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Key Factors for Successful Development and Implementation of Electronic Data Capture in Clinical Trials

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Abstract

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Drug development in general and clinical trials in particular is expensive and time consuming processes. One mandatory procedure in clinical trials are data collection, about 15 years ago almost all data were collected with a paper based approach but with new digitalised technology for data collection the process were about to become more efficient in regard to time, cost and quality of data. However the adoption rate of these systems for data collection were much lower than anticipated and most previous research points toward poorly developed products as the main reason for the adoption failure. Nevertheless, these systems have become more user friendly and efficient and today almost all studies use Electronic Data Capture (EDC) as the primary method for data collection. This project aim to investigate if the reason for the slow diffusion was a result of poorly developed products or if there are external factors such as social or organisational aspects that caused this delay. Semi structured interviews were conducted with 15 informants who works with EDC systems daily and are professionals within this industry. The result indicates that the slow diffusion is partly caused by initially bad systems that in turn might have caused a resistance among the end users and partly caused by slow decision organisations such as multinational pharmaceutical companies. The advice given to the project owner who intends to acquire this market is to focus on electronic Patient Reported Outcome (ePRO), which is a tool used by individual patients for self-reporting of data in clinical trials. ePRO is an extension of the EDC systems and must be user friendly for the patients and easy to connect to other systems. The company should rather focus on small Contract Research Organisation (CRO) as main customers rather than Big Pharma. Big Pharma often conduct multinational studies and decisions regarding the protocol and how data is to be collected are centrally decided. Since the project owner is a newly started, small firm with limited experience of clinical trials my advice would be to target CROs that conduct smaller studies.

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Abbreviations

ARO	Academic Research Organisation
AE	Adverse Event
CRF	Case Report Form
CERB	Central Ethical Review Board
CDM	Clinical Data Management
CDMS	Clinical Data Management System
CRA	Clinical Research Associate
CTA	Clinical Trial Assistant
CTMS	Clinical Trial Management System
CRO	Contract Research Organisation
DSMB	Data and Safety Monitoring Board
DCF	Data Clarification Form
DoH	Declaration of Helsinki
DOI	Diffusion of Innovation
DELTA	Dynamically Extendable platform for Long-Term Assessment
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EMR	Electronic Medical Records
ePRO	electronic Patient Reported Outcome
EMA	European Medical Agency
FIM	First in Man
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GUI	Graphical User Interface
IEC	Independent Ethics Committee
IVRS	Interactive Voice Response System
ICH	International Conference on Harmonisation
IRB	International Review Board
IB	Investigators Brochure
MPA	Medical Product Agency
MDS-UPDRS	Movement Disorder Societies Unified Parkinson's Disease Rating Scale
NME	New Molecular Entities
PDC	Paper-based Data Collection
PANDA	Parkinson's Disease Digital Assessment
PK/PD	Pharmacokinetic and pharmacodynamic
POC	Proof of Concept
QoL	Quality of Life
RDE	Remote Data Entry
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
21CFR11	Title 21, CFR part 11
WMA	World Medical Association

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1 Introduction

The health care system along with the pharmaceutical industry is facing a major transformation, not only do we live longer and thereby require more care and more pharmaceuticals, new research indicate that we also require diverse treatments due to the differences in our genetic material. This is what is commonly known as personalised medicine. Several fields in this industry are changing and most of these processes are part of a more personalised vision of health care so it seems like all these changes can be included in the same medical model, which in this project is referred to as personalised medicine.

Personalised medicine can thereby include the change of patient-physician relationship, which is drastically shifting from a physician-centred care towards a more patient-centred care. Patients are becoming more eager to learn about their illnesses and they are also becoming more involved in their own diagnoses and treatments. This change might be a result of the large amount of information about disorders and new treatments that today easily can be accessed by practically anyone. This new form of relationship, where patients are in control of their own treatment and have more to say in the discussion of future care has shown a great increase in patients Quality of Life (QoL).

QoL is a subjective parameter based on questions about the patient's perceived situation but it is nonetheless becoming more important both during diagnosis and also when evaluating the efficacy of new drugs. The clinical assessments, especially in a clinical trial setting are shifting more towards soft parameters such as QoL evaluations rather than hard laboratory parameters. This aspect is becoming more important also when applying for registration of new drugs and when evaluating new drugs in a longer perspective in regard to health economy and public welfare.

At the same time the medical industry is going through major changes due to advanced molecular methods that allows individualised treatments based on the patients' genetic material. The diversity of individuals' DNA can cause different responses to the same drug. This includes both the effect of the drug and the side effects of the drug. The appropriate substance and dose for one individual can result in side effects and toxicity for another and by knowing the patients genome it is possible to customise each patient's treatment and make sure that everyone gets the best care they can get.

Both patient centralised care, the importance of QoL and human genetics are examples of how the health care is becoming more personalised. Another aspect of the transformation the industry is facing lies within new technology and concepts such as telemedicine or mobile health. This makes it possible to give patients the opportunity to become more responsible for their own health and well-being. The telemedicine market is rapidly growing, today the market is estimated to US\$ 843 million and by 2019 it is expected to reach a value of US\$ 2.9 billion (Winter Green Research 2013).

The project owner has now developed an application in an attempt to acquire this fast growing market and this is where the assignment was originated. However, this particular project will rather concern how a modulated version of the product can be used in clinical drug development to reduce time and cost for data collection. To understand the features of the product the next section will describe the origin of the assignment.

1.1 The origin of the assignment

Animech Technologies is a company specialised in software development and communication that, in collaboration with the Knowledge Foundation, Uppsala University and Dalarna University, has developed a digital application called Parkinson's Disease Digital Assessment (PANDA). As the name implies this application is a digital patient diary that facilitates monitoring of patients living with Parkinson's disease. The application will increase the communication between patients and physicians while giving each patient a chance to engage and take responsibility for their own well-being. PANDA is a test battery consisting of self-assessment questions and motor tests, including tapping and spiral drawing that aim to monitor patients living with Parkinson's disease in their own homes. The system is validated and registered as a CE-marked medical device class 1 (Westin et al. 2009), which indicates that it is a low risk, non-invasive medical apparatus (MEDDEV June 2010 2. 4/1 Rev. 9). PANDA is able to deliver decision support information based on patients' current symptom profiles and symptom history to the treating physician and present this data for an individualized evaluation (Westin et al. 2009). This is not to be seen as a substitute for regular medical appointments but as a complementary diagnostic tool to improve the patient evaluation.

Parkinson's disease is a progressive neurodegenerative disorder that affects cells in substantia nigra, which results in loss of dopamine that in turn influences motor function. Common symptoms are consequently stiffness, tremor and bradykinesia characterised by difficulties in initiating movement. People living with Parkinson's disease often become worse over time. However, the progression of the disease is not steady, which means that the dose of the

treatment needs frequent adjustments. (Ray Chaudhuri, Clough & Sethi 2011). Dose adjustments are often done after patient assessment at the clinic and for many patients this means long and burdensome trips to the hospital. When patients with Parkinson's disease are in what is known as off- mode, i.e. when dopamine levels are low and patients experience excessive stiffness, tremor and bradykinesia, even the most basic daily tasks are difficult to perform. An additional problem with medical appointments, where the physician only sees the patient for a short period of time during one day, is that patients who have an appointment with a physician tend to be very precise with their own medication. This behaviour might be a combination of what is known as "pleasing the doctor" and worries about not being able to get to the clinic for evaluation. This gives a distorted perception of how well treated these patients are. An evaluation of patients in their own homes, when they live their normal lives and forget drug administration and doesn't perform their daily physical therapy would present a more accurate picture of the patient's medical status.

The evaluation method used by the physicians to assess patients with Parkinson's disease at the clinic is called Movement Disorder Societies Unified Parkinson's Disease Rating Scale (MDS-UPDRS). This method is well documented and used in various countries all over the world and it is also considered the standard method for evaluation of therapies for Parkinson's disease in clinical research, according to the European Medical Agency (EMA) (EMA/CHMP/330418/2012 rev. 2). MDS-UPDRS primarily consists of patient self-assessment and analysis of patient motor movement patterns using questionnaires and doctor's eyes respectively. Movement patterns is analysed while the patient is performing simple motor exercises and in addition MDS-UPDRS includes interviewing the patients about their general condition during the last days or weeks and as one can imagine this is not easy to estimate. One of the benefits with PANDA is that all questions are asked in real time. PANDA includes both self-assessment questions about the patients' perceived condition since the last test and various motor tests, such as; two-box tapping, four-box tapping and spiral drawing, see figure 1. All tests are connected to a smart phone with touch screen, only for use in this manner. The application will remind patients to perform these tests once every four hours during one week. PANDA will during this week collect, send, process and present data in a platform called cenPAD, with a user-friendly interface. This interface present data in a simple graph for the physician to analyse, which will provide the physician with long-term information about patient status instead of the short-term information given at the medical appointment. Since patients with Parkinson's disease often have both good and bad periods during one day a short-term assessment could result in inaccurate dose adjustment. PANDA was originally evaluated with two patients to demonstrate Proof of Concept (POC) as well as compliance and usability in a clinical trial and the

result show good patient compliance. According to the nurses who participated in the study the usability was acceptable (Westin et al. 2009). To validate the test battery a trial with 35 stable and fluctuating patients with Parkinson's disease was conducted. This trial included usage of PANDA, MDS-UPDRS, which is mainly QoL questionnaire developed specifically for cognitive assessment of patients with Parkinson's disease and the results indicate an adequate correlation and test-retest reliability (Westin et al. 2012)

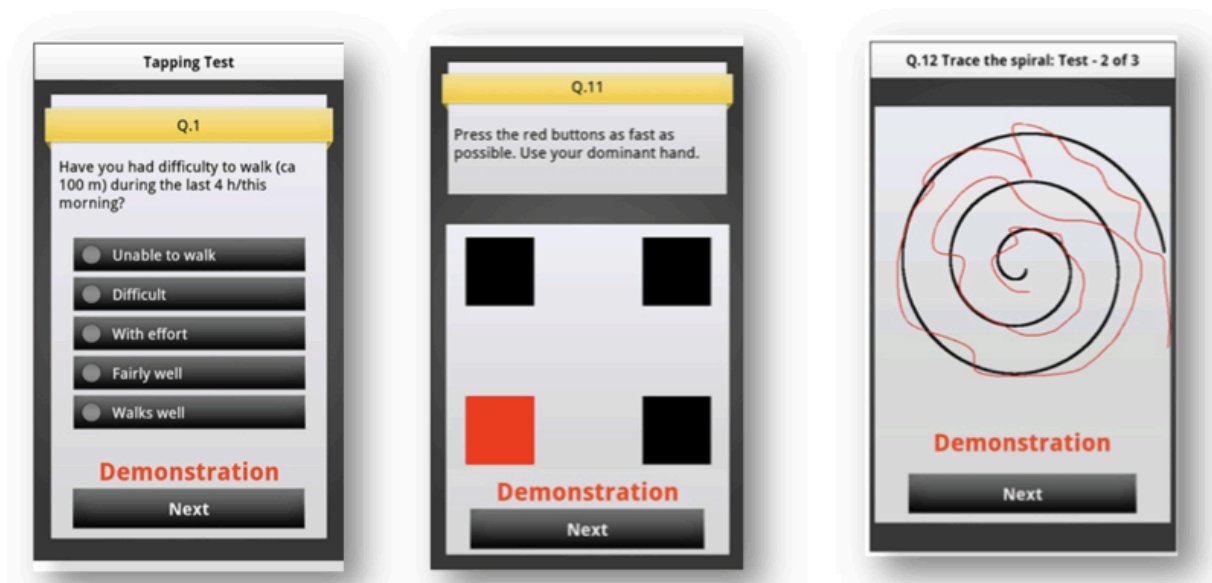


Figure 1. PANDA includes both self-assessment questions about patients perceived condition and various motor tests, such as, four-box tapping and spiral drawing.

PANDA is now the main product of the newly established subsidiary firm, Cenvigo AB. Cenvigos idea of business is to use a standard model to introduce digital tools such as PANDA in health care, self care and in the future also in clinical drug development. All data will be presented on the same platform, cenPAD. The business plan also includes helping small firms or academia to implement or develop their technology, ideas or products in health care using this model and connecting it to cenPAD. Advantages with having the same platform and only connect different technologies to it is that the physician is familiar with the interface and can easily navigate and understand the data, weather it is data from PANDA or Product X that is presented. The work of implementing PANDA and cenPAD at Akademiska Hospital in Uppsala and Karolinska Hospital in Stockholm is as a first step, as well as creating a business plan and a standard model for implementation and launch of new technology is an ongoing work.

To be able to use PANDA in other situations or in other patient groups the tests need to be adjustable. The work of creating a generic platform for use in, for example clinical trials was carried out during the fall of 2013. This platform is named Dynamically Extendable platform for Long-Term Assessment (DELTA) and enables development of various tests that easily can be added to the DELTA system without need of changing the entire system (Ebbeson, Evertson & Risch 2013).

This generic platform could be used to create tests for use in clinical trials for drug development as a tool for participating patients. Patients could easily report study data from within their own homes, saving the study personnel both time and money. The above explains the origin of this project but in order to further continue, a background on drug development and clinical trials are necessary.

1.2 Drug development and clinical trials

Drug development can be divided into three processes, the first being drug discovery, the second being preclinical research and the third being clinical research. The first process, in which new drug candidates are discovered, can be seen as basic research and the aim is to detect molecules that have the potential to become a new drug. To find these molecules a method called high throughput screening is often used. This method will analyse chemical structures in silico using a database containing a library of molecules that is analysed to determine if there is a compound that will be able to modify the chosen drug target. The molecules then need to be adjusted to increase affinity and specificity for that specific target (Hill & Rang 2013 s 95).

The next process in drug development is preclinical research, which takes place in a laboratory environment where the drug candidate is studied both in vitro and in vivo. The in vivo studies are conducted in animal models, one rodent and one non-rodent to assess if the substance's has the required effect- and safety properties. If the drug has required effect, it is further investigated in toxicity studies to examine at which dose the drug is toxic. Preclinical research also includes pharmacological studies to examine the pharmacokinetic and pharmacodynamic (PK/PD) properties of the drug (Hill & Rang 2013, s 204). All preclinical studies must be conducted according to the regulatory guidelines known as Good Laboratory Practice (GLP), which is a system designed to assure quality of preclinical studies in regard to conduction, archiving and reporting (EU-directive 2001/83/EC).

Clinical trials are studies on healthy volunteers or patients, where pharmaceuticals and/or medical devices are tested in terms of safety and efficacy. The owner of a clinical trial is known as a sponsor, who is often a pharmaceutical company. Although, almost all clinical studies, parts of or whole studies, are outsourced and conducted by Contract Research Organisations (CRO), which are consulting companies specialised in conducting clinical trials. Furthermore, a clinical investigator must be involved in the study and an investigator must be a physician or other qualified health care professional. The studies are most often conducted at a clinic, commonly known as an investigator site, with easy access to patients living with the condition that the drug aims to ease or cure. The physician, who is conducting the trial, i.e. the investigator is responsible for the patients' well-being and other concerns at the clinic, while the sponsor is responsible for everything concerning the drug. The sponsor is also liable to regulatory authorities (Lemne & Lafolie 2009, s 13-19).

Clinical research consists of four phases characterised by the purpose of the study. Most drugs goes through a series of studies in each phase and these might overlap or run parallel. During phase I, also known as the exploratory phase the study is conducted in healthy volunteers manly to confirm or disprove the results from the preclinical studies. The purposes of these studies are also to identify PK/PD properties of the drug in humans, to identify appropriate doses and to evaluate unwanted effects. In phase II or the explanatory phase, the drug is for the first time given to patients with the condition that the drug aim to ease or cure. The study population is small and consist of approximately 10 to 100 patients depending on the study design. The aim is to find the lowest dose where the drug has effect and to show POC. In phase III or the confirmatory study the study population increases and the study is designed to resemble the reality as far as possible. To get the new treatment registered and launched an application for registration must be transmitted to the regulatory authorities, providing that the results indicate superiority or non-inferiority to the standard of care. All studies conducted after registration, such as studies of long-term side effects are categorised as phase IV trials (Lemne & Lafolie 2009, pp. 10-12).

Perhaps the most important feature of clinical trials is the Clinical Data Management (CDM). Data management in clinical trials boils down to three individual processes; collecting data, cleaning data and managing data.

The traditional way of collecting data in clinical trials is by using a paper-based Case Report Form (CRF), which is a patient specific document where all study related data from that patient is assembled (Lemne & Lafolie 2009, p. 47). The collection of data using paper CRFs requires

multiple steps of data handling before it reaches the data management unit of the sponsor and the process may take up to 9 months, which delays the entire drug development process. The time consuming procedure is one disadvantage with the traditional paper-based data handling system, another and perhaps an even more critical disadvantage is quality. Due to the multiple step process there is a great risk for misplaced data, which could lead to possible loss of important information (Sahoo & Bhatt, 2004) and in the end a false negative result, which in statistics is commonly known as a type II error (Bring & Taube 2006 p. 148-149).

Quality, time and cost are the three main reasons why pharmaceutical industries and CROs continue to look for new innovative methods and techniques to improve data management in clinical trials. Electronic Data Capture (EDC) compared to Paper-based Data Capture (PDC) is a system that enables collection of data via an electronic CRF (eCRF) and it allows managing of data immediately after collection. eCRFs makes it possible for the investigator, instead of the data management unit of the sponsor, to make the entries. This takes place at the study site and has several advantages compared to paper based CRFs in regard to quality, time and costs (Sahoo & Bhatt, 2004). These benefits include greater accuracy, fewer queries, decreased paper record storage and timelier population of the study database. Nevertheless, implementation of digital systems like EDC in clinical trials has been a slow progression and Welker (2007) describes a number of barriers, which could explain this fact. This is further discussed in the theoretical background. As early as 2004 EDC was considered to be the preferred technology with significant advantages compared to existing methods.

