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Implementation of Clinical Trials Regulation EU no 536/2014 to Clinical Operations -organisation's working procedures

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New Clinical Trials Regulation EU no 536/2014 (EU CTR) will be implemented fully in European Union in January 2022. New regulation will introduce major changes in a way clinical trials are conducted in EU area. Organisations conducting clinical trials need to be prepared for the changes the new regulation will bring.

The purpose of this qualitative study was to support implementation of Clinical Trial Regulation to Company X operational procedures. The objective was to find out how should Company X Clinical Operations Finland -organisation amend their working procedures to meet the new regulation requirements. Focus was identified to be in start-up process of the trial.

This study used PDCA (Plan, Do, Check, Act) approach as this model is used to embedding the continuous improvement in organisations. Purposive data sampling was used. Data for this study was collected by interviewing five experts on trial start-up process at Company X. Data collected was analyzed by using deductive content analysis.

As expected, results showed that there are operational procedures that are impacted when new regulation enters into force. Certain tasks currently done will be diminished at country level as clinical trial submission will be done centrally for all participating EU countries. Some tasks will remain the same but new regulation is setting stricter timelines while some tasks are not affected at all.

The results lead to the conclusion that there are certain working procedures that should be improved to better meet the requirements from new regulation. These procedures rely mostly on submission document preparation.

Keywords	clinical trial, regulation, study start-up, implementation, working procedure

Contents

List of Abbreviations

CSL	Country Study Lead
CRA	Clinical Research Associate
CTA	Clinical Trial Assistant
CTIS	Clinical Trials Information System
CTPS	Clinical Trial Planning System
CTR	Clinical Trial Regulation
CV	Curriculum Vitae
EMA	European Medicines Agency
EU	European Union
FIMEA	Finnish Medicines Agency
FPFV	First Patient First Visit
GCP	Good Clinical Practice
IMPACT	International Management Package for the Administration of Clinical Trials
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reactions
TUKIJA	National committee on Medical Research Ethics

1 Introduction

The way clinical trials are conducted in the European Union (EU) will undergo a major change when the new Clinical Trial Regulation (CTR) is implemented. The goal of the new regulation is to harmonize the way clinical trials are conducted in EU countries. Instead of single country approval process there will be streamlined application procedure via EU portal. This means that all the EU countries participating the trial will submit their regulatory and ethics committee submission documents at the same time with single application. Submission documents will be divided to two parts. Part I dossier will contain general information on the trial (such as study protocol, information related to investigational product etc.). Part II dossier will include information regarding sites participating the trial and documents provided to the study subjects (patients participating the trial). In other word Part II dossier consists of country specific submission documents from participating country. (Clinical Trial Regulation. European Medicines Agency.)

Clinical Trial Regulation was entered into force in 2014. However full implementation has not yet happened as Clinical Trials Information System (CTIS), which is the portal used for communication between the study sponsors and authorities, is not ready. At the moment system enhancement is ongoing and agile development is ongoing. (Clinical Trial Regulation. European Medicines Agency.) New Clinical Trial Regulation will be implemented to Finnish legislation. New Act is currently under preparation and first opinion round ended 15 Sep 2017. (Lääketieteellisiä tutkimuksia koskeva lakiehdotus lausunnolle. 2017.) Second opinion round was completed in 2018 and Act was introduced to parliament in March 2020. Approval is still pending as more information on certain topics has been requested from different committees. Information on targeted approval date is not published. (Asian käsittelytiedot HE 18/2020 vp. 2020.)

Changes implemented with the new regulation requires changes in the operational aspects at the companies conducting clinical trials. The setting of this Master thesis is one life science company acting in the field of clinical trials. In this Master thesis we call it Company X. At Company X internal “EU Clinical Trial Regulation Implementation Project” ensures company’s overall readiness for the implementation. Project provides the framework by which countries provide their Part II documents for clinical trial - submission in the EU. Country readiness is not in scope of the project. Ensuring that

Company X country organisations are ready and have local processes in place is the responsibility of Clinical Operations –organisation within the respective countries.

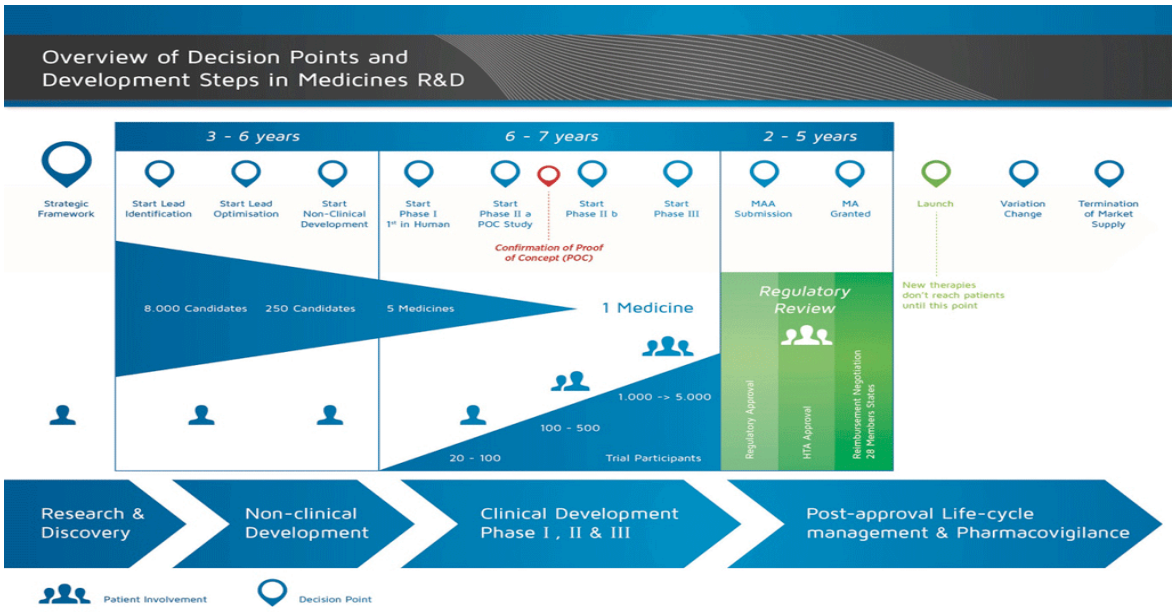
Clinical Operations Finland –organisation at Company X is responsible for clinical trials conducted in Finland. Responsibilities include obtaining the necessary approvals at country level. Currently Finland is considered as one of the fastest countries within the EU in start-up activities (including Regulatory Authority and Ethics Committee approval). This advantage will be partly lost when all the EU countries will submit and receive their approvals at the same time. Timelines for the submissions under the new regulation will be very tight and Clinical Operations Finland –organisation needs to ensure that it is able to keep the timelines and remains the preferred “first in line” - country for the upcoming trials. Purpose of this research is to support the implementation of Clinical Trial Regulation to organisation's operational procedures. Aim is to develop a recommendation on how they should organize their procedures and operations to ensure new regulation requirements are met.

2 Theoretical background

2.1 Clinical trial

Drug development is time consuming and expensive process. It takes approximately 10-12 years to get the new drug on the market. As soon as new potential compound is identified there are many pre-clinical testing done and if compound is proofed to be safe and have an effect, testing with the humans may begin. This is the point when clinical trials start.

According to Guideline for Good Clinical Practice E6(R2) (2017) = GCP definition for Clinical trial 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. The terms clinical trial and clinical study are synonymous." In other words, clinical trials are research in which new medication effects on humans are investigated.



Picture 1. Overview of the medicines development process (Making a medicine. Step 1: Pre-discovery. 2015.) EUPATI: Copyrights licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Clinical development is divided into three phases. During the phase I there are small number of study participants and the purpose is to proof safety and dosage of the new medicine. During the phase 2 efficacy and side effects are investigated and if the new medicine is found to be safe and beneficial, it will move to phase 3. Phase 3 trials are large, involving even thousands of patients. Purpose of this phase is to verify efficacy and monitoring the adverse reactions of a new medication. (Step 3: Clinical Research. 2018.) Clinical trials are usually multinational global studies where same study protocol is initiated and followed in many countries simultaneously.

2.2 European Medicines Agency (EMA)

The European Medicines Agency (EMA) was founded in 1995 to ensure efficacy and safety of human and veterinary medicines across Europe. Executive Director is the legal representative of the agency. EMA is governed by Management Board with 36 members. Management board has representative from each EU member state. In addition, there are representative(s) from European Commission, European Parliament plus patients', doctors', and veterinarians' organisations. Management Board is responsible for budgetary and planning matters, the appointment of Executive Director

and monitoring of Agency's performance. In addition to Agency staff that is supporting the Executive Director in fulfilling his responsibilities, EMA has scientific committees responsible for evaluating the medicines throughout the whole lifecycle of the product. There are also other working parties and groups supporting the scientific issues as a consultant. (Who we are. 2017.)

EMA oversees the scientific evaluation, supervision, and safety monitoring of medicinal products in European Union (EU). The Agency is facilitating the development and access to medicines within EU area to enable timely patient access to new medicines. EMA is responsible for evaluating the applications for marketing authorisation in Europe. Pharmaceutical companies are submitting a single marketing authorisation application to EMA and once it is approved, a centralised marketing authorisation is valid in all EU member states. EMA is also monitoring the safety of the medicines authorised in the EU across the whole lifecycle of the medicine. Also, important task for the Agency is to provide information about the medicines to healthcare professionals and patients. (What we do. EMA European Medicines Agency.)

2.3 Clinical Trial Regulation EU no. 536/2014

EU Clinical Trial Regulation has been created to protect rights, safety, and wellbeing of trial subjects. Aim is also to ensure that results of the trials are credible. Marketing authorization for new medicines within EU area necessitates that all clinical trials included in the authorization application fulfils the requirements of regulation. (Clinical trials in human medicines. European Medicines Agency.)

