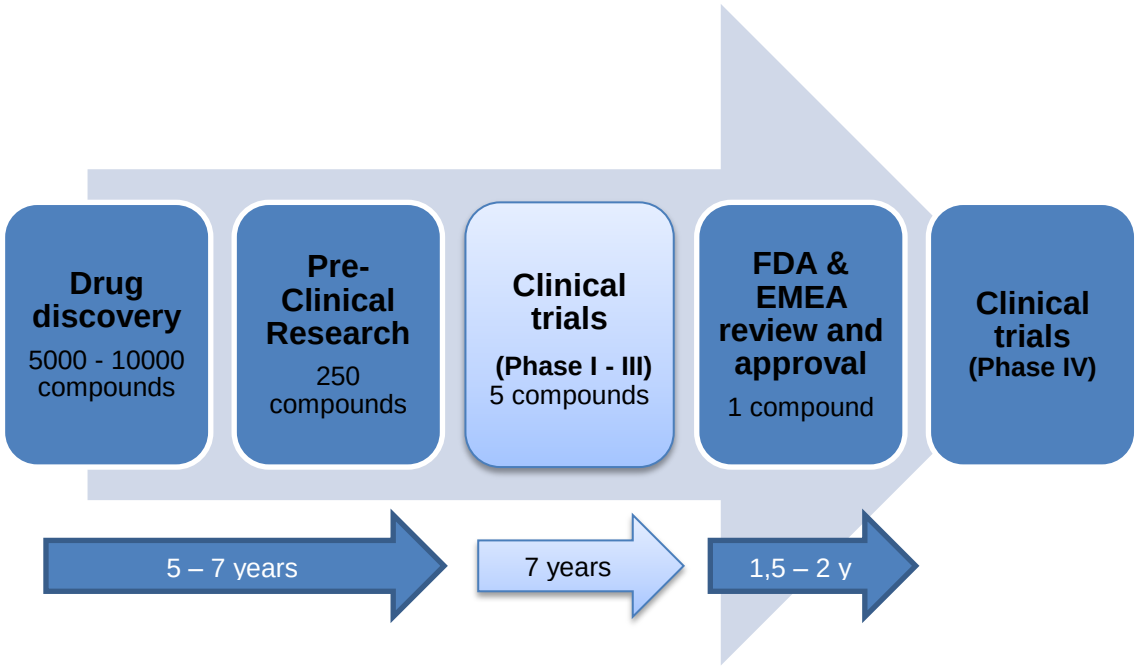

Figure 1. Drug development process

2.1.1 Definition of Clinical Trial

Good Clinical Practice (1996) is an international, ethical and scientific quality standard for trials which involve the participation of human subjects. The guideline should be followed while conducting clinical trials or other investigations that may have impact on safety and well-being of human subjects and are intended to be submitted to regulatory authorities. The definition of a clinical trial in GCP (1996) is “any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy”.

In Medical Research Act 488/1999 in chapter 1, section 2 clinical trial means “intervention research on persons for the purpose of finding out effects of medicinal product in human being as well as its absorption, distribution, metabolism or excretion in the human body”. In Fimea administrative regulation (2012) clinical trial is defined as an interventional study conducted with human subjects in order to discover the effects of medicinal products in human subjects or their pharmacokinetics in the human organism or both.

Before a clinical trial can start in Finland a favourable opinion from Ethics Committee (EC) and approval from Finnish Medicine Agency (Fimea) must be obtained. In case Fimea has not requested additional clarifications and 60 days from commence of trial evaluation process has past, trial can be started without a specific approval from Fimea. Also notifications of termination or completion of clinical trial and summary of trial results are provided to Fimea and EC within timelines given in the legislation. Once a year during the time clinical trial is ongoing in Finland, sponsor is obligated to provide Fimea and EC a list of occurred suspected serious adverse reactions and evaluation of overall safety aspects of trial. Report is signed by a person responsible for the trial. The person responsible for the trial in Finland is selected by the sponsor and is a physician or dentist with adequate professional and scientific qualifications. The person responsible for the trial ensures that personnel conducting trial is competent and conditions are safe and all local and international legislations are taken into consideration during the clinical trial process. (Fimea 2012, 13; Laki lääketieteellisestä tukimuksesta 488/1999).

2.1.2 Field of Clinical Trials in Finland

Research and science have always had an important role in Finnish welfare. High educational level has guaranteed competence and expertise, good patient registers are available and Finnish people have had a positive attitude towards research operations. Finland has a long tradition in clinical trials and international pharmaceutical companies have valued operational environment and competence in Finland in clinical trial sector. (Alkio 2012, 9)

Pharma Industry Finland (PIF) is following statistics in clinical trials and as noticed in figure 2, number of ongoing clinical trials in Finland has decreased since 2008. Also the number of people participating in clinical trials as clinical trial subjects has decreased as presented in figure 3. In 2014 approximately 82% of initiated clinical trials in Finland

were sponsored by pharmaceutical companies and 70% of trials notified to Fimea were international multicentre trials meaning that trial is conducted according to the same protocol but in different trial sites and by more than one investigator in different parts of the world (Fimea 2015).

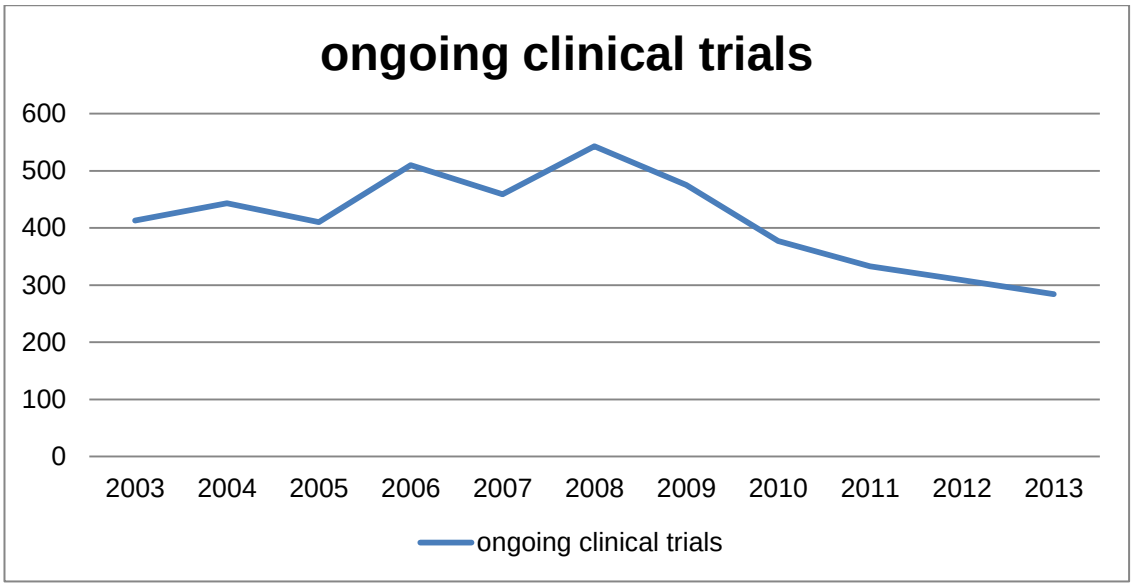

Figure 2: Ongoing clinical trials conducted by PIF member companies in Finland (modified from Pharma Industry Finland 2014b)

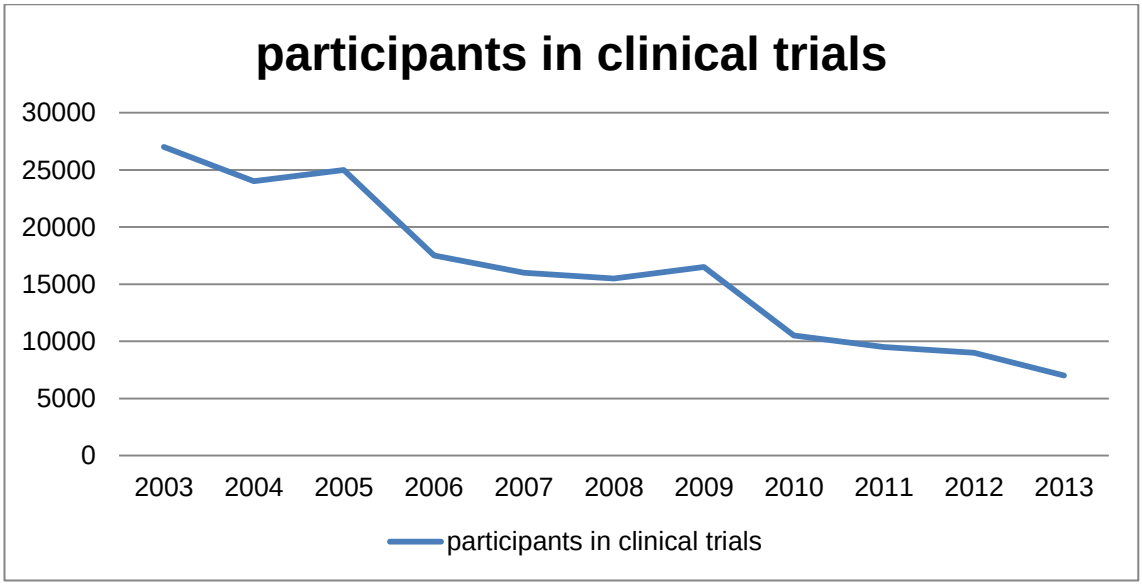

Figure 3. Number of participants in clinical trials in Finland without vaccine trials (Modified from Pharma Industry Finland 2014a)

Factors influencing to decrease in amount of clinical trials in Finland can be categorized to three groups. At first Finland has lost competitive position as an attractive country to conduct clinical trials. Clinical trials have globally transferred especially to

Eastern Europe, Asia and South America, because those areas have potential pharmaceutical markets and price-quality ratio has improved. (Lääketeollisuus 2012: 12-13; Smed – Getz 2014: 2; Vogel – Getz 2009)

The position of investigators in Finland is also challenging. Experienced investigators are aging and junior doctors are less motivated to participate in clinical trials as investigators. Junior doctors may not have competence in research because educational training focuses to patient care. Health care environment has also decreased time and personnel resources from medical research field. Lack of encouragement and the level of compensation is demotivating. Also the increased use of CROs in clinical trial management has transferred trials to countries where CROs have strong networks. (Lääketeollisuus ry 2012: 14-16) Centralizing functions as a trend among international pharmaceutical companies may lead to situations where Finland is seen as a part of Nordic countries rather than an independent player (Työ- ja elinkeinoministeriö 2014: 21). Patients in Finland have had positive attitude towards participation in clinical trials, but this attitude is also changing. Participation in clinical trials is time-consuming and people have access to health care and medications also without clinical trial participation. (Lääketeollisuus ry 2012: 16)

The second category concerns the growing trend towards non-intervention studies (NIS). Non-intervention trials are typically studies which are done after medicine has been approved to markets (phase IV trials). Trial data in non-intervention studies is usually collected from patient databases, registers and interviews. Differing from many other countries, in Finland interviews have been construed as intervention and trials that include interviews need to have same kind of approval procedures as traditional phase I – III clinical trials. This construction together with a difficult access to patient databases and strict data privacy policy has ruled Finland out from NIS markets. Third reason for decreasing number of clinical trials in Finland is difficulties in business and finance environment in Finland. Number of new enterprises in research sector has decreased. Entrepreneurship is not supported in academic environment, lack of peer networks and business knowledge make starting processes burdensome and difficult. (Lääketeollisuus ry 2012: 18-20)

According to Alkio (2012) despite of competence in research sector, Finland has not succeeded in wide-scale commercialization of this knowhow. Possibilities of growth in pharmaceutical sector are potential in both employment and economical point of view.

In 2010 there were five pharmaceutical companies among “top 10” organizations investing to research and development (R&D). To get Finland back to a desired country of investments for pharmaceutical companies the Finnish Ministry of Social Affairs and Welfare, the Ministry of Employment and Economy, the Ministry of Education and Culture, The Finnish Funding Agency for Innovations (TEKES) and Academy of Finland published a growth strategy of research and innovation in health sector (Työ- ja elinkeinoministeriö 2014). The purpose was to identify development needs in innovation ecosystem in order to get competitive advantage for Finland as an attractive business partner in health sector. The strategy points out the global nature of R&D sector. Global networking among research communities and markets and the role of entrepreneurs in commercialization are vital factors also when national ecosystem is regenerated. The aim is to get 20% annual growth in national and international research investments and to get private investments increase 2, 5 times during next ten years in Finland.

2.2 Sponsor

Definition of Sponsor in GCP (1996) is “an individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of a clinical trial”. In Finland every clinical trial must have a sponsor. In case an outside party only participates in financing clinical trial, investigator and financing party may agree that investigator takes care of responsibilities of the sponsor. (Laki lääketieteellisestä tutkimuksesta 488/1999 §2.)

Sponsor is responsible for utilizing qualified personnel to supervise the conduct of the trial, to handle and verify the trial data, to conduct the statistical analysis and to prepare trial reports. The sponsor should designate medical personnel to advise on trial related medical questions or problems. Prior to start of any clinical trial, sponsor should ensure that safety and efficacy data from preclinical studies are available to support human exposure and to evaluate safety of investigational product on the ongoing bases. The sponsor ensures that investigational products are properly manufactured and transported. The sponsor also provides instructions to the proper handling and storage of products and maintains a system for the disposition of unused investigational products. (GCP 1996.)