When using paper-based CRFs the investigator records data and a sponsor representative will need to monitor the work at the clinic and conduct a Source Data Verification (SDV) to assure validity of data. All CRFs are then sent to the data management team, who complete the data entry. If queries arise, Data Clarification Forms (DCFs) are sent back to the clinic and first when all DCFs are resolved and the data are complete and free from errors it is called a clean file. A clean file means that the clinical part of the study is finished and the database is locked for statistical analyses (Sahoo & Bhatt, 2004).

1.3 Problematization

As stated earlier the drug development process in general and the conduction of clinical trials in particular is unsustainable today. Cost, size and timeline increases for each trial. According to a study conducted by Insel (2012) only about 1 out of 10 000 potential drug candidates reaches FDA approval.

When a target is chosen in the initial drug discovery phase there are about 10.000 potential drugs that can be considered candidates for further research. After the high throughput screening only about 250 compounds remain and subsequent to the preclinical phase and several in vitro and in vivo studies there are approximately five compounds out of the original 10 000. These five potential candidates are further studied in a clinical setting, in which approximately one reaches Food and Drug Administration (FDA) approval, see figure 2. The failure rate for new drugs is more than 95 % (Insel, 2012)

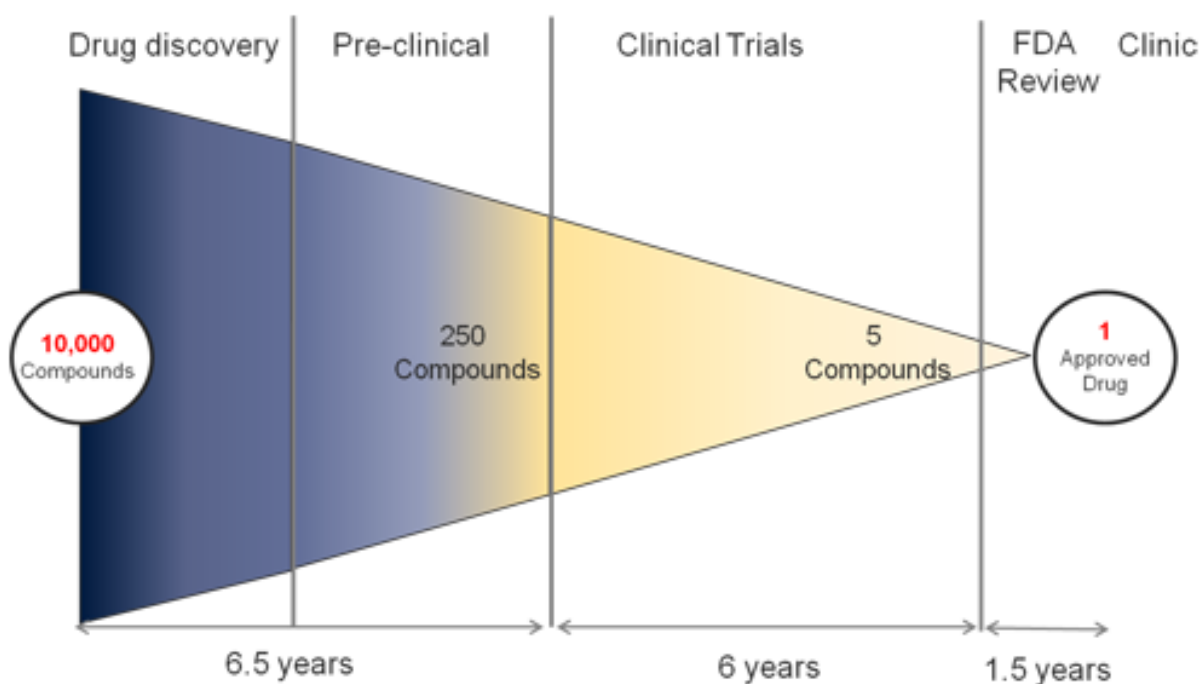


Figure 2. About 1 out of 10 000 potential drug candidates reaches FDA approval and this indicates a fail rate of more than 95 % (Insel 2012)

So drug discovery and drug development are high risk but potentially also high rewarding activities. An analysis conducted by Forbes in 2013 proves that development of one single treatment could cost up to \$ 350 million before the drug reaches the market. When including costs for all the substances that failed to meet the safety- and efficacy criteria the pharmaceutical

companies spend up to \$ 5 billion to get one single drug on the market (Forbes 2013). The time for this process from filing a patent to marketing approval is estimated to 10 – 20 years depending on the study, with an average lead-time of 9 – 12 years (Dickson 2009). Clinical trial is the last part of the drug development process. This process, in which pharmaceuticals and/or medical devices are tested in humans to assure safety and efficacy, is the most expensive and time-consuming part. During the process from the first First in Man (FIM) study to the last large phase III study a pharmaceutical company have spent an average of 10 years. However, 95 % of all drugs fail to be both effective and safe and therefore these studies are terminated (Forbes 2013). Bright Focus Foundation (2013) describes this phenomenon as ‘An Uphill Battle’ where every step is more difficult than the last, see figure 3. Previous research shows that digitalisation of different processes of clinical trials can save CROs and pharmaceutical companies both time and money, by reducing the time of data collection (Walther 2011) and increasing compliance and quality (Sahoo & Bhatt 2003).

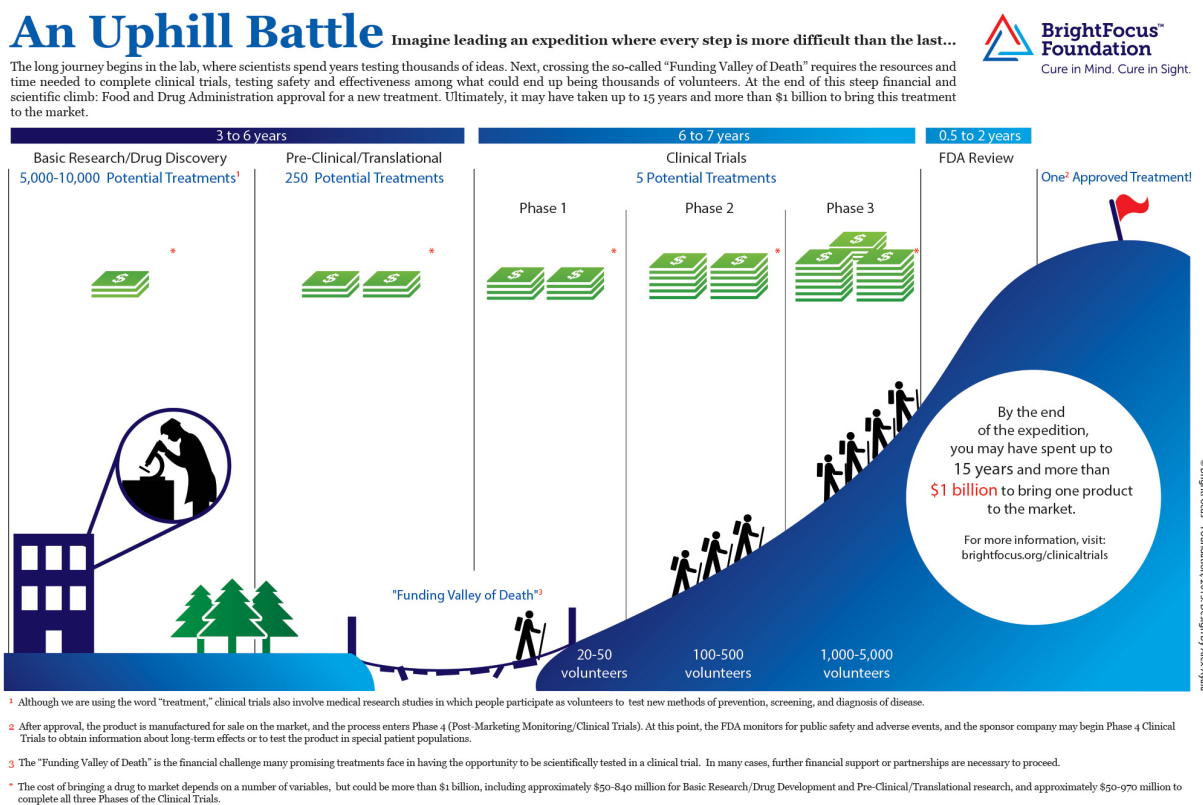


Figure 3. The cost increases with each phase of the clinical trial process. (Bright Focus Foundation 2013)

1.4 Aim and scope

EDC, in opposite to manually collected data is not a new phenomenon. This technology has been available in 15-20 years. However, even though the rate of EDC systems in clinical trials are increasing, the progression have been slower than anticipated.

Since the ability to collect data electronically in clinical trials already exists and the advantages of using this system is well documented, this is probably not a question of a pure technical problem. Perhaps it is rather a problem that addresses a more practical issue of usability or maybe a social, cultural, regulatory or organisational problem. It appear that the diffusion of this method for use in data management was a slower process than the industry expected and it is not as widely spread nor as developed as some people thought it would be in 2014. During this project I hope to gain a deeper understanding of the diffusion of this innovation and chart what barriers a company trying to acquire this market is facing and why the adoption of this innovation has been slower than anticipated.

The particular problem for the project client is weather to acquire the market for digital applications in clinical trials or not and also what they need to bear in mind if they do. Before Cenvigo can enter this market they need to know what difficulties they are facing and what the solutions might be and based on this the aim is defined as follows.

The aim of this project is to trace the evolution of ePRO/EDC systems, identify what external factors that affects the adoption and what the future trends and needs are and based on this provide Cenvigo with an advice regarding development of an ePRO/EDC system.

To meet this demand the study is divided into three research questions, which will address both (1.) the product evolution (2.) the environmental implications and (3.) the business advice for Cenvigo.

1. *What is the difference between PDC, early EDC systems and EDC systems today?*

This question aims to address the history of ePRO/EDC systems in clinical trials. In order to investigate if the slow diffusion is a result of unsuccessful development of the product, I intend to trace the evolution of the product and assess what the growing pains of the technology might be. If the problem is a result of unsuccessful development, it can be considered a more product related problem. In addition I will investigate the differences with the precursor PDC.

The next question will address another dimension of the problem and aim to reveal if the slow diffusion is related to how the product was implemented and used in a clinical trial setting.

2. *What potential external parameters can affect the adoption of ePRO/EDC systems when these are implemented in clinical trials?*

This question will address potential problems within the adopting organisation and potential regulatory requirements that must be met when implementing ePRO/EDC systems.

The other part of the advice is based on the next question and will primarily focus on customer needs and this question can be considered the foundation to a market survey or a needs analysis.

3. *What are the future market needs and trends in regard to features of systems for data collection in clinical trials?*

This question has a clear business perspective and lays the foundation for the business advice to Cenvigo.

1.5 Delimitations

This project focuses mainly on the collection of data and the first step of the data management process. The systems used in clinical trials today are so much more than just a data collection tool but in this study the collection is the main focus. In this project I have chosen to call it EDC but the whole system in which you create protocols, build trials and write reports are called Clinical Trial Management Systems (CTMS) and these sorts of systems is only briefly discussed with the informants. In addition I have chosen to exclude all technical details concerning how to programme these systems and how to technically assure that data is securely transferred.

Furthermore, I have chosen to focus less on the business perspective, such as market shares, revenue and whether Cenvigo will benefit from acquiring this market. Here I will only present Cenvigo with an advice on what to bear in mind when developing this product. This advice is based on how these products were developed in the past and how it was adopted, what environmental factors that affects the adoption and what the future needs and trends seems to be for data collection in clinical trial.

1.6 Disposition

In section 1, the introduction, I will provide the reader with background information, both on why Animech Technologies took part in the development of PANDA and also the background for this particular project and the new indication for the application, which is in a clinical trial setting. To understand the aim of this study it is also necessary to provide the reader with a brief introduction to the clinical drug development process, which also will be presented in this section. In section 2 I describe the methodological approach taken in the study. Section 3, Key concepts of data management in clinical trials is the theoretical background and is based on the result from a literature study conducted, particularly on EDC in comparison to PDC but also on what characterises the industry in general. The theoretical framework is based on Everett Rogers (1983) theory on diffusion of innovation and this is presented from an EDC perspective in section 4. Section 5 contains the empirical result from the interviews conducted during this study. This section is divided into 4 subsections based on the research questions presented to meet the study aim. These subsections are (1) the difference between EDC and PDC and (2) key factors for a successful EDC system. These two subsections aim to answer the first research question and have a clear product perspective. The next subsection (3) is the environmental impact on implementation of ePRO/EDC system and it aim to answer the second research question. This subsection is further divided, based on the responses from the informants, into social, organisational and regulatory problems and the purpose is to analyse if it is an environmental problem rather than a product problem that was causing the slow diffusion. In subsection (4) the result from what can be considered a need analysis will be presented and in the last subsection the result from more ePRO specific questions will be presented.

In the next section (6) the empirical result is analysed using the theoretical framework and a conclusion is also presented. A discussion about the general problems presented in the introduction will be held in the last section (7) and in the discussion a business advice for Cenvigo concerning their product PANDA will also be presented and discussed.

2 Methodological approach

During the initial discussion with the project owner the project description consisted of a market analysis to furnish the project owner with a business plan for launch and future development of Dynamically Extendable platform for Long-Term Assessment (DELTA) as an electronic Patient Reported Outcome (ePRO) tool. The project owner intends to acquire the market for digital applications for use in healthcare and self-care as part of a new trend called telemedicine, where home-care at a distance is the main focus. Now the company would like to know if it is profitable to also acquire the clinical trial market and that was where this project originally started.

The generic application DELTA and the software CenPad on which data from different applications is displayed could in the future work as ePRO and an EDC-system respectively. However the work of developing an EDC-system from cenPAD is an extensive work and has not yet started. That is why the focus of this project shifted from a typical market analysis of the market for ePRO in clinical trials towards a general mapping of barriers and solutions for successful implementation of ePRO tool and EDC-systems in clinical trials.

As discussed above, the original purpose of this study was to investigate if the market for digital applications in clinical trials is lucrative and if Cenvigo would benefit from acquiring this market but after studying the latest research literature within the field another problem arose.

The digital technology used in clinical trials today have existed in more than 20 years but the diffusion of EDC systems and ePRO tools was much slower than anticipated (Sahoo & Bhatt, 2004). Therefore the problem statement and the aim of the study were adjusted and the problematization finally resulted in a question of why the technology wasn't as successful as researchers first expected.

In order to understand the slow rate of diffusion I identified two dimensions to this problem; (1) the product itself i.e. the development and evolution of ePRO/EDC systems as a product and (2) the environment i.e. the external factors that could affect implementation of these systems. If the low adoption rate is a result of ineffective ePRO/EDC systems, this could indicate that the slow diffusion is a problem related to the product rather than related to how the product was implemented and used in a clinical trial setting.

Based on these two dimensions the project resulted in an examination of ePRO/EDC systems and the product evolution as well as an examination of external factors that might affect implementation. Based on these two dimensions and the research questions presented on page 15 and 16, I will during this project gain a deeper understanding of the reason why the market progression was much slower than anticipated. In addition, I will aim to map out the future market trends and needs of data collection in clinical trials, which will be the foundation of the business advice for Cenvigo. This two-sided aim gave the project the scientific level that is required in a master thesis and at the same time delivered a more substantial or specific advice regarding the case to the project owner.

2.1 Study design

The relation between theory and empirical result can be described as either deductive or inductive. Bryman (2013, pp. 27-29) describe deductive theory as generation of a hypothesis based on previous knowledge. The hypothesis is in turn the foundation on which data is generated and based upon. With appropriate data collection it should be possible to discard or approve the generated hypothesis and redefine theory. This approach is more common in quantitative research, which is perhaps more associated with natural sciences while the inductive approach is often seen in qualitative research perhaps more associated with social sciences. An inductive approach is characterised by generation of theory, based on empirical results rather than the opposite (Bryman 2013, pp. 27-29).

This project does not have a clear deductive or inductive approach. However, Alvehus (2013, p. 109) describes that the most common way to relate to theory and empirical data is with an abductive approach, which is with a combination of deductive and inductive theory (Alvehus 2013, p.109). From one perspective, the aim of this study indicates an inductive approach and is based on qualitative research with a limited number of interviews. The empirical result from this, as a case study could generate a hypothesis of why the diffusion rate of EDC/ePRO systems was slower than anticipated. On the other hand, two dimensions to this problem with slow diffusion rate were already identified; the first two research questions imply two potential reasons for the slow diffusion rate. These dimensions were described in the section above and could be considered a hypothesis. So perhaps an abductive approach is more appropriate description of the relationship between theory and empirical data in this study.

The design of this project is a case study where different organisations such as Contract Research Organisations (CROs) Academic Research Organisations (AROs), pharmaceutical

companies and clinics are studied in terms of adoption and use of ePRO/EDC-systems. In more general terms it can be considered a case of implementation and diffusion of technical innovations in technologically resistant organisations.

Yin describes different cases when it is appropriate to use what he refers to as single-case studies, one of these are the typical case which refers to a study of an average project among others (Yin 2003, p. 41). This project indicates an approach of *average case as a single case study* since the adoption of EDC can be seen as adoption of any technology in a technology resistant organisation. The single case approach is taken mostly due to the large amount of resources that a multiple case study demands (Yin 2003).