European Clinical Trial Regulation 536/2014 entered into the force 16 Jun 2014. Although the full implementation timeline is dependent on EU clinical trials portal and database which is still under development. (Clinical trials. European Commission.) Current go-alive date was released to 31 Jan 2022 on 12 Mar 2021. This should give all the relevant parties (clinical trial sponsors, authorities, and other organisations) reasonable time to prepare for implementation in its full. At the same time EMA published an extensive training program for supporting the implementation. (EMA Management Board - highlights of March 2021 meeting.)

The main purpose of the regulation and the portal is to harmonize the rules for conducting clinical trials throughout the EU. Based on regulation only single submission

is needed for gaining authorisation approval of clinical trial in EU area. All information in the data base is publicly accessible so it provides transparency on clinical trials data. There are certain criteria for limited accessibility, such as protection of commercially confidential information, personal data etc. In addition to transparency, regulation simplifies the rules for safety reporting by providing possibility to submit safety related data such as safety reports and SUSARs (suspected unexpected serious adverse reactions) through database. (Clinical trials. European Commission.)

New regulation introduces major changes to the processes and procedures in conducting the clinical trials in EU. Objective of the new CTR is to make EU area attractive for the research. This will be done by fostering the innovation, making trial application process simpler and faster without risking the safety and rights of the subjects participating the trials. Regulation covers interventional clinical trials with medicinal products for human use and introduces the new category of low-interventional trials. (Marcal 2019.) Goal is to make start of the trials easier especially in the cases when trial is planned to be conducted in many EU countries. New regulation will also harmonize the processes throughout the member states and reduce conflicting interpretations and mode of operations. (Konttinen & Närhi 2017.)

2.4 Finnish legislation concerning clinical trials

Finnish Medicines Agency (Fimea) is responsible for supervising and developing the pharmaceutical sector in Finland. Mission of Fimea is to ensure that medicines marketed and used in Finland meet the requirements for efficacy, safety, and quality. Fimea is operating as a part of the European Medicines Regulatory Network. Fimea is the national competent supervisory authority for clinical trials on medicinal products and Fimea must be notified of interventional clinical trials conducted in Finland. (Tietoa Fimeasta. Lääkealan turvallisuus- ja kehittämiskeskus Fimea.)

Fimea has published an Administrative regulation 8/2019 about Clinical Trials on medicinal products based on Medicines Act and Act on Medical Research. Administrative regulation to implement European Parliament Directive 2001/20/EC and European Commission Directive 2005/28/EC was published in 2012 and updated version was released in 2019 with the main change on submitting all the material related to clinical trials via electronic portal. Administrative regulation is providing detailed instructions on how the clinical trial is submitted to Fimea and what are the

requirements and documents to be used in submission. It also defines what kind of follow up information needs to be submitted during the trial conduct. (Määräys, Kliiniset lääketutkimukset 8/2019.)

Clinical trials in Finland are governed by the Act on Medical Research (488/1999). Finnish legislation in force must be followed when clinical trial is conducted in Finland. Administrative regulation defines that all the following needs to be taken into account:

- Act on Medical Research (488/1999) and Decree on Medical Research (986/1999) and the subsidiary regulations issued in pursuance thereof
- Medicines Act (395/1987)
- Act on Patient Status and Rights (785/1992)
- Data Protection Act (1050/2018)
- General Data Protection Regulation (2016/679)
- Gene Technology Act (377/1995) and Decree (928/2004)
- Patient Injuries Act (585/1986)
- Act on the Medical Use of Human Organs and Tissues (101/2001)

In addition, ICH E6 (R2) Good Clinical Practice (international ethical and scientific quality standard for trials involving human subjects) as well as World Medical Association's Declaration of Helsinki (ethical principles for medical research involving human subjects) must be followed. (Määräys, Kliiniset lääketutkimukset 8/2019.)

Clinical Trial Regulation EU no. 536/2014 will be implemented to the Finnish legislation. Government of Finland has provided a proposal of new act on clinical trials (HE 18/2020) to parliament on 12 Mar 2020. Procedure is still pending in parliament and some additional statements has been requested from Social Affairs and Health Committee (situation 21 Mar 2021). New act will enter into force when Clinical Trial Regulation is implemented fully. (Asian käsittelytiedot HE 18/2020 vp. 2020.)

2.5 Start-up activities in Clinical Trials

Before the clinical trial can start recruiting subjects into the trial, there are many steps that need to be completed by the trial sponsor. At Company X Country Study Lead (CSL) is responsible for country clinical trial activities for assigned trial. Following

picture presents the main categories of start-up activities for CSL. All these will be explained in more detail in the following paragraphs.

Picture 2. Start-up activities for Country Study Lead at Company X

2.5.1 Regulatory Authority submission

Before any clinical trial related activities can be conducted at the study site, a notification to Regulatory Authority, Fimea (Finnish Medicines Agency) needs to be submitted. Notification is done by submitting the Clinical Trial Application Form that is available on the EMA EudraCT database. There are certain documents that need to be included in the submission package to the authorities and these are specified in Fimea's Administrative Regulation 8/2019 chapter 6: "Documents to be appended to the notification". In case Fimea does not approve the conduct of the trial, it will ask further clarification in writing within 60 days from commence of the evaluation of the trial. If clarification has not been requested within 60 days, trial can be started. (Määräys, Kliiniset lääketutkimukset 8/2019.)

Regulatory department is responsible for Regulatory Authorities (Fimea in Finland) communication and submissions at Company X in Finland. Submission for the clinical trial is done in close collaboration with the Country Study Lead (CSL). CSL is

responsible for providing the country specific documents required by Fimea to Regulatory department for submission.

2.5.2 Ethics Committee submission

Favorable opinion from the ethics committee needs to be obtained beforehand for the trial. In Finland TUKIJA (National committee on Medical Research Ethics) is responsible for issuing opinions on the ethics of clinical trials. It can also delegate the task to the regional ethics committee. Ethics committee needs to issue opinion within 60 days of arrival of acceptable application. Ethics committee may request further clarification once and handling of application will continue once clarifications are received. (Valtakunnallisen lääketieteellisen tutkimuseettisen toimikunnan toimintaohje. 2021.)

It is also specifically defined by TUKIJA in the operating procedures guideline "Valtakunnallisen lääketieteellisen tutkimuseettisen toimikunnan toimintaohje" which documents, and statements need to be submitted with the application. All patient facing material used for the study needs to be approved by the ethics committee. At Company X Country Study Lead (CSL) is responsible for preparation and submission of application for an assigned trial.

2.5.3 Budget and Contracts negotiation

Country Study Lead (CSL) is accountable for planning, managing, and tracking local study budget. Before trial can start at the study site, contract needs to be finalized. CSL is responsible for contract and budget negotiations with the study sites and other local vendors with the support of Contract Associate.

2.5.4 System Updates

There are company internal electronic systems that needs to be updated as the progression of the trial is followed through these systems. One important system to be updated is Impact (International Management Package for the Administration of Clinical Trials) as this is the system for planning and managing the clinical trials internally. Systems are used to follow up the study status and study events throughout the trial.

2.5.5 Investigator Meeting and Site Initiation

Before the trial can start there are many tasks that needs to be completed at the study site (e.g. hospital or private health care provider that is conducting the trial). It needs to be ensured and documented that the site staff performing the trial are adequately trained for the study. There needs to be certain essential documents in place at site. Essential documents needed for a study are defined in Good Clinical Practice (GCP).

Usually, a big global investigator meeting is held before the study starts to train the study sites for trial. Coordination of the site staff meeting arrangements is done by the country study team. In addition to Investigator meeting, sites are visited before the permission to recruit patients is given. These visits are called as Site Initiation Visits. Purpose for this visit is to ensure that all the site staff is understanding the study protocol and its requirements, operational steps are in place and everyone is properly trained based on their role and responsibilities in a study. Site Initiation Visit is usually conducted by CRA (Clinical Research Associate) responsible for the site.

2.6 The changes Clinical Trial Regulation EU no. 536/2014 cause for procedures in study start-up in Finland

New Clinical Trial Regulation requirements will be implemented to the Finnish legislation by introducing the new Act for Clinical Trials. The new act will bring changes compared to the current procedures. In the future Fimea will be the responsible for providing national approval for the study. Evaluation will be done in cooperation with National ethics committee Tukija, which will be the only ethics committee to evaluate clinical trial applications in Finland (currently this is done by the national ethics committee or delegated to regional ethics committee). Submission of the documents will be done through EU Clinical Trials Information System (CTIS). (Hallituksen esitys HE 18/2020 vp. 2020.)

This chapter is not covering all the changes that new regulation and act will implement but only the ones that are affecting the study start-up activities in relation to CSL work. This will be done by main categories identified for start-up activities CSLs are responsible for.

2.6.1 Regulatory and Ethics committee submission

Major impact of the regulation will be the application process change from country internal submissions to one single submission covering all EU member states. This means in practice that submission will be done via EU portal (CTIS system) and all member state authorities will have access to the system. Submission assessment will be coordinated between the member states and in the end, one single decision will be given. (Marcal 2019.) Assessment process will be partly conducted at the EU level and partly locally in participating member state. Assessment of the trial will be done in two parts. Part I, scientific part, which relates to current Regulatory Authority submission, is submitted to EU portal once and assessment of the dossier is coordinated between the participating member states and one single decision is given that covers all the participating countries within EU. (Konttinen & Närhi 2017.)