Sponsor's responsibility is to select investigators who conduct the clinical trials (GCP 1996). U.S. Food and Drug Administration (FDA 2013) have recommended the factor's sponsors should consider when selecting investigators for the clinical trials. Previous experience with investigator and site, workload of the investigator and study staff and resources available at the study site should be considered. Key components when initiating clinical trial at site are ensuring that investigator and site staff understand responsibilities, study process and procedures, regulatory requirements and sponsor's process for monitoring the clinical trial. According to GCP (1996) to verify that rights and well-being of trial subjects are protected, reported data is accurate, complete and verifiable from source documents and trial is conducted in compliance with approved protocol, GCP and regulatory requirements sponsor should appoint monitors for the trial and ensure that the trial is adequately monitored. It is sponsor's responsibility to determine appropriate extent and nature of monitoring. A monitor, usually called Clinical Research Associate (CRA) as job title, should be familiar with investigational product, the trial protocol, informed consent form and other written information to be provided to the subjects, sponsor's standard operating procedures (SOPs), GCP and regulatory requirements. The monitor is the main link of communication between the sponsor and the investigator. GCP defines responsibilities of the monitor and the monitor should submit a written report to the sponsor after each trial related contact with the investigator.

Regulatory authorities, European Medicine Agency (EMA) and U.S. Food and Drug Administration (FDA), have published guidelines for risk-based quality management in clinical trials on 2013. Increasing costs, complexity of clinical trials, variability in investigator experience, trial site infrastructure, treatment choices and standards of health care and increasing use of electronic systems and records have created new challenges to clinical trial oversight and quality management. (European Medicine Agency, 2013; FDA, 2013.)

Monitoring is one of the quality control tools. Traditionally sponsors have conducted on-site monitoring visits at approximately 4-8 weeks interval with 100% verification of all data at the trial site. On-site monitoring has been used to identify missing data and discrepancies between source data and data provided to the sponsor, to verify that source documentation exists, and to assess the quality of processes. On-site visits have played important role in training and in providing feedback to trial personnel. Increased use of electronic records and technical solutions has made increasing amount of clini-

cal trial data remotely available. Therefore recommendations of centralized and risk-based monitoring approach have been issued. The idea is to focus on the most critical data elements and processes to achieve study objectives, decrease on-site visits and direct on-site visits to the higher risk sites. Resent evaluations have suggested that centralized monitoring can identify the most of the on-site monitoring findings. The use of routine review of submitted data, statistical analysis to identify data trends and analyzing site characteristics can help in identifying significant concerns, higher risk clinical sites and ensure human subject protection and data quality across trial sites. (European Medicine Agency, 2013; FDA, 2013.)

In global survey (Avoca 2014) both sponsors and CROs reported the use of data driven approaches in clinical trial activities. Greater portion of CRO respondents reported making at least moderate advances of it over the past two years in clinical trial activities than sponsor respondents. A majority of sponsor respondents indicated that CROs are making significant or essential contributions to the use of data driven approaches in four key areas: site selection, region selection, monitoring and patient recruitment. CROs acknowledged that sponsors have contributed their adoption of new data driven approach by helping them to understand general approaches and by making data available. Although significant advancements were made in the movement towards more data driven approaches in clinical trials, additional progress is needed to realize the full potential of new approaches. Both sponsors and service providers should develop tailored strategies to guide investments in this area with clear priorities regarding capabilities needed in-house and with those that are best fulfilled via cooperation with service providers like CROs.

Time optimization in a long and expensive clinical trial process may narrow sponsor´s focus on ongoing trials and especially on patient recruitment and data collection phase of the trial. Post-trial initiatives and interaction are not utilized as effectively as possible. Post-trial communications between trial partners like investigators and CRO representatives could give a possibility to share general reflections and feedback about the trial. Current cooperation processes and increased management layers including integrated CRO partners restricts valuable knowledge-transfer between sponsors and investigators. Due to restrictions investigators are not able to get enough information about the final outcome of the trials and sponsors are not able to develop processes or identify opportunities for optimizing future and ongoing trials. Feedback could also reveal in-

formation about user´s experience in investigative product that might be relevant for clinical practice in future. (Smed – Getz 2013: 80-85; Smed – Getz 2014: 1.)

2.3 Investigator

Investigator is a person responsible for the conduct of the clinical trial at a trial site. Investigator should be qualified by education and experience and provide evidence of such qualification to assume responsibility for the proper conduct of the clinical trial. In case trial is conducted by a trial team, investigator is the responsible leader of the team. The responsible leader is usually called as “Principal Investigator”. Principal investigator should maintain a list of the personnel at the trial site to whom she/he has delegated trial-related duties. Investigator should be able to demonstrate availability of potential suitable trial subjects and adequate staff and time resources to conduct trial properly and safely. Investigator is responsible for trial-related medical decisions and also ensures that adequate medical care is provided to the trial subject. (GCP, 1996.)

Investigator should conduct clinical trial in compliance with an approved protocol. Deviations from the protocol should be agreed with the sponsor and ethics committee beforehand unless deviation is made to eliminate immediate hazard to trial subject. All deviations should be documented and explained. Prior to the participation in clinical trial, written informed consent should be signed and dated by the subject or the subject’s legally representative and by investigator or a person designated by investigator who conducted the informed consent discussion. Copy of the informed consent form should be provided to the subject. Exceptions and variations from this process should be described in protocol and to be approved by Ethics Committee. (GCP 1996.)

According to GCP (1996) investigator is responsible for investigational products at the trial site, including storing products according to instructions from the sponsor, keeping records and inventory of the products and ensuring investigational products are used only accordance to an approved protocol. Investigator is also responsible for explaining the proper use of products to trial subjects and he/she should check that instructions have been followed. Investigator is responsible for data and safety reporting to the sponsor. Data should be consistent with source documents and according to Finnish legislation (Fimea, 2012: 14) clinical trial documents must be archived at least for 15 years.

Clinical trials are typically conducted in two different type of clinical trial sites; academic and independent. Trial site types differ from organizational structure and incentives for conducting clinical trials. Independent trial sites are specialized in conducting clinical trials. As the trial site personnel are not occupied with daily clinical practice, they are highly professionalized around clinical trial processes. At the academic trial sites personnel are often engaged also in other activities related to the health sector. Academic trial sites have previously dominated the clinical trial environment, but over the last 20 years industrialization of site organizations has been globally observed. (Smed – Getz 2014: 2)

Investigators and investigative sites are important actors in drug development process as they may have input into study design, they have access to trial participants and they are also a critical source for information about clinical practice experiences. Participating in clinical trials offer opportunities for investigating doctors to learn more about novel medication and learn how to apply drug after launching. (Smed – Getz 2013: 80; Smed – Getz 2014: 1.) Investigators have indicated that primary motivator to participate in clinical trials as investigator is an opportunity to be involved in the research of innovative medical treatments. Research has shown that older investigators who had participated in high percentage of CRO managed trials preferred working directly with sponsor. Other investigators had no preference or they preferred more CROs. (Glass, 2009.).

Turnover rate among investigators conducting clinical trials is significant. Globally 35 – 55% of investigators gave up doing research after first clinical trial and this fact increases and escalates costs of sponsors for site selection, qualification and training of new investigators and trial start-up. Reasons for turnover rate may be categorized for three groups: 1) system and organization related 2) Trial related and 3) Physician related reasons. System and organization related reasons include time needed for research-related work, discussions with patients, grant applications, costs, facilities and infrastructure and requirements of sponsor. Trial related reasons include lack of rationale for the research, increasing complexity of trials, costs not covered by sponsor and inferior trial drugs compared to standard therapy. Physician related reasons include lack of interest in the research topic, unfamiliarity with trial procedures, lack of support staff and disruption to clinical practice. Investigators have reported completing contractual and regulatory documents, recruiting patients, budgeting and getting paid on time, completing feasibility surveys and reporting adverse events as the most bur-

densome activities in clinical trials. Also interacting with trial monitors, tracking clinical supplies and retaining patients in the study were burdensome especially for inexperienced investigators. (Cascade – Sears – Nixon 2015.)

2.4 Contract Research Organization (CRO)

Contract Research Organization is a person or a commercial, an academic or other organization contracted by the sponsor to perform sponsor's trial-related duties and functions. Although the sponsor transfers duties and functions to CRO, the ultimate responsibility for the quality and integrity of the trial data resides with the sponsor. (GCP 1996.) In Guidance for Industry FDA (2013: 18) recommended that sponsor and CRO prospectively establish a clear understanding of responsibilities and expectations for the conduct of transferred obligations. An appropriate process of relevant and timely information sharing should be in place.

2.4.1 Outsourcing Clinical Trials

History of CROs can be traced to the pharmaceutical expansion after World War II. Outsourcing of sponsor's duties and functions has increased enormously since 1990s. It was estimated that over 90% of pharmaceutical companies had outsourced at least some of the clinical trial activities by 1993. In 2010 largest pharmaceutical companies outsourced almost 100% of Phase IIIB and IV trials and laboratory services to CROs and service providers. Use of CROs in all therapeutic areas and clinical trial phases increased 44% between 2007 and 2011. (Bryde – Joby 2007: 364; Henderson 2013; Petryna 2011: 953-954.)

According to Tarnainen (2012) in 2009 there were 26 CRO companies operating in Finland. 15 companies were founded in Finland and all of them in western countries. Based on the information on trade register 22 of 26 CROs had less than 50 employees. According to the companies' websites the most common services CROs in Finland provided were regulatory support, medical writing, training, clinical trial monitoring, protocol writing, data management and project management. Same activities are the most outsourced also globally (Vogel – Getz 2009).

The main reasons for increased outsourcing are high and rising costs of clinical phase of drug development. Pharmaceutical companies face challenges and competition. Therefore ability to reduce and share risks and uncertainty are drivers for outsourcing. Companies are seeking ways to manage clinical trials more effectively and efficiently and to introduce new drugs faster to the markets. Pharmaceutical companies also aim to focus to their core competence: marketing medicinal products. Outsourcing of research and development has become a management issue, because formerly R&D has been seen as a part of business that should always be kept in-house, but now the boundaries of the companies are coming more open. Outsourcing of at least those parts of R&D that are not seen as core activities has become possible and even inevitable. (Bryde – Joby 2007: 363; Tarnainen 2011: 7-8; Suomi 2012; Vogel – Getz 2009.)

Clinical trials are transferred to countries where treatment naïve population is available. People in western countries are saturated with treatments and produce too many drug-drug interactions. This makes them less usable for showing effectiveness of a specific drug. (Petryna 2011; Vogel – Getz 2009.) By outsourcing clinical trial activities, pharmaceutical companies are able to expand their area of operations without need to establish permanent premises in countries (Tarnainen 2011: 8). For smaller companies outsourcing is needed to get access and flexibility to required staff and skills as they cannot afford to build up their own internal resources (Contract Pharma 2014; Mehta – Peters 2007: 30; Suomi 2012; Vogel – Getz 2009).

Outsourcing of R&D has also risks. Outsourcing company may come dependent on the supplier and loose knowhow and overall market performance. (Suomi 2012.) At the moment pharmaceutical companies are downsizing R&D departments and as a result the expertise and the knowledge about clinical trial management is increasingly going outside the companies. In this situation CROs are able to hire professionals who come directly from pharmaceutical industry and know how to conduct trials the way sponsor companies want to handle them. (Reese 2011.) Integration of CROs to clinical trial processes may also compromise relationship between sites and sponsors as the previous direct relationship has been changed to more distant relationship (Smed – Getz 2013: 84).

In literature two types of outsourcing are defined in field of clinical trials; strategic and tactical outsourcing. Tactical outsourcing is a variation of fee-for-service contracts and more short-term and used on a project-by-project basis. Tactical outsourcing refers to

transactional and opportunistic relationship between the sponsor and CRO. Strategic outsourcing involves formal long-term partnership with selected CRO/CROs. The aim is to build partnership based on trust, form closer ties and business integration, share objectives and build long-term business stability and save money. Trend among sponsor organizations is to develop relationship with CROs to more strategic outsourcing approach. (Bryde and Joby 2007: 364-365; Contract Pharma 2014; Henderson 2013; Smed – Getz 2013: 84; Vogel – Getz 2009).

The four elements that characterize strategic outsourcing are (1) close link between the outsourcing processes and the key success factors of the company, (2) transfer of the ownership of a previously internalized business function, (3) long-term commitment and contract between company and supplier, (4) existing contractual definition of obligations and service level (Suomi 2012). Four most important attributes for strategic partnership in 2013 were history of quality, cultural fit, partnership philosophy and cost. The most important service provider overall not just strategic attributes were overall value, prior positive experience with the provider, risk management, project management quality, therapeutic expertise and contingency planning. (Henderson 2013.)

2.4.2 Sponsor – CRO Relationship

Despite the outsourcing type, the sponsor – CRO relationship is vulnerable to problems where interest of pharmaceutical company and CRO may be misaligned and both parties act in their own best interest (Bryde - Joby 2007: 364-365). Azoulay et al (2010) from Massachusetts Institute of Technology showed that despite the efforts to build embedded relations between a pharmaceutical company and CRO, relations were chronically underperforming, adversarial and short-lived. Level of commitment from sponsors to their contract organizations was a critical factor which was often missed by sponsor's managers. Firms were dealing with large number of CROs and they were constantly changing suppliers. This reflected the situation of negative commitment and was demotivating to the CRO partner to make investments specific to client or satisfy client-level demands. Feelings of mistrust impacted to pharmaceutical firms' assessment of the chronically underperforming CROs. Perception of underperformance led to the need for ongoing monitoring of CRO teams and increased costs and decreased effectiveness. The sponsors have been dissatisfied with oversight of service providers, the governance of quality, communication and availability of quality personnel for projects and efficiency and timeliness in achieving clean data (Avoca 2011).