Case studies are often related to qualitative research and an inductive theoretical approach. One case can generate a hypothesis but the external validity is often low and one can argue that a general conclusion to other cases cannot be drawn from the result of only one case study (Bryman 2013, p. 51). However, it is a good way of generating a hypothesis that might be the foundation to further research within the field.

Validity and reliability are keystones for the evaluation of qualitative research according to some researchers (LeCompte & Goetz 1982), others believe that qualitative research should be evaluated according to other concepts such as trustworthiness and authenticity (Lincoln & Guba 1985) Reliability is the degree to which the result would be the same if the study were to be conducted again or if the results are influenced by extraordinary conditions. Since it is impossible to freeze a social context the results are bound to be biased in a qualitative research. The internal reliability describe how well the members of a research team agree on how the results should be interpreted (Bryman & Bell 2013 p .351) but since this project only include one researcher internal reliability is not applicable.

Validity describes how well the results from one study can be generalised to the whole population. The external validity is often low in qualitative studies due to frequent use of case as a method and a limited sample size, just as in this study. As discussed previously the external validity in this study must be considered low and the result, since it is a case, could only function as a generator of a hypothesis of the whole population i.e. all technologically resistant organisations. This means that the result from this study will only answer to why diffusion rate of ePRO/EDC systems was low in the organisations studied here and cannot be generalised to why diffusion rate of technological innovation would be slow in technologically resistant

organisations in general. However, the result from this study could function as a hypothesis to this but that will not be discussed further in this project.

2.2 Research method

The nature of the formulated questions implies a qualitative approach. A quantitative approach would demand a large sample size and it would probably be difficult to find an appropriate number of participants since the research question requires certain knowledge within the field. A literature study of previous research on implementation of ePRO/EDC-systems was conducted. Also, interviews were held with professionals within the field. By interviewing a number of professionals that work with EDC-systems or ePRO-tools daily in different ways I hoped to gain information about what the problems with these systems were, both when the first systems were launched and also what problems and benefits these systems have today.

2.2.1 Literature study

A comprehensive literature study of implementation of ePRO tools and EDC-systems was conducted to receive further knowledge about previous research within the field. The database mainly used for this purpose was PubMed and to receive a comprehensive result publications from the beginning of 2000 up till today were included in the literature study. Search words frequently used were; EDC, ePRO, Clinical Trials, Telemedicine, This theoretical background is presented in section 3. *Key concepts of data management in clinical trials*, while the result from the literature study of theories about diffusion of technological innovation is presented in section 4. *Theoretical framework*.

The problematization and the previous research presented in the theoretical background, together with my pre understanding of the topic, was the foundation for the choice of study design.

The second research question includes an investigation of ethical and regulatory problems that might arise when developing an ePRO/EDC system. To get this part as accurate and up to date as possible this section is not based on the interviews but on an additional literature study of regulatory requirements concerning ePRO/EDC systems. This included primarily regulatory documents from the Food and Drug Administration (FDA) and European Medical Agency (EMA) and the result from this literature study will also be part of the result and empirical material.

2.2.2 Interviews

The collection of empirical data consisted mainly of interviews with people working with different types of EDC-systems, with different parts of EDC-systems and also in different stage of the clinical trial process. To get a general idea of the past and current status and also future needs semi structured interviews were held with informants from CROs and pharmaceutical companies, which are the most frequent user of EDC-systems and many companies have created their own. By conducting these interviews I aimed to acquire a deeper understanding of what drives successful implementation of EDC-systems and what features are important to distinguish EDC-systems and eCRF from a paper-based approach.

16 interviews were conducted with participants from ten different organisations. The first twelve interviews were held face-to-face, most of them in an office environment while the last four interviews were conducted using a qualitative questionnaire, see annex 1. All participants that gave their consent were recorded and the recordings were used when the results and citations were written.

The focal point of this study is fairly explicit and therefore the interviews were conducted in a semi-structured manner instead of unstructured. Unstructured interviews are more beneficial in explorative studies while semi-structured interviews could well be used for studies with a clear focus and a specific issue. The latter method also simplifies comparisons between empirical results. (Bryman 2013, p. 416). Since the interviews were conducted with informants from different companies, in different positions and with different experience of EDC-systems and PRO-tools, semi-structured interviews with a research guide of the main discussion topics and questions seemed legit for the purpose. The research guide was used as a somewhat of a template for the interviews, which allowed flexibility at the same time as every aspect of important topics and questions were addressed. Bryman (2013, p. 413) consider semi-structured interviews most beneficial when investigating different organisations with several units due to the possibility of making comparisons.

2.2.3 Sampling

All participants are professionals, working within clinical research and they were selected using a chain sampling or snowball method. This method is effective given that people tend to be more prone to participate if they know that someone working within their field recommended them. However, there are disadvantages with this method, Alvehus (2013 p. 68) points out the risk of receiving misrepresentative data, as many of the participants know each other. Since

participants from a chain sampling tend to have the same opinion about the issue there is a great risk that the question is not being as widely elucidated as one would wish for. To reduce the risk of bias most participants interviewed are senior professionals within the field currently in managerial occupations. The informants are working within different processes of EDC and interviews were conducted with several different professionals such as Clinical Trial Assistants (CTA), Clinical Research Associates (CRA), Data Managers, Project Managers and Line Managers. For detailed descriptions about the informants please see section 5.1.

2.3 Ethical implications

Ethical implications considered in this project included informed consent, voluntariness and personal integrity. All participants were fully informed about the purpose of the study and they were also told that they could choose not to answer a question and at any time terminate the interview if they were uncomfortable. The interviews were recorded, if the participant allowed it and it was clearly stated that the recording was for personal use only. If a participant were cited in this report, the participant gave their permission first. Only a verbal consent was collected and the confidentiality of the participants' personal information, such as name and work position, was handled according to individual agreements with each participant. No names of companies are mentioned in this report.

2.4 Method for analysing empirical data

The Interviews were transcribed and all data were sorted according to five categories with appropriate subcategories; difference between PDC and EDC, difference between the first EDC systems and EDC systems that are used today, external factors that have affected the adoption of EDC, the future of data collection and last data about ePRO and PANDA. Sorting data is a good method for finding corresponding categories or categories that in other ways are related (Alvehus 2013, p. 110). The next step in the analysis process was to reduce the empirical material. Data that wasn't essential for the five selected categories were not presented but data that was considered ambiguous were of course presented if it concerned the main issues. Since empirical material often include contradictions it is important that all relevant data is presented to not receive a misleading result (Alvehus 2013 p. 112).

2.5 Choice of theoretical framework

As previously described the main focus of the project lays within the diffusion of a technical innovation and how mature the market and the product has become since EDC systems were first launched. What's special with this market is that the customer is not the end user and the end user does not get charged. The customers, who are CROs and pharmaceutical companies, are quite used to technically advanced tools and systems but the end users however are often not used to digital technologies. The end users are nurses at the clinical or patients who participates in the study.

The theoretical framework will therefore focus mainly on theories about adoption and diffusion of technological innovation and Rogers (1983) theories on diffusion of innovation will be the foundation for the analysis of the empirical data.

3 Key concepts of data collection in clinical trials

This section is the result from the literature study conducted to summarize the latest research within the field of data management in clinical trials and this theoretical background will clarify the basics of clinical trials in general and data collection in particular. It will also give a broad perspective of the latest research of implementation of electronic Patient Reported Outcomes (ePRO) and Electronic Data Capture (EDC) systems in clinical trials.

This section is divided into 3 parts; the first will describe *the process of Data Collection* (section 3.1) and the importance of efficient *Case Report Forms* (section 3.1.1) on which data is collected. When this form or document is electronic it is named eCRF, which is part of a system called *Electronic Data Capture* (section 3.1.3). When data is entered by the patients, whether it is on a paper or electronically into an EDC system it is called *Patient Reported Outcome* and this is described in section 3.1.4. The second part (*section 3.2*) describes potential barriers of implementation of EDC systems in a clinical trial setting. The last part (section 3.3) includes the typical features of the market as well as cost, time and quality assurance of the drug development process.

3.1 The process of clinical data management

The process of clinical trials and data management were briefly described in the introduction and this section will provide a deeper understanding of the key concepts of data management in clinical trials.

In 2004, Sahoo & Bhatt (2004) stated that current method for data collection in clinical trials is in most cases a manual process. They refer to this process as Paper-based Data Collection (PDC). Data collection occurs at the clinic, which can also be referred to as clinical sites. Patients that participate in clinical trials visit the clinic frequently and the rate of visits is predetermined in the study protocol, which is specific for each clinical trial. At the clinic, data is collected on a Case Report Form (CRF) and to validate that all data are accurate Source Data Verification (SDV) is conducted by a representative from the sponsor, if this data is collected electronically the method is called Electronic Data Capture (EDC) rather than PDC.

3.1.1 Case Report Form

In a PDC study patient data is collected and documented on a Case Report Form (CRF), which is a patient specific document where all study related data from one patient is assembled (Babre 2011). This document contains everything from efficacy data, which is data related to the objective of the study, to safety data and information about concomitant medication and Adverse Events (AE). Safety data is often a collection of symptoms related to the study drug. However, it is difficult to determine what symptoms are related to the drug and what symptoms are not. Therefore all adverse events, which are events or symptoms that might be related to the study medication is documented and after evaluation the investigator and the sponsor can upgrade it to a related AE but all events are documented even if there is no correlation to the study drug. The International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) define AEs as:

“Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.”

(ICH Topic E6; Good Clinical Practice)

AEs are important to document due to safety reasons and to synchronize these it is important that all events are reported in the same terms. There are databases containing the right terms, which are often a diagnosis and not a symptom. The same databases exist for concomitant medication.

3.1.2 Source Data Verification

To assure quality and accuracy of data, a Clinical Research Associate (CRA) also called a monitor, who is a sponsor representative from either a pharmaceutical company or from the Contract Research Organisation (CRO) are sent to the clinic to conduct monitor visits. These visits include Source Data Verification (SDV) and collection of completed CRFs (Sahoo & Bhatt 2004). Source data must be crosschecked with the data in the CRF and according to ICH-GCP source data is defined as:

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

It is important to know what is approved as source data or source documents for the SDV to be accurate. The monitor visits differ depending on how data is collected in clinical trials, if the study uses PDC or EDC. The traditional way of data capturing, using a paper-based method is much more time consuming. Monitor visits also include inspection of signatures, informed consents, unchecked boxes and other potential errors. When errors are resolved the monitor collects all CRFs and bring them to the sponsors Clinical Data Management (CDM) team (Babre 2011). CDM is a cross-functional division, vital for high quality data. When using a PDC process all data is entered into a Clinical Data Management System (CDMS) manually, often with a double data entry method for quality control meaning that two people enter the same data and all entries are thereafter cross-referenced for errors. Errors or queries must be sent to the clinic for resolution via a Data Clarification Form (DCF) (Sahoo & Bhatt 2004). As one can imagine, this paper-based process is both expensive and time consuming. A study conducted in 2011 show that the average cost per DCF is about US\$ 80 – 120 and resolution of one query takes about 5-8 days from sending a DCF to receiving a signed resolution in a traditional PDC study. First when all queries are resolved the CDM team can lock the data file (Babre 2011). The lead-time from collection of data to clean, ready-to-lock-data is 6 – 9 months when using a traditional paper-based system (Sahoo & Bhatt 2004). The time and costs in clinical trials today, as well as for 10 years ago are unsustainable and the search for more effective ways to collect data is an ongoing process. EDC has according to most research shown to be very effective in reducing both time and cost.

3.1.3 Electronic Data Capture

3.1.3.1 Development

A precursor of EDC was introduced in the mid 1980s, as a result from the introduction of personal computers. Before it was possible to use PC for data capture in clinical trials, all data was collected on paper and sent to a centralised sponsor-owned facility where all data was computerised. This precursor allowed for study personnel at the site to collect and capture data in a decentralised manner. Data was regularly, daily or weekly transferred to the sponsor via the phone line and depending on the data volume it could take quite some time. This way of collecting clinical data became known as Remote Data Entry (RDE) and the RDE software was installed locally on computers with modems (Marks 2004). In the late 1990s a web-based solution to collection of clinical data capture was initiated and the acronym was changed from

RDE to EDC - Electronic Data Capture. The difference between RDE and EDC lays mostly in the way data is transferred. Investigators still used paper for collecting data and computerised it using an EDC-system but instead of transferring data to the sponsor via phone, the Internet was used. This resulted in more rapid and frequent transfers and hopes of a more efficient data management process (Marks 2014). EDC-systems today are connected to an electronic CRF (eCRF) as opposed to paper-based CRF. In 2004 Sahoo & Bhatt (2004) declared that EDC is the new mantra of data capturing but according to the authors, paper CRF is still considered the current way of conducting clinical trials. Kush (2006) conducted a study that indicated that only one third of all clinical studies was using an EDC-system. Today that number seems to have increased.

Many studies, comparing EDC systems with the traditional way of capture data in clinical trials were published during the mid of 2000s (Marks 2004; Sahoo & Bhatt 2004; Welker 2007) when it was clear that the method hadn't spread as fast as anticipated. One thing that all their research has in common is that it shows that EDC is in most cases superior to PDC in regard to cost, time or efficacy. However there are quite a few barriers or issues that is important to bear in mind.

3.1.3.2 Advantages with EDC

Raviteja and Ishal Gupta (2013) propose 4 main reasons for implementing an EDC system in clinical trials. The first being real time data access. As soon as data is gathered from the patient at the investigator site it is possible for the sponsor to view the data. EDC systems also makes it possible to transfer data more efficiently and thereby reducing the time it takes for the drug to reach the market. The third benefit of using EDC in clinical trial is of a more practical nature. When a paper-based method is used, the amount of paper CRFs are enormous and by using eCRFs instead, the sponsor overcomes all the shipping of CRFs from the investigator sites. The last reason is described as synergy between serious adverse effect reporting and the database (Raviteja & Gupta 2013). Serious adverse events (SAE) are, by ICH-GCP defined as:

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- *results in death*
- *is life-threatening*
- *requires inpatient hospitalisation or prolongation of existing hospitalisation,*
- *results in persistent or significant disability/incapacity, or*
- *is a congenital anomaly/birth defect.*

If SAEs occur during the trial it is important that those are reported within the timeframe determined by the European Medical Agency (EMA). This is very important from a safety perspective.

One study shows that the interaction between the investigator or study nurse and the patient can be compromised while using an EDC system. The interviews with patients were found unnatural when the interviewee had to turn away from the patient to a keyboard to document data directly to a computer. This disadvantage was tested in regard to error rates, time and cost in a study published by Walther et al. (2011). Interviews with study subjects were conducted to compare traditional PDC with four different EDC devices; PDA, telephone, tablet and netbook, which is a small lightweight laptop. These interviews were based on a typical CRF and the answers were registered by the interviewee on one of the four devices or on paper. The different ways of data capture were compared in regard to error rates, duration of interviews and data entry and costs. The results from this study indicate that while EDC interviews takes slightly longer, data becomes available immediately, which in the end makes EDC much more time efficient than PDC. In regard to error rates, this study shows that the netbook and PC performed better than PDA and telephone interviews as a prolongation of EDC systems. So even if the interaction is compromised EDC show better results.

The writers propose that if EDC systems are well designed and appropriate training are offered to study personnel it could reduce errors, time and costs associated with data entry and correction of data (Walther 2011). Mitchell et al (2011) concur that most errors that appear in CRFs are from transaction of data from a paper-based source to an EDC system. With early training on how to make direct data entry to an eCRF, the writers mean that a major reduction of errors due to transaction mistakes can be accomplished (Mitchel et al. 2011). This is confirmed both by Raviteja and Gupta (2013) and Sahoo & Bhatt (2004) that agree that one of the most important benefit with EDC is that eCRF enables control during the first entry of data. It is possible to include checks for unchecked boxes or implausible data, which results in reduction of errors (Sahoo & Bhatt 2004). The decrease of errors results in less queries (Raviteja & Gupta 2013) and reduced time spent on DCF and query resolution (Sahoo & Bhatt 2004). Another advantage with instant data entry is that there is no need for CRF retrievals, manual data entry at a central site or data cleaning, which are all very time consuming processes (Sahoo & Bhatt 2004). Another important benefit with the instant data entry is that it allows fast transfer, which in turn allows sponsor to access data more quickly (Raviteja & Gupta 2013). If data reaches

sponsor more quickly it is easier for the sponsor to report events to the authorities (Sahoo & Bhatt 2004) and to make quick decisions about the study (Raviteja & Gupta 2013).

These decisions are often related to patient safety and might in worst case regard termination of the study. Since many studies are double blind there are often a Data and Safety Monitoring Board (DSMB) connected to the study. This board works as advisers on behalf of sponsor to assure that the study is not continuing if the results indicate that termination of the trial is the best decision. However, the board does not have the authority to decide if a study should be terminated, only the sponsor is allowed to make a decision like that.

By making all data entries at site it is possible to get access to data immediately after it is entered. This is not only important for decision making but also for monitoring and SDV. Immediate access and most important, access from any location makes it possible for the CRA, who does the monitoring to pre-monitor the site from a central location, to assure that all CRFs are filled out before going to the clinic to conduct SDV.

To summarise the advantages with EDC compared to PDC, most researcher agree that EDC is superior to PDC in regard to time, cost and data quality, or perhaps reduction of errors which in turn results in reduction of time. Nevertheless depending on the study design, for example if it is a small study with only a few participants the PDC could be beneficial in regard to time and cost when the time it takes to build the study and install and learn the system is included.