Part II dossier relates to current Ethics committee submission and is assessed in the concerned member state. Submission of the documents for Part II dossier is through CTIS portal simultaneously with Part I dossier or after the Part I dossier approval is received. Part II dossier consists of ethical aspects and local requirements. Part II documents are assessed in local ethics committee and there will be one single decision per member state. (Tenti & Simonetti & Bochiccio & Martinelli 2018.) There are defined timelines for each phase: validation, assessment, query responses and decision. Final timeline for decision depends on what type of medication is in use and if the maximum assessment timeframe is used. Timeframe for providing answers for queries received is maximum 12 days. (Konttinen & Närhi 2017.)

2.6.2 Study documents

Local Finland requirements for Part II submission documents are not yet known at the time of finalizing this research. Although it has been said that Finland will follow the EU requirements and does not add any additional requirements. Part II dossier in general includes:

- Informed consent form and subject information leaflet
- Compensation arrangements
- Suitability of investigators and facilities
- Proof of insurance or indemnification

- Data protection rules
- Proof of fee payments

(Kirk 2017).

Documents can be submitted in English (as previously) for evaluation in Finland. Patient facing material needs to be submitted in Finnish or Swedish. (Hallituksen esitys HE 18/2020 vp. 2020.)

As in the future there will be only one national ethics committee that will evaluate the clinical trials in Finland, it harmonizes the process. EMA has published the templates for Part 2 dossier submission and stated that these templated should be followed when regulation transitional period is ended. Member states are advised to implement them as such or adapt them according to national requirements if applicable. Sponsors are instructed to follow the national guidelines from member state when submitting an application. (EudraLex - Volume 10 - Clinical Trials Guidelines.)

There is currently a template created by Tukija that has been used for Informed consent form and subject information leaflet in clinical trials. Template is published in Tukija's web pages and current version is "Malliasiakirja_tiedote kliinisestä lääketutkimuksesta ja suostumus_29.5.2018.docx". According to the template, the form can be maximum of 5 pages long and it contains a lot of mandatory text defined in the template. However, it allows to create a separate document to provide more instructions and/or clarifications on procedures done during the trial. (Tutkittavalle annettava tiedote kliinisestä lääketutkimuksesta ja suostumusmalli. 2018.) Experience has shown that such a document is always created to provide a clear and necessary information to study participants on the trial. EMA has not provided any template for informed consent as it must be according to local requirements in each member state. Handling of personal data in clinical trials will be based on law instead of consent. By this change it will be ensured that already collected data can be used in analysis even the study participant withdraws her/his consent. This is needed to secure the reliability of a trial and ensuring that drugs to be on the market are safe to use. (Hallituksen esitys HE 18/2020 vp. 2020.)

In Finland there is a requirement by the law to nominate National Researcher in charge for each trial who is responsible for overall conduct of the trial in a country.

Requirement will be removed from the law and instead of this, a study sponsor holds the overall responsibility of study conduct. Principal Investigator at each study site remains responsible for fulfilling all the requirements at respected site. (Hallituksen esitys HE 18/2020 vp. 2020.)

Digitalization is also taken into consideration when preparing the new Act. New act will enable the usage of digital mode of operations when possible in relation to ethics considerations. This could include for example electronic Patient Information and Informed consent form. (Hallituksen esitys HE 18/2020 vp. 2020.)

2.6.3 Other activities

EU CTR and a new Act does not affect directly to the CSL tasks related to study budget and investigator site contracts, electronic systems or study site start-up activities. As these are company internal procedures, there may be some changes in SOPs, instructions, procedures, responsibilities, or systems related to these tasks. Site start-up activities will remain as a responsibility of CRA but CSL will be heavily involved in site initiation activities.

2.7 EU Clinical Trial Regulation Implementation planning

Deloitte has published an article in 2018 for industry to advise how to build a successful program around EU Clinical Trial Regulation. According to this article organisations should prepare for the implementation of CTR not only by focusing on readiness of data landscape but also on Clinical Operations and Regulatory Affairs perspective. Deloitte has identified key operational processes at the company side that will be mostly affected by the regulation. Requirement for the companies is to enhance the existing processes and organisation to meet the needs of the regulation. (EU Clinical Trial Regulation, Building a successful programme. Deloitte 2018.)

There is no "one size fits all" approach for implementing the new regulation for the pharmaceutical companies as business models and operational landscape is different in every company. Deloitte has published a five steps approach for CTR implementation:

1. Identify the regulatory impact to the enterprise
As EU CTR implementation is affecting to whole lifecycle of a clinical trial, companies should perform a comprehensive impact assessment for the entire landscape. Assessment should include areas related to Processes (within an organisation and existing third party services), Organisation (organisational structure and people), Data (completeness, quality and provision of existing data and documents), Technology (landscape such as Clinical Trial Management - and Document Management Systems) and Time (deadlines for different processes).

2. Asses CTR gap and readiness
In order to understand the gap and readiness of an organisation, the detailed assessment of the current situation is needed by conducting interviews and analysing the existing data and documents.

3. Defining the CTR strategy and roadmap
Realistic roadmap harmonized with the overall strategy and vision ensures effective implementation. This should include grouping and prioritizing of activities, resource analysis and logical analysis.

4. Setup a CTR programme
By identifying all key stakeholders and involving them into process and culture change is ensuring smooth transition. Wide awareness and understanding ensures effective adoption, transformation, and support for the program.

5. Implement enterprise-wide transformation
Major impact for implementing a new CTR is changing the existing processes and procedures. In order to do this effectively, current operating procedures and other documents guiding the work needs to be updated and/or created to meet the new regulation requirements. Enterprise wide governance of processes and procedures ensures consistent adoption of the change.

(EU Clinical Trial Regulation, Building a successful programme. Deloitte 2018.)

3 Purpose, aim and research objectives

Purpose

To support implementation of Clinical Trial Regulation to Company X's Clinical Operations Finland -organisation operational procedures.

Aim

To develop a recommendation how Clinical Operations –organisation in Finland should organize their working procedures and operations to ensure new regulation (especially Part II dossier) requirements and fast start-up timelines in clinical trials are met.

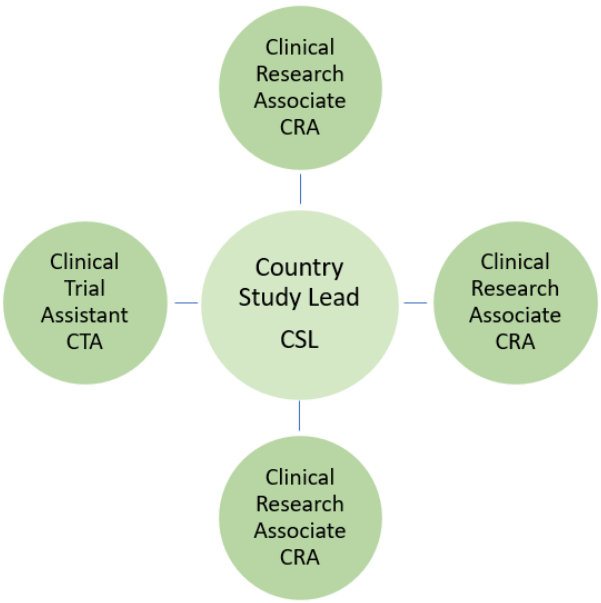
Research objective

How should Clinical Operations Finland -organisation amend their working procedures to meet the new regulation requirements?

4 Setting

Company X is a life science company that operates globally. Clinical Operations Finland –organisation at Company X is responsible for managing clinical trials conducted in Finland. Vast majority of the trials are global trials, meaning that the same trial is ongoing in many countries worldwide simultaneously. There are global SOPs (Standard Operating Procedures) that guides the internal procedures in different trial phases. SOPs are ensuring that processes are same despite of location. Country Clinical Operations organisation is responsible for following these global SOPs and implementing and following the local instructions / SOPs based on local requirements.

Country study teams are managing the trials and consist of a Country Study Lead (CSL) who is responsible for overall trial conduct in Finland, Clinical Research Associate(s) (CRA) who are responsible for dedicated study site(s) and a Clinical Trial Assistant (CTA) who is supporting the team on administrative tasks. Country study team is actively in contact with global study management team (responsible for a trial management globally).



Picture 3: Example of the country study team at Company X

Country Study Lead (CSL) is accountable and responsible for overall country clinical trial activities in assigned trial. CSL oversees overall progress (timelines, study subject enrollment, budget, quality etc.) from the very beginning of the trial to the archival phase. One of the main responsibilities is to ensure ethical, regulatory and SOP compliance. CSL is responsible for overseeing country start-up activities and contributes to completion of all necessary study documents for ethics and regulatory approval according to agreed timelines and ensuring all legal, regulatory and company internal requirements are met.

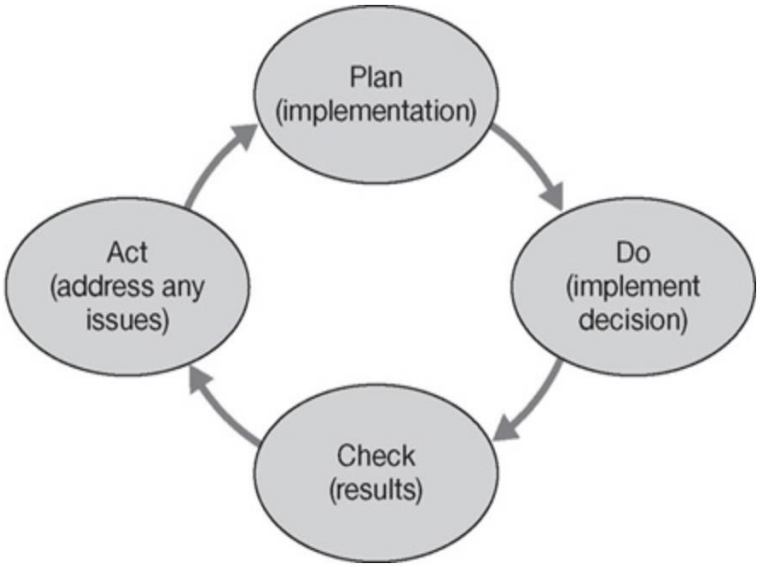
Regulatory department is responsible for Regulatory Authorities communication and submissions (Fimea in Finland). Submission for the clinical trial is done in close collaboration with the CSL.