Results (Azoulay et al 2010) also showed that internal and external clinical trial personnel were allocated to the trials in different ways. In-house monitors at sponsor firms were assigned to single project at the time and it was very likely that the same monitor (CRA) with experience of the drug was assigned to follow-up study as well. External CRO monitors were assigned to multiple projects, multiple clients and shifted across the projects as needed. These working practices allowed in-house monitors to have “a sense of project ownership” and in contrast perception of uncommitted CRO monitors. Sponsors still expected the same level of loyalty and performance from temporary CRO staff than from their own permanent staff. Unrealistic and unreasonable expectations led to disappointment and mistrust. The practice of using CROs to fill in the employment caps was not officially announced although it was publicly recognized. The drug development process is predicated on the idea that clinical trials are impervious to the influence of non-medical factors. It would be problematic for sponsor to admit that organizational arrangements may have influenced to data production and outcomes of clinical trials. Trend to invest towards higher-level strategic partnership has improved satisfaction. Sponsor organizations have realized that CROs are not just extension of staff but really a part of the clinical research team and high-level relationship is possible only if there is mutual respect, cooperation and honesty. (Henderson 2013; McKay - Syrop - Calaprice-Whitty 2011.)

In terms of quality, sponsors have been satisfied with CROs compliance with written procedures, data quality and integrity and audit plans and execution. Sponsors are more comfortable with quality in Western and Central Europe and North America than in Asia, Latin America and Africa. It is noted that service providers assume they are providing higher quality than sponsor feels they receive. Main causes for issues with quality and gap in perception between sponsors and providers seems to be cost pressures on the industry and inability of providers to consistently perform to their potential due to constraints placed by sponsors. (Avoca 2011.) If CROs are paid and punished according to task-specific schedule, attention of CRO monitors is directed from knowledge production to data-processing and speed of execution of tasks. Therefore CRO employees have been characterized as “data mules” that receive less training and are overworked. This may lead to burnout and turnover. A high turnover rate of CRO monitors has been issued among sponsors. (Azoulay et al. 2010.)

One key finding in study of Azoulay et al. (2010) was difference in the information flow. CROs relied on formal reporting mechanism and the information was likely to be lost or

get filtered before it reached the sponsor. Information flowed more freely in pharmaceutical companies. Communication and information sharing seem to be areas where improvement is still needed. According to Contract Pharma (2014) survey, sponsors are expecting more proactivity and feedback from CROs about their processes and methods to be able to improve functions. They also describe lack of transparency in communication and they hope that service providers share also mistakes and problems with them in time. CROs are complaining that they do not get enough information from the sponsor to get work done properly. They would like to get more upfront information from the sponsor.

Mixed communication channels between sponsors, CROs and investigators create insufficient and poor information and knowledge flow. Trial site personnel are communicating simultaneously with managers from sponsor and CRO, CRAs and sales department representatives. Diffused communication channels hinder the development of personal and engaged professional relationship which may improve and encourage free flow of both tacit and formal information. Designation of single point of contact may create clear information flow structure and ensure knowledge transfer more efficiently. (Smed – Getz 2013: 85-86.)

Early and complete integration of CRO into clinical trial program, proactive quality management for example the use of written quality agreements, setting up effective governance and oversight structure and setting up metrics to measure performance are seen as factors that ensure quality and optimal performance and increase sponsor´s overall satisfaction with work performed by CRO (Avoca 2011; McKay et al 2011). CROs desire to have more input to protocol design and planning state of clinical trials. Sponsors still prefer outsourcing trial execution although early partnership offers benefits. One of the benefits is better communication and collaboration between sponsor and CRO. Early partnership allows establishing a dialog that enables both parties to set realistic expectations and to build trust. Collaborative environment gives the ability for CRO to take ownership and accountability with decisions and actions and contribute to each component of clinical trials. CROs are also experts in study management and have a hands-on knowledge about the clinical trial sites due to ongoing relationship with the sites. This gives an opportunity for CROs to evaluate a protocol logistically and see if study is doable. Early cooperation also enables sponsors and CROs to prepare flexible and realistic budgets. (Reese 2011.)

2.5 Cooperation

Working together with someone or with another company or organization to the same goal or to achieve something are definitions given to word “cooperation” (Oxford dictionary, 2014; Cambridge Dictionary 2014). Also a synonym word “collaboration” is commonly used in English literature when writer is describing situation where people are working together to create, achieve or produce something. Cooperation was chosen as a key word for this research, because in business language definition refer also to “being willing to be helpful and to do what someone asks you to do” (Cambridge Dictionary, 2014). Cooperation involves decision making among interdependent parties, joint ownership of decisions and collective responsible for outcomes (Peters – Manz, 2007: 119).

Cooperation has been researched from many scientific perspectives and it is a challenging phenomenon which has been understood in many ways. Cooperation is contextual as context guides the nature and appearance of cooperation. (Aira, 2012: 30.) In this research cooperation between people working in different organizations; clinical trial sites and CROs is in focus. Interorganizational cooperation can be seen as a set of communicative processes where individuals representing different organizations work interdependently (Keyton – Ford – Smith, 2008: 381). The focus in this research is on organizational representatives not in organizations. In this type of cooperation individuals are responsible to their organizations and have organizational resources. These factors influence what messages surface. Representatives may not have a prior relationship and they must develop structures and processes for creating relationships, identifying goals, sharing information and making decisions. (Keyton et al 2008: 381.) In the context of this thesis CRO representative has a complexed role; she/he is representing two organizations, the sponsor and CRO to investigators.

According to Aira (2012) communication in interpersonal relationships creates shapes and maintains cooperation and the same definition is used for cooperation in this research. In cooperation shared goals are inevitable and communication is needed to find the shared goals. Cooperation is a voluntary choice and purposive and active collaboration process originates from need and desire to create something new or resolve a problem. The process is dynamic and requires active input from both participants. One of the most important factors in cooperation is trust. Trust is built in interaction. Disagreements and problematic situations may reduce trust, but successful problem

resolving may increase it. When people are cooperating and interacting, they become dependent on each other. Too close or too distant interactive relationship may be harmful for cooperation. If an individual in cooperation system is changed, there is a need to build a new relationship and trust with new representative. (Aira, 2012: 132-136.)

In the context of clinical trials investigators and CRO representatives are interacting and cooperating both face-to-face and by technologically mediated collaboration. As mentioned in chapter 2.2, the trend is to decrease on-site visits to trial sites and to increase usage of technological solutions in the sponsor – investigator cooperation. Modern technology enables interaction and collaboration, but it does not guarantee it. In hectic work life and busy schedules, tasks with deadlines are prioritized and communication with business partners decreases. Active communication is also required in a dispersed cooperation. For a successful cooperation, a good interpersonal communication is more important than the geographical location of parties. (Aira, 2012: 143-145.)

3 Purpose, Aim and Research Objectives

A worldwide trend is to increase usage of Contract Research Organizations in conduct of clinical trials. The purpose of this Master's Thesis is to increase knowledge about cooperation between Contract Research Organizations and investigators in the field of clinical trials. The results of the research will help CROs to identify development needs and to improve procedures related to clinical trials and cooperation. The aim of the research is to describe how investigators in Finland are experiencing cooperation with Contract Research Organizations. Objective is to find out answers to following research questions:

1.) What kind of positive experiences investigators have in cooperation with CROs?
2.) What kind of negative experiences investigators have in cooperation with CROs?

4 Materials and Methods

4.1 Research Method

This research has a qualitative approach and conventional inductive content analysis is used as data analysis method. In content analysis data is describing the phenomenon and intention is to find meanings from the fragmental data and describe those meanings in an explicit and compact way. Inductive content analysis is a three phase process including reduction of data, clustering data and abstraction of data. (Tuomi – Sarajärvi, 2013: 104 – 108). Data analysis process of this research is described in chapter 4.5 Data Analysis.

4.2 Sampling

The purposive sampling technique was used in this research. In qualitative research persons chosen as sources have experience and/or knowledge in theme under research and based on their expertise researcher expects them to provide the best possible information (Tuomi – Sarajärvi, 2013: 86; Pitkäranta, 2010: 114). To find out the experiences about cooperation with CRO companies, I asked permission to interview doctors working with clinical trial from one private health care provider, Hospital District of Pirkanmaa and Hospital District of Helsinki and Uusimaa, although working organizations of interviewees are not revealed in Master's Thesis. After a discussion with coordinator of Hospital District of Helsinki and Uusimaa I decided to leave investigators from that hospital district out from this research due to complicated approval and interview request processes.

After getting approvals, interview request letters in Finnish (appendix 1) were sent via email to 10 potential interviewees during 08Jan2015 - 03Feb2015. Criteria for selection were at least five years' experience in clinical trials and experience in collaboration with CRO. Receivers of the interview request letters were selected from my investigator contacts gathered during eight years working experience in clinical trial field as Clinical Research Associate and I also got some recommendations from colleagues' and two interviewees recommended their colleagues'. According to Eriksson and Kovalainen (2008: 52) it is quite a legitimate alternative in business research to conduct research with the people that are familiar to researcher or at least have direct or indirect contact

with them. I obtained six answers via email with interest to participate in this research and face-to-face interviews were scheduled for convenient time and place chosen by investigators. Due to interviews I spent 33 hours in buses and travelled 2330 kilometres across Finland.

4.3 Data Collection

To collect investigators' experiences in cooperation with CROs, six in-depth face-to-face interviews were performed during 15Jan2015 – 19Feb2015. To give an opportunity for interviewees to express themselves with the most natural way, interviews were performed in Finnish. Times and places for interviews were chosen by interviewees. In-depth interview was chosen as it is a research technique to reveal a vivid picture of the participant's perspective on the topic under research. It is a non-structured method and the only topic of the interview defined and questions are open-ended. During in-depth interview conversation and questions are related to purpose and aim of the study and research question. (Mack - Woodsong - MacQueen - Guest - Namey 2005: 29; Pitkäranta 2010: 107; Tuomi - Sarajärvi 2012: 75.)

In the beginning of the appointment I told interviewees briefly what and where I am studying and the purpose of my research. They were able to ask questions if they wanted to. I told them that I have no specific questions or themes which we need to go through, but the purpose was that they can freely, openly and honestly tell me what kind of positive and negative experiences they have in cooperation with Contract Research Organizations. I told that during the conversation I may ask some specifying questions. I also informed that all names and places revealed during interview are masked when I write interviews word by word to my computer. This was important for two reasons: first was to keep anonymity and second reason was that interviewees were able to speak openly without a need to be worried about their expressions. I told that interview is recorded with the recording application in my mobile phone. Before starting interview and recording, interviewee and I signed informed consent form (appendix 3).

The duration of the interviews varied from 33 to 60 minutes and all together I obtained 5 hours in recordings. I transcribed recordings word by word within 3 days from the interview and obtained 50 pages of written material in Arial font 11 and with line spacing 1,5. I evaluated data collection as successful. After four interviews I began to see

that same kinds of experiences were repeated in the interviews. In that point I had already made appointments for two more interviews and I decided not to send new interview requests until I have made six interviews to see if the data really is repeating itself and it can be assumed that new interviews will not provide new information for the research. After six interviews I was confirmed that this sample was appropriate and saturation had been fulfilled as described by Tuomi and Sarajärvi (2012: 87).

During the interviews I focused on listening and did not make any written notes, but after every interview I made notes about the atmosphere during interview and what was my impression about the interview session as whole. Based on those notes, the atmosphere in interview sessions was cosy and trustful as interviewees were able to reveal their experiences openly and honestly. Five out of six interviewees were investigators I had had prior work relationship during some point of my career in clinical trial field. I noticed that investigators with whom I had worked for several years and we were quite familiar with each other, it was more difficult to keep conversation in a topic and theme of this research. In those situations I needed to guide interview more to keep it on a theme. After listening to interviews many times from the recorder I evaluated that I managed to do that quite professionally and early enough, so most of the time the interviews were focused on the research questions.

4.4 Data Analysis

After every interview I listened to recording ones or twice before I transcribed it literally. I printed transcriptions and read them once or twice to get an impression and overview about the data as a whole. After reading the data, I started to underline sentences and phrases (group of words from one or more sentences standing together as conceptual unit) that answered to my research questions. I copied those underlined sentences and phrases to separate document and these became meaning units of the research data. I reduced meaning units to include only relevant for the research. These condensed meanings were listed on a separate document that included all condensed meanings from every interview. I gave different colours for all interviewees so I was still able to follow from which interview listed meaning was originally taken from.

After reduction I started to make theme clusters from condensed meanings. In this point I did not separate positive, negative or neutral meanings, but I grouped all meanings concerning the same theme together. After first clustering I printed documents out

and read them through. In some cases I went back to original interview to check that the theme group was correct. During that process I made some regroupings. After I was satisfied with theme groups, I started to group condensed meanings in theme clusters according to my research questions and gave names to created subcategories. I continued to cluster subcategories to categories and from categories I abstracted three themes to describe my research subject; “Positive experiences related to cooperation with CRA”, “Negative experiences related to cooperation with CRA” and “Experiences related to CRO position and operational environment”.