3.1.3.3 Disadvantages with EDC

In studies comparing PDC and EDC, it is clear that EDC has advantages compared to PDC but this fairly new way of collecting data has quite many disadvantages as well.

Raviteja & Gupta (2013) points out a few technical problems that must be sorted out before using an EDC system and the disadvantages that comes with it. Depending on the system it is important that all software needed is installed on each PC, this is a time consuming process and it is not sure that the study benefits from using EDC systems if it takes too much time to set it up. In other systems, the use of EDC requires Internet connection in the remote area. Most EDC systems today seems to be web-based so this is often not a big issue but if studies are conducted in certain countries it could be a major problem.

When using EDC for collection of data it is important that all electronic devices that are used are regularly validated to assure accuracy and if data is transferred using the Internet it is also

important to validate that all data is secure. The regulatory requirement regarding data security is further discussed in the empirical section, compliance with the Title 21, CFR part 11 (21 CFR 11) of the code of federal regulations, which applies to the electronic records and electronic signatures, will also be discussed in the empirical section.

Marks (2004) conducted a study in which he compares the clinical trial industry with the airline and bank industry. Both banks and airline industries have successfully moved on from paper-based system to secure and efficient global data transfer. Paper copies are available in these industries but they are not essential. So, why is the clinical trial industry so reluctant to change? Marks (2004) proposes three reasons for this; FDA, lack of mobile hardware and attitude. In 2004 when this study was conducted the FDA provided guidelines with requirements for data capturing with electronic systems, it was however much confusion over these guidelines due to requirements for the source documents (Marks 2004). Source documents were often paper-based so the guidelines had to be rewritten and today FDA states that electronic data can be considered source data. This includes data that only exists in eCRFs, laboratory results and results from medical devices that transcribe data directly into the eCRF or EDC database. If data are documented on paper in addition to the eCRF, the data on paper-based document are to be considered source data (FDA Guidance for Industry Electronic Source Data in Clinical Investigations 2013.)

The second reason according to Marks (2004) is the lack of mobile hardware but today this cannot be considered a real problem since the technology has change substantially since 2004. The last reason of why the pharmaceutical industry is reluctant to change is, according to Marks (2004), attitude. He believes that monitors, who are validating collected data, are the source of this negative attitude. Since the manual validation process has been a part of the monitors work ever since the centralised computerisation through RDE and later EDC he believe that the monitors need to realize that they will still be required even though their tasks and work processes will change.

3.1.4 Patient Reported Outcome

To take the use of EDC even further a prolongation of the EDC system was developed for patients to entry part of their data themselves. When patients make their own data entry with an electronic device it is referred to as electronic Patient Reported Outcomes (ePRO). PRO has been used for a long time in clinical trials but unfortunately the compliance with these paper based PRO are not good. When comparing ePRO and paper based PRO the compliance is considerably

higher with the ePRO. ePRO can include electronic patient diaries in which the patients report some of the study data themselves. What data that can be reported with the use of ePRO is of course protocol dependent. An implementation study of PRO was conducted in 2014 to validate the development and implementation of a certain PRO system developed for use in pragmatic trials. Pragmatic trials are supposed to mimic the reality as opposed to explanatory trials where the settings are highly controlled. It was concluded in this study that the implementation was successful (Cramon et al. 2014)

3.2 Implementation of electronic systems in clinical trials

Studies that aim to evaluate barriers for implementation of EDC systems were also conducted during the mid 2000s. One article, often cited in other publications, is based on a literature study conducted by James A Welker in 2007. According to Welker, the user input is crucial when implementing a new system. Often, input is only obtained from a small user group, more technically oriented than process oriented. This frequently results in failure of implementation. Welker believe this could be avoided by obtaining input from all participating parties of the clinical trial. By including both CRO, sponsor and the investigator site the user motivation and thereby the chance of a successful implementation will increase. To further increase user motivation, all end user must know that the new technology will add to overall productivity and profitability and it is therefore important to educate all parties of the implementation process. This is especially important at investigator sites with a flat organisational structure. Welker also points out the importance of technical support as well as a well-designed Graphical User Interface (GUI) (Welker 2007).

3.3 Cost of drug discovery and drug development

The first two steps in the drug discovery and drug development process are, in terms of time and costs often included in the concept of preclinical research. According to a review by Steven Morgan et.al (2011), which aimed to systematically assess published estimates of costs for development of new drugs, the preclinical research stands for approximately 20 % of the total costs. That means that the clinical trials stands for 80 % of the total drug development cost. This study compared a number of original articles from different time periods to evaluate the development of costs over time.

Drugs first tested during a period from 1990 to 2003 had an average preclinical capitalised cost of US\$ 164.7 million, while the same drugs had an average clinical capitalised cost of US\$ 573.0 million (Morgan et al. 2011). A review published in nature in January 2012 confirms that the

preclinical costs for New Molecular Entities (NME) and biologics stands for approximately 1/5 of the total expenditures per drug, 17 % to be exact. The preclinical cost for drugs approved from 1990-2008 is according to Allison approximately USD\$186 million and the clinical cost is about US\$ 189 million (Allison 2012). However, if you include the cost for allocated failures, which is US\$ 866 million the average total capitalised costs for drugs developed during a time period from 1990 to 2003 is US\$ 1.241 million (Allison 2012).

According to the study by Morgan, the variation of average cost between the 13 original studies was 9-fold and changes over time indicate that the cost have increased from a total average of USD\$92 million for drugs developed in the 1960s and 1970s to USD\$737 million for drugs developed in 1990s and 2000s. All figures were converted to year 2009 US dollars (Morgan et al. 2011). Part of this increase seems to be caused by higher costs at each stage of the process due to higher requirements from the authorities. Another reason for this increase seems to be related to failure of drugs in later stages of the process. The longer the study continues the more expensive the drug becomes so the cost for drug development is, throughout the study phases growing at an exponential rate (Morgan et al. 2011).

4 Theoretical framework

The central concept of this project lies within diffusion of technological innovation. Therefore theories about adoption, implementation and diffusion of technological innovations, with authors such as Everett Rogers, Melissa Shilling and Tornatzky and Fleisher are included in the theoretical framework. These theories will be used in the conduction of the analysis of the empirical material, in an attempt to describe why the diffusion of the technology has been slow. A comparison between the collected data and previous research on important factors for diffusion of innovation will give a comprehensive analysis of the empirical data.

4.1 Diffusion of innovation

Several researchers have defined technological diffusion or Diffusion of Innovation (DOI). The central meaning of the expression similar but in order to understand the theories used in this section I will present the different definitions formulated by some of the main researchers within the field.

Everett Rogers (1983), whose theories on DOI will be the foundation for this theoretical framework, proposed a model he defines DOI as:

"a process by which an innovation is communicated through certain channels over time among the members of a social system."

(Rogers 1983 p. 5)

Further definitions of the expression was established by Peres, Muller and Mahajan (2010) who describes diffusion of innovation as:

"the process of the market penetration of new products and services that is driven by social influences, which include all interdependencies among consumers that affect various market players with or without their explicit knowledge."

(Peres, Muller & Mahajan 2010)

As stated earlier, Rogers' theories about diffusion will be the foundation for the theoretical framework. The focus will primarily be on the variables that according to him determine the rate of adoption, since rate of adoption or diffusion is the main research question for this project. To understand what drives the adoption of innovation it is of great importance to understand how technology is adopted, which will be presented in section 4.2. In addition it is important to know what characterises technological diffusion. To understand this, the definition proposed by Rogers (1983) will be used. His definition contains four elements that characterises DOI and these are therefore of importance to further define. *These are innovation, communication channels, time and social systems.*

4.1.1 Innovation

Rogers describe the innovation as an idea that is perceived as new. Newness does not necessarily need to be objectively new, it is enough that the idea seems new to the individual, to be an innovation according to Rogers (1983, p. 11). Innovations are categorized into radical versus incremental innovations and product versus process innovations. A radical innovation is very different from all prior solutions while incremental innovations can be seen as more of fine adjustments to existing inventions (Shilling, 2014). Electronic Data Capture (EDC) systems can be seen as a product innovation for the company who develops and puts the system on the market but a process innovation for the customer who will use it. In many cases one Contract Research Organisations (CRO) can take on both roles, partly as producer and distributor and partly as customer, as many CROs design their own system due to lack of suitable systems on the market. EDC and electronic Patient Reported Outcome (ePRO) were radical innovations for data handling in clinical trials when it was first launched, competing with paper Case Report Form (CRF) and manual data entry. However, the leading edge EDC systems that are used today, which are connected to other databases such as randomisation centres and laboratories are rather to be seen as incremental innovations to the first EDC system.

Rogers have identified several attributes that are common in successful innovations, which are further presented in section 4.2.2 Attributes for adoption of innovation.

4.1.2 Communication channels

The second element in the definition presented by Rogers is communication channels. When Rogers discuss channels he define it as the means by which messages get from one individual to another. It seem that homophily, two people that are a like communicate more frequently and can thereby increase the communication and also adoption of an innovation. Rogers explains this as group belonging, similar people often have the same interests and belong to the same social group. The problem with this is that these people often have the same values and the

communication doesn't get as effective in regard to adoption of innovation. Heterophily, which is more common, would perhaps increase the communication more but they often doesn't speak the same language and doesn't see innovations in the same way.

4.1.3 Time

When discussing DOI and adoption of new technology, time is one of the most important aspects. Time can be related to the time it takes to decide if the innovation is worth adopting, the innovation decision process and also the time it takes for different categories of the social system to adopt an innovation. In the next section 4.2 Adoption of innovation, these different categories based on time of adoption will be discussed.

4.1.4 Social system

Rogers (1983, pp. 110) define a social system as *a set of interrelated units that are engaged in joint problem solving to accomplish a common goal*. The relationship between social system and adoption can be a question about for example system norms and culture. When discussing what affects rate of adoption it seems that the structure of the social system is of great importance and this will further be discussed in section 4.2.2 Attributes for adoption of innovation. What causes this rate of adoption seems to not only lie within social systems but different elements as well. The type of innovation-decisions seems to be one of these factors and this will together with other elements also be discussed in the section 4.2.2.

4.2 Adoption of innovation

4.2.1 Rate of adoption

When a new technology is introduced to the market the number of adopters is initially low often due to unfamiliarity but as the time passes and the technology becomes better understood the number of adopters will increase. By plotting the percentage of adopters in a population against the time the technology has been on the market an S-curve will appear. This curve is often used to describe diffusion of innovation (Schilling, 2014). Everett Rogers proposed this model for diffusion in 1962, in which he describes DOI as a theory of how, why and at what rate new ideas and technology is spread through cultures operating at the individual and firm level.

The technology diffusion is described in terms of different user categories from innovators to laggards. These five categories of individuals are described by plotting either the cumulative

number of adopters against time to receive the s-shaped curve or by plotting market share against time to receive a bell shaped curve (Rogers 1983, p. 243). The five categories of adopters are; innovators, early adopters, early majority, late majority and laggards.

To better understand why some innovative technologies are successful while other innovations fail, researchers has tried to explain and characterise the different stages of technological innovation. Utterback and Abarnathy proposed one model to describe the cycle of innovation in 1995. They detected two distinct phases on which the cycle is based; the fluid phase and the specific phase. The fluid phase is characterised by uncertainty, uncertainty about both the technology and about the market. A firm within this phase works primarily with different product designs to find product features and form factors that meet the customers desired quality. When the customers have reached consensus in this matter a dominant design is set and the innovation enters a new phase, the specific phase. Utterback and Abarnathy imply that the specific phase is a phase where all innovations are focused on the specific dominant design. A firm within this phase works primarily with process innovation and incremental change to improve the dominant design (Shilling, 2014).

4.2.2 Variables determining rate of adoption

4.2.2.1 Attributes for adoption of innovation

But what is it that decides whether an innovation will be rapidly adopted or even adopted at all? Rogers (Rogers 1983) suggest based on previous research five attributes that describe an innovation and how it affects the adoption rate. These attributes that describe the product itself are: relative advantage, compatibility, complexity, trialability and observability.

4.2.2.1.1 Relative advantage

...Relative advantage is the degree to which an innovation is perceived as being better than the idea it supersedes.

(Rogers 1983, p. 213)

Rogers describes that the relative advantage depends on the characteristics of innovation. It can be for example economic or social advantages. In this case I believe it is a question only about economic advantage and the social aspects probably don't have anything to do with it since there is no gain in social status when using an EDC-system, not for the CRO, nor for the clinic. There are different aspects of economic advantage; it can be a question of economic profitability, low initial cost, a decrease in discomfort, a saving in time and effort and also how soon the

reward is gained. Rogers describes the latter as the problem for preventive innovations, which at some level EDC also can be classified as. Preventive innovations is characterised by something that is adopted in order to avoid unwanted consequences, here that could be long lead time for data management.

Rogers also describe the importance of informing potential adopters about the relative advantage with the innovation. The exchange of this sort of information and evaluation is one of the central point of a diffusion process and probably the best indicator of the rate of innovation. However it seems like it doesn't matter whether the innovation has greater objective advantage, it seems like it is rather a question if the innovation has a perceived advantage to the idea it supersedes.

4.2.2.1.2 Compatibility

Compatibility is the degree to which an innovation is perceived as consistent with the existing values past experience and need of potential adopters.

(Rogers 1983, p. 223)

Compatibility is characterised by how well the adopters perceive the innovation as consistent with existing sociocultural values, past experience and need for new innovations. (Rogers 1983, p. 224) This might have been a problem during the implementation of the first EDC systems, when PDC was considered the safe standard method. If the idea goes well with the social norms and values that already exist, the diffusion rate will be much faster than if the innovation goes against the existing values. So, if this is the case with EDC systems this could have been one of the reasons why the diffusion was slower. However, past experience seems to also have impact on how new innovations are adopted. If the innovation is preceded by an idea that caused a negative view, the new innovation will more likely be causing a negative response as well. Previous experience is often the standard used to interpret new ideas and therefore the compatibility with previously introduced ideas can both speed up and delay the adoption (Rogers 1983, p. 224). If the first EDC systems were poorly developed and slowed down the data collection process the innovation was probably perceived as a negative expansion of the data collection process. This phenomenon is known as Innovation negativism and describes that if an innovation fails to meet the expectations of potential adopters it is more likely that the adopter

will refuse a similar innovation in the future (Rogers 1983, p. 225). Perhaps this might be one of the reasons for the slow diffusion rate of ePRO/EDC.

Another dimension to this attribute of compatibility is according to Rogers the clients need for an innovation. If the need for the innovation exists among clients the adoption rate will of course increase. However clients might not know that they have needs for a new technology and recommending solutions to a problem that the clients don't know exists is probably the most difficult part of implementing new innovations (Rogers 1983, p. 225). Since the clients who are making the decisions about buying EDC systems isn't the same people as the end users there might be a conflict of interest in regard to needs. The management team might realize that the processes needs to be improved but the end users at the clinic might just only see the increase in cost and time that it brings in the initiation phase.

Studies have also shown that if innovations are presented to clients in clusters or packages they are adopted more easily.

4.2.2.1.3 Complexity

Complexity is the degree to which an innovation is perceived as relatively difficult to understand and use.

(Rogers 1983, p. 230)

Complexity might be the feature in focus here. This describes the degree to which an innovation is perceived as complex and hard to use. The complexity is negatively related to the rate of adoption. New ideas that are simple to understand and doesn't require any extra skills or learning time is adopted faster than a complex product. Several studies indicate that this parameter is perhaps the single most important for rapid adoption when presenting a new innovation (Rogers 1983 p.231).

4.2.2.1.4 Trialability

Trialability is the degree to which an innovation may be experimented with on a limited basis.

(Rogers 1983, p. 231)

This attribute is perhaps the one least interesting for this project. Trialability is as stated above the ability to try and experiment with it. This is according to Rogers more important for innovators and early adopters than for laggards. Laggards are surrounded by the early adopter categories that have already adopted and experimented with the innovation therefore the trial is less important for these. According to Rogers, trialability is positively related to rate of adoption but however, there is no strong evidence for this correlation. In the case with ePRO/EDC the trialability, or the degree to which it can be changed and experimented with is crucial, since that is required to be able to use it in different studies. Therefore this attribute does not seem to apply to the project presented here as much as the other attributes.

4.2.2.1.5 Observability

Observability is the degree to which the results of an innovation are visible to others.

(Rogers 1983, p. 232)

This attribute is positively related to the rate of adoption. As one can imagine, the easier the user see results the more likely are they to adopt (Rogers 1983, p. 232). With this in mind there is a chance that the end users of ePRO/EDC systems aren't able to observe the results of this innovation. Could this perhaps also be related to the slow diffusion rate? Rogers describes software as a technological innovation that might be hard to observe, in comparison to hardware that often is a physical device.

4.2.2.2 Type of innovation-decision

Rogers (1983, p. 29) describes three types of innovation decisions and these are; optional innovation-decisions, where the adopter has the main influence on the choice, collective innovation-decisions where the adopters have some influence on the choice and authority innovation-decision where adopter has almost no influence on the choice. The last two are perhaps more common in organisations and within the government. This could be an important aspect to the analysis in this project since the adopters and end-users don't have much to say in the decision process. The three types of innovation-decisions will be thoroughly presented below.

4.2.2.2.1 Optional

Optional innovation-decisions are characterised by the individual choice. One individual will, regardless of the other members of the social system make an innovation decision. However, often is the individual affected by the social system in some way.

4.2.2.2.2 Collective

This type of innovation decision is characterised by a united choice made by all units of the social system together.