5 Materials and Methodology

This section is presenting the methodology used to describe the research design, research setting, data collection and data analysis.

5.1 Research Design

This study is using PDCA (Plan, Do, Check, Act) cycle approach. PDCA is the model that is widely used as embedding the culture of continuous improvement in organisations. Model was introduced by Shewhart and further developed by Deming. Model has been said to be the fundamental concept for problem solving and making changes and improvements. Model consist of 4 stages:



Picture 4: PDCA Cycle (Grath 2015: Chapter 66.)

1. Plan

Plan is the stage where the problem is being identified and clarified. In this stage the potential for improvement is identified. At this stage the clear and detailed plan for implementation is created and “what” and “how” is defined. (Hesley 2017:102-105.)

To be able to create a plan for implementation in this research, topics and material for theoretical background were collected. Guidelines from European Medicines Agency (EMA) and information about implementing the regulation to Finnish legislation from different sources (Ministry of Social Affairs and Health, National Committee on Medical Research Ethics (TUKIJA), Finnish Medicines Agency (FIMEA) etc.) were reviewed to get a clear picture on how the processes will change in Finland when new Clinical Trial Regulation EU no. 536/2014 is fully implemented.

Planning is the phase when qualitative data is collected. In this research data was collected by interviewing the selected relevant employees to identify the current procedures for preparing the ethics committee submission package and other start-up activities (e.g. contracting, initiating the study sites). Basic principles and operating procedures were already known but assumption was that there are variations in practical work and how the working tasks are distributed among the team members. Five individuals were included in the interviews. Interviews were conducted in Finnish. Personal informed consent forms to use the data collected during the interviews were asked from the participants.

2. Do

Do stage is about conducting the planned actions to achieve the results. At this stage it is important to ensure that the implementation is following the plan and avoid rushing into action. (Hesley 2017:102-105.) At this stage data collected during the interview was analyzed. Purpose was to identify the need for changes and determine the procedures that need to be changed when the new regulation is in use: Current procedures vs. new regulation requirements.

3. Check

Check stage (also called study) is to confirm what has been identified during Do stage. At this stage it is important to ensure that the problem is solved and confirm that it was solved in the expected level. Important is also learning from the process. This was highlighted by the creators of this model as it is the learning that provides the long-term benefits to the organisation. (Hesley 2017:102-105.) For this research as soon as the need for changes were identified, the most relevant processes requiring attention were defined and proposal on how Clinical Operations -organisation in Finland should

organize their working procedures and operations to ensure new regulation requirements and fast start-up timelines in clinical trials are met was developed.

4. Act

Act is the final stage of the cycle. If the outcome of the previous stages was successful, the new process should be standardized and shared with others. If the results were not as expected, then the cycle should be reviewed. There should be an understanding of what went wrong in order to learn from mistake. (Hesley 2017:102-105.) For this research the identified processed for improvement during the check stage are presented. Final implementation of the suggested processes is left to the organisation to decide how to implement those in practice.

5.2 Sampling

Purposive sampling was used for this research. This sampling method was chosen as it was only appropriate method for getting reliable answers to research questions that requires special expertise on the subject. Selection criteria for participants was that they have performed site start-up activities at Company X and were working in that role at the time of interviews. All candidates who fulfilled these criteria were invited to participate. All the persons interviewed are experts in their field and have several years' experience working in clinical trials. Total of five persons volunteered and were interviewed for this research. As there were a limited number of potential respondents, anonymity was a challenge. Therefore, no background information was collected during the interviews. Interview was selected as a method to be used as no other method would provide such a detailed information about the processes.

5.3 Data Collection

Interviews were conducted as face-to-face semi-structured interview. Semi structured interview was selected as an interview method as it allows conversation to roam around the topic rather than sticking into very limiting questions. This method is providing insight into things that could not have been anticipated beforehand. It also allows in-depth discussion around the topic and clarifying questions when needed. (Adams 2015.) Themes to be discussed during the interview were taken from the main categories of start-up activities for CSL presented in picture 2. Interviews started with

the main question on the process and tasks within each theme followed by clarifying questions and questions on what is working well and what should be improved. Thematic interview guide used for this research is presented in attachment 3.

During the actual phase of data collection, the researcher identified, selected, and recruited the participants for interview. Inclusion criteria was to select the persons who are conducting and responsible for start-up activities and were willing to participate the interview. Researcher then set the interview schedule according to interviewees' availability by sending the meeting invitation letter. The researcher met the participants face to face in the meeting room and formal interview was conducted. In the beginning of interview researcher explained the participant the purpose and the aim of the interview and the research. Also, main themes of the interview were explained. Informed consent form was given and signed by the participant. Participants were encouraged to ask questions both before and after signing the consent. Anonymity of the interviewees was secured, and no names or other personal data was collected or recorded.

Interviews were recorded by using an audio recorder app in mobile phone. Duration of the interviews varied from 20 minutes to 45 minutes, total duration for all interviews was 2 hours 49 minutes. All the verbalizations were transcribed literally after the interview. Notes were not taken during the interviews to keep focus on listening and making the clarifying questions.

5.4 Analysis

The interview data was analyzed using deductive content analysis. According to Kyngäs and Kaakinen: "Deductive content analysis is an analytical method that aims to test existing categories, concepts, models, theories, or hypotheses in a new context, i.e. with new data." When using the deductive method, the analysis is based on theoretical structure and earlier theoretical knowledge (Kyngäs & Kaakinen 2020). Deductive content analysis moves from broad generalizations to specific observations. Analysis of the data is driven by already known theory and research questions are set based on themes or categories defined during the theoretical part of the research. Collected material is reported based on predefined theory. (Tuomi & Sarajärvi 2018: 118-124.) As this research had qualitative research approach with predefined themes,

selecting the deductive content analysis approach was relevant. In the following paragraphs I will explain in more detail how this was done in this research.

At the first phase interviews were listened and transcribed literally by using Microsoft Word -word processor. As a result, there were total of 32 pages of transcription data from the interviews (Times New Roman, font size 12, line spacing 1.0). Interviews were printed out and read couple of times to get the overview of the topics discussed. After the individual interviews were read, second version of interviews was compiled. In this new version all the interviews were cut in sections and one document was created to include all the responses and comments from all 5 interviews. Responses and comments were grouped under the predefined themes (main categories of start-up activities) that were used during the interview. Responses were color coded so that it would be possible to identify which responses belong to a certain interviewee. In some cases, grouping was a challenging task, as themes were mixed, and flow of the interview was jumping from one theme to another and backwards. After compiling the interviews, the whole package was read multiple times in order to understand the whole content and to start identifying the similarities and differences within the responses within the themes.

The purpose of the interviews was to identify the current procedures for start-up activities and clarify what is working well and what could be improved. Based on this, next step of the analysis was to identify the sentences and phrases that are answering to and is relevant to the research question. This was done by predefined theme and a new version with condensed meanings was created. Color codes for interviewees were kept the same as in previous version to ensure reliability and traceability. Microsoft Excel was used to this phase of the analysis to be able to sort and filter the themes and categories. As soon as condensed meanings were created, completed, and checked, main categories under each theme were created and furthermore divided on the subcategories. Categorization was checked multiple times before results were reported and some minor corrections were done even during the reporting phase. Also checking against the original transcribed interview data was done, if needed, to confirm the connection to the original data.

6 Results and Findings

This chapter presents and analyses the data that was gathered during the interviews. The presentation of the results and findings is arranged according to the predefined themes used in interviews. There were six predefined main themes that were divided to main categories and subcategories. The table 1 shows these themes, categories, and subcategories and these are explained in more detail in the following chapters 6.1 - 6.6.

Table 1. CSL start-up activities in clinical trials.

	THEME	MAIN CATEGORY	SUB CATEGORY
CSL Start-up activities in clinical trials	Regulatory Submission	Co operation with Regulatory Department	Communication between CSL and Regulatory Department
			Timing of submission
		Timelines for Regulatory Submission	Global study team Impact on submission timelines
			Local team plans for submission timelines
		Regulatory Submission Documentation	Documents provided by global study team
			Documents prepared locally
	Ethics Committee Submission	Submission process to Ethics Committee	Submission package coordination
			Cooperation with relevant parties
		Documentation for Ethics committee submission	Document preparation process
			Cooperation on preparing the documents
	Study documents	Document preparation	Documents provided by the global study team
			Co peration in document preparation
		Translation of the documents	Translation process
			Cooperation with translation agencies
		Patient Information and Informed Consent form	Translation of Patient Information and Informed Consent form
			Review process
	Budget and Contracts	Country budget planning	Process for budget planning
			Cooperation related to budget planning
		Contract negotiations with study sites	Process for contract negotiations
			Cooperation on contract negotiations
	Electronic systems	Electronic systems in general	Electronic systems usability
			Information received from electronic systems
		Updating the electronic systems	Responsibility on updating the electronic systems
			Information updated to the electronic systems
	Study site start up activities	Investigator Meeting	Investigator meeting arrangements
			Attending investigator meeting
		Site Initiation Visit	Site Initiation visit conduct
			Investigator Site File

6.1 Regulatory submission

Regulatory department is responsible for submission to Regulatory Authorities. As soon as study is confirmed to Finland, a kickoff meeting between CSL and Regulatory department contact person is held to plan and agree submission timelines and to discuss the details on submission. CSL initiates this meeting. During the submission phase, CSL and Regulatory department is in contact by phone, e-mail or additional meetings on needed basis.