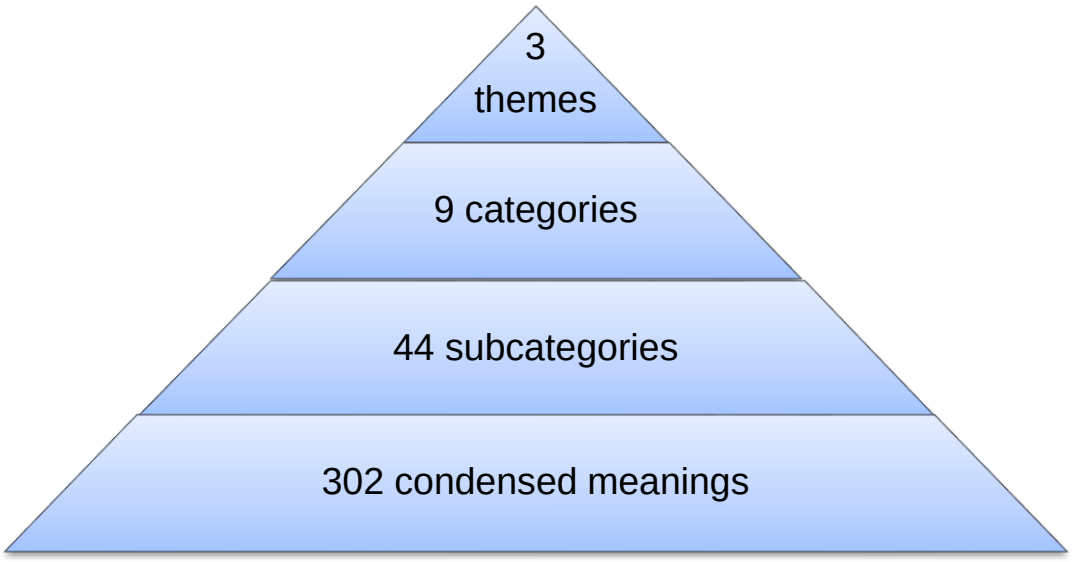

Figure 4: Data reduction process in numbers

After processing data to themes, I once again went back to the original interviews and read them through to verify that I had not missed anything and that themes were describing original data. Data reduction was also checked by an instructor. Few minor changes in condensed meaning clustering were made due to these check-ups.

5 Results

5.1 Background Information of the Interviewees

Due to a limited number of potential interviewee the anonymity is a challenge. Therefore minimal background information was collected from the investigators. Six interviewed doctors were specialist physicians representing five different therapeutic areas.

One interviewee was female and five were males. Interviews were conducted in five different towns in Finland. Five interviews were conducted at a private clinic and one in a public hospital. Four out of six interviewees had experience in clinical trials from both private and public sector and two had only experience from private clinics. Experience in clinical trial field varied from 8 to 35 years and all interviewees had been in a role of Principal Investigator in clinical trials operated by CRO.

Most of the investigators told spontaneously about their motivations to be involved in clinical trials. From the rest of the investigators I asked about their motivators. All of the investigators told that most motivating factor was to be in the frontline, ability to see what new is happening. Clinical trials gave doctors an opportunity to learn more about disease and therapeutic area for which a new drug is developed for and an opportunity to familiarize themselves to novel therapies. Based on knowledge gained from clinical trials they already knew how the drug is functioning, how to use it and for which patient group it is most suitable for when the drug is on markets.

> "Tykkään olla siinä niinkun etulinjassa ja nähdä, että miten lääke toimii ennenkun se on apteekissa, et sit kun se on apteekissa mä tiedän ihan tarkalleen, et siihen on tullut sellanen hunch et kelle potilaalle kannattaa juuri kyseistä lääkettä edes kokeilla… tää on niin jollain tavalla kiehtovaa" (Interview 2)

> "I like to be in frontline and see how medicine is functioning before it comes available in pharmacy, so when it is available in pharmacy I know exactly, I have got a hunch to which patients this particular drug is even worth to try… This is somehow fascinating" (free translation)

Doctors also saw clinical trials as the only safe way to get new medicines available to patients. Some of the doctors felt that it was an ethical duty of the doctor and hospital to participate in treatment development so that novel and better treatments will be available for the patients. Clinical trials gave also variation to basic practice and long and intensive patient-doctor relationships in clinical trials were rewarding.

5.2 Collecting Positive and Negative Experiences during Interviews

I started all the interviews by asking when interviewee has started working in the clinical trial field and have they noticed the trend to increase CRO usage in clinical trials. In most of the interviews investigators started to share their opinion and experiences in cooperation with CROs without further questions. Most of the investigators started with negative experiences. I noticed that in all interviews there was no need to ask about

negative experiences, those were expressed spontaneously. When I asked about positive experiences some of the interviewees thought that there must be some positive experiences, but they were not able to recall them as the negative experiences were on the top of their minds. But eventually all the interviews included both positive and negative experiences. Although many negative experiences were shared, investigators expressed that they do not bear ill will to anyone or want to harm no one. They expressed regret at lack of positive experiences. Like one of the interviewed investigator expressed:

> "Tarkoitan sitä, ettei oo tarkotus tuottaa kellekään mitään vaivaa tai pahaa mieltä, mutta jokainenhan meistä tulkitsee maailmaa omien kokemusten pohjalta ja kokemukset on tän tyyppisiä ni ei siltä voi välttyä" (Interview 3)

> "I mean that there's no intention to cause any trouble or give offence to anyone, but every one of us interpret world through our own experiences and if experiences are like this, it cannot be avoided" (free translation)

I understood that it was also in investigators interest to develop cooperation to more positive direction and that is why they expressed that this research was important. In following chapters I will describe investigators´ experiences by themes obtained from data analysis.

5.3 Positive Experiences Related to Cooperation with CRA

Cooperation with CRA was understandably the most discussed topic during interviews. CRA is the main contact between investigator and sponsor and CRA may be the only sponsor representative that has face-to-face contact with investigator and other site personnel during clinical trial project. There were altogether 88 condensed meanings describing positive experiences related to cooperation with CRA and these were clustered to 11 subcategories and to three categories (Figure 5).

Theme:	Positive experiences related to cooperation with CRA		
Categories:	1) CRA is working together with trial site personnel	2) CRA is qualified	3) CRA works in a businesslike manner
Subcategories:	CRA is ready to help	CRA is a specialist	Monitoring is done in a businesslike manner
	Tasks are handled together	CRA is an insider in pharmacompany	Decrease in monitoring frequency is not problematic
	Mutual understanding		Enough training is available
	Communication and information flow smoothly		Tasks are handled properly
			Personality effects on cooperation

Figure 5. Positive experiences related to cooperation with CRA: theme, categories and subcategories

5.3.1 CRA is Working together with Trial Site Personnel

The first category in the theme "Positive experiences related to cooperation with CRA" is derived from four subcategories; CRA is ready to help, Tasks are handled together, Mutual understanding and Communication and information flow smoothly.

Investigators expressed in interviews that in their point of view it is CRA's duty to help them with problems and questions. Investigators have the most positive experiences in cooperation with CRAs who are helpful, willing to help and who assist site personnel and resolve issues.

> "Semmonen monitori on hyvä, josta niinku heti huomaa, et se on niinku avulias ja valmis auttamaan, koska ainahan tulee semmosta kysymistä. Et se on niinku se ensimmäinen, et siel on se valmius auttaa ja ratkaista ongelmia, jos ei heti jollain puhelinsoitolla tai muulla selviä, niin sit se selvitetään seuraavana päivänä tai sit joka tapauksessa." (Interview 4)

> ""From the good monitor you can right away notice that she/he is helpful and ready to help, because there will always be questions, That is the first thing that there is a willingness to help and resolve problems, if not right away by phone or some other way, the issue will be resolved on a next day or eventually anyway." (free translation)

Investigators wanted to describe clinical trials as a cooperation project and teamwork where CRA and site personnel are planning and executing trials together. They had positive experiences related to face-to-face meetings in the initiation phase of trial, where operational plans are settled and agreed together with CRA. During the trial execution investigators were satisfied if problems were resolved together and corrections for documents and trial data were discussed and corrected in cooperation with CRA. Investigators wanted to have CRA's assistance and guidance to be able to do their own part of the duties correctly.

> "Ne tehdään yhdessä. Normaali käytäntö on niin, että se monitori, niin aamulla yleensä sen nään kun se tulee jos suinkin on mahollista ja sitten mä tuun muutaman tunnin päästä käymään ja sitten tarkistetaan ne liput ja laput ja ne korjataan samaan aikaan yhdessä, niin sillon mä tiedän millä tavalla tää ihminen haluaa tän homman hoitaa ja sitten se on niinkun kerralla pois päiväjärjestyksestä." (Interview 6)

> "Those are done together. Normal procedure is that I meet the monitor usually in the morning when she/he arrives if possible and then I come few hours later and we check notes and post-its and we correct them right away together. That is the way to see how this person wants to handle these tasks and then they are handled correctly right away." (free translation)

Successful clinical trials are conducted in a good cooperation. A good collaboration motivates investigators and site personnel to do their best in patient recruitment and data generation. It also motivates investigators to participate in new, future trials and in that way it also has an impact on amount of trials running in Finland in future.

Investigators experienced that mutual understanding about clinical trials as cooperative project is important. They wanted CRA to tell what kind of expectation CRA, CRO and sponsor have on them. One of the interviewees said that sharing CRO's aims and objectives could help investigators to understand why certain metrics, timelines and statistics are important for CRA´s organization. It would help investigators and CROs to understand collaborator's perspective and help to achieve goals together.

> "Mun mielestä ihan site initiation visitin yhteydessä vaan niinku näytettäis, että mitkä on niinku CRO-firman ja sponsorin tavotteet… ja sitten tota mitkä on niinkun toimeksiantajan kannalta tärkeet asiat… Et avattais tavallaa se kortti: tähän me pyritään ja tää ois niinkun meijän kannalta optimaalista niin se vois avata tutkijan silmiä, et ai jaa, no eipä tullu mieleenkään." (Interview 2)

> "In my opinion during site initiation visit one should show objectives of CRO and sponsor… and what is important in a sponsor's aspect… So someone shows the cards: this is our goal and this would be optimal for us. That might open investigator's eyes that ok, I did not even think about that" (free translation)

All the interviewees shared an experience that CRAs are easily available by telephone and email and contacts with CRA have been successful. Issues were usually resolved on telephone. Situations where CRA was not reached were rare. Contacts with CRA were principally satisfying and investigators felt no need to have contacts with sponsor personnel if communication with CRO-CRA was functioning. If there were some disagreements, they were resolved in discussions.

In situations where CRA was changed during trial execution, investigators felt that information from former CRA to new one was transferred, at least if change was planned and CRAs had possibility to work together for some time before actual trial handover. Although information was transferred there might have been a sort of uncertainty period before the new CRA had full knowledge about the trial, but according to interviewees it did not generally effect on cooperation or cause problems. Investigators also thought that it was depending on person how given information was processed and used. A CRA change may have also positive effects on trial. In long projects the new CRA may energize and inspire site personnel to continue in the project with new enthusiasm.

5.3.2 CRA is Qualified

Second category in theme “Positive experiences related to cooperation with CRA” is derived from two subcategories; CRA is a Specialist and CRA is an insider in pharmacompany. Investigators brought out appreciation for CRA’s competent in trial management. They indicated that working with a competent and acquainted CRA makes cooperation easier and motivates trial site for better performance. Qualified CRA has knowledge in trial processes and management, therapeutic area, other diseases and medications. With qualified CRA misunderstandings and false interpretations of source data are avoided. Investigators felt that it is important to ensure CRAs competent in the beginning of the trial process and this is the responsibility of CRO and sponsor.

> “Monitoroijan asiantuntemus on kans ihan tärkeä. Että on semmonen kokemus monitoroijallaki niin sehän on suureks avuks. Siis tämmösen tutkimuksen vetämisestä, myös tietysti sen meneillä olevan tutkimuksen sisällöstä ja muusta, mut sen lisäks kuinka ne tutkimukset hoidetaan ja erityisesti ne semmoset ongelmatapaukset, et sielt tulee vastaus heti niin sitä kyllä minä arvostan” (Interview 4)

> “Monitor´s competent is also important, it is big help if monitor has experience in leading clinical trial and also in content of ongoing trial and other things, but also

> about clinical trial management and specially how to handle issues, so that resolutions come right away. That´s what I appreciate" (free translation)

To get proper competence and acquaintance, investigators thought that CRA needs to be somehow inside in a pharmaceutical company or at least insider position has benefits. In insider position the CRA is able to get general view of the drug development process. The commitment and acquaintance of pharmaceutical company to certain therapeutic area or molecule enables insider to get more information about the subject in focus. In situations where CRA from CRO is working as in-house CRA in a pharmaceutical company there is no difference between sponsor's own CRAs and CRO-CRAs in aspect of cooperation. Investigators were satisfied with in-house CRA arrangement.