4.2.2.2.3 Authority

This type of decision is often made by a small number of individuals, often people possessing power and status. It seems to be the standard type of decision making in large hierarchic organisations.

4.2.2.3 *Nature of the social system*

The nature of the social system seems crucial when adopting a new technology. Values and norms that are a great part of a social system can sometimes be a barrier for change. Norms can be both cultural and religious and can influence social groups of all perspectives, for example entire nations to small villages or a religious community. There are parts of a social system that are more important to observe than others. These are the opinion leaders and change agents. Opinion leaders are often informal leaders who take on a role as the innovator. However, the majority of the social system often perceives this person as peculiar but his/hers role in the diffusion process within a social system is still to move it forward if the norm allows it, otherwise it seem like it rather has the opposite effect (Rogers 1983).

4.3 Adoption at firm level

It is important to separate theories about diffusion of innovation on an individual level from diffusion of innovation at a firm level. Rogers (1983, pp 55 - 61) present a theory on what drives this diffusion or innovativeness at firm level. He states three individual factors that he believes are of importance. These three variables are (1) individual characteristics, which describe the leaders attitude towards the innovation, (2) the internal characteristics of the organisational structure, which includes 6 parameters that affect innovativeness of a firm and last (3) the external characteristics of the organisation that refers to system openness.

The 6 parameters that describe how internal characteristics of the organisational structure can affect the innovativeness of a firm is: (1), *centralization* that describes power and control in an organization. Centralised control has a negative correlation with innovativeness and according to Rogers the range of new ideas seems restricted when only a few leaders are dominant. (2), the second variable is *complexity*. Complexity stands for the rate of occupational specialities and expertise within a firm. Organisations that have a high number of members with special knowledge and formal training tend to have a higher rate of new and innovative ideas but even though complexity brings innovativeness to a firm it also complicates the implementation. Rogers mean that complexity might make it hard to achieve consensus between the group members. (3), the next parameter described by Rogers is *formalisation* that refers to how prone the organisation is to follow rules. By following rules the effect will be the opposite compared to an organisation associated with complexity, formalisation inhibits the creativity and the development of new ideas but it encourages implementation of it. The (4th) variable is called *interconnectedness* and it explains how the units in a social network are connected. Well-connected networks where ideas can flow easily have a positive correlation to the organisations innovativeness. (5), *organisational slack* is defined as an actual or potential cushion of resources which allows an organisation to adapt to pressures for internal changes and to initiate strategic changes to respond to the external environment (Bourgeois 1981) and it has a positive correlation to innovativeness in an organisation. The last, (6th) parameter is *size*. Several studies indicate that size has a positive correlation to innovativeness. Rogers argues if it is the actual size of the firm that makes it successful or if it is a surrogate variable such as total resources, slack resources, and organisational structure or something else. Tornatzky & Fleisher (1990) developed another theory about how innovations are adopted and spread across a population. This theory is also described at firm level and the focus is on Technology, Organisation and Environment (TOE). TOE was originally developed and presented in Information Technology (IT) studies and the authors identified these three aspects that are of importance for a company in an implementation process. The two theories presented by Rogers (1983) and Tornatzky & Fleisher (1990) are identical in regard to the technology variable and the organization variable. However, compared to Rogers's theory on DOI, the TOE framework adds another dimension to the model - the environment. The environment represents the external context in which a firm operate and include the industry characteristics, market structure, competitors, regulatory requirements, technology support and infrastructure.

5 Empirical data

The empirical data is, based on the three research questions, divided into three parts. These three parts are arranged and presented in the same order as the research questions formulated to meet the aim of the study, which primarily concerns the slow diffusion of electronic Patient Reported Outcome (ePRO) and Electronic Data Capture (EDC) systems in clinical trials. The first research question concern the product development and evolution of the system, the product in this case refers to ePRO/EDC systems in general and not Parkinson's Disease Digital Application (PANDA) or Dynamically Extendable platform for Long-Term Assessment (DELTA) as a case. The purpose of this question was to investigate if the reason for the slow diffusion was a result of a poorly developed product and if it is the evolution of the product that has increased the adoption rate over the last years. The response from the interviews showed several important features for successful EDC system, which are presented in section 5.3. To further understand the evolution of EDC it is important to understand how it is different from Paper-based Data Capture (PDC). The difference between EDC and the precursor PDC is presented in section 5.2.

The second research question concern the environment of the innovation and the purpose of this question were to investigate if the slow diffusion rather is a result of any problems during implementation. The empirical data is divided into three separate areas based on the informants' responses. These areas concern the innovations environment and how each area can affect the implementation and I have chosen to divide them into social, organisational and regulatory issues. These three areas can cause different problems for the implementation process and will further be discussed in section 5.4

The third research question has a clear business perspective and can be considered somewhat of an analysis of customer needs. Here, PANDA will also be discussed as a case of ePRO for use in clinical trials

5.1 Informants

Interviews with the informants were carried out during the spring of 2014. All informants are anonymous and only connected to a participant number but for the sake of the analysis a general work title that corresponds with their actual work title is added to the participant number. Also, the type of organisation; pharmaceutical company, Contract Research Organisation (CRO), Academic Research Organization (ARO) or Hospital is also stated for the sake of the analysis. 3 different pharmaceutical companies and 5 CROs, were represented. The other participants

either work at a hospital or in an ARO. The first 13 participants were interviewed face to face and the last 4 were interviewed by e-mail using a qualitative questionnaire.

5.1.1 Face-to-face interviews

Informant 1, Investigator, Hospital

The informant works as a physician and researcher at a hospital, he/she was involved in the development of PANDA. This interview had a clear focus on PRO with PANDA as a case.

Informant 2, Manager, Pharmaceutical Company

The informant has many years of experience in this industry and this interview had a clear focus on the future of data management in clinical trials.

Informant 3, Manager, CRO

The informant has worked in this industry for many years and CRO I is in the forefront when it comes to digitalisation. The interview focused on important features needed to create successful systems.

Informant 4, former Country Manager, CRO

The informant has previously worked as both CRA and project manager in clinical trials for a CRO. The interviewed focused on his/hers previous experience from EDC systems in that role. The discussion included practical features of the system and advantages compared to PDC. Her role as a project manager at the hospital does not include work with clinical trials.

Informant 5, Clinical Trial Manager, ARO

The informant has worked in the industry for many years and this was a very educating interview in regard to processes around data collection in clinical trials.

Informant 6, Data Manager, ARO

The informant has worked in the industry for about 10 years and this was also a very educating interview but in regard to processes around data management in clinical trials.

Informant 7, Clinical Trial Assistant, Pharmaceutical Company

The informant has worked in the industry for about one year and the interview included a long discussion about the importance of user-friendly systems.

Informant 8, Clinical Trial Assistant, Pharmaceutical Company

This informant has also worked in the industry for about one year and the interview was conducted with Informant 8 and as stated above, it included a long discussion about user friendliness.

Informant 9, Clinical Research Associate, CRO

The informant has worked in the industry for about three years and the interview ended up in a comparison between EDC and PDC. The discussion primarily regarded practical features.

Informant 10, Project Manager, CRO

The informant has worked in the industry for about 15 years and the most of the discussion was about these systems in a larger context and how it affects the client which most often is a large pharmaceutical company.

Informant 11, Manager, CRO

The informant has previously worked as CRA and gave input in regard to how different systems are built both from the CRAs points of view and the client's point of view. This informant works in a managing role where he/she has frequent client contact.

Informant 12, senior Clinical Research Associate, CRO

Perhaps the most important interview in regard to user-friendliness. This informant has been in the industry for many years and he/she has seen how the data collection method have evolved from PDC via poorly developed EDC systems to the fairly effective EDC systems that are available today.

5.1.2 E-mail interviews

These interviews were conducted via e-mail correspondence using a survey with semi-structured questions. The survey reminded of the interview guide with three focus areas based on the research questions; the difference between PDC, early EDC systems and EDC systems today, the external factors that affect EDC and last the future of data collection in clinical trials. In addition background questions were asked to establish their perspective and previous experience and knowledge.

Informant 13, Manager, Pharmaceutical Company

Informant 14, Project Manager, Pharmaceutical Company

Informant 15, Medical Manager, Pharmaceutical Company

Informant 16, Study nurse, CRO

5.2 The difference between EDC and PDC

After conducting the literature study on EDC and how it is different from PDC the result seemed unambiguous. It was obvious that EDC was the superior method for data capturing. Therefore it seemed important to get that confirmed from the informants participating in this study. Even though this section doesn't respond directly to any of the research question it is important to show these results. It gives a deeper understanding of the incitements to carry out a change of data collection method.

5.2.1 Difference for the company conducting the trial

When did EDC become the standard method for collection of data? This question seems to confuse the informants and the responses are very vague. This could be a result of fairly young informants who haven't been working within the industry for that long. But even the older informants who have worked within this industry for more than 15 years seem to be unsure about this. It seems like EDC adoption has been a slow increase, a creeping process rather than a distinct change of method.

... eCRFs were used in some of our projects as early as 2001 or 2002 and the participants were also using e-diaries back then but it was first during 2008 that EDC systems were initiated as the standard method for data collection.

(Informant 5, Clinical Trial Manager, ARO)

... All studies that are initiated today are electronic trials, however in studies that were initiated more than 5 years ago we still work with PDC.

(Informant 7, Clinical Trial Assistant, Pharmaceutical Company)

... Today only a few studies are paper based but in 2004 PDC was the standard method and if we were to use eCRF in a study that was more of an exception.

(Informant 10, Project Manager, CRO)

The development of new systems seems to favour the use of EDC and it is without doubt the future of data collection in clinical trials. The senior CRA are perhaps the individuals who can find most advantages with the use of paper CRFs but even them believe that EDC are here to stay.

...There is not a chance that the industry will ever return to PDC even though there were advantages with that way of capturing data.

(Informant 12, senior Clinical Research Associate, CRO)

All informants agreed on the fact that in the long run EDC as it works today is superior to PDC both in regard to time, cost and quality of data. However, the level of superiority seems to depend on the features of the study.

5.2.1.1 Cost and time

Many EDC systems are expensive to licence and above all to implement. All EDC systems require some sort of training which can, depending on the system take a couple of days up to a week to learn for each individual and since all involved personnel must take the course before using the system a lot of money will be spent only on education of the system.

When conducting early phase I studies the number of patients or study participants are relatively low and the amount of data that is collected is therefore naturally not as extensive as for large multinational trials with more than 10 000 patients.

...In small-scale studies, like the ones I work with we only use paper CRFs, the digital systems are too expensive, which mean that we don't gain from using EDC in these studies. I only work with small phase I studies and the largest study I have ever worked in included 39 patients and that is probably why I haven't worked directly with EDC systems

(Informant 5, Clinical Trial Manager, ARO)

Another informant that works for a company that developed their system in house claim that with their system almost all studies gain both time and money, education time and licensing cost

included. However, the reason for this seems to be the low cost for licensing this system and he also explains one exception.

...We developed our own product because we were tired of poorly developed digital systems and paper. It was never our purpose to grant other licensees for our product but after a couple of years other CROs were getting interested and we became licensor of the system that we developed in house. The reason for our success is that the system is very cost efficient. We can honestly say that practically any study benefits economically by using our system. As I see it there is only one exception. If the duration of the study is long and the study is conducted in many countries with multiple clinics but with only a few patients per site, only then will you benefit economically from PDC.

(Informant 3, Manager, CRO)

Small studies, when the numbers of recruited patients are low, seem to benefit economically from PDC rather than EDC. It makes sense that in large phase III studies with more than 10 000 patient it is a great advantage to have a good EDC system since the amount of data that is collected is so high. Even if it takes months to build the eCRF and educate all personnel, that time and money is gained in the end. However the expenses when using EDC is large in the beginning of the project instead of in the end as with PDC. One of the informants presents this as a potential explanation for why small companies often hesitate to use EDC.

...It seems like small companies doesn't see the advantage of EDC in the long run and uses PDC because of the initial expenses that EDC entails.

(Informant 9, Clinical Research Associate, CRO)

5.2.1.2 Quality

The quality of data is also an advantage with the EDC. Quality refers primarily to the rate of errors or missing data and even if PDC often include double data entry and cross-referencing to assure quality the human factor cannot be disregarded. This was explained by one of the CRAs.

...The quality of collected data tends to be higher when digital tools are used, perhaps because there are less room for interpretation. Since different data managers often works differently the human factor cannot be disregarded when working with PDC. In addition, different sites sometimes enter data differently and these errors tend to decrease with the digitalisation.

(Informant 9, Clinical Research Associate, CRO)

If the database contains a high amount of errors the study will require more patients to show the same superiority as if the data were correct, this requires longer lead-time and higher costs. Before starting a clinical study a thorough calculation of the sample size that is needed to show superiority to the standard of care is conducted and if data is missing the calculation will be misrepresented. This calculation is required by the ethical committee, they will not allow a study that recruits more patients than necessary. It is considered unethical to put more patients in danger when it is not needed. At the same time it is unethical to conduct studies with fewer patients than needed since this increases the risk for a type II error in the same way as missing data will and if that happens, the patients who participated in the study were put in danger for no reason. Quality advantages will further be presented in the next section.

5.2.1.3 Disadvantages

The advantages with EDC are obvious but some of the informants have also stated some disadvantages with this way of capturing data. The technical issues seem to be concerning the informants. If the system for some reason cannot be logged on to there is a risk of missing data.

...For EDC to work efficiently the program must either be installed on all computers used in the study or the system must be internet-based. Today, most systems are internet-based which in turn requires a good Internet connection at all sites. This is probably one of the reasons why countries in Africa are underrepresented in clinical trials.

(Informant 10, Project Manager, CRO)

Archiving might be another issue since it can be problematic to guarantee that data is safely stored and archived in an EDC study. All study related data must be stored at sponsor for at least 10 years after the study is terminated, this is decided by EMEA and FDA has more indefinite roles about archiving. How can we guarantee that all data isn't just destroyed?

5.2.2 Practical difference for each role in the process

In the previous section I explained the main difference with EDC compared to PDC in the perspective of the company conducting the trial in more general terms but this section will rather focus on the practical differences with EDC compared to PDC for each professional in the process. As I see it, based on the informants responses there are four roles in the clinical drug development process that are practically affected by the way data is captured. These are the

study personnel at the clinic, which is often the study nurse or the investigator, the CRA who does monitoring visits to conduct SDV, the data manager who is responsible for cleaning and handling of data and last but not least the project manager. I will, based on the responses from the informants explain the main differences between PDC and EDC in terms of these four professional roles.

5.2.2.1 Study personnel at the clinic

The difference between PDC and EDC at the clinic seem to have the largest impact on the moment where the patient or study participant is interviewed and later when all data is being entered. With a paper based CRF the interview with the patient is considered comfortable and it is possible for the study nurse to write all answers directly into the CRF. With EDC the interviews seem to be conducted in the same manner, the study nurse often uses some sort of notepad during her interview with the patient to write down the answers by hand and later transferring them to the eCRF on a computer. With this extra step for the study nurse the interviews take longer time. The reason why the interviewer doesn't enter data directly on a computer seems to be a practical issue.

... The reason why study personnel doesn't enter data directly into a eCRF could perhaps depend on the location of the nearest computer, sometimes the interviews are conducted in a room without computer or it could also be a case of perceived interaction loss with the patient when a computer is used.

(Informant 12, senior Clinical Research Associate, CRO)

The general opinion seems to be that PDC is a simpler process for the personnel at the clinic since all CRFs are stored on a shelf and no login or passwords are needed. The collection of data is also simpler since the study nurse or in some cases the investigator only write the answers by hand directly into the CRF. The advantage with PDC is explained by one of the senior CRAs that worked most of his life with PDC.

... With PDC the CRF is easier to access, everything is just sitting on a shelf and no password and less training is needed. Moreover, it is easier for the study nurse or investigator to fill out a paper based CRF and the interaction with patients is not lost. In regard to access, PDC is easier for us CRAs as well.

(Informant 12, senior Clinical Research Associate, CRO)

From what the informants have expressed, here stops the advantages with PDC for individual professionals. EDC on the other hand seem to favour the CRO or pharmaceutical company rather than the clinic and furthermore it seems like the CRAs that conduct SDV at the clinic on behalf of the sponsor benefits perhaps the most from EDC. Their job assignments seem to have shifted during the implementation of EDC.

5.2.2.2 CRA or monitor

The general opinion from the informants who currently work or who have previously worked as CRAs is that EDC have primarily two advantages; logic checks and remote monitoring. The monitor or CRA seem to be one of those involved in data collection and data cleaning whose work assignments have changed the most. With PDC the CRAs work assignments consisted mostly of monitoring CRFs for mistakes like for example wrong date of visit, unchecked boxes, missing signatures and such. With EDC, there is no need for this because of the logic checks that are incorporated in the systems today. Logic checks are a great advantage, these checks forces the person who enters data to fill out everything correctly before moving on to the next page. With logic checks it is also possible to obtain a warning if you use the wrong format for data for example if height is entered in cm instead of meter. A warning can also be obtained the data isn't plausible, for example if 290 cm is entered as height. This works for different pages in the same eCRF as well, if male is entered when the eCRF is asking for gender a warning will appear if you are trying to enter pregnant on the next page. This goes for different visits as well, in most systems it is possible to receive a warning if it is entered in the eCRF from the first visit that the patient never smoked and during the second visit the patient states that he/she quit smoking two years ago.

Risk based monitoring is an advantage with EDC since it allows the CRA to monitor data before going to the clinic, this also allows screening of data to detect systematic errors. By conducting risk based monitoring it is possible to detect which questions or fields in the eCRF that is problematic. Or perhaps to detect if there is a specific site that might need more monitoring.