There were 3 main categories identified within the Regulatory submission and main categories were divided into 2 subcategories. Tasks during the Regulatory submission relate to cooperation, timelines, and documentation. Main categories and subcategories are presented in the table 2.

Table 2. Regulatory submission categories.

THEME	MAIN CATEGORY	SUB CATEGORY
Regulatory Submission	Co operation with Regulatory Department	Communication between CLM and Regulatory Department
		Timing of submission
	Timelines for Regulatory Submission	Global study team Impact on submission timelines
		Local team plans for submission timelines
	Regulatory Submission Documentation	Documents provided by global study team
		Documents prepared locally

Cooperation with Regulatory department

Overall cooperation with the Regulatory department was perceived as positive experience and easygoing.

> *Hyvin sujuu yhteistyö, sähköpostilla ja nähään. Toisaalta se on kiva että ne on tässä samassa rakennuksessa niin pystyy hyvin kommunikoimaan. Ei ole ollut ongelmia, hyvin saa vastauksia ja mitä tarvii toimittaa.*

> *Cooperation goes well by email and face to face meetings. On the other hand, it is nice that they are in this same building and this helps communication. There have been no problems, all answers are received as well as information on what needs to be delivered. (free translation)*

Communication between the CSL and Regulatory department is active throughout the submission phase. Communication is maintained by e-mail exchange and meetings.

CSLs feel that information needed from Regulatory department is received accordingly. It was also identified that cooperation requires active involvement from both parties. In some cases, the feeling was that the CSL is more active member and cooperation is based on which documents and when Regulatory department needs for submission. Sometimes CSLs were not fully aware of reasoning for the Regulatory department decisions on timing of submission.

Timelines for Regulatory submission

Timelines for Regulatory submission is dependent on global study management team who is providing study specific documents for submission (submission package). Country study team receives well in advance planned date for submission package availability and is able plan the local timelines based on this. Regulatory department receives the information and planned timelines also from their own global function and it is not always clear to the CSL where these plans are based on. This is the reason why CSL should be in contact with the Regulatory department as soon as information on study start is received to agree local target date for submission.

> *Siis meille tulee globaalitiimiltä tietenkin aikataulut että milloin ne toimittaa submissiopaketin ja siitä tulee sitten lähinnä ne aikataulut. Muodostuu se milloin on FPFV ja milloin pitää olla tehtynä ne ja sen mukaan sitten suunnitellaan ja kaikki pitäisi saada sitten tehtyä siinä välissä.*
>
> *So, we will, of course, have schedules from the global team on when they will deliver the submission package and that is basically the timeline. Based on this it is formed when FPFV (First Patient First Visit) will be and when everything needs to be completed. Then we should get everything done in between. (free translation)*

Regulatory submission documentation

Documents needed for the Regulatory submission are provided by the global study management team. Some documents that are received, are used as such for the submission but some documents require local modifications or translation. Some documents are created also locally. CSL is responsible for local documents needed for the submission. CSL is in contact with the Regulatory department to confirm which

documents needs to be provided. Sometimes it is unclear to CSL which documents Regulatory department is receiving directly from their own function and which documents needs to be provided by CSL. Regulatory department is submitting the package to the authorities at agreed timepoint.

> *Regulatory osasto saa sieltä omasta organisaatiostaan kyllä ne tiedot ja materiaalit. Minulta tarvitaan päätutkijan CVt ja protokollan allekirjoitussivut ja käännetyt potilastiedotteet.*
>
> *Regulatory department receives the information and materials from their own organisation. I need to provide Principal Investigators CVs and protocol signature pages and translated patient information and informed consent documents. (free translation)*

6.2 Ethics Committee submission

CSL is responsible for Ethics committee submission for a study. There were 2 main categories identified within the Ethics committee submission and main categories were divided into 2 subcategories. Tasks during the Ethics committee submission relate submission process and documentation. Main categories and subcategories are presented in the table 3.

Table 3. Ethics Committee submission categories.

THEME	MAIN CATEGORY	SUB CATEGORY
Ethics Committee Submission	Submission process to Ethics Committee	Submission package coordination
		Cooperation with relevant parties
	Documentation for Ethics committee submission	Document preparation process
		Cooperation on preparing the documents

Submission process to Ethics committee

As soon as study has been confirmed to start in Finland by the global study team, CSL submits preliminary notification of the study to TUKIJA (Central Ethics Committee). After the notification, preparations for collecting and coordinating the Ethics committee submission package documentation starts. Submission package preparation is time consuming task and requires a lot of work as lot of documents are needed for the submission. There are often tight target timelines for submission, and this created pressure for CSL. Challenge for the CSL in Ethics committee submission preparation is

the timelines and availability of documents. Most common reason for submission delay, evaluated by CSLs, is that final documents are not available from the global study team by the set target date.

In order to get the submission package ready, it requires a lot of cooperation with other parties. Some documents needed for the submission is collected from the study site personnel and National researcher in charge of the trial. Also, cooperation with the translation agency is critical for meeting the submission timeline and usually translation timelines are agreed well beforehand with the agency. As the collection and preparation of the submission package is so extensive and time critical, CSLs feel that it would be beneficial to have at least 2 persons involved in the process.

> *Ja tietysti submissiossa on hyvä jos siihen saa toisen henkilön mukaan, varsinkin nyt kun siinä on ollut niin paljon ihan konkreettista paperityötä kun tehdään paperisubmissioita. Mutta nythän se tulee sitten aikatavalla muuttumaan kun mennään elektroniseen submissioon. Tosin samat dokumentithan sinne pitää kuitenkin toimittaa.*
>
> *And, of course, it's good to get another person involved in submission, especially now that there's been so much concrete paperwork involved when preparing submissions. But now it will change over time when we go into electronic submission. However, the same documents must be submitted there. (free translation)*

Documentation for Ethics Committee submission

CSL is responsible for collecting the Ethics Committee submission package and coordinating the translation of the documents. All the patient facing material needs to be translated into local language and modified according to local requirements.

> *No mähän teen sen submission CSLnä ja sehän alkaa jo sitten siinä vaiheessa kun ollaan saatu tutkimustiimiltä dokumentit. Se alkaa niiden käännöstehtävien osalta: protokollaan yhteenvetoa, potilastiedotteet, kontaktikortit; kaikki materiaali joka toimitetaan tutkittavalle käännätetään ja sitten sitä kootaan pikkuhiljaa sitä pakettia ihan ohjeiden mukaan.*

> *Tehdään se lausuntohakemus ja siinä on liiteluettelot ja kerätään ne dokumentit sen mukaisesti.*
>
> *Well, I do the submission as a CSL, and it starts when we have received the documents from the study team. It starts with translation tasks: protocol synopsis, patient information sheets, contact cards; all the material that is delivered to the study subject is translated. Then the submission package is gradually assembled according to the instructions. The application form is completed, and it contains the list of needed documents and these are collected accordingly. (free translation)*

Document preparation requires cooperation with many parties from the CSL. Translation of the documents is agreed with the translation agency. Contract Associate is supporting CSL by providing advice on practical matters related to data protection and insurance questions. Contract Associate also acts as a link between CSL and Legal department on issues that require legal input. This is seen as very beneficial as she/he is expert on this field.

In addition to internal cooperation, National researcher in charge of the trial is obliged to give input on certain submission documents. CSL is cooperating with the National researcher in charge and ensures that all the documents that needs input is received. Overall, the impression is that cooperation is good but there are personal variations. Sometimes it is challenging for CSL to get the needed input within the set timelines as they may be hard to reach and busy with other tasks.

6.3 Study documents

CSL is responsible for preparing and collecting and modifying the documentation needed for the start of a study. This is demanding and time-consuming task and requires cooperation with many parties.

There were three main categories identified within the Study documents and main categories were divided into two subcategories each. Tasks concerning study documents relate to Document preparation, translation of the documents and Patient Information and Informed Consent Form. Main categories and subcategories are presented in the table 4.

Table 4. Study documents categories.

THEME	MAIN CATEGORY	SUB CATEGORY
Study documents	Document preparation	Documents provided by the global study team
		Co peration in document preparation
	Translation of the documents	Translation process
		Cooperation with translation agencies
	Patient Information and Informed Consent form	Translation of Patient Information and Informed Consent form
		Review process

Document preparation

CSL receives information on planned date when submission documentation is available from the global study team. Local timelines for submissions and preparations are planned based on this information. Material is received in English and all the patient facing material needs to be translated in local language (for Finland in Finnish and Swedish). Some documents may come readily translated via global translation vendor, this may include questionnaires, patient diaries etc. In this case CSL is checking the translation quality and provides feedback if needed. This is very time-consuming task and timelines are often very tight for review.

Sometimes it may occur that updates are applied to documents and new versions received after the initial delivery. CSLs feel that this causes delays in country start-up timelines and increases workload.

> *No jos tulee muuttuneita dokumentteja niin se tietysti vähän hidastaa aina sitä aikataulua. Sitten se täytyy kääntäjälle laittaa tai jos se on joku yksi sana niin sen voi ehkä itsekin korjata. Mutta se versiointi on sitten aika tarkkaa että pysyy kärryillä.*
>
> *If there are changes in the documents, it of course always slows down the schedule. Then it must be sent to the translator or if it is only one word then maybe you can fix it yourself. But you need to be accurate with versioning that you'll stay on track. (free translation)*

CSLs wish that study documents could be received from the global study team earlier which would leave more time for preparations. If documents or translations are not received within the needed timeline, submission and start of the trial in a country may delay.

Although the CSL is responsible for the submission and documents related to that, it is done in cooperation with other team members and relevant stakeholders. As some documents are also required from the study sites, study team agrees who will collect the needed documentation. CSLs feels that it would be also beneficial to involve multiple persons in reviewing the study documents before the actual submission is done.