> "Vaik mä en tiedä mist firmasta on vuokrattu, mut sit on se etu, et on sisemmällä siinä firmassa, että ei oo niinku päälle liimattu tämmönen niinku välikappale, joka joutuu aina kysyy kaiken firmasta vaan on sisällä siinä ja pystyy ihan omiakin nopeita ratkasuja heittää, jos tulee jotain ongelmia, et se on mun mielestä ihan toimiva systeemi." (Interview 2)

> "Although I don't know from which firm she/he is contracted, but there is a benefit that she/he is inside in firm, that she/he is not just an obvious connecting piece, who needs to ask everything from the firm, but she/he is insider and able to make own decisions in situations where issues appears. In my opinion, this system is practical." (free translation)

5.3.3 Work is done in a Businesslike Manner

The third category in theme "Positive experiences related to cooperation with CRA" is derived from five subcategories; Monitoring is done in a businesslike manner, Decrease in monitoring frequency is not problematic, Enough training is available and Tasks are handled properly, Personality effects on cooperation. In the interviews investigators expressed satisfaction towards monitoring visits conducted by CRA. They felt that monitoring visits have been generally conducted in business-like manner and there were no differences between CROs. All the interviewees were experienced investigators and they felt that decrease in amount of monitoring visits is not influencing in cooperation and is not a problem for an experienced investigator and site personnel. Monitoring visit frequency could be prolonged if trial site was familiar with clinical trial processes and CRA was available for technologically mediated communication. For inexperienced investigator decrease in visits may cause increased workload.

> "Siinä ei o nyt ollu kauheesti ongelmaa, varmaan liittyy kokemukseenki. Mä tiedän ne tavalliset sudenkuopat, tiedän mitä kirjataan ja näin poispäin, ettei tuu hirveesti töitä, vaikka tääl CRA ois pari päivää paiskis töitä… Mut vähemmän koke-

> neelle se voi olla, et tota sit tulee niin hirveesti kirjattavaa ja korjattavaa ja muuta tämmöst näin niin niinku nääkähtää siihen ja sit motivaatio laskee.” (Interview 2)

> “It´s not problematic, it may be related to experience. I know the usual pitfalls, I know what to document and so on, so it does not cause lots of work although CRA is working here for couple of days… But for less experienced it may be. There will be so much recording and correcting and other that kind of tasks and it causes exhaustion and then motivation decreases.” (free translation)

The interviewed investigators were quite satisfied with the training they have received for the clinical trials. Trainings are increasingly done via internet instead of former face-to-face investigator meetings and investigators experienced some benefits in this change. Trainings via internet are available for completion at any convenient time. Overall experience was that training obtained via internet and during site initiation phase by CRA was enough at least for experienced investigators. Investigators were satisfied with increased frequency in monitoring visits in the beginning of the trial. It prevented systematic error occurrence and gave opportunities for further training. Benefits of global or local investigator meetings were networking and ability to practical training and guidance.

Cooperation between investigators and CRAs is an interpersonal cooperation between two personalities and chemistry between personalities influences on cooperation. Personality effects on working methods of both collaborators and also to attitude to work and quality of work. Investigators stated that difficulties due to unfitting chemistry were not dependent on company or professional skills, it was purely related to persons. Although personal characteristics have influence on cooperation and willingness to cooperate investigators appreciated that duties and tasks were performed in cooperation in a business-like manner. Professional attitude towards collaborators including open and decorous communication was functional. The most important thing was that work is done properly. Overall experience of the investigators was that with most of the CRAs chemistries have matched and there were only rare individual cases where differences in personalities have caused major problems.

> “Tutkiminen on työtä ja tota työtovereihin suhtaudutaan niinkun työtovereihin suhtaudutaan elikkä asiallisesti ja ammatillisesti ja se yleensä toimii kauheen hyvin” (Interview 2)

> ”Research is work and work colleagues are treated as workmates; properly and professionally and it works usually very well” (free translation)

5.4 Negative Experiences Related to Cooperation with CRA

Attitude of interviewed investigators towards CRAs was appreciative and positive but they shared also negative experiences related to cooperation with CRA. There were 82 condensed meanings describing negative experiences related to cooperation with CRA and these were clustered to 13 subcategories and two categories (figure 6).

Theme:	**Negative experiences related to cooperation with CRA**	
Categories:	1) CRA´s working method is not satisfactory	2) Site is left alone with increased workload
Subcategories:	CRA is not committed to resolve issues	Tasks are transferred to sites
	CRA is not completing tasks	CRA is lacking knowledge
	CRA is task oriented	CRA is not helping
	CRA is lacking service attitude	Resolving technical problems is time consuming
	Contacts are pending	Lack of personal guidance
	CRA´s working method is annoying	Practical training for technology is needed
	CRA gives only negative feedback to site	

Figure 6: Negative experiences related to cooperation with CRA: theme, categories and subcategories

5.4.1 CRA's Working Method is not satisfactory

The first category in theme "Negative experiences related to cooperation with CRA" is derived from seven subcategories; CRA is not committed to resolve issues, CRA is not completing tasks, CRA is task oriented, CRA is lacking service attitude, Contacts are pending, CRA´s working method is annoying, CRA gives only negative feedback to site.

Investigators were disappointed and frustrated in situations where CRA was not committed to resolve issues related to trial. There were differences between CRAs in level of engagement and commitment. Investigators had experienced that CRO-CRAs were not as committed and engaged as sponsor's own CRAs. Based on their experiences monitors of CROs did not have time or motivation to solve issues. It was not in CRAs' interest to further affairs in timely manner. CRAs did not take responsibility or ownership on trials and tasks they were involved in. Investigators gave a reason for lack of

commitment and motivation from outsider position of CRO-CRA; if the CRA is not able to see the whole picture she/he is not seeing the effect of actions or lack of actions to wholeness.

> “Kun tulee joku ongelma eteen, sen selvittäminen sujuu helpommin kun on tämmönen sitoutunut ihminen, joka sit ymmärtää, et tää pysähtyy nyt tää prosessi, jos ei tätä asiaa hoideta ja sillon se vaikuttaa siihen myös ajallisesti. kun taas tää CRO ulkopuolinen ihminen sille ei merkitse niin paljon kuin hyvin ajallisesti ja asiallisesti se asia sujuu vaan hän sitten selvittää kun jaksaa, kerkiää ja on kiinnostunut.” (interview 3)

> ”When an issue appears, resolving is easier with committed person, who understands that this process will freeze if the issue is not handled and then it has also temporal effect. But if there is a CRO outsider it does not matter to that person how properly and timely manner things are handled, but she/he resolves them when there is time, interest or willingness” (free translation)

Investigators had experienced unfulfilled promises when CRAs have left tasks uncompleted or refuse to complete tasks. Investigators reported that lack of service attitude and lack of interest of CRAs complicate work of site personnel. Site personnel have a feeling that CRA should not be bothered with the issues. If CRA is only interested in her/his own tasks it influences negatively in cooperation. Sometimes CRAs had justified their unwillingness to do something with rules and regulations. Differences in interpretation of rules and requirements caused friction between investigators and CRAs. Investigators had experienced rigid interpretation and meticulousness by monitor. On the opinion of one of the interviewees investigators are sometimes falsely blaming CRAs for pedantry although it is investigator who has not understood GCP or other regulations.

Investigators became annoyed and frustrated when monitor was not able to detect systematic error in site’s actions on time, especially if it caused lots of extra work or had an effect on patient’s eligibility in trial. Investigators also reported that some of the monitors had no understanding for unintended mistakes made by site personnel. Site personnel received only negative feedback and monitor visited site only in situations where site had made something wrong or actions were pending. If site personnel conducted clinical trial satisfactory, site was left alone and not even positive feedback was received.

> “Jokainen haluu työstänsä jonkunlaisen palautteen, eikä se palaute voi olla sitä, et kun teet väärin niin sit tulee ihminen, joka sanoo: ”Te ootte tehny väärin”. Sit kun me on tehty hyvin, ni me ei saada muuta kun tehdä sitä työtämme. Tottakai me ollaan tyytyväisiä, et me ollaan tehty oikein asiat ja näin, mut joku vois sen kertooki meille.” (interview 1)

> "Everyone wants to receive feedback and it can´t be so that when we have made a mistake then a person comes and says: "You have made a mistake". And if we have performed well, we receive nothing. We just continue our work. Of course we are satisfied that we have completed tasks correctly and so, but someone could also tell us that." (free translation)

Investigators understood CRA's duty to remind them about not completed trial tasks but, CRA's style or attitude to do it may influence negatively on cooperation and investigator's motivation. CRA's style to dictate tasks and duties to site personnel was annoying and one investigator reported experience in army like commanding by CRA.

> "Ne vaan sit ilmottaa, et tämä pitäis laittaa sinne eikä niinkun se et hei voitaisko me yhdessä kattoo tää. Tulee vaan niinku semmonen niinku armeijamainen olo "toi on teijän tehtävä, toi on teijän tehtävä, toi on tehtävä, ei mul oo aikaa enkä mä saa tulla teille"… (interview 1)

> "They just inform that this should be put in there not that can we look at this together. It feels like in the army: "This is your job, this is your job, this must be done, I don't have time and I'm not allowed to come to visit you" (free translation)

As described in chapter 5.1.1 investigators generally experienced that CRAs were reachable but they had also experiences in situations where unavailability had effected on cooperation negatively. In conflicts and in situations where CRA was lacking knowledge or was not able or willing to ask advices from upper management, investigators had felt that CRAs have avoided contacts. Also if CRA was located in other country than Finland reachability was more difficult. Delays in contacts caused uncertainty and unawareness among site personnel.

5.4.2 Site is Left Alone with Increased Workload

The second category in theme "Negative experiences related to cooperation with CRA" is derived from six subcategories; Tasks are transferred to sites, CRA is lacking knowledge, CRA is not helping, Resolving technical problems is time consuming, Lack of personal guidance and Practical training for technology is needed. Interviewed investigators had noticed that the workload of site personnel has increased. They did not necessarily feel trend as deterioration, but as some of the investigators indicated it was unfair if in budget negotiation phase of trial, investigator was not aware of all expected duties and tasks, but relied on former experiences and some new responsibilities revealed during trial execution phase.

> “Olin tässä neuvottelussa varmaan niin hölmö, että mä lupasin semmoseen pienempään (palkkioon), koska mä en siinä vaiheessa tienny sitä, että miten paljon mun pitää tehdä semmosta ekstra hommaa, jonka monitori on mulle aikasemmin tehny” (Interview 6)

> “In this negotiation I was so stupid, that I agreed to lower (fee), because in that time I didn’t know how much extra work I need to do, work that has previously been completed by monitor” (free translation)

It was especially duties and tasks which have previously been performed by CRA that have been transferred to the site’s responsibility. Tasks included printing documents, ordering supplies, shipping documents and equipment, archiving and resolving technical issues with helpdesks. Investigators, who had had clinical trials which included technical equipment, felt frustration with problems occurring with poorly designed devices. Resolving technical issues took time, increased technologically mediated communication and pressure in cooperation with CRA. Investigators felt that they were left alone with dysfunctional devices and there was no local help or guidance available with equipment. CRAs guided investigators to contact global helpdesk with the issues and investigators were not comfortable to communicate technical problems in English. Some of the investigators had experienced that helpdesk had not resolved problem in proper time or at all. Investigators hoped to get practical training for technical devices and applications. Web-based training and written guidance were not enough. The best way to learn was to get personal training from local, competent CRA in their own language.

Investigators reported same kind of lacking in local help with other new tasks. Finding instructions and guidance were time consuming and there was no help available from CRA. CRA’s role was only to monitor that trial responsibilities have been performed correctly by site personnel. Lack of help was demotivating as investigators felt that they needed to learn everything by trial and error. Some of the investigators expressed their concern over inadequate trial data due to lack of guidance. CRA was not able to guide or teach because they were also inadequately trained or they were inexperienced.

> “Nyt kun sä soitat tommoselle ulkopuoliselle CRA:lle, joka käy täällä kerran, kaks ja sit se on vaan niinku puhelimen päässä, sehän sanoo: ”No koittakaa ratkasta, jos ette osaa niin soittakaa helpdeskiin. Te ootte tehny nyt jotain väärin, mut mä en osaa auttaa”. Eikä ne osaa siis. (interview 1)

> “Now when you call to outsider CRA, who visits us ones or twice and then is only available by phone, she/he says: “Try to resolve it, if you can’t resolve it call to helpdesk. You have done something wrong, but I can’t help you”. And they actually don’t have the knowledge. (free translation)

5.5 Experiences Related to CRO's Position and Operational Environment

The third category includes experiences related to CRO's position in between sponsor and investigator and generally to operational environment. Although the aim of this research is to describe experiences related to cooperation with CRO, some environmental aspects need to be taken into consideration. There were 132 condensed meanings in this category and these were clustered to 20 subcategories and four categories (figure 7).