... There is a lot going on in the world of data management right now with risk based monitoring and control of data entering with logic checks. However, the work of SDV can never be completely replaced by a digital solution.

(Informant 5, Clinical Trial Manager, ARO)

... I have worked with paper but the advantages with EDC are great, with remote monitoring I can see trends even before I get to site. With paper based CRFs there are a lot that needs to be corrected but with EDC and all the logic checks that work as block for inaccurate data saves both the clinic and the CRO time.

(Informant 9, Clinical Research Associate, CRO)

... Another important advantage with EDC is the improvement of working conditions for the CRA, it might seem trifling but each patients CRF can weigh up to 2.5 kg and several patients at each site during each visit can result in unnecessarily hard work. Besides it is also expensive to send these enormous amounts of documents back and forth.

(Informant 4, former Country Manager, CRO)

When data is verified it is sent to the data manager that seems to be another part that benefits from EDC.

5.2.2.3 Data Manager

The difference for data managers when PDC was replaced with EDC was primarily the need to send DCFs. DCFs are queries sent to back to the clinic for clarification. In PDC studies these are time consuming and sometimes only a question of unclear data due to poor handwriting or an unchecked box. With EDC most of these queries are resolved even before it gets to the clinic because of the logic checks incorporated in the system.

... With the paper based process is more continues work, after each monitoring visit the completed CRFs are obliterated so no changes can be done. If data needs to be clarified a DCF must be sent to the clinic and the database can only be locked once all DCFs are resolved. With EDC the data is cleaned much faster.

(Informant 9, Clinical Research Associate, CRO)

Data management is often involved in the construction of an eCRF because even if the system is licensed by another company the eCRF must be build based on the protocol for each study. Many informants have pointed out the importance of involving both the data manager and the statistics early in this process because they tend to think in number and figures even before the study is initiated.

5.2.2.4 Project Manager

For the project manager, the greatest difference between EDC and PDC as I see it, seems to be control. It is easy to control how the recruitment is going for each clinic and they get a better overall picture of the trial.

...With an EDC system the project manager can look at all data in real time and there is no need for the project manager to wait for the monitor to file a report before finding out if there is a problem.

(Informant 4, former Country Manager, CRO)

5.3 Key factors for a successful EDC system

Based on the interviews the development of EDC systems seems to have come quite far and practically every study that is initiated today include electronic Case Report Forms (eCRF) with the exception of small phase I studies as I discussed in the previous section. Based on the responses, I have identified a few areas including different factors that seem to be of great importance for successful EDC systems.

Some of these factors seem to be highly developed already in most systems, while some factors are missing or must be improved. Could these missing or under developed features be responsible for this innovations slow diffusion rate or is it the improvement of the now highly developed features that are the reason that these systems were adopted at all.

5.3.1 User friendly system

One aspect that has come up in all of the interviews is that the systems must be user-friendlier. I believe that this means that EDC must not be more difficult or time consuming than PDC, EDC should be just as easy as collecting data on paper.

... The system must be intuitive and fast.

(Informant 4, former Country Manager, CRO)

... The work processes must be effective and fast. It is also of great importance, more than some developers seem to understand, that the graphical user interface is appealing.

(Informant 3, Manager, CRO)

... The system must be easy to build studies in and it must be easy to work with both for the people building the studies and for the people who are going to work in the system during data collection. It is also important that it is clear what data you will get out of it. In addition it is important that it is user-friendly for the study personnel at the clinics, it must be easy to work with and self-instructive.

(Informant 6, Data manager, ARO)

... I don't see that there is a major difference between the systems I have used during my 3 years in the business, most systems are only different when it comes to the user interface. I would say that the interface is important but the single most important feature is user friendliness and all systems I have used are relatively intuitive.

(Informant 9, Clinical Research Associate, CRO)

... Big Pharma want efficient flexible systems. It must be easy to learn how the system works, as well as building studies in it. Equally important is the ability to access the data and do real-time template graphics for quality and safety monitoring.

(Informant 2, Manager, Pharmaceutical Company)

... Our company is trying new EDC-systems, the one we have has a boring user interface, it is not user friendly and it is not a workable solution.

(Informant 7, Clinical Trial Assistant, Pharmaceutical Company)

... Previous systems that we have used and the one we have on licence today hasn't been user friendly, it is slow and it is not at all self-instructive. Today many systems have matured and many of these characteristics have been fixed so we are changing one of our major systems now.

(Informant 10, Project Manager, CRO)

Based on the responses from the informants six characteristics that are of importance when designing a user-friendly system was formulated. These are; effectiveness, speed, intuitivity, easy to learn, appealing graphical user interface interview interaction. I chose to add the last characteristic based on the discussion in the last section. Interview interaction is not something that was lifted as a problem when user friendliness was discussed but perhaps this is a reflection of the fact that no study nurses were interviewed during this project.

Effectiveness is here described as the ability to get different choices based on answers to previous questions. It should be just as easy find a specific page in an EDC system as in a paper based CRF. To take this even further, an EDC system that is more effective than using PDC would be a great advantage. Based on the interviews this is one of the greatest benefits with a digital system. If the box for concomitant medication is checked the system will automatically send you to another page were details about this can be filled out.

Speed can also be related to the effectiveness, for a system to be effective it needs to have the power to switch between different pages fast. Even though this is a pure technical feature it is crucial for user friendliness. The informants seem to be annoyed with slow systems and also, once again the end user for these systems are in most cases study nurses and patients that doesn't have the time for slow systems, however this doesn't seem to be a major problem with the EDC systems today.

The system must be intuitive. It is important to remember that the end users are often patients and personnel who might not be experienced users of digital applications. However, intuitivity in EDC systems is one of the things that seem to be improving.

... I have worked with several systems during my 3 years in the industry and they are all easy to work with and intuitive.

(Informant 9, Clinical Research Associate, CRO)

If the system is intuitive it will also be much easier and quicker for the end users to learn. Another aspect is that it in addition must be easy to set up new studies, build eCRFs and manage clinical studies in the same system. One informant expressed in which way the system must be easy to administer on role based levels.

Data manager: easy to define and set-up a new study

Study nurse: easy to enter data

Clinical trial Manager: easy to project lead the study via the database system

Monitor: easy to monitor and query the data for quality assurance, graphical interface important.

Sponsor and investigator: easy access to blinded data in the study, to investigate unwanted safety signals (e.g. serious LAB data out of normal range), preferably with real-time template graphics and last, easy access to patient recruitment status.

(Informant 2, Manager, Pharmaceutical Company)

Building studies is often more technically demanding than working with the finished eCRF and it seems like many of the licensors provide this service to companies without in house data management. One informant that together with colleagues have developed their own systems stated that:

... Our system was originally developed about 10 years ago but with the latest version we have developed an intuitive system, which has also reduced the education time, both for the end user and the management. The education time was previously a couple of days but now it takes only a couple of hours.

(Informant 3, Manager, CRO)

A graphical user interface, that is appealing and easy to follow seems more important than one could imagine. In this case GUI is equal to the eCRF and a well-designed GUI seems according to the informants highly related to user friendliness. Most informants stated that the early systems GUI were out-dated and boring to work with. An appealing, simple GUI with graphics and colour coding that are easy to understand and easy to follow seems to be a winning concept.

As I described previously there is a great risk for loss of interview interaction when using eCRF instead of the paper based solution. This problem was not recognized by any of the participants in this study, however it is important to bear this in mind especially when deciding if the system should be Internet based or not. If a system is Internet based it could be easier to solves this interaction loss problem than if the system is installed on a desktop.

5.3.2 Efficient system

One of the informants was asked about important features of eCRFs and he/she expressed this in what I consider an explicit and comprehensive manner.

... The important thing when developing an eCRF is that it adds something that a paper-based CRF doesn't. It is important that it is not just a paper based CRF in a computer.

(Informant 4, former Country Manager, CRO)

In opposite to user-friendliness that seems to address the issue that EDC must not be more difficult than PDC, this section will rather address the issue that EDC must add features that cannot be accomplished with PDC. This might seem obvious but some of the first systems had eCRFs that were just transferred from paper. Based on the interviews a couple of features that add something to an eCRF and makes it more than just a paper based CRF on a computer were identified. These features are; logic checks, audit trail, remote monitoring, redirection and real time data.

As discussed in the section comparing EDC with PDC, this is perhaps the greatest advantage with the use of EDC and well-constructed eCRFs. However the informants agree that from the beginning, the eCRFs did not have these logic checks to the same extent. Some systems might have had the ability to block the next page if any field was unfilled but the logic in these checks, the ability to detect if data is plausible came later. When the paper CRF is transferred directly into a computer without adding any features it just becomes more complicated and time-consuming.

... The most important thing to remember when an EDC system is designed is that it must bring something that paper CRFs doesn't. An eCRF that is basically a paper based CRF on a computer doesn't add anything and will only takes the study personnel longer time to work with. It is important that each click gives different choices. For example, if the box for concomitant medication is checked it is important that the system immediately open up a new space where details about these drugs can be filled out. The logic checks are also crucial.

(Informant 4, former Country Manager, CRO)

Also discussed in the section comparing EDC with PDC, remote monitoring gives the CRA an opportunity to monitor some data before going to the clinic. It is also a good way to keep track of systematic errors at particular clinics or perhaps for single patients. This could for example be that at one clinic, all patients have much higher glucose levels than at the other sites in the same study and that could mean that this clinic takes the blood samples after breakfast instead of before. It is possible to detect these types of mistakes with remote monitoring and it gives the CRA an opportunity to clarify the purpose of the glucose test and how they should conduct it. Before more errors occur.

Audit trail is another advantage and can be used as a digital trace to keep record of who is responsible for specific data entry or changes in the database. Audit trail is a crucial function and one of the regulatory requirements regarding EDC.

Redirection is an extension of what I in the previous section called effectiveness. With redirection I mean that the system will automatically give you choices based on what the previous answer was and that the segment that doesn't concern the patient in question is hidden in that particular eCRF. The difference, as I see it between effectiveness and redirection is that effectiveness explains that it should be just as easy to navigate between sections and pages in the eCRF as it is when a paper based CRF is used. With redirection a new feature is added that isn't possible to gain with a paper-based solution such as hidden segments or choices based on previous answers.

5.3.3 Communication with other systems

In the beginning of the adoption of EDC most system were insufficient and communication with other systems were not possible. The systems that are leading edge today are often connected to other study related systems and this can be very beneficial both from a practical perspective, meaning that data doesn't have to be entered as many times manually and also from a more general perspective meaning that it is easier to create reports and to get a better overall view of the project.

Based on the interviews I have identified systems that could be beneficial to connect an EDC system to. These are in house systems such as Interactive Voice Response Systems (IVRS), Clinical Trial Management Systems (CTMS), quality registries, Electronic Medical Records (EMR) and systems containing laboratory data.

Almost every organisation uses some sort of IVRS in their studies today. IVRS controls for example the randomisation, blinding and drug count. Connecting these sorts of systems to an EDC system can be very beneficial since it keeps track of patient related information. However there are still many systems that are not connected to the EDC system. It can be for example the CTMS, which is the system, that project managers control most of their work and it includes overall information about different studies conducted by the organisation and also budget and information about contracts with sponsors.

... Since most of these organisations are gigantic multinational companies that conduct multiple studies at once, connecting all systems would result in one huge system and that might only cause more harm than good.

(Informant 10, Project Manager, CRO)

Many systems today but far from all are connected to a central lab and lab data can be directly transferred to the EDC database or the eCRF. The respondents all agreed that this is very valuable and time saving.

... If it isn't possible to create a system that automatically sends laboratory data to the eCRF or the study database it must at least be easy to enter the data manually, for example scanning of the test results.

(Informant 5, Clinical Trial Manager, ARO)

Quality registries are registries that the health care industry uses to improve the quality of care. Registers for different conditions and different treatments exist and based on these it is possible to compare how well the treatment is working for different people. This together with EMR has been discussed as the future in clinical research. If it were possible to connect the EDC directly to the EMR that would be a huge improvement and one step further to only enter patient data once. This seems unusual today, if it exists at all but it will be further discussed in section 8. *future trends and needs.*

5.3.4 Technical features

Many of the informants have expressed thoughts about the technical features of EDC systems. Since most of the informants and myself has little to no knowledge about IT, this project doesn't include details on how data must be collected, transferred and managed for it to be compliant

with regulations. This project only include information on why it is important that it is collected, handled and managed properly, the rest is up to the programmer building the system.

Data safety is probably the most important thing to keep in mind when designing EDC systems. All electronic systems must be compliant to all regulations. Because this is such important section 5.4.3 *Regulatory and ethical requirements*, is dedicated only to regulatory requirements. However, if EDC systems are licensed from a well-established licensor this should not be an issue since all systems must be tested and valid for use in clinical trials and for handling of personal data.

As one of the CRAs acknowledged, paper based CRFs are a lot easier to access and a pen is all that is needed to perform an interview with a patient. For the nurses who already have multiple logins this might be a reason for study nurses to be resistant to the digitalisation. Based on the tone from this interview it seem like this is an issue for the CRA as well, perhaps a minor issue but he/she still gives the impression that all these logins to different systems are inconvenient. Another technical matter that must be taken into account is system updates. As all systems EDC requires updates and support and it is important that these updates can be done without interfering with the usage of the system. One informant suggested that updates should be conducted during night-time.

5.4 The environmental impact on implementation of ePRO/EDC systems

Up until now the empirical result have focused mainly on the attributes of the product itself and not as much on the context of the implementation and adoption. It could be that it is the product itself that has caused this slow diffusion but I wanted to investigate if it might have been due to external factors. I have identified three levels where external factors could have caused the slow diffusion. These are social or cultural factors, which primarily concern the end users at the clinic, organisational factors that primarily concern the sponsor or CRO and last ethical and regulatory factors that primarily concern FDA and EMEA.

5.4.1 Social/cultural problems

The end users of this product are the study personnel at the clinic such as investigators and study nurses. Based on the interviews it seems like the opposition to digitalisation comes especially from the clinic. However most informants doesn't see this as a major issue. The CRAs and the data managers are also end users but none of the informants believe that there has ever been as resistance among sponsor or CRO representatives. Nevertheless, when looking at a

sponsor as a whole organisation instead of only individual representatives it seem like there might have been a resistance to the change of method after all but that is further discussed in the next section about organisational issues.

Some of the informants seem to have noticed a resistance towards EDC and digitalisation in general from the personnel at the clinic. However it doesn't seem as a big problem.

One thing to bear in mind here is that no one who works as a study nurse or investigator was interviewed with focus on these questions. The responses here are mainly from representatives from sponsors or CROs.

... For older people who work with clinical trials there can be a resistance against digitalisation due to unfamiliarity to technology. In addition, almost all helpdesks are in English, which also can be troublesome for this group of people. It is impossible to get helpdesks in all native languages since most studies are located in several different countries but with the same helpdesk. To get one person for each country would be to expensive if it is even possible. Therefore it is important that the CRA can function as an intermediary.

(Informant 9, Clinical Research Associate, CRO)

... When EDC was introduced the most resistance came from older investigators but this was barely in issue since the investigator in most studies just sign the eCRF when it is completed.

(Informant 11, Manager, CRO)

... Whether the study personnel at the clinic is resistant or not completely depend on the patient's and the personnel's maturity when it comes to digitalisation.

(Informant 5, Clinical Trial Manager, ARO)

... I believe that resistance from the clinic is a question about changing habits. This can be difficult for certain people but I think that everyone who works in this industry have realised that the industry is constantly changing and the ones who have a problem with that have already left. Another issue is that many

people still find computers unsafe and unreliable while paper-based documents are considered safe and easy to work with.

(Informant 10, Project Manager, CRO)

Some of the informants haven't noticed any problems from the end users and believe that the problem to the slow diffusion must lie within the development of the product.

... EDC was positively received at the sites and end from my experience user motivation is not a problem. Since the study personnel agree on how the study is conducted by signing a contract they will conduct their part of the agreement and accept the method used in the trial.

(Informant 3, Manager, CRO)

... The people working at the clinics have also matured when it comes to computerisation since more and more uses EDC and many clinics have electronic health records as well. If there is some sort of resistance today it is only from older people. In 2004, there were greater resistance towards EDC but I believe that depended more on the product. All clinics needed a laptop with the program installed and there were always problems with the network at the hospitals. Today it is better programs and everything is Internet based.

(Informant 10, Project Manager, CRO)

To avoid any unnecessary resistance from the sites some of the respondents believe that it is important to motivate the end users and involve them in the development while other state that feedback on the system is received in terms of indirect feedback through the CRA.

... To motivate them it is important for the CRA to state how much time the nurses will save when avoiding entry errors and queries. It is also important to support the clinic and take time to guide them through the eCRF.

(Informant 9, Clinical Research Associate, CRO)

5.4.2 Organisational problems

In this section the organisational problems will be discussed. Could the reason for the slow diffusion lie within the decision of the sponsor, which in most cases are a pharmaceutical company, or the CRO?

It seems like the decisions can be made both by the sponsor and by the CRO. As with many of the other issues, it depends on the sponsor who is the client. In general it seems like a big sponsor for example one of the big pharmaceutical companies often use their own systems. Especially if it is a study that is suppose to run in multiple countries and perhaps with multiple CROs. The decision about what systems to use in these large companies are often taken on a central level. However, if the sponsor is a two man company with one product, perhaps a medical device. Their specialty is most likely not clinical trials and in these cases the decision could be delegated completely to the CRO. In cases where the sponsor is a small biotech company that has developed one product, the knowledge about clinical trials and all regulatory requirements is often inadequate and the need for full service CROs are much greater.