Translation of the documents

As already mentioned previously, all patient facing documents needs to be translated to the local language. It is also a requirement that study protocol synopsis is provided to the Ethics committee in local language. CSL provides the documents requiring translation to a local translation agency. Translation agency then translates the documents and provides the translations and translation related documents (e.g. translation verification certificate) to CSL. CSL then reviews the translated material. CSLs feels that it would be beneficial if there would be another reviewer as well for translation to avoid mistakes in details.

> *No jotain sellaista helpotusta niihin käännöksiin ja niiden oikolukemiseen kaipaisi. Pääsääntöisesti olen tehnyt ne aina ihan yksin että jos siinä olisi vaikka assari joka voisi lukea ja tarkistaa niin sittetn ainakin välttyisi sellaiselta että menee vahingossa väärä versio tai on footerissa joku kirjoitusvirhe ja sitten joutuu sen takia tekemään uusia versioita. Sellaista apua mä kaipaisin ehdottomasti.*
>
> *Well, I would need help for translations and proofreading them. Mainly I have done them all alone. If there would be assistant or someone who could read and review, it would help avoiding mistakes in versioning or typos in document footers. I would definitely need that kind of help. (free translation)*

Overall cooperation with the local translation agencies is working well and CSLs are satisfied with the quality of translations. Sometimes translation agencies are crowded, and it is difficult to get the needed timeslot for translations before the submission target date. This may lead to delay in submission.

Patient Information and Informed Consent Form

Patient Information and Informed Consent Form modification is complicated process and requires eye for details. Master version that is received from the global study team is very different format than local requirement by ethics committee for Finland. Patient Information and Informed Consent form master version is long document and version for Finland must be shortened and modified to meet the local requirements. Translation agency is converting the master version of Patient Information and Informed Consent Form to local template.

> *Masterversio on meillä todella pitkä ja siinä on toistoa todella paljon. Mutta se Suomen versio tulee tosi paljon lyhennettynä ja sitten liitteissä loput. Meillä on aika hyvät kääntäjät ja he tekee sen jo aika pitkälle valmiiksi. Mutta sittenhän se pitää kuitenkin tarkistaa että siellä on kaikki tarvittavat asiat mukana.*
>
> *We have a really long master template and there is a lot of repetition. The Finnish version is really abbreviated and then the rest of the information is put on appendix. We have pretty good translators and they are already doing the conversion. But then it must be checked that all the necessary things are included. (free translation)*

When the translation is received from the translation agency, CSL reviews translated Patient Information and Informed Consent form for consistency. As per company requirements, translated version of Patient Information and Informed Consent - document undergo a review process internally. CSL coordinates the internal review with relevant departments as applicable. Purpose of the internal review is to ensure that translated version is fulfilling the local requirements. Patient Information and Informed Consent Form internal review process is working well in the opinion of CSLs although sometimes it may take time to get responses.

CSL is also working in close collaboration with National researcher in charge to finalize the local versions of Patient Information and Informed Consent Forms. When all the review is complete and document is considered final, CSL completes the needed internal forms to document the review and Patient Information and Informed Consent form is ready to be submitted.

It may happen that updated version of Patient Information and Informed Consent form is received from a global study management team while completion of the initial version is ongoing. When this happens, it may cause delay in finalizing the document and lead delay in submission and study start in a country. CSLs stated that the earlier the master template is received; it eases the time pressure for submission timelines.

6.4 Budget and Contracts

CSL is responsible for study budget on at country level and completion of investigator site contracts for the study. Budget planning is started at very early stage of a study and task is followed up throughout the whole study lifecycle. Negotiation with the study sites is started as soon as site is confirmed to the study and contract must be signed before site can start patient recruitment.

There were two main categories identified within the Budget and contracts and main categories were divided into two subcategories. Tasks concerning budgeting and contracts relate to country budget planning and contract negotiations with the study sites. Main categories and subcategories are presented in the table 5.

Table 5. Budget and Contracts categories.

THEME	MAIN CATEGORY	SUB CATEGORY
Budget and Contracts	Country budget planning	Process for budget planning
		Cooperation related to budget planning
	Contract negotiations with study sites	Process for contract negotiations
		Cooperation on contract negotiations

Country budget planning

Budget planning is started in early phase of the study start-up. Budget is estimated and followed up in CTPS (Clinical Trial Planning System) and the system is updated according to CSL feedback. Initial budget planning is done based on fair market value figures. Country budget consists of amounts paid to the study sites for conducting the study and country related costs like ethics committee fees and translation fees. CSL has regular meetings with CTPS expert on budget related updates in CTPS system throughout the whole study duration.

> *Mutta budjetti on aina sellainen palapeli. Se on ns helppo kun on samalla indikaatioalueella niin vähän tietää niitä hintoja - - Meillä CTPS ihminen*

täyttääkin sen teknisen puolen niin kyllä se on se CSL jonka pitää tietää ne summat suurinpiirtein. Budjetin suunnittelu menee samaan aikaan kaiken submissioiden sun muiden kanssa niin kyllä se on aikamoista veivaamista ja varsinkin jos on monta keskusta.

But budget is always the kind of a puzzle. It is easy when there is the same indication area so you kind of know the prices - - CTPS expert is taking care of technical side but it is the CSL who need to know about the sums. Budget planning goes hand in hand with all the submissions and others so yes, it is quite a demanding task and especially if there are many study sites. (free translation)

Contract negotiations with study sites

CSL is responsible for contract negotiations with the study sites but Contract Associate is conducting the actual negotiations with the study sites. As soon as confirmation for study start has been received, CSL informs Contract Associate about the study start to initiate contract negotiation planning. Contract negotiations are done in close collaboration with the Contract Associate and the CSL. When the local budget plan is set, Contract Associate is sending contract template and budget proposal to study sites for comments and negotiates the details. Contract Associate provides updates on budget and contract negotiation progress to CSL. In case of issues CSL is involved to discussions. When agreement with the study site is reached, Contract Associate is responsible for collecting signatures. Contracts are signed electronically.

Kyllä ihan ensimmäisiä asioita on että ilmoitetaan Contract ihmiselle että nyt meillä on alkamassa tutkimus. Ja kun me ollaan vahvistettu ne saitit tietenkin eli site selectionit niin sopimusneuvottelut täytyy saada lähtemään heti käyntiin, että se on ihan ehdoton. Nykyisin aika usein tarvitaan myös ulkopuolisia sopimuksia, esimerkiksi kuvantamisiin liittyen. Niissä kaikissa contract henkilöllä on älyttömän suuri panos ja osaaminen.

Yes, the very first thing is to inform the Contract Associate that now we are starting the study. And once we've confirmed the sites, then the contract negotiations need to get started right away, that's absolutely

must. Nowadays, external contracts are also often needed, for example in connection with imaging. In all of them, the contract associate has an extremely large contribution and expertise. (free translation)

Contract and budget negotiations vary a lot based on study complexity and between the study sites. CSLs appreciate Contract Associate for conducting the contract negotiations with the study sites as it requires special expertise. Cooperation between CSL and Contract Associate is working well. Sometimes CSLs feel that they are not fully aware of contract negotiation progress in their studies as Contract Associate is conducting the actual negotiations.

6.5 Electronic Systems

There are multiple electronic systems that CSL and study team needs to update throughout the study. Some systems are used internally to track the progress and status of a study or system used for filing the study essential documents (Trial Master File). There are also systems that both internal study team as well as study site personnel has access. One example of this kind of system is electronic case report form -system where study site is entering the protocol required information on each trial patient. Other example could be the IXRS system that tracks the study medication logistics. On top of these there are usually other electronic systems in use based on trial set up like electronic patient diaries, laboratory systems, training portals etc.

There were two main categories identified within the Electronic Systems and main categories were divided into two subcategories. Tasks concerning systems relate to general issues and system updates. Main categories and subcategories are presented in the table 6.

Table 6. Electronic systems categories.

THEME	MAIN CATEGORY	SUB CATEGORY
Electronic systems	Electronic systems in general	Electronic systems usability
		Information received from electronic systems
	Updating the electronic systems	Responsibility on updating the electronic systems
		Information updated to the electronic systems

Electronic systems in general

CSL has access to multiple systems. Systems can be used to follow up the study status, study progress and data collected in the study. There are different kind of reports that can be run from the different systems to track or collect information on specific issues related to a study. Systems are not always seen as user friendly and there are challenges in finding the relevant instructions. As there are many systems it is also challenging to remember all the passwords as almost every system has different log in detail.

> *Toivomus että voisi olla sellainen että olisi yksi tunnistautuminen kun menee tutkimukseen esim sormenjäljellä ja kaikki aukeaa sieltä ettei tarvitse enää erillisiä salasanoja. Meillä on varmaan kaikilla listoja salasanoista ja ne vaihtuu kokoajan ja keskuksen henkilökunta, heilläkin on aikapaljon ongelmia salasanojen kanssa.*

> *I wish that there would be one authentication for a study, for example with a fingerprint and everything opens from there and you no longer need separate passwords. Probably all of us are having lists of passwords and they need to be changed all the time. And the study site staff, they also have a lot of problems with passwords too. (free translation)*

Updating the electronic systems

It is very important to keep electronic systems up to date from the very beginning of the study. Responsibilities for updates is discussed, agreed, and delegated within the study team. Common rule is that CSL is responsible for country level updates like important country event dates and patient enrollment planning. CRA is responsible for site level updates. CTA is also having a big responsibility especially for filing the essential study documents to electronic Trial Master File. In the beginning of study CSL is coordinating different study related electronic systems and ensures that all study team members have access to relevant study systems.

> *CSL syöttää country asiat mutta sitten keskuskohtaisia CRA syöttää ja sen voi sopia tiimissä että miten se tehdään. Jos on iso tiimi niin onko*

helpompi että yksittäinen ihminen sen tekee vai onko jokainen itse. Vähän vaihtelee.