Theme:	**Experiences related to CRO´s position and operational environment**			
Category:	1) CRO is using sites to get profit	2) CRO-Sponsor contract causes difficulties	3) CRO´s working method is not satisfactory	4) Operational environment influences in cooperation
Subcategories:	CRO is treating sites as a resource	Handling tasks is more difficult when CRO is in between	Prior experiences influence in willingness to participate in trials	Sponsor´s actions are influencing to general picture
	CRO maximizes profit at the expense of site	CRO contract is limiting CRA´s work	There are differences between CROs	Increased CRO usage is problematic
		Unclear duty delegation complicates situations	Insufficient processes in CROs increase difficulties	Challenges in operational environment influence in cooperation
		Variation is getting research results	CRO is lacking local knowledge	Handling tasks with technology has increased
			Development need in feedback collection	Technology is not utilized
			Amount of fruitless work is notable	Same re-trainings are annoying
			Too many emails	
			High turnover rate	

Figure 7. Experiences related to CRO position and operational environment: Themes, categories and subcategories

5.5.1 CRO is using Sites to get Profit

The first category in theme “Experiences related to CRO´s position and operational environment” is derived from two subcategories; CRO is using sites as a resource and CRO maximizes profit at the expense of site. Some of the interviewed investigators experienced that CRO was not treating investigators and other site personnel as equal cooperation partners. CRO was focusing on its own interest and utilized site as a resource that provides material to CRO and then CRO sells material to sponsor. CRO was not so interested in how things are experienced at the trial site. They just wanted to use them as mediums to get income and profit. Working directly with sponsor has been more like equal partnership. Investigators had understood that CROs have a contract with sponsors to conduct trial for certain sum of money. From that total sum CRO was paying investigator and site fees and more they paid, less they gained profit. Investigators understood CRO’s willingness to make profit, but they felt that CRO was doing it on expense of site. They had experienced that investigator fees were lower in CRO handled trials.

> “Semmonen tunne tulee kun näistä siis tutkimuspalkkiosta neuvotellaan niin siinä tulee vähän semmonen kuva, et siinä sen tutkijalääkärin osuus niinku minimoituu, jää niinku pienemmäks. Se CRO-firma vie siitä tietysti tietyn osan. Ja tota se on ihan ymmärrettävää, haluaahan he tietysti palkkion itekin.” (interview 4)

> “The kind of feeling comes when trial fees are negotiated that investigator’s share is minimized, it settles to lower level. CRO-firm takes of course own share and it is understandable, of course they also want to have payment too.” (free translation)

Investigators also indicated that CRO’s profit maximizing made financial agreement negotiations more complicated and it was difficult to get compensation for extra work needed during the trial, if that was not foreseen during negotiations. Extra work included problem resolving, unscheduled patient visits and assessments due to safety reasons and working hours spent to preparations and patient screening. One of the investigators suspected that CRAs did not always complete all the tasks they were expected to complete at site, but they still invoiced sponsor at maximal level.

5.5.2 CRO-Sponsor Contract causes Difficulties

The second category in theme “Experiences related to CRO´s position and operational environment” is derived from four subcategories; Handling tasks is more difficult when

CRO is in between, CRO contract is limiting CRA´s work, Unclear duty delegation complicates situations and Variation in getting trial results. Contract between sponsor and CRO concerning clinical trial conduct has an effect also on cooperation between CRO and investigator. CRO gets instructions and frames to work from sponsor and investigators felt that it was complicated to discuss or negotiate with CRO about the issues that were not in CRO's hands to decide. Financial agreement negotiations were typical situations mentioned by investigators. Negotiations were prolonged when CRO was in between due to need of CRO to ask every detail from sponsor. Especially if the sponsor was located outside of Finland, delays were expected. Cooperation was rigid and autocratic also with CROs that had management located outside of Finland.

CRO's position in between sponsor and investigator and unclear duty delegation between CRO and sponsor complicated cooperation. Investigators were annoyed if they needed to share and explain the same information to both collaborators. It gave an idea that it was not clearly agreed between sponsor and CRO who was responsible for communicating certain subjects with trial site. Investigators had experiences also in situations where decisions were delayed due to uncertainties in responsibilities. Either issue was transferred from one person to another and again to another or different persons from CRO or sponsor organization wanted to comment and make arguments to the issue and it was unclear who was responsible for the final decision. Resolving issues in that kind of atmosphere was complicated, bureaucratic and time consuming.

> "Mä kysyin sitä asiaa monitorilta, monitori kysyi sitten sieltä CRO-firman joltain asiantuntijalääkäriltä ja sitten sitä kysytään sieltä sponsorilta, et se niinkun kiertaa ja kaartaa… Sitten tulee lisäkysymyksiä tulee siltä CRO-ihmiseltä, sitten siltä varsinaiselta sponsorilta ja kaikilta siitä välimuodosta, et viis ihmistä laittaa mulle meiliä… Sillä tavalla se voi niinkun levitä." (interview 6)

> "I asked from the monitor, monitor asked from CRO´s some kind of medical adviser and then it is asked from sponsor, so it goes around and around… Then further questions are presented by CRO-person, sponsor and by everyone else in the middle, so five persons were sending me emails… In that way it may get around." (free translation)

The contract between sponsor and CRO has also effect on CRA's work. Investigators indicated that contract defined strictly tasks for CRA and time that CRA was able to spent for task completion. Due to agreement CRAs were not able to visit trial site, CRAs had no time resources and were only doing tasks they were paid to do by sponsor. These experiences have led to situation where investigator need to ensure what kind of terms CRA has during the trial before investigator agrees to participate in trial.

> “Täytyy niinku varmistaa se et miten tää menee tää monitorihomma. Et kummonen ihminen siihen tulee ja mimmoset ehdot sillä on. Tähän saakka on kauheen vähän kiinnitetty siihen huomioo, mut näit on ollu näit niin sanottuja ulkopuolisia monitorointeja, jotka on voisko sanoo herättäny pientä närää puolin ja toisin niin kyl nyt enemmän ja enemmän rupee miettimään” (interview 1)

> “We need to ensure how monitoring will go. So who is coming and what kind of terms monitor has. Until now we have not paid attention to that, but we have had these outsiders’ monitorings that has divided both parties so this needs to be taken more and more into account” (free translation)

Sometimes it has been difficult for site personnel to perceive allocation of responsibilities between operators. CRO represents sponsor and CRA may represent CRO which is paying her/his salary but CRA also represents sponsor in the trial process. Especially in trials where CRA is the only face-to-face contact from sponsor’s site, investigator may expect response and involvement in duties she/he is not responsible according to CRO-sponsor agreement. This may cause confusion, frustration and conflicts in cooperation.

Unfinished contract negotiations between sponsor and CROs have caused extra work for investigators. If sponsor had not yet decided to which CRO clinical trial is outsourced, different CROs may contact investigator with feasibility assessments concerning the same trial.

In trials where CRO’s responsibility ends before trial is officially closed, investigators have experienced confusion especially with archiving. Although archiving site documents is investigator’s responsibility, investigators felt that they need some guidance with it. There was also development need in getting results of clinical trials. Investigators were interested in to hear about the overall feedback and results of the trial. Although receiving results have improved, there were still some delays in it. Investigators had noticed that trial closure meeting where results were usually discussed, have not been arranged anymore.

5.5.3 CRO’s Working Method is not satisfactory

The third category in theme “Experiences Related to CRO´s Position and Operational Environment” is derived from eight subcategories; Prior experience influence in willingness to participate in trials, There are differences between CROs, Insuffisient processes in CROs increase difficulties, CRO is lacking local knowledge, Development need in

feedback collection, Amount of fruitless work is notable, Too many emails and High turnover rate.

Based on experiences of the interviewed investigators, there are differences between CROs. Quality in monitoring activities and working method varied between organizations. Previous experiences related to certain CRO had an effect on willingness to cooperate with this organization in the future. Overall experience was that turnover rate of CRAs was quite high in CROs. Although CRA turnover was not affecting dramatically on cooperation as described in chapter 5.1.1, investigators preferred to have the same CRA during whole trial process. Some of the investigators thought that a high turnover rate was a consequence from poor working climate and lack of team spirit inside CRO. In cases investigators were considering participation in clinical trial and had information that a certain CRO is conducting the trial, it caused some extra evaluation, but it was not primary factor for final decision. Study design and molecule under development were more important. But investigators revealed that they had a kind of blacklist of disfavoured CROs in mind.

> "Jos siitä CRO-firmasta on jotain kokemuksia, mitkä ei oo ollu niin hyviä niin se vaikuttaa paljon asiaan. Mut tota jos on semmonen hyvä CRO-firma, josta niinkun on ehkä kokemuksia, niin ei se ratkaisevasti silloin vaikuta, mutta aina pikkusen se vaikuttaa joka tapauksessa. Et vähän on empivämpi siinä ja se täytyy olla se tutkimus muuten mielenkiintoinen ja hyvä." (interview 4)

> "If there are some negative experiences about certain CRO-firm it influences a lot, but if CRO-firm has a good reputation, it isn´t decisive, but it influences somehow anyway, causes some hesitation and trial need to be otherwise interesting and desirable. (free translation)

Insufficient or inflexible processes inside CROs prevented smooth cooperation. Especially in big international organizations, where different people are completing different tasks there were challenges in continuous information flow inside CRO.

> "Siinä firmassa yks hoitaa sopimusneuvottelut, toinen selvittää asioita monitorin kanssa, kolmas ihminen ehkä selvittää joitakin ihan käytännön asioita ja näin se niinkun leviää kun jokisen eväät… Se tieto ei heillä kulkenu, et esimerkiks sopimusneuvottelut katkes yks kaks noin viideks viikoks, joka johtu siitä, että se ihminen, joka hoiti niitä niin oli sairastunu… nää muut yritti hoitaa niitä omia asioita, joita ei voinu hoitaa ku ei ollu sopimusta, et vähän vaikee!" (Interview 6)

> "In that firm one person is negotiating agreements, one is handling things with monitor, one is figuring out practical matters, so it spreads out… Information was not spread. For example agreement negotiations paused suddenly for five weeks due to sick leave of negotiator… Others tried to handle their duties but they could not do that because there wasn't signed agreement. It was difficult!" (free translation)

Inflexibility in processes also prevented the usage of meaningful and site specific solutions in cooperation. As example one of the investigators told that in feasibility assessments every investigator receives same kind of multi-page assessment form although many questions in form are not suitable or relevant for local practice in Finland. Investigators expressed that CROs were lacking local knowledge and CRO's actions and propositions were based on false assumption. Lack of local knowledge appeared in unfamiliarity with local health care and treatment practices, compensation policies, patient database availabilities and investigator's motives to participate in clinical trials. Some of the investigators experienced that CROs assumed conduction of clinical trials to be core task of the investigators and that investigator have countless hours to spend for the duties in trial. There were also more fruitless experiences with CROs in trial negotiations that did not lead to trial agreement than with sponsor. According to investigators insufficient processes and lack of local knowledge were partially reason for amount of fruitless work in cooperation with CRO.

Inflexibility in email communication was also experienced as every message relevant or not was sent to the Principal Investigator. One of the investigators indicated that CRO outsourced responsibility to investigator by sending email about every minor detail. Frustration for increasing amount of emails was mentioned also in other interviews. Investigators preferred more targeting in email communication. Investigators hoped to have messages only relevant for them and the other messages should be allocated to relevant personnel. Investigators were concerned that important messages were lost in mass of emails and they were not able to prioritize or evaluate relevancy of every message.

> "Sitten kun on kymmeniä uusia sähköposteja viikonlopun jälkeen niin sitten tulee aina mieleen, et eiks joku vois tän muutenkin hoitaa tän asian… Niihin täytyy suhtautua aika niinkun kovalla kädellä sitten siihen, niitä vaan putsataan sieltä pois ja siinä saattaa sit joku tärkeempikin viesti mennä ja se on huono juttu, mut niitä ei pysty niinkun, jonkun pitäis kuitenkin ne priorisoida, mikä vaatii jotain responssia ja mikä ei." (interview 5)

> "Then when you have dozen new emails after weekend it always comes in mind that could there be some else way to handle this… You need to react in quite a hard way and just delete those away and in that process some important messages may be wasted and that's bad. Someone should prioritize them, which one needs response and which one doesn't."

The same kind of targeting was desired for trainings. For an experienced investigator it was frustrating and annoying to go through same trainings in the beginning of every

trial. Investigators understood need for refreshment training and appreciated if shorter version was an option instead of long training sessions designed for beginners.

Investigators were willing to give feedback related to clinical trials. They had given it spontaneously especially in situations where a development need was identified. Some of the investigators told that they had completed feedback surveys provided by CRO, but there has not been systematic feedback collection process in place. Investigators experienced that feedback collection and feedback discussions would help to develop cooperation and trial processes and were willing to participate in feedback collection. They were also willing to obtain feedback about trial site and their own operations.

5.5.4 Operational Environment influences in Cooperation

The fourth category in theme “Experiences related to CRO position and operational environment” is derived from six subcategories; Sponsor´s actions are influencing to general picture, Increasing CRO usage is problematic, Challenges in operational environment influence in cooperation, Handling tasks with technology has increased, Technology is not utilized and same trainings are annoying.

All of the interviewed investigators had noticed a trend of increasing usage of CROs also in Finland. One of the investigators recalled, that in 1990s all of the trials he participated in were monitored by sponsor and nowadays all his four ongoing and three coming trials were monitored by CRO personnel. Most of the investigators indicated that integrating CROs to clinical trial processes was not successful and it increased problems. Growth of CRO usage has been a notable change in the field of clinical trials. Pharmaceutical companies may achieve financial advantages from outsourcing, but investigators thought that it may influence negatively on investigators willingness to participate in clinical trials. Many investigators mentioned awareness of decreased number of clinical trials conducted in Finland and they were concerned about the trend. Personally they had not experienced decrease in clinical trials. They reported that there were enough clinical trials available for them.