... What system that is used in a trial depends on the sponsor and some sponsors want to use their own systems while other prefer if the CRO decides what system to use. The sponsor is the customer and always has the last say in how a trial should be conducted.

(Informant 11, Manager, CRO)

In the beginning of EDC adoption there was a resistance from some of the big pharmaceutical companies. It seems like this mainly was a result of not knowing how much time and cost there was to gain. Today the resistance is not from EDC systems in general but the change of EDC systems. Even if some of the existing systems are bad it takes a lot for a big pharmaceutical company or a multinational CRO to change a system that is already implemented

If a big multinational company were to change the system they use for data collection and management it can have serious consequences. Not only do they need to educate the entire organisation in the new system they need to find a system that they are certain is going to be more effective than the one they already have.

The more users there are in the organisation the more time and money will the sponsor gain from changing a bad system. In conclusion, the more users the more incitements for change.

5.4.3 Regulatory and ethical requirements

Before starting a clinical study, a trial application must be sent to the regulatory authorities, which in US is the Food and Drug Administration (FDA) and in Sweden that is the Medical Product Agency (sv. läkemedelsverket). In addition applications must be sent to the International Review Board (IRB) or Independent Ethics Committee (IEC) for approval. In Sweden that is the Central Ethical Review Board (sv. etikprövningsnämnden).

When developing an EDC-system it is central that it is compliant with all federal regulations. In the United States the responsible agency is FDA, which is an agency within the United States Department of Health and Human Services. In Europe the responsible agency is European Medical Agency (EMA).

... FDA are responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics and products that emit radiation.

Title 21, CFR part 11 (21CFR11) is FDA's guidelines on electronic records and electronic signatures. The corresponding guideline from the European Medical Agency (EMA) is Good Manufacturing Practice (GMPs) - Annex 11, Computerised Systems (Annex 11). These two guidelines are probably the most essential when developing EDC systems. However, when discussing regulatory and ethical requirements in clinical trials the single most important principals regarding clinical research is the Declaration of Helsinki. These three principals will be presented in this section.

Declaration of Helsinki

All studies must be carried out according to the World Medical Association's Declaration of Helsinki, which describe ethical principles for medical research involving human subjects. The Declaration of Helsinki (DoH) was developed and adopted in 1964. The original version of the DoH was based on the Nuremberg code that was assembled as a result of the horrifying experiments carried out on victims from concentration camps in Nazi Germany. In the first paragraph of the DoH it is declared that:

... the World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

This is the far most important regulatory requirement to comply with when conducting clinical trials.

Since 1964, 9 amendments were made to the DoH, the last one in October 2013. Carlson et al. (2004) investigated the revisions of the DoH from 1964 to 2002 and it indicates a great increase in word count, especially for the first revision in 1975 and in the later revision from 2000. The number of years since last revision is steadily decreasing from about 10-15 years in the 60s and 70s to about 2-5 years during the 2000s. Both the increase in word count and the decrease in number of years since last revision indicate the importance of ethics in clinical research. Perhaps the most important feature of the DoH is the paragraph of voluntarily participation that clearly states that all individuals participating in a clinical trial must receive oral and written information about the trial, both risks and benefits and first when the investigator is sure that the patient understands the information both investigator and patients sign and dates an informed consent (Lemne 1991).

Regulations on computerised systems

A study on how to develop regulatory compliant eCRFs was conducted in 2009. In this study the regulatory requirements for computerised systems were divided into procedural and technical requirements and a comparison between the guidelines from FDA and the guidelines from EMEA show a significant similarity. The procedural requirements include; study protocol, the protocol must include all data that the system will handle and this is to be considered source data. Standard Operating Procedures (SOPs), it is clearly stated that SOPs and controls must be applied for all electronic data handling, this should also include documentation of what software and hardware are used for all activities. The last procedural requirement concerns archiving of electronic records, which is the investigators responsibility for (FDA 2007; EMEA 2002)

The technical requirements from FDA and EMEA concerns authorisation and audit trail to assure that access are limited to authorised operators and to keep track of all data activities, including when changes were made and by whom. Data validation and system integrity is also incorporated in FDAs guidelines, which refers to consistent system checks to assure data quality

and data validity and also to keep integrity of data and protect against data loss during for example system updates (FDA 2007, Guidance for industry: Computerized systems used in clinical investigations; EMEA 2002, ICH Topic E 6 guideline for good clinical practice: Note for guidance on good clinical practice).

In this case study, which focused mainly on technical requirements it was concluded that acceptance from agencies such as FDA and EMEA depends heavily on the ability to verify validity and quality of data. Therefore, following the recommendations provided by these agencies are crucial for data acceptance from electronic trials, especially for decision purposes (Ene-Iordache et al 2009).

Title 21, CFR part 11 and Annex 11

21 CFR 11 of the code of federal regulations was published in 1997 and updated and republished in 2007, it applies to the electronic records and electronic signatures. This guideline must be met by all EDC-systems and it is recommended to acquire expert interpretation prior to developing and implementing an EDC-system. These systems should meet the requirements by the same quality as PDC and electronic signatures should be equal to handwritten signatures. It is not only EDC systems but all computerised systems that must meet the regulatory requirements and in addition the systems must also be compliant with the study protocol (FDA 21CFR11 2013). The requirements for Europe are included in the International Conference on Harmonisation (ICH), topic E6 guideline for Good Clinical Practice (GCP), which were published in 2002. A comparison between these two guidelines indicates two common areas; electronic signatures and controls for closed systems. Electronic signatures part 11 goes beyond Annex 11. In Annex 11 it is stated that; electronic signatures have the same impact as handwritten signatures, is linked to the specific record and should include time and date of the signature. Title 21 Part 11 however contains several sections not included in Annex 11. In conclusion Annex 11 has a broader scope than 21CFR11 and covers areas not included in this guideline.

ICH-GCP

All clinical trial processes must also be conducted in compliance with International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) (EU-direktiv 2005/28/EC). ICH-GCP is international guidelines for conduction of clinical trials and these guidelines were developed for clinical trials to be conducted in the same manner independent of the country it is conducted in.

Local regulations

In addition it is crucial that all electronic systems are compliant with all applicable local regulations. This section refers to local regulations in Sweden only.

Investigator is responsible for all documents containing information about patients, such as name, phone number, address or personal ID number. This information is not to be seen by sponsor/CRO or any other party not involved in the study with one exception, the monitor. He/she is the only representative from sponsor/CRO that has personal access to patient specific documents but only after confidentiality agreement is signed. This all according to the Swedish law regarding subject confidentiality (SFS 2098:204. Personuppgiftslag. Stockholm: Justitiedepartementet). The investigator is also responsible for all documentation on the study and must keep it according to Swedish law regarding archiving (SFS 1990:782. Arkivlagen. Stockholm: Kulturdepartementet SFS 1991:446. Arkivförordning. Stockholm: Kulturdepartementet) and the Public Access to Information and Secrecy Act (SFS 2009:400. Offentlighet och sekretesslag. Stockholm: Justitiedepartementet).

5.5 electronic Patient Reported Outcome (ePRO)

(DELTA) is an example of an electronic Patient Reported Outcome (ePRO) tool. The informants were asked questions about important features of ePRO in general and also about DELTA and Cenvigo as a case. The empiric result from that part of the interview will be specified in this section. As a reminder, ePRO is data that the patients digitally report themselves directly into the eCRF or the database. This can be done either at the clinic or within the patient's own home, both scenarios are considered ePRO.

5.5.1 ePRO in general

The use of ePRO or e-diaries seems common in many trials. The informants have stated some advantages with ePRO compared to paper-based PRO.

... The patients are using an e-diary in one of the studies that I am involved in. These diaries include two types of data, (1) time of drug administration and (2) data related to an end point that the patients are able to enter themselves, it is related to urine samples. It also includes a reminder and the ability to send information directly to the patients. No Adverse Events (AEs) are entered in the

e-diary since AEs must be entered in a standardised manner and it would be too difficult to handle data on site if the patients entered AEs themselves. However, it could be good for the patients to use the e-diary to document AEs to remember when they occurred and how they felt and then bring the e-diary as a reminder to next visit at the clinic when the study nurse will ask about this.

If the study includes end points that require data to be reported frequently, e-diaries are a good resource. Paper diaries are hopeless in these cases and it is primarily because of bad compliance. If data are missing or seems implausible it is impossible to question the patients perception of a certain event because the patient will in all probability not remember this when he/she is asked later at the clinic. With an e-diary it is possible to send a follow up question immediately if data are missing. If data are missing it is uncertain why it is missing and no presumptions are allowed here. Did the patient take the drug but forgot to fill out the paper diary or did he/she forget the drug entirely?

(Informant 9, Clinical Research Associate, CRO)

... I have experienced PRO both electronically and in a paper-based form. From my experience, compliance is always better when a device is handed out. Perhaps the patients are more responsive when they receive an actual device provided that it is as easy to use as possible.

(Informant 4, former Country Manager, CRO)

... Using e-diaries for PRO can save a lot of time during patient visits, these questionnaires are often very extensive and it is preferred if patients conduct these at home. In the study I am involved in we have 12 PROs and 9 of them are included in the electronic device and compliance are about 80 %, which is a fairly good number.

(Informant 8, Clinical Trial Assistant, Pharmaceutical Company)

From the responses I conclude that compliance is the major advantage with ePRO and as long as the device are easy to use, even for the older people enrolled in clinical studies ePRO is a great tool. Nevertheless, as always when patients report how they feel there is always a risk of inaccurate data due a desire of “pleasing the doctor”, even of the patients are interviewed at site.

... There is one problem with PRO, there is no way of knowing how honest the patients are when filling out forms or entering data into a digital device. This is of course a problem even if the patients are interviewed at the clinic. Here are

two examples: The patient might state that “-Yes doctor, I took 2 pills a day every day” and when counting the pills this seems accurate but it is not uncommon that the patient have discarded the forgotten pills the morning of the visit just to please the doctor. Also, the doctor could ask if the patient has experienced any symptoms and the patient would clearly state that he/she has been great since last visit. Then, when the good-looking doctor leaves the room the patient reluctantly tells the nurse that he/she did have diarrhoea last week. However the need for 100 % compliance is more important in early phase studies and the need for continuous data is more important when studies are long and the patients are responsible for administer the drug themselves.

(Informant 5, Clinical Trial Manager, ARO)

5.5.2 DELTA and PANDA

If DELTA were to be used as an ePRO tool in clinical trials the most important thing to assure is that it is compliant with all regulatory requirements and that it is validated. Since DELTA are developed to be used as a template it is important that all tests that are included in this generic platform are in fact valid methods to use In a clinical trial setting.

If PANDA were to be used in clinical trials this would require that the therapeutic area are Neurological diseases and primarily Parkinson’s disease since the method is validated for Parkinson’s and nothing else at the moment. However, no clinical trials today use MDS-UPDRS as the primary end point, it is always doctors opinion that is most important. Nevertheless, MDS-UPDRS is used as secondary end points and since there is a correlation between MDS-UPDRS and PANDA (Westin, 2009) PANDA could perhaps be used in clinical trials.

... PANDA could, from a legal and regulatory perspective be used to measure efficacy in clinical studies of drugs for Parkinson’s disease. However, the problem with PANDA today is the credibility, the credibility is not nearly as high for PANDA as it is for other well-established methods. PANDA could perhaps be a tool for ePRO in trials in the future but today it is more appropriate to use DELTA just as an e-diary instead.

(Informant 1, Investigator, Hospital)

... To be able use PANDA in a clinical trial for patients with Parkinson’s disease it is important that it gain credibility. To gain credibility it is crucial to get a first

customer who can stick their neck out for the product to really prove Proof of Concept.

(Informant 3, Manager, CRO)

5.6 The future of data management in clinical trials

In this section the result from the needs analysis will be presented. This section aim to answer to the third aim, which have a clear business perspective rather than research perspective. All informants where asked about what they thought would be the future of data collection in clinical trials.

In addition I asked what features they require from these systems today. CRO and pharmaceutical companies need the systems to be well developed today. From what I have understood, user friendliness is most important apart from being compliant with regulatory authorities of course. The features required from systems today are the pretty much the features summit in section 5.3 *Key factors for successful EDC systems* and therefore these data will not be presented again but only discussed in the analysis in the next section, 6.1 *Analysis of empirical data*.

The responses from the question about the future of data management were diverse. Some responses focused on the collection at site while other informants talked about data management on a global study level. Based on these responses the results were divided into two focus areas; simplicity and communication with other systems.

5.6.1 Simplicity

Most informants agree that EDC must be efficient and flexible system. Below are some citations that describe how the informants imagine the EDC systems improvement in the future.

... The EDC systems that I have worked with lack an eCRF completion guideline. The information on how to fill out the eCRF must be incorporated in the system. It would make it easier if study specific information was clearly stated in the eCRF, for example if hypertension should be entered as hypertension, high blood pressure or HBP.

(Informant 9, Clinical Research Associate, CRO)

... The dream would be if data was only entered once and before you know it all collected data is in their right place and no manual data entry is ever needed and if all systems worked at all times and no technical issues occurred. I realise that this is a utopia, but that would be the dream.

(Informant 5, Clinical Trial Manager, ARO)

... It would be nice if only one system could be used for all activities. However there is so many levels of management that this would require huge systems from the upper level of economy and study management to project management, safety and regulatory in each countries to individual sites and patients.

(Informant 10, Project Manager, CRO)

5.6.2 Communication with other systems

Many of the informants talked about communication when asked about the future of data collection. Communication is summarised in this and can be seen as communication with other databases as well as communication with other devices.

... In the future I believe that all data will be collected on iPads, or another similar digital format instead of using paper or a desktop. With this method no interview interaction is lost and it is easier for the study nurse to collect electronic data.

(Informant 8, Clinical Trial Assistant, Pharmaceutical Company)

... I believe that the processes of data collection will continue in the same manner that is seen today but with the addition of much more efficient systems.

(Informant 13, Manager, Pharmaceutical Company)

... I believe that there will be more specific options available on the market, options that are user-friendlier for the study personnel. The study personnel will probably use iPads and applications in their data collection. These applications could also be used to help investigators to locate suitable patients at other clinics.

(Informant 14, Medical Manager, Pharmaceutical Company)

Many informants also think that we are going to see more of real time data collection, meaning collection of data from patients more frequently and not just during their weekly or monthly visit. This data will most likely be obtained using some sort of digital application.

... I believe that we will receive enormous amount of data in the future due to frequent collection of patient data. Real time collection will give a more comprehensive representation of the reality instead of giving just a snapshot. However, this postulates an explicit study objective and it is important to remember not to collect data that is just "nice to have". "Nice to have" data is not only unethical but it is also time consuming and there is a great risk of more "nice to have" data when the data is easy to collect.

(Informant 4, former Country Manager, CRO)

... I believe that the rate of self-reported patient data will go up but there is definitely a risk in collecting too much data. You must know exactly why you are collecting the data and what you are going to use the specific data for.

(Informant 9, Clinical Research Associate, CRO)

Register research is another aspect that was frequently discussed during the interviews as the future of data collection. Quality registries are databases containing standardised data from a specific patient group on a regional level. These registries are used to improve health care and by observing different parameters it is possible to detect differences within the health care across the country.

... In the future I hope it will be possible to easily transfer data between registries and EDC systems, as it is today data must be exported, adjusted and transferred to a new database within the EDC system.

(Informant 5, Clinical Trial Manager, ARO)

Conduction of register research is increasing perhaps as a result of less demanding requirements from regulatory authorities, compared to interventional studies. The amount of data that can be collected in these registries is huge and one could compare these studies to phase IV studies, they are similar in their characteristics in regard to sample size and time line.

... Systems connected to Electronic Medical Records (EMR) does not exist today I would say that collection of data from EMR is about 5 – 10 years away.

(Informant 3, Manager, CRO)

... It would be possible to connect EDC to EMR if it is compliant with all regulatory and ethical requirements. It could however be hard to connect one EDC system to all the different EMR systems that exists today but if there is someone who can find an IT-solution that works in 44 countries at 900 clinics it would not be a problem to collect data from EMR.

(Informant 10, Project Manager, CRO)

6 Analysis of empirical data

When comparing Electronic Data Capture (EDC) with Paper-based Data Collection (PDC) it is clear that EDC can accomplish much more in regard to data management in clinical trials. Since all informants agree that EDC is the better choice, it is hard to believe that the diffusion was as slow as it was. Analysing the empirical data collected in this study, with the premises described in the theoretical framework based on Rogers (1983) theories on variables that determine rate of adoption, will present a deeper understanding of what might have caused this slow diffusion.

This section will cover the analysis of the empirical data using the theoretical framework to evaluate data and generate a conclusion that responds to the research questions the thereby the aim. To make the analysis easy to follow it will follow the structure of the three research questions presented below and also in section 1.4 *Aim and Scope*.

1. *What is the difference between PDC, early EDC systems and EDC systems today?*
2. *What potential external parameters can affect the adoption of ePRO/EDC systems when these are implemented in clinical trials?*
3. *What are the future market needs and trends when it comes to data management in clinical trials?*

The first research question will be analysed primarily with Rogers theories on attributes of innovation, the second research question, which in the empirical result is divided into three areas; social, organisational and regulatory will be analysed together using Rogers (1983) theories on the nature of the social system and theories on adoption at firm level and type of innovation decision. The third question will not be analysed only discussed in section 7.

Discussion and future advice for Cenvigo.