The CSL enters country level items but site related is entered by CRA. It can be agreed with the team that how it is done. If there is a big team is it easier for one person to do it or is everyone doing themselves. It varies a bit. (free translation)

6.6 Study site start-up activities

Clinical Research Associate (CRA) is responsible for assigned study sites. However, CSL is involved in the start-up activities with the sites.

There were two main categories identified within the Site start-up activities and main categories were divided into two subcategories. Tasks concerning systems relate to investigator meeting and site initiation visit. Main categories and subcategories are presented in the table 7.

Table 7. Site start-up activities categories.

THEME	MAIN CATEGORY	SUB CATEGORY
Study site start up activities	Investigator Meeting	Investigator meeting arrangements
		Attending investigator meeting
	Site Initiation Visit	Site Initiation visit conduct
		Investigator Site File

Investigator meeting

Usually in the beginning of the study, Investigator meeting is arranged. Meeting can be arranged as face to face meeting or as virtual meeting. Study sites from different countries are participating the same regional meeting (for example Europe region sites). Global study management team is responsible for setting up the investigator meeting, but country study team ensures that study sites from the respective country are invited. CSL is responsible for ensuring that all relevant site staff is invited to Investigator meeting and all the arrangements related to meeting are done properly. CSL in cooperation with CTA and CRA(s) arranges Investigator meeting related issues for site staff. CSL and CRAs are also participating the meeting together with relevant study site staff and CSL acts as a host for the country study team during the meeting.

Kun vahvistuu päivämäärä tutkijakokoukseen niin mä ilmoitan niille tutkijoille ja tutkimushenkilökunnalle joita sinne tullaan kutsumaan. Että nyt tämä on. Sitten siihen liittyy ilmottautumislinkit ja usein tässä vaiheessa jos on CTA niin hoitaa matkajärjestelyt. Tavallansa sitten kun olet siellä kokouksessa niin sulla on maatiimi siellä.

As soon as the date for the meeting is confirmed, I inform investigators and other site staff that will be invited. That now this is. Then it involves registration links and often at this point, if there is a CTA, she takes care of the travel arrangements. Then when you're there in a meeting you have a country team there. (free translation)

Site Initiation Visit

Purpose of the Site initiation visit is to confirm that all site staff is appropriately trained for the study and site has all the equipment etc. needed in place to start patient recruitment. CRA is responsible for conducting the site initiation visit. CSL is responsible for ensuring that visits are done according to planned timelines. Even the CRA is responsible for the visit, CSL often participates the visit and is planning the visit activities in cooperation with the CRA.

Global study team is providing training material for Site Initiation Visits. Usually the material that is received is very long and requires modifications from country study team to meet the training needs for the site. Country study team agrees who will prepare the material for Site Initiation Visits.

In addition to training material, country study team is preparing investigator site files for the study. Investigator site file includes the essential study documents that must be maintained throughout the study. Part of the documents are received from the global study team and part of the documents are prepared by the country study team. It is the CSLs responsibility to ensure that all the documents are included. CTA prepares the folders for the sites. Sometimes it is not clear for the CSL which documents are provided by the global study management team and which of the documents needs to be prepared in the country level.

Kyllä globaalitiimiltä tulee materiaalia mutta CSL muokkaa aina vähän sen mukaan miten se on tarkoituksenmukainen Suomessa. Yhdessä CRAn kanssa. Että se olisi helppo koulutuspaketti. Yleensä tiimissä yhdessä tehdään eikä oteta suoraan globaalin tiimin materiaalia. Ensinnäkin sitä on niin järkyttävän paljon sitä materiaalia että sitä täytyy kohdentaa.

Yes, there is material from the global team, but CSL always modifies it a bit to fit for Finland needs. Together with the CRA. So that it would be easy training package. Usually it is team effort and material provided from the global team is not used as such. First, there is so much material that it needs to be targeted. (free translation)

7 Discussion

Context of this master's thesis is topical at the moment. Even the EU Clinical Trial Regulation implementation has been postponed many times, it is inevitable that it will be implemented and organisations conducting clinical trials must be prepared for the implementation. As mentioned in the chapter 2.3, purpose of the regulation and the portal is to harmonize the rules for conducting clinical trials throughout the EU; thus, making EU area attractive for conducting the clinical trials. According to EMA, around 4000 clinical trials are authorized per year in European Union member states and average of two member states participating the trial. Trials that are conducted in multiple member states are benefiting most when the new regulation is fully implemented. (Clinical trials in human medicines. European Medicines Agency.)

Further in this chapter I will present the discussion of the results by focusing on main themes used in presenting the study results in chapter 6. Results and Findings. Results and findings are compared against the changes the new regulation will bring to the start-up activities in operational level. Further in this chapter Limitations (7.2), trustworthiness (7.3) and ethical considerations (7.4) are reviewed.

7.1 Changes in start-up activities for CSL due to new regulation

New regulation introduces many changes to the processes and procedures in conducting the clinical trials in EU. Major impact of the regulation implementation will

be to clinical trial application process that will be centralized throughout the EU. (Marcal 2019.) When the new regulation is implemented fully, in practice this will mean that CSLs are no longer actively participating the Regulatory Authority submission. As the submission will be done centrally to all participating EU member states, no documents prepared locally are needed for the Part I submission. All Part I documents will be the same for all countries and assessment is coordinated between the participating member states. (Konttinen & Närhi 2017.) In practice this means less interaction between the Regulatory department and the CSL. Cooperation with Regulatory department was perceived as positive experience, on the other hand there were some unclarity on timelines and document delivery for the submission. CSL role on the Regulatory Authority submission will be diminish due to the change in submission process.

When the studies are submitted under the regulation, Part II of the submission is comparable to current Ethics committee submission. Part II dossier will be submitted centrally via CTIS portal but assessed in each respective country. (Konttinen & Närhi 2017.) Country study team will have a major responsibility for preparation and completion of documentation needed for the Part II submission. Based on the new regulation, timeframe for providing answers to the queries received from the authorities is maximum of 12 calendar days (Konttinen & Närhi 2017). This will be a challenge as it is tight, especially in the situations there are lot of corrections or justifications requested. In CSL perspective, the submission process will be changed as CSL is no longer conducting the actual submission but collecting the documentation for central submission. In practice this will not bring a big change to actual preparation work. Translations of patient facing material needs to be coordinated and checked. Responsibility of having all the documents finalized by the due date remains. Currently CSL is planning the submission timelines based on document availability from the global study team and Ethics committee deadlines for submitting the package for evaluation. In the future submission will be done centrally in parallel for all EU member states. In practice this will mean a common deadline for final submission documents for all the EU countries participating the study. CSLs perceived the collection and preparation of submission package extensive, time consuming and critical. It was suggested to have at least 2 persons involved in process. As the timelines for responding to the possible queries during the assessment period is tight, it is well justified to have proper back up arrangements in place to ensure responses in time.

Local Finland requirement for Part II submission documents are not yet known although the assumption is that EU requirements are followed, and no additional national requirements are implemented. When the regulation is implemented, there will be only one Ethics committee, TUKIJA, assessing the clinical trials in Finland (Hallituksen esitys HE 18/2020 vp. 2020.). This will harmonize the process as in the current situation different ethics committees have had variations for requesting the corrections to the documents. CSL is responsible for collecting the submission package, coordinating the translation of the documents, and ensuring that the documents are according to local requirements. CSLs are perceiving this as a very time consuming and see this as critical part for successful submission, it would be beneficial to involve multiple persons in review process. There are many parties involved when submission documentation is prepared, including translation agencies, study site personnel, National researcher in charge and other team members / departments as applicable. When new act is implemented, the requirement for National researcher in charge will be removed (Hallituksen esitys HE 18/2020 vp. 2020). This will simplify and fasten the process for finalizing the documentation as no input for submission is needed from her/him.

7.2 Start-up activities for CSL that will not change due to new regulation

Even though new regulation will bring many changes, some of the tasks in start-up process for CSL will remain the same. As there still will be documents prepared or modified locally in local languages, cooperation with translation agencies is continuing. CSLs are satisfied with cooperation with the local translation agencies and quality of the translations they are providing. Translation agencies in use are sometimes crowded and are not able to provide a translation timeslot in requested time. This may lead to delay in submission document preparations. Likely there will be a national template for Patient Information and Informed Consent Form in the future as well. Translation agencies are playing the important role in converting the global template into local requirements. CSL is responsible for reviewing the translation and coordinating the internal review rounds.

New regulation does not directly affect on CSL tasks on study budget and investigator site contracts, electronic systems, or study start-up activities. CSL still remains responsible for these tasks and they are ongoing in parallel with submission preparations. Contract Associate is in very close collaboration with the CSLs

throughout the budget planning and site contracting process. This is highly appreciated by the CSLs as these tasks requires a special expertise.

Study status is followed by electronic systems starting at very beginning of the start. CSLs are very committed to keep the systems up to date all the time but are struggling with multiple systems not interacting with each other and not being very user friendly. Country study team members are agreeing the responsibilities for updates in the beginning of the study. CRA holds the main responsibility on study site start-up activities and ensuring that study site is trained properly for the study and that they have all the equipment etc. needed for the study. CSL is supporting the CRAs and ensures that sites are initiated according the planned timeline and that all the material needed for site initiations are available. Site start-up activities are performed in close collaboration with the whole country team.