Sponsor’s decisions and actions have an influence on CRO operations. CRO is representing sponsor and acting accordance with contract between CRO and sponsor. Sponsor’s working methods and guidance determine some kind of frame to CRO operations and reflect to cooperation between investigator and CRO:

> “Semmonen yks vähän poikkeava kokemus oli, kun oli “ulkomaalainen” yritys, joka teki, sponsori oli “ulkomaalainen” ja se jotenki niiden toimintatavat kyllä poikkes ihan olennaisesti muista… Mä jotenkin tulkitsin, et se oli sekä sponsorin erilaisesta toimintatavasta, että siihen… Kyllä se oli enemmän sponsoriin liittyvä, koska siin oli semmonen CRO-yritys, joka on sitten muissa yhteyksissä toiminu toisella tavalla, et ei se varmaan ollu siitä CRO:sta kiinni” (interview 5)

> “Kind of exceptional experience was when there was a “foreign” company, sponsor was from “other country” and its working methods were exceptional compared to others… Somehow I interpreted that it was related to different working method of sponsor… Yes, it was more depending on sponsor as the same CRO has worked on another way in other trials, so it wasn’t related to CRO.” (free translation, country mentioned in interview was masked in quotation)

Although there were negative experiences related to communication with both CRO and sponsor prescribed in chapter 5.3.2, some of the investigators experienced that in certain situations it is beneficial to have sponsor’s involvement during a trial process. Visible involvement generated a feeling of security. Investigators felt that they were able to return to sponsor if there were problems with CRO cooperation. Sometimes sponsor was involved in problematic issue resolving and that was appreciated.

Strategic decisions of a sponsor have an impact on general view on clinical trial field. Investigators had noticed that pharmaceutical companies outsourced trials which were strategically unimportant for them. Strategic unimportance may influence on sponsor’s motivation to invest on a trial and at site level it has appeared in poor technical solutions, incomplete trial process planning and uncertainty in putting project into effect and carrying on as planned.

> “Kyllä on tullu vähän vaikutelma, että semmoset sekundääriset hankkeet herkemmin ulkoistetaan, jollonka sen niinkun toteutuminen on hiukan epävarmaa. Semmostakin on niinku tapahtunu, et on väännetty sopimuksista ja suunnitelmista tosi pitkään ja sitten vaan yhtäkkiä projekti niinku lopetetaan ja se on tosi turhauttavaa kyllä.” (Interview 5)

> ”The kind of impression has come that secondary projects are outsourced so putting them into effect is slightly uncertain. It has happened that we have had long agreement negotiations and planning and then suddenly project is aborted. It is really frustrating. (free translation)

As described in chapter 5.3.3 investigators experienced fruitless work with CRO due to internal processes, but sponsor’s operations have also influence on that. Some of the investigators indicated that sponsors’ way to invite to bid CROs for trials has an impact on amount of fruitless work. As there have been many small companies with high turnover rate and without stable relationship with certain sponsor, the knowledge in trials and sponsor’s working methods were undeveloped.

Investigators indicated also that it is not only the field of clinical trials which has had changes and new challenges. They were experiencing increasing challenges also in their general practice. In addition to challenges in daily duties, the challenges in a research field were experienced demanding and demotivating. Investigators expressed that a successful cooperation was required, appreciated and meaningful in diverted and complicated environment.

Investigators had noticed that technologically mediated cooperation has increased. Web-based solutions have enabled information sharing in real time and made issue resolving possible despite long distance. Technologically mediated solutions have enhanced cooperation possibilities and have not decreased communication.

> “Ei se (teknologiavälitteinen viestintä) ainakaan vaikeuttanut sitä asiaa (yhteydenpitoa) ole, ehkä jopa nopeuttanu joittenki asioitten kohdalla, kun ei se vaadi sitä et monitorin pitää matkustaa Helsingistä tänne monta tuntia, vaan me sitetaan ja sanotaan sille ja se sanoo, et se selvittää asiaa ja laittaa viestiä netin kautta tai soittamalla niin ei se ainakaan huonontanu sitä sillä tavalla.” (interview 3)

> ”It (technologically mediated communication) has not made it (communication) more difficult, perhaps even expedited it in some situations, because it is not required for monitor to travel hours from Helsinki to trial site, but we can call and report and monitor says that she/he will resolve the issue and send a message via email or call. So it has not at least made communication worse.” (free translation)

Negative experiences related to technologically mediated cooperation and communication were concerning increased email communication and described in chapter 5.3.3 and increased transfer of duties from CRA to investigator including printing electronic documents at the site as described in chapter 5.2.2. Investigators also experienced that technology has not been yet fully utilized. The development and utilization of electronic databases and web-based trainings were mentioned as development needs in the interviews.

> ”Tällä hetkellä tehdään vähän niinkun sulkakynä-paperisysteemiä vaan sähköisesti monella tapaa, mikä on turhauttavaa”

> ”At the moment electronic ”guill and paper” system is in use in many ways and it’s frustrating.” (free translation)

6 Discussion

Context of this Master´s Thesis is fairly topical issue at the moment. Finland´s national public service broadcasting company Yle (2015) released news on 06Apr2015 concerning decreasing number of clinical trials in Finland and its effects on Finnish patients. Decrease in number of clinical trials decreases quality of health care and patients´ ability to get novel therapies. Finland is losing frontline position in taking novel treatments into the clinical practice. Positive news is slight increase in number of clinical trials in the beginning of year 2015 and this trend was also noticed by investigators interviewed for this Master´s Thesis.

The world of clinical trials is international and global. As pointed out in chapter 2.1.1 global trends are influencing in field of clinical trials in Finland in general and also in individual level as results of this research have shown. Although there are differences between nations, there are many similarities. For example interviewed investigators in Finland shared same kind of primary motivator to participate in clinical trials as their colleagues in other countries (Glass 2009); to learn about new medical treatments prior to launch.

As the clinical trials are not conducted in isolation, changes in operational environment have an influence on circumstances of clinical trial operations. Worldwide financial challenges are increasing outsourcing in many other industrial sectors not just in pharmaceutical industry. Investigators reported many challenges that are resulted from outsourcing clinical trials. Perhaps it is unrealistic and even unnecessary to try to go back to “the old times” where sponsors were conducting clinical trials with their own headcounts. More important is to focus on improving cooperation between sponsors and CROs and also cooperation between CROs and investigators. Based on the results of this research there are lots of improvement needs and some of them should be easily resolved.

Increasing utilization of technology is trend in every sector. There are lots of advantages in technological solutions usage and all of the technology available is not fully utilized yet. In the interviews investigators complained about the need to perform same trainings several times and about completing same feasibility assessments. There are already many global support-function approaches available that could be time and cost saving solutions for all parties. There are web-based trainings where certificate of com-

pleted training can be uploaded and accessed by multiple study sponsors and cross-pharma repositories of essential documents and CVs of investigators (Cascade et al 2015). Sponsors and CROs just need to implement these to their practice. But there are also many challenges in technical solutions. Technical problems were causing lots of extra work for site personnel in clinical trial sites and help for these issues was not always easily available.

Further in this chapter I will discuss research results by focusing on two main themes; investigators´ experiences in cooperation with CRAs (6.1) and experiences in cooperation with CROs (6.2). In chapters 6.3 and 6.4 trustworthiness of this research and ethical considerations are in focus.

6.1 Investigators´ Experiences in Cooperation with CRAs

It was revealed in the interviews that investigators appreciated qualified CRAs and were willing to work in cooperation with CRAs. Cooperation only happens if both cooperation parties are actively giving their time and resources and sharing goals and responsibilities (Aira 2012: 50). Investigators valued cooperation with CRAs who have time for issue resolving, who were available for contacts and who were seeing clinical trial project as teamwork with clinical trial site personnel. Sharing and setting goals together increased mutual understanding. As Aira (2012) pointed out in her research, successful cooperation is created in regular interpersonal interaction by building trust, maintaining interpersonal relationships and keeping balance between distance and closeness. Results of this research support Aira´s study. Investigators described positive experiences in cooperation when in the beginning of the trial project CRA visited trial site more frequently. Same approach was suggested in Cascade et al (2015) research to reduce feeling of burdensomeness of clinical trials among investigators. During visits investigators were able to familiarize themselves with CRA and trial and were able to get confirmation and trust that they were conducting project correctly. Although on-site visits were less frequent after study start, built interpersonal relationship was maintained by telephone and email contacts and there were no more need for close face-to-face cooperation.

Investigators valued CRAs´ competence in clinical trial project management and knowledge of medical and medicinal content of the trial. These qualifications are also requirements for trial monitor in GCP (1994). Investigators had also experienced that

some of the CRAs were lacking knowledge or were not willing to share their knowledge with site personnel. As pointed out also in study of Azoulay et al (2010) monitors of CROs were lacking “sense of project ownership” and focused rather to individual tasks than to the project as a whole. Task orientation may arise from the CRO-sponsor contract. If CRA is trained and appointed to complete only certain tasks but is not involved or implemented to whole trial process it is more difficult to see the influence of own actions to the whole project. So task orientation is not only grow up from monitors own attitude, but also from attitude, guidance and information received from both CRO and sponsor.

Workplace relationships are constructed around work related tasks, but in successful collaboration goals are achieved and it can be observed in behaviour, satisfaction and attitude of collaborators (Aira 2012). Investigators reported that mutual understanding was gained by sharing expectations and goals and also by understanding challenges each collaborator is facing. Although chemistry between collaborators had influence on cooperation, it was more important to investigators that tasks were handled properly and businesslike manner rather than close friendship-like relationship with the monitor. Similar findings were obtained in Aira´s research. Attitude of the CRAs influenced on cooperation and investigators´ motivation to conduct research. CRA´s willingness to help and work together with site personnel increased investigators´ motivation to contribute to clinical trials. If CRA was focusing only to her/his own tasks, refusing to assist and avoiding communication or using commanding, unkind tone in communication, investigators´ motivation was decreased.

6.2 Investigators´ Experiences in Cooperation with CROs

In the research of Azoulay et all (2010) and in global surveys by The Avoca Group and Contract Pharma CRO – Sponsor relationships have revealed to be complicated. Business orientation of the organizations is different; for sponsor clinical trials are R&D cost and income and profit is gained from developed medicines when they are launched in to the market. CRO is getting income and profit from the clinical trials. Orientation may lead to situation where CRO is using clinical trial sites as resource to get profit and ignoring investigators needs, interests and opinions. For a pharmaceutical company investigator can be a valuable long-time partner as the cooperation continues also after drug is on markets. It should be remembered in sponsor organization that CRO is rep-

resenting sponsor at the clinical trial site and negative experiences in cooperation with CRO may reflect as negative association towards sponsor and its products.

Previous research has showed that lack of embeddedness between sponsor and CRO hindered efficient partnership building. It was shown in the results of this Master´s Thesis that difficulties in sponsor – CRO relationship reflects to CRO - investigator relationship. Contractual stipulations limits CRO´s and CRA´s work, complicates communication and clinical trial agreement negotiations at least if duty delegation is not clearly stated. Lack of commitment among CRO CRAs was influencing negatively on cooperation. Investigators had noticed also high turnover rate among the CRAs in CRO. Being embedded in the organization is associated with reduced intention to leave or actual leaving (Mitchell – Holton – Lee – Sablynski – Erez 2001: 1118). Embeddedness may increase when sponsors are contracting CROs as strategic partners and CRAs are included as in-house CRAs in the pharmaceutical company. In-house CRA strategy may also increase local knowledge as in-house CRAs are able to increase knowledge in sponsor company´s operations, gain benefit from closer teamwork with sponsor representatives and utilize knowledge from sponsor´s prior experiences and projects. This trend of strategic partnership is increasing and based on the results of this research moving to that direction is the correct way.

Nowadays organizations are operating via emails and even though efficiency and effectiveness of emails are high, there is still need for implementation improvement (Sikula – Dodds – Sikula 2012: 8). Investigators were concerned and annoyed about enormous amount of email communication from CRO representatives that hindered their ability to focus on the relevant information and to notice important messages. Based on the results of this research need for implementation improving in emails in this context is essential in aspects of cooperation and reliable clinical trial data. Although absolute rules for email communication are not available, implementation of email etiquette presented by Sikula et al (2012) should be considered. The most important thing is to send email only to those who need to know of its content. Based on description of investigators, emails are sent to everyone and sender is forwarding responsibility of importance evaluation to receiver. In the initiation phase of the clinical trial, discussion about proper email procedures tailored for the site could improve cooperation and ensure that important and relevant messages are acknowledged at clinical trial site. Also indicating in subject line what the email is about and if the information

is important and critical to operations and limited length of email message are crucial (Sikula et al 2012).

In the results of Smed and Getz (2013) research lack of systematic feedback collection was noticed. The results of this Master´s Thesis support this finding. Lack of regular feedback collection prevents development of processes based on lessons learned from the prior experiences. Mixed communication process where investigators and other site personnel are communicating with many different representatives from CRO and sponsor organization hinder the knowledge flow as the representatives may not be aware of the information other representatives are giving to and gaining from the site. Investigators reported failures in internal and interorganizational communication flow in and between CROs and sponsors. Failures restraining feedback utilization in a process development were also reported by Azoulay et al (2010). Although sponsors wanted to get feedback from the CROs, information was filtered before it reached applicable persons. There are lots of simple, easy to use feedback collection tools available and implementation of this kind of tools should be taken into consideration for ongoing feedback collection in clinical trial operations.

6.3 Trustworthiness

Usage of classic evaluation criteria in qualitative research has several problems. Therefore classical reliability and validity was substituted originally by Lincoln and Guba on 1985 with concept of trustworthiness and it is presented in book of Eriksson and Kovalainen (2008: 294). Concept includes four aspects; credibility, transferability, dependability and conformability. I am using concept of trustworthiness in evaluation of this research.