6.1 Attribute of ePRO/EDC systems affecting rate of adoption

As described in the theoretical framework, Rogers (1983) suggests five attributes of an innovation that is of importance for the adoption rate. These attributes will be used as the foundation when describing and analysing the empirical data in regard to the product and research question 1. In addition the result from this analysis is summarised and presented in table I.

Relative advantage

Rogers (1983) states that the relative advantage is the degree to which an innovation is perceived as being better than the idea it supersedes and that relative advantage is positively related to the rate of adoption. All informants agreed that EDC is better than the idea it supersedes, PDC at least in regard to economic profitability. Since the relative advantage is strong this should indicate a high rate of adoption. However, as Rogers discusses the relative advantage includes several sub dimensions such as the degree of economic profitability, low initial cost, a decrease in discomfort, savings in time and effort and also the immediacy of the reward. Economic profitability is clearly higher for EDC than PDC but in regard to the other sub dimensions the results does not enable unambiguous interpretation.

The initial cost for most of these systems are high and the reward is not immediate, the reward is rather seen at the end of the trial through shorter lead-time for each new drug. The discomfort speaks both for and against adoption. According to the informants the study nurses and the CRAs could be the personnel for whom it is easier to just use paper based CRFs for collection of data. Nevertheless, data managers and project managers seems to perceive a decreased discomfort since the workload seem to decrease and the control seems to increase. However, it is important to remember that none of these roles are directly involved in the decision of whether to adopt the system or not.

After analysis of the empirical data collected in this matter I would still say that ePRO/EDC systems, even the early once have a relative advantage compared to PDC

Compatibility

Compatibility is another attribute that Rogers (1983) believe affect the rate of adoption. Whether EDC is compatible to consisting sociocultural values and beliefs or not seem to have changed throughout the diffusion of EDC. From what I interpret from the interviews the

compatibility to sociocultural values and beliefs might be one of the major reasons for this slow adoption. However, it is not on an individual level but rather the major reason for why the business management team was resistant to change at first. The drug industry was described as a slow industry with an already existent resistance towards digitalisation. Computerised systems was described as scary and unreliable and first when it was scientifically proven to provide high quality data to lower costs and decreased time lines the management teams were convinced.

Whether EDC is compatible with previously introduced ideas can be discussed. The first EDC systems might have been so poorly developed that it retarded the future rate of adoption. If bad EDC is what the new EDC systems are compared with there will naturally be a negative evaluation of the new systems as well. Could the first poorly developed systems be the reason for why the improved systems didn't have the diffusion rate anticipated?

The last dimension of compatibility is discussed in terms of whether the innovation is compatible with needs or not. Based on the interviews I interpret that there are defiantly needs for more efficient systems for data collection in clinical trials. The compatibility is positively related to the rate of adoption of the innovation but in the case of EDC the compatibility might just not have been compatible enough, at least not for the business management.

Complexity

Complexity is the degree to which an innovation is perceived as complex. The first EDC systems appear to have been very complex and not as user friendly as one might wish for. However this doesn't seem like a problem today when people are more used to technology and the user friendliness of these systems have improved. Although, the complex systems introduced 20 years ago might have harmed the reputation for the user-friendly systems that is on the market today. As stated before, the compatibility with previously introduced ideas might harm the new innovation if previous experiences were bad. Complexity is negatively related to the rate of adoption and based on the empirical data, the first EDC systems was complex and might have retarded the rate of adoption.

Trialability

Trialability is the degree to which an innovation can be experimented with on a limited basis. Even though it is crucial that the ePRO/EDC system can be adjusted to each trial, that is a required feature rather than an attribute that can be accustomed. In addition it is important that the system is validated and well established before any pharmaceutical company or CRO adopts

it therefore the adjustable parts must of course be validated as well. Consequently it would probably be too complicated to add features just for the trialability. Since that is positively related to the rate of adoption, this attribute also speaks against a high diffusion rate.

Observability

Observability is last of Rogers (1983) attributes. EDC systems are software and compared to devices such as ePRO, the major part of EDC systems is not observable in the same manner. However according to the empirical result, the GUI seems to be one of the most important features when implementing an EDC system. Since observability is positively related to the rate of adoption this indicates that a well designed EDC system with an appealing GUI should be easily adopted. From another point of view, this attribute could be interpreted as the degree to which the end result of the innovation can be observed. With this understanding, the EDC system does not have a high observability since it will take until the end of the study before the result of the innovation is visible. Also, since the early EDC systems were poorly developed in regard to GUI I would say that this innovation lack observability.

Attributes	Positively/Negatively related to adoption	Attributes of ePRO/EDC systems	Increased/decreased adoption rate
<i>Relative advantage</i>	Positive	x	Increased
<i>Compatibility</i>	Positive	-	Decreased
<i>Complexity</i>	Negative	x	Decreased
<i>Trialability</i>	Positive	-	Decreased
<i>Observability</i>	Positive	-	Decreased

Table 1. These five attributes are suggested to impact the rate of adoption and the third column indicates whether these attributes can be found in early EDC systems or not. It is also presented in this table whether this would increase or decrease the rate of adoption.

The reason for the slow diffusion seems to be related to the attributes of EDC systems as a product. I believe that this primarily concern sub dimension discussed within the attribute relative advantage. Even though EDC is better than the idea it supersedes it is the sub dimensions to this attribute that speaks against a rapid adoption. The sub dimensions, such as initial cost, discomfort and immediacy of the reward all indicates a low adoption rate. EDC seems to have been the better choice in theory but in reality it failed to meet customer's demands.

6.2 External factors affecting rate of EDC adoption

In this section, the external factors will be discussed based on Rogers' (1983) theories about innovation in organisations. External factors in this case are factors not related to the actual product but rather to the company adopting it or the environment in which it is seen. In the empirical results this part of the study was divided into three areas; social, organisational and regulatory. However, only the social and organisational aspects will be presented and analysed here. The regulatory and ethical aspects won't be analysed, since this section is primarily based on Swedish and international laws and guideline this will only be discussed in section 7

Discussion and business advice for Cenvigo.

Social aspects

The social aspect of this question were supposed to be addressed with Rogers' (1983) theories on innovation and nature of social system, which includes more soft parameters, As Rogers discuss, the social systems seem crucial when it comes to adopting new innovations, especially informal leaders. The interviews were never so specific that information about leaders in the organisation was discussed.

Organisational aspects

The organisational aspect is perhaps the most comprehensive in this analysis and here Rogers' (1983) theories on organisational innovativeness and innovation-decisions will be used. As presented in section 4.3 Rogers (1983) describes three parameters that affect the adoption at firm level; individual characteristics, internal characteristics and external characteristics. The results of this analysis is summarised in table II.

The individual characteristics refer to the leaders attitude towards innovation. Since the informants have very different roles in the decision process it is hard to make any conclusions in regard to this but I believe that it is safe to say that those who have the decision making organ close seem to have experienced a faster implementation process than those who works for a large pharmaceutical company, either as an employer or a customer with the decision organ in another country. The leaders attitude also seems to correlate with the size of the company. Large pharmaceutical companies seem to have more resistant leaders than small CROs but on the other hand, small CROs also have less to lose when implementing a new system. Change of system in multinational companies seems to require much more resources. In conclusion, the individual characteristics of the leaders are hard to determine in the cases studied here.

This can also be related to *centralisation*, which is one of the six internal characteristics that describe where the decisions are made. If the decisions are centrally made it has a negative correlation to innovativeness in an organisation. According to the informants large pharmaceutical companies that make this type of decision centralised experiences a longer lead-time to implementation. It is of course natural to take your time and carefully chose or develop a system when one system change will affect a large company is such extensive matter.

Complexity is another variable of the individual characteristics according to Rogers (1983) and all of the organisations that are involved in this project should be considered complex. Complexity stands for the rate of specialised occupations and I reckon that the pharmaceutical industry is an organisation that consists of a high number of members with knowledge and formal training. Complexity has a positive correlation with innovativeness in an organisation but this can also complicate the implementation process. I interpret that this is one of the main reasons for this slow diffusion, the complexity of these large organisations.

Formalization is the next variable and here I believe that it is safe to say that this industry is probably one of the most formal there is. Most of the informants pointed out, several times during the interviews that the single most important thing is validity and to fulfil all regulatory and ethical requirements. As Rogers (1983) states, formalisation inhibits the creativity but in opposite to complexity, formalisation enhances implementation process of the innovation.

Another variable that speaks against a rapid implementation process is *interconnectedness*. These large pharmaceutical companies seem to be quite hierarchic and many informants have stated that the decision is not ours to make. Informants working at CROs state that when a large pharmaceutical company is the customer the last word on what system to be used is always in their hands. Informants working at pharmaceutical companies with head quarters in other countries state that the decision is made at a centralized level and cannot be directly influenced by only the Swedish office, which makes sense since multinational studies must use the same system for data to be easily comparable.

The last two of Rogers's attributes that affect adoption at firm level is *organisational slack* and *size*. Since many different organisations were studied here these parameters are hard to draw conclusions from since this differ between the companies. In general the large pharmaceutical companies should according to Rogers have adopted the innovation faster than the small companies, which seem to correlate with the empirical data from this study.

Adoption at firm level	Positively/Negatively related to adoption	The Organisation	Increased/decreased adoption rate
Individual characteristics	If the leader is positive it is related to adoption.		
Internal characteristics			
<i>Centralization</i>	Negatively	-	Increased
<i>Complexity</i>	Positively	+	Increased
<i>Formalisation</i>	Negatively	-	Increased
<i>Interconnectedness</i>	Positively	-	Decreased
<i>Organisational slack</i>	Positively	No conclusion	
<i>Size</i>	Positively	+	Increased

Table II. The characteristics that have impact on the adoption at firm level are presented in this table together with a comparison to the organisations represented in this study.

6.3 Conclusion

I conclude that the reason for the slow diffusion of EDC within clinical trials seems to be a combination of the product itself i.e. the EDC system and the organisations that the system is intended to be implemented in. The EDC systems were originally poorly developed and this might have retarded the adoption rate of this type of systems. However this seems to have changed and today EDC is by far considered the most efficient method for data collection.

The organisations in which EDC systems are meant to be implemented are often large, complex organisations with a centralised decision making organ that are prone to follow rules. Within the industry the rules are many and the room for innovation is small but the largest problem is perhaps an issue regarding costs. It seems like the cost an organisation must invest to implement a system is so extensive that the process will take time. The organisation must decide how they want to solve the data collection issue and since the consequences when implementing a system for an entire multinational organisation that require certain standards can be crucial this is not something that is discussed and decided during a coffee break.

The future of data collection in clinical trials is efficient systems that allow connection with other types of databases for a reduction of data entry multiple times.

7 Discussion and business advice for Cenvigo

As discussed in the introduction, drug development in general and clinical trials in particular is unbearable today. With the use of EDC systems the cost and time line for each newly developed drug could largely decrease. Since the slow diffusion seem to be a result of slow organisational decisions in combination with a mediocre first generation product the future for data collection with EDC as the standard method are looks promising.

I believe that the giants within the EDC industry will continue to occupy market shares. Within the pharmaceutical industry it seems like the single most important thing is validity and this speaks against small companies trying to acquire the market, the new entrants into the market does not fight against PDC anymore, they fight against well established developers of EDC. Besides, most developers have substantial experience within the industry, about clinical trial processes and about data collection. When developing an EDC system, I believe that this is crucial.

7.1 Business advice for Cenvigo

As mentioned in the discussion, the EDC industry will not be easy to acquire for a small business with limited experience of clinical trials. Therefore my advice for Cenvigo is to focus on developing systems or device that can be connected to EDC. By developing systems that allows for patients to enter their own data, either manually or by automatic transfer from one device to the EDC database, they can create their own niche that better harmonises with their original business idea. Cenvigos business idea includes providing the health care industry with digital tools for efficient diagnostic, monitoring and treatment and since ePRO is closer to the clinical environment and the patients this is a more suitable approach for Cenvigo to take. Since PRO probably is the future of data collection in clinical trials and perhaps also within health care this seem more appropriate than trying to develop an EDC system. My advice is that Cenvigo put their focus on PROs for hospitals and companies.

This is what I suggest for Cenvigo, be creative and develop solutions for data collection, where data is easily transferred directly from the patient to the EDC database. As stated before, PRO seems to be the future of data collection in clinical trials, the advantages of following a patient during a longer period of time seems to be intriguing for the clinical researchers. By being

creative and connecting already existing device such as body scales or blood glucose meters to the EDC database, the clinical management team will have the ability to monitor patients more frequently. This could be of interest for the patient's physician as well and perhaps implementing the system or tool in a regular clinical setting first will give the system or tool the credibility needed for use in clinical trials. Important to remember is that if the purpose of the data collection is to measure blood pressure every 4th week and the clinical researchers realises that this could be measured daily, by the patients themselves, credibility would not be an issue. As long as it is possible to assure that the result would be the same if blood pressure was measured by a nurse at the clinic or with the device that the patient can bring home I don't see a problem with the credibility at all. However in the PANDA case it is the method itself that is new and hasn't received the credibility that is needed for use in clinical trials, yet. Perhaps this is an objective for future study. When PANDA is implemented in a regular clinical setting, how long before this method of tapping and spiral drawing has reached the geographical spread and gains the credibility that it is possible to use in clinical trials.

As discussed in the section above, the easiest way to acquire the market seems to be by using a standardised method with high credibility, such as measuring of blood pressure or glucose levels and use these methods in a new digitalised manner.

Questionnaires are popular to use in clinical trials and there are many companies that have created standardised forms, which are sold to different studies. Since most questionnaires are already validated and most have high credibility in the eyes of EMEA and FDA, self-assessment questionnaires could be method that could easily be integrated in an eDiary. Perhaps a company creating these questionnaires would be a suitable business partner for Cenvigo.

It could also be of interest to partner up with one of the giants within EDC development. By collaborating with a CRO or pharmaceutical company the data collection methods could be customised to each trial. CRO or pharmaceutical companies would know long before the initiation phase what type of tool or method that will be used in the study and Cenvigo could in this phase offer a consultation of what elements of the data collection that they have the ability to improve.

8 References

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9 Annex I

Kvalitativ enkät om EDC i kliniska prövningar

Jag gör mitt examensarbete på ett nystartat företag som heter Cenvigo. Cenvigo arbetar för att ta fram IT-lösningar för vård på distans och har bl.a. utvecklat en applikation som ska hjälpa läkare att monitorera patienter med Parkinsons sjukdom i hemmiljö. En vidareutveckling av denna applikation har nu tagits fram för att användas i kliniska prövningar för insamling av data direkt från patienten, så kallad electronic Patient Reported Outcome (ePRO). Syftet med min undersökning är att studera utvecklingen av EDC-system och ePRO-verktyg i kliniska prövningar. Detta är en kvalitativ enkätintervju så svara gärna så utförligt du kan. Om du önskar vara anonym i uppsatsen så är detta okej men fyll gärna i de personliga uppgifterna nedan och skriv sedan *önskar vara anonym*.

Namn:

Företag:

Antal år i branschen:

Nuvarande yrkestitel:

Tidigare branchrelaterade yrkestitlar:

1. När började ni använda er av EDC-system med eCRF i kliniska prövningar?
2. Hur stor andel av era prövningar görs med EDC-system idag och skiljer sig detta mellan olika prövningsfaser?
3. Har du, inom företaget eller i ett annat företag, använt dig av olika EDC-system? Hur skiljer sig i så fall dessa system åt, vilka fördelar respektive nackdelar kan du se med respektive system?
4. Använder företaget andra databaserade lösningar som t.ex. ePRO, IVRS eller CTMS, pratar dessa system i så fall med varandra eller krävs manuell överföring av data?
5. Vilka fördelar kan du se med att använda EDC-system jämfört med pappersbaserad datainsamling?
6. Vilka fördelar kan du se med att använda pappersbaserad datainsamling jämfört med EDC-system?

7. Fanns det ett motstånd när EDC-system skulle implementeras i era prövningar? Var fanns i så fall motståndet (ex. klinik/CRO/sponsor/monitor/data management) och vad gällde motståndet i första hand?
8. Vem tar beslut om vilka system som ska implementeras och hur motiveras slutanvändarna?
9. Vilka barnsjukdomar finns i dessa system och vilka förändringar respektive förbättringar behöver göras för att öka användarvänligheten?
10. Tekniken för den här typen av datainsamling har funnits under väldigt lång tid och fördelarna är många men ändå har spridningen av tekniken gått förvånansvärt långsamt, vad tror du detta beror på?
11. Hur tror du datahanteringen i kliniska prövningar kommer se ut om 10 år?
12. För att effektivisera datainsamlingen ytterligare kan viss datainsamling göras av patienten själv. Det kan gälla både patientdagböcker, QoL-frågeformulär eller något annan typ av data. Görs detta elektroniskt eller via papper i era studier?
13. Om PRO har använts både i elektronisk form och i pappersform, har ni upptäckt någon skillnad vad gäller compliance eller andra fördelar/nackdelar med respektive form?
14. Skulle insamling av mätdata från instrument som patienten själv kan hantera, t.ex. blodsockermätare eller våg där all data går direkt in i ett eCRF vara av intresse att använda i era prövningar? Vilka är fördelarna respektive riskerna med att samla in data på detta sätt?
15. Om ni skulle köpa in en ny elektronisk lösning för inhämtning av data direkt från patienten, vad skulle ni kräva respektive önska av systemet?
16. Hur ser ert behov av lösningar för elektronisk datainsamling ut idag?
17. Cenvigo arbetar med att hitta lösningar för effektiv och säker datainsamling. Är ni intresserade av att bli kontaktade av Cenvigo där vi kan berätta mer om vår verksamhet och diskutera vad vi kan göra för er?