7.3 Limitations

There are some limitations in this study that needs to be considered. These limitations are the small sample size and timing of the study. Interviews for this study were conducted October-November 2019. Total of five persons were interviewed which is a relatively small number. According to Tuomi & Sarajärvi (2018) sample size in qualitative research is vague and there is no unambiguous answer to this question. However, in this research there were limited number of suitable participants as the participation required the special expertise on the field. During the thesis process, COVID-19 outbreak, and restrictions due to that, caused the situation when the researcher had to put the thesis work on hold due to high workload in other responsibilities. As the timeline for completing the thesis work was stretched, there might have been possibility to add few more participants to the interviews, but it was not done to speed up the completion of the thesis. Despite of small number of interviewees, clear similarity on responses was observed. Based on this, increasing the number of participants probably would not have significant impact on study results.

7.4 Trustworthiness

There are no specific unambiguous instructions how to evaluate trustworthiness in qualitative research. Trustworthiness in qualitative research can be evaluated by reviewing the following: collection of data, selection of research participants,

relationship between the participants and the researcher, timetable of the research, analysis of the research, reliability of the research and reporting of the research. Criteria for evaluating quality in qualitative research can be assessed within the concept of credibility, transferability, dependability, and confirmability. (Tuomi & Sarajärvi 2018: 118-124.) Trustworthiness for this research is evaluated according to these concepts.

Credibility of the research can be ensured by four strategies: prolonged engagement, persistent observation, triangulation, and member check. Researcher is determining which of these strategies are applicable for evaluating the credibility. Prolonged engagement is defined by lasting presence during the observation and investing the sufficient time for become familiar with the setting and context. Persistent observation strategy identifies the elements that are most relevant to the problem. Triangulation is defined by using different sources for data, investigators, and methods. Member check is when data is fed back to the original source. (Korstjensa & Moser 2018.) In this research, researcher already had knowledge on context as she has worked with clinical trials for several years. However, researcher is not working herself in a role that conducts study start-up activities. Therefore, it was possible to take the needed distance to perform the research in valid credibility. Thorough familiarization was done for theoretical background before the interviews. During the familiarization, thematic interview guide was developed. Semi-structured interview was selected as a method of collecting the data as it allows participants express their thoughts freely and at the same time allows interviewer to ask clarifying questions. As the purpose for this research was to support a specific organisation, it was not considered relevant to look for participants outside the organisation. During the data analysis phase, research supervisor reviewed the draft analysis few times and modifications based on feedback received were implemented. Data was color coded during the analysis phase so that it was always possible to check the original source to confirm the correct understanding when categorization of data was done.

Strategy for defining transferability is "Thick description" when behavior, experiences and their context is explained. Researchers responsibility is to provide description of the participants and the process so that reader can assess the transferability of the research. (Korstjensa & Moser 2018). Description of the study setting, participant and the interview process is included to this master's thesis. Also, background information

of the organisation and relevant topics around research question is explained to give clear picture of the whole setting.

Dependability and confirmability mean that research steps are described transparently from the start of the research project to reporting of the findings. Researcher need to secure that analysis process in in line with accepted standards and meet the aspects of neutrality. Interpretation of the data must be grounded to the data instead of researcher's own preferences. This is confirmed by audit trail. (Korstjensa & Moser 2018). In this research selected research methods are explained. Data analysis method and process is described in detail. Reported study results rely strictly on the collected data and are traceable. According to consent, original recorded interviews and transcription data will be destroyed 1 year after the publication of this master's thesis.

7.5 Ethical considerations

According to European code of conduct for research integrity (2017), scientific and scholarly research must follow the good research practices. These practices are based on fundamental principles of research integrity. These principles are reliability, honesty, respect, and accountability.

When conducting the work-oriented development work, aim for the work needs to be according to high morals, development work needs to be conducted honestly, carefully, and precisely. Result of the development work needs to be practically useful. (Ojasalo & Moilanen & Ritalahti 2018: 48-49.) Evaluating this specific development work, there is a clear need for it. New regulation implementation is inevitable, and the organisation needs to be ready when the implementation deadline is reached. This also justifies the use of selected interviewees in this research settings as information regarding the processes on a practical level is needed to be able to assess the need for a change.

All parties involved in this thesis (interviewees) were treated in a fair, respectfully, and confidential way. Consent to participate was collected from the participants involved in the interviews. Thesis purpose and aim was explained to the participants beforehand. Participation to interview was voluntary, and participants had the right to cancel their participation at any time. Anonymity of the interviewees was secured, and no names or other personal data was collected or recorded.

8 Conclusion

The purpose of this research was to support implementation of Clinical Trial Regulation to Company X's Clinical Operations Finland organisation's operational procedures. The objective was to find out how should Clinical Operations Finland -organisation amend their working procedures to meet the new regulation requirements.

Assumption for this research is that role of the CSL is remaining as it has been responsible for start-up activities within the assigned study in a country. However, there might be a change to overall process for study start-up activities in global level and specialized roles for start-up activities introduced. As mentioned in the Introduction section, there is Company X internal "EU Clinical Trial Regulation Implementation Project" ongoing that ensures overall readiness for the implementation. Even the country readiness is not in the scope of this project, it will surely bring changes that are affecting the country study start-up activities. How it will affect on CSL tasks and responsibilities in study start-up activities is not yet fully known by the country organisations.

Findings showed that there are certain working procedures that should be improved to better meet the requirements and changes new regulation will bring. Based on the results two main areas were identified:

1. Proper back up plan for document preparation and submission process:

- To ensure documents for submission are valid and correct
- To ensure meeting the timelines for submission preparation and providing response to potential queries during the assessment phase.

2. Ensuring local translations can be delivered on time

- To ensure meeting the timelines for delivering the submission documents and responses to the queries.

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Invitation Letter to Interviewees

Implementation of the new Clinical Trial Regulation EU no. 536/2014 to Clinical Operations Finland -organization local processes

Hei,

Kliinisten lääketutkimusten EU-asetus (536/2014) hyväksyttiin16.4.2014. Asetuksen tavoitteena on yhdenmukaistaa kliinisten lääketutkimusten tekemistä Euroopan Unioinin alueella. Erityisesti kliinisten tutkimusten lupamenettelyyn tulee suuria muutoksia, kun asetuksen myötä otetaan käyttöön ns. yhden luukun periaatteella toimiva lupaportaali ja kliinisten tutkimusten tietokanta. Asetuksen täysi soveltaminen käytäntöön riippuu tämän eurooppalaisen tietokannan valmistumisesta.

XXX:lla on käynnissä sisäinen projekti asetuksen implementointiin liittyen. Projektin tarkoituksena on varmistaa yrityksen valmius toimia asetuksen mukaisesti sen voimaan tullessa. Maakohtaiset Clinical Operations -osastot ovat vastuussa siitä, että heillä on paikallinen valmius vastata tulevan asetuksen vaatimuksiin.

Teen Metropolia Ammattikorkeakoulussa Helsingissä ylempään ammattikorkeakoulu-opintoihin (Master´s Degree Programme in Health Business Management) liittyvää opinnäytetyötä kliinisen lääketutkimusten EU-asetuksen implementoinnista Clinical Operations Finland -osastolla. Tutkimuksen tarkoituksena on tukea asetuksen täytäntöönpanoa osaston paikallisiin toimintoihin liittyen. Tavoitteena on luoda suunnitelma ja/tai suositus siitä miten osaston tulisi organisoida paikallisia toimintatapoja ja toimintoja siten, että varmistetaan uuden asetuksen vaatimusten täyttyminen. Päättötyötä ohjaa yliopettaja, Dosentti FT Eija Metsälä (osoite: Metropolia Ammattikorkeakoulu, Mannerheimintie 172, Helsinki ja puhelinnumero: 050 3478177).

Pyydän Teitä osallistumaan tutkimukseen, koska toimit avainroolissa Clinical Operations -osastolla tutkimusten läpiviennin kannalta, erityisesti tutkimuksen aloitusvaiheessa. Tutkimukseen osallistuminen on täysin vapaaehtoista ja voitte halutessanne perua osallistumisenne missä vaiheessa tahansa tutkimuksen aikana. Henkilöllisyytenne ei tule muiden kuin minun tietooni. Ainoat tutkimusta varten kerättävät taustatiedot ovat ammattinimikkeenne ja osasto, jossa työskentelet.

Mikäli päätätte osallistua tutkimukseen, pyydän Teitä hyväksymään haastattelun kalenterikutsun. Tutkimusaineiston keruu tapahtuu noin tunnin kestävässä henkilökohtaisessa haastattelussa. Haastattelu nauhoitetaan ja nauhoitukset sekä niistä kirjoitetut kirjalliset versiot säilytetään luottamuksellisesti ja tuhotaan vuoden kuluttua opinnäytetyön julkaisemisesta. Haastattelut on tarkoitus järjestää loka- ja marraskuun 2019 aikana.

Ystävällisin terveisin
Eija Salminen

Consent

Implementation of the new Clinical Trial Regulation EU no. 536/2014 to Clinical Operations Finland -organization local processes

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:

_____

Tutkittavan allekirjoitus

_____

Tutkittavan nimenselvennys

_____

Aika ja paikka

Suostumuksen vastaanottaja:

_____

Tutkijan allekirjoitus

_____

Tutkijan nimenselvennys

_____

Aika ja paikka

Thematic Interview Guide

To identify the current start up processes for a clinical trial at Company X.

Theme	**Main question**	**Sub questions** for all main questions
Regulatory submission	What is the process and your tasks in Regulatory authority (Fimea) submission?	**What is working well?** **What should be improved?**
Ethics committee submission	What is the process and your tasks in ethics committee submission?	
Study documents/ patient material preparation	What is the process and your tasks in study documents / patient material preparation?	
Budget & Contracts	What is the process and your tasks in budget and site contract negotiations?	
Electronic Systems	What is the process and your tasks in updating the electronic systems?	
Investigator meeting and site initiation arrangements	How is Investigator meeting arrangements done and what are your tasks related to this?	
Other	Is there any other tasks/procedures you would like to raise up related to start up activities?	