Dependability means responsibility of researcher to prove that process of research has been logical, traceable and documented (Eriksson – Kovalainen 2008: 294). I have described sampling, data collection and analysis process in details in chapter 4. Size of sample was only six persons. Group of interviewees was heterogeneous. They represented different therapeutic areas, were from different towns, clinics and hospitals and most of them had experience on clinical trial conduction in different environments in private and public health care organizations. The biggest health care organization conducting clinical trials, Hospital District of Helsinki and Uusimaa was left outside from this research due to complicated processes of organization. Including this hospital dis-

trict would have increased credibility of this research. It would have been interesting to hear if experiences were still similar. After six interviews in other parts of Finland, saturation was reached and no more interviews were expected to provide new information to research topic.

In-depth interview as a data collection method was chosen due to only few prior research concerning phenomenon were available. It would have been too leading to choose themes of interview in forehand. To succeed in interview it is recommended that interviewees are aware at least of the subject of the interview before the interview (Tuomi – Sarajärvi 2013: 73). In an interview request letter to investigators I gave investigators information about aim and purpose of the research and data collection method and also in the beginning of the interview I repeated the information. During one of the interviews I sensed that interviewee was expecting more specific questions from researcher. In that interview it was more difficult not to lead conversation to certain topics. Other interviewees had evidently recalled experiences related to CRO cooperation prior to interview as they spoke more spontaneously about the topic during the interview. One of the interviewees was slightly uncomfortable with recording in the beginning of the interview but was relaxed eventually. Despite of these experiences in my evaluation processes of the research were appropriate and successful.

In evaluation of credibility researcher´s familiarity with research topic and ability to interpret collected data are under focus (Eriksson – Kovalainen 2008: 294). I have eight years' experience in field of clinical trials as a CRA. I have worked in CRO and at sponsor so I was already acquainted with the context when I started my research. During research process I was on fulltime study leave, so I was able to take distance to CRA´s work. I assume this was the best solution as I was able to make a research as an outsider but still had knowledge of context including context specific phrases, roles and responsibilities. During analysis process I often thought that it would have been difficult for a total outsider to understand meanings of some wordings interviewees used, but for me abbreviations and metaphors were understandable. At the end of every interview I asked permission to contact interviewees afterwards if I had some questions concerning content of interview. All the interviewees gave permission, but I did not feel the need to ask any further clarifications during analysis process.

Prior to interviews, I considered if former work relationship with most of the interviewees would have an influence on the results. After interviews I evaluated former rela-

tionship to have more benefits than barriers in the final results. Interviewees had trust on me from the beginning of the interview so they were able to share their true experiences about the research topic. I did not feel that they were uncomfortable for example in revealing negative experiences concerning CRAs because of my background. I tried to express my gratitude towards all kinds of experiences and valued their opinions without need of criticising. Interview with interviewee I had not former relationship with did not deviate from the other interviews and that supported my evaluation on credibility.

Conformability refers to idea that data and interpretations are truthful (Eriksson - Kovalainen 2008: 294). During analysis process I really focused on the idea, that subcategories and categories were describing the original content of the interviews and experiences investigators shared. Before I started to do the reduction of data, I listened to the original recordings and read transcriptions several times, so collected data was familiar to me. I also went back to original data several times during analysis process to ensure analysis was interpreting original data. In chapter 6 I have included some quotations to result presentation so readers may also evaluate that data and interpretations are truthful and not just imagination.

Trustworthiness is also evaluated through transferability. Are there connections between this research and previous research results and also if same kind of similarity could be found in other research contexts. (Eriksson – Kovalainen 2008: 294.) Cooperation occurs in many contexts and cooperation has always some context related elements. Results of this research support previous researches made in clinical trial field and about cooperation as discussed in chapters 6.1 and 6.2.

The purpose of the qualitative research is not to make statistical generalization. Purpose is to describe and give theoretically sensible construction for phenomenon. (Tuomi – Sarajärvi 2013: 85) Construction of the cooperation between investigators and CROs described in the results of this research is based on experiences of experienced investigators. In the interviews I did not define any time period for the experiences. Investigators were able to share experiences during their whole career in clinical trial field. In my specifying questions during interview I did not ask them to estimate when experiences they described have happened. This may have effected on the results so that all of the experiences may not describe the present situation.

Other limitation is also connected to interviewees and selection criteria; investigators were very experienced in conducting clinical trials. Results are therefore describing experiences of experienced investigators and generalization to all investigators is not appropriate. As many investigators indicated some of the changes in clinical trial field like decrease in amount of monitoring visits or decrease in face-to-face trainings were not causing problems to experienced investigators but might do that for inexperienced investigators. In future research experiences of inexperienced investigators should be also studied to get wider construction of the phenomenon.

6.4 Ethical Considerations

Commitment to ethicality should guide the whole research process and is linked to credibility and trustworthy of the research (Tuomi – Sarajärvi 2013: 127). Personal integrity of researcher may be evaluated from logic of the research process (Eriksson – Kovalainen 2008: 72). In this Master´s Thesis I have described research process in details in chapter 4 so the reader is also able to evaluate process and logic in it from ethical perspective.

Anonymity and privacy of research participants should be the first priority for the researcher and research should not bring any harm to participants (Eriksson – Kovalainen 2008: 72-74). I have kept identities of interviewees only in my knowledge. Names and places of interviews are documented in signed informed consents and those are kept in lockable storage with no access to unauthorized persons. Informed consents are stored for one year after research report is finalized and informed consents are destroyed appropriately.

Permissions for interviews were also asked from institutes and companies in which investigators were working. Identities of investigators I sent a request for interview were not revealed to companies or organizations. Companies and organizations are not mentioned in this research report except hospital district of Pirkanmaa as it was required in permission to research. Investigator interviewed in that hospital district was informed about requirement prior interview started and investigator did not feel it harming. Investigators and my colleagues recommended investigators for the interviews. I did not reveal to referees if I had contacted recommended investigators or if they had agreed to participate in research.

Voluntary participation is an important ethical principle (Eriksson – Kovalainen 2008: 70-71). Primary contact with investigators was via email when I asked their willingness to participate in this research. Investigators were able to choose if they responded or not. I did not repeat my request, I did not want to put pressure on investigators that had not responded to my enquiry. Those who agreed to participate had an opportunity to ask me about the research before they signed the informed consent. They were also informed to have possibility to withdraw from the research at any time before research report is final.

After I had written first version of result chapter (chapter 6), I sent selected quotations to relevant interviewees with short description about the result I have linked quotations to via email, so they were able to comment before quotations were published in final version of Master´s Thesis. Some strongly dialectical wordings were changed to more general language on a request of interviewees, but original meaning or content of quotations were not changed. This procedure increased both anonymity and self-determination of research participants, but did not have an effect on research results.

7 Conclusions

The purpose of this research was to increase knowledge about cooperation between investigators and contract research organizations in the field of clinical trials by describing how investigators are experiencing cooperation. The objective was to find out what kind of positive and negative experiences investigators have in cooperation with CROs. There are only few prior researches available about investigators´ experiences and this research increases knowledge in this area. Results bring up elements that make cooperation positive experience and also reveal development needs in cooperation between investigators and CROs.

There is a need for discussion and training inside CRO about working methods with trial site personnel. Everyone working in the field of clinical trials should have the same goal; to ensure that patients have access to novel, properly developed and researched treatments also in the future. Clinical trials should be seen as a cooperative project where every actor has their own roles, tasks and responsibilities, but the goal is the same and it is achieved only by successful cooperation. In this research only investiga-

tors experiences were collected. To get overall picture about cooperation between investigators and CROs, also experiences of CRO representatives should be studied.

As pointed out in chapter 6.3, results of this research reveals experiences of experienced investigators. Interviewed investigators were familiar with clinical trial procedures and need for guidance and training for example is different than it is for inexperienced investigators. Results might have been different if experiences of inexperienced investigators were researched or would they? This is the second suggestion for further research.

Based on the results of this research I already made some suggestions in chapter 6 about development needs with email etiquette and collecting feedback. There is also need to evaluate processes inside CROs and between sponsor and CRO to gain more streamlined and also more flexible processes for clinical trial operations. Proper processes save time and money and can provide a competitive advantage for the firms in the high cost and long-lasting drug development process.

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Letter to Investigators

Hyvä Tutkijalääkäri,

Kliinisten lääketutkimusten ulkoistaminen tutkimuspalveluyrityksille (CRO) on 1980-luvulta alkaen ollut ja on edelleen kasvava suuntaus lääketeollisuuden parissa. Lääkeyhtiöiden ja tutkimuspalveluyritysten välistä yhteistyötä seurataan erityisesti alan konsulttiyritysten toimesta vuosittain, mutta tutkijalääkäreiden ja tutkimuspalveluyritysten välisestä yhteistyöstä on vain niukasti tutkittua tietoa saatavilla.

Teen Metropolia Ammattikorkeakoulussa Helsingissä ylempiin ammattikorkeakouluopintoihin (Master´s Degree Programme in Health Business Management) liittyvää opinnäytetyötä tutkijalääkäreiden ja tutkimuspalveluyritysten välisestä yhteistyöstä. Tutkimuksen tarkoituksena on saada tietoa tutkijalääkäreiden kokemuksista CRO-yhteistyöstä. Tavoitteena on kuvata millaisia myönteisiä ja kielteisiä kokemuksia tutkijalääkäreillä on yhteistyöstä tutkimuspalveluyritysten kanssa Suomessa. Tutkimuksen tuloksia voidaan hyödyntää tutkimuspalveluyritysten toiminnan sekä eri sektoreita edustavien terveydenhuoltoalan organisaatioiden kanssa tehtävän yhteistyön kehittämiseen. Päättötyötä ohjaa yliopettaja, FT Eija Metsälä (osoite: Metropolia Ammattikorkeakoulu, Mannerheimintie 172, Helsinki ja puhelinnumero: 050 3478177).

Pyydän Teitä osallistumaan tutkimukseen, koska joko omien tutkimuskoordinaattorina (CRA) toimimieni vuosien tai kollegoiltani tai toisilta tutkijalääkäreiltä saamieni suositusten mukaan Teillä on kokemusta tutkijalääkärinä toimimisesta kliinisissä lääketutkimuksissa sekä kokemusta yhteistyöstä CRO:n kanssa. Tutkimukseen osallistuminen on täysin vapaaehtoista ja voitte halutessanne perua osallistumisenne missä vaiheessa tahansa tutkimuksen aikana. Henkilöllisyytenne ja toimipaikkanne eivät tule muiden kuin minun tietooni. Ainoat tutkimusta varten kerättävät taustatiedot ovat sukupuolenne ja kokemuksenne kliinisistä lääketutkimuksista vuosina.

Mikäli päätätte osallistua tutkimukseen, pyydän Teitä ottamaan yhteyttä minuun puhelimitse tai sähköpostitse (yhteystiedot alla). Tutkimusaineiston keruu tapahtuu noin tunnin kestävässä henkilökohtaisessa haastattelussa. Haastattelu nauhoitetaan ja nauhoitukset sekä niistä kirjoitetut kirjalliset versiot säilytetään luottamuksellisesti salasanan takana ja tuhotaan vuoden kuluttua opinnäytetyön julkaisemisesta. Haastattelut on tarkoitus järjestää tammi- ja helmikuun 2015 aikana.

Ystävällisin terveisin

Jaana Hynynen
Puhelin: 040 5243886
Sähköposti: jaana.hynynen@metropolia.fi

Structure of Interviews

Guiding interview questions:

- In case you are asked to participate as an investigator to clinical trial that has feasible protocol and contract research organization is managing the trial, what are your thoughts about cooperation with CRO?
- What kind of positive experiences do you have about cooperation with CRO?
- What kind of positive experiences do you have about cooperation with CRO?

Haastattelu runko:

- Jos saatte pyynnön osallistua tutkijalääkärinä kliiniseen lääketutkimukseen, jonka tutkimussuunnitelma on toteuttamiskelpoinen ja tutkimusta hoitaa tutkimuspalveluyritys, millaisia ajatuksia yhteistyö tutkimuspalveluyrityksen kanssa herättää?
- Millaisia myönteisiä kokemuksia teillä on yhteistyöstä CRO:n kanssa?
- Millaisia kielteisiä kokemuksia teillä on yhteistyöstä CRO:n kanssa?

INFORMED CONSENT FORM

TUTKITTAVAN SUOSTUMUS

Cooperation between Investigators and CROs – Investigators´ Experiences in Clinical Trials in Finland

Minua on pyydetty osallistumaan yllämainittuun tieteelliseen tutkimukseen ja olen saanut sekä kirjallista että suullista tietoa tutkimuksesta ja mahdollisuuden esittää siitä tutkijalle kysymyksiä.

Ymmärrän, että tutkimukseen osallistuminen on vapaaehtoista ja että minulla on oikeus kieltäytyä siitä sekä perua suostumukseni milloin tahansa syytä ilmoittamatta. Ymmärrän myös, että tiedot käsitellään luottamuksellisesti.

Suostun osallistumaan tutkimukseen: **Suostumuksen vastaanottaja:**

_____	_____
tutkittavan allekirjoitus	tutkijan allekirjoitus
_____	_____
nimenselvennys	nimenselvennys
_____	_____
aika ja paikka	aika ja paikka