Conceptualization of a medical data collection system intended for decentralized clinical trials

Caroline Zander and Klara Indebetou

2022

LUND UNIVERSITY

SONY

Faculty of Engineering LTH
Supervisor: Martin Stridh
Examiner: Frida Sandberg

Sony Network Communication Europe
Supervisors: Anders Strömberg,
Claes Nilsson & Johan Rocklind

Master Thesis in
Biomedical Engineering
Department of Biomedical Engineering

Conceptualization of a medical data collection system intended for decentralized clinical trials - A Master Thesis

Subject: Degree Project in Biomedical Engineering (BMEM01)
Division: Department of Biomedical Engineering
Supervisor: Martin Stridh
Co-supervisors: Anders Strömberg, Claes Nilsson & Johan Rocklind at Sony Network Communication Europe
Examiner: Frida Sandberg

Department of Biomedical Engineering
Faculty of Engineering LTH
Lund University
P.O. Box 118
SE-221 00 Lund
Sweden

Abstract

Developing and getting a new medicine approved is a long and expensive process and it would therefore be beneficial if it could be streamlined. In order to control the effect and safety of a new treatment, clinical trials are performed. Traditionally, these have been performed at physical clinics, but with digitalization the option to collect clinical data remotely has been presented.

This thesis investigates how a system for collecting clinical data remotely could be designed to comply with existing regulations and at the same time facilitate the work for clinical trial personnel. An extensive list of requirements such a system would have to fulfill was therefore compiled through a literature review and interviews. Based on a selection of these requirements a prototype was developed. The prototype was then evaluated through five interviews where usability testing was performed. The evaluation showed that all test subjects were able to complete the usability tasks in the system and that they gave the system a rating of 8/10 points on average. This thesis also contains a section on considerations to have in mind when implementing a clinical trial data collection system.

Acknowledgments

First of all we would like to thank everyone at Sony that has supported and guided us throughout this project. We would like to give special thanks to Anders Strömberg, Johan Rocklind, Claes Nilsson and Anna Jakobsson for all the encouragement and useful input you have given us.

We would also like to thank our supervisor at LTH, Martin Stridh, for all your advice and inspiration.

Finally we would also like to express our gratitude towards all the interview subjects who have devoted both time and effort towards our project, it would not have been possible without you.

Contents

List of abbreviations

API - Application Programming Interface
CRF - Case Report Form
CRO - Contract Research Organization
CTD - Clinical Trial Data
DBD - Digital Biomarker Device
DCT - Decentralized Clinical Trial
DIM - Decentralized Intervention Method
EHR - Electronic Health Records
EMR - Electronic Medical Records
FDA - Food and Drug Administration
GCP - Good Clinical Practice
ICH - The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IMP - Investigational Medical Product
IoT - Internet of Things
LTE Cat-M - Long-Term Evolution category M
PPG - Photoplethysmography
RPM - Remote Patient Monitoring
SMPA - Swedish Medical Pharmacy Agency (Läkemedelsverket)
SNCE - Sony Network Communication Europe
TMF - Trial Master File
VCT - Virtual Clinical Trial

1 Introduction

In this section the background of this thesis project is presented and the purpose and the research objectives are defined.

1.1 Background

Developing and getting a new medicine approved is a time consuming and expensive process. On average, it costs $1336 million [1] and takes about 12 years [2]. Thus, it would be favorable if the process could be streamlined as much as possible. To prove that a new treatment or medicine is safe and effective is done by conducting a clinical trial [2]. During the clinical trial, it is determined how the medicine is absorbed, metabolized and excreted. Furthermore, the effectiveness of the medicine is established. To accomplish this, large amounts of data must be collected from multiple study participants [3]. One of the main challenges during clinical trials has always been to recruit enough study participants and one of the main reasons why people decline to participate is the time the trial would consume [4]. It would therefore be advantageous to reduce the time spent at the clinic by collecting data from wherever the participants are located so that they do not have to spend time traveling to the clinic. This would be especially beneficial during a pandemic such as COVID-19 when travel restrictions have at times been imposed. It would also be useful during normal circumstances as it allows for a bigger reach and the possibility to recruit participants that live in more rural areas [5].

When data is collected outside of a study clinic the trial is said to be decentralized or virtual. To collect data for a decentralized clinical trial (DCT) a remote patient monitoring (RPM) system could be used [6, 7]. One way to monitor patients remotely is through a digital biomarker solution. The Health Solution Division at Sony Network Communication Europe (SNCE) has developed such a solution called mSafety which will be used as an example for remote data collection in this thesis. The mSafety system consists of two parts, a digital biomarker device (DBD) worn on the wrist to collect data and a secure cloud to store and manage the data. The DBD has embedded sensors which allows the system to calculate for example the users heart rate, heart rate variability, activity and sleep. Furthermore, the wearable allows customization of the data collection by connecting to other sensors. The mSafety system has, among other things, previously been used to monitor patients with kidney failure and diabetes [8]. Sony is now exploring the op-

portunity to use the mSafety system to collect data remotely during clinical trials. They are therefore interested in identifying user needs and regulatory requirements placed upon such a system, and henceforth they call for a design example of a digital system that fulfills these.

1.2 Purpose and Goal

The purpose of the thesis is to define requirements and create a prototype of a digital system that allows qualified personnel to safely and efficiently access medical data collected remotely during a clinical trial. Furthermore, the thesis aims to compile a summary of considerations to have in mind when implementing a DCT. This thesis hopes to facilitate the implementation of remote patient monitoring systems in a clinical trial setting and contribute to the general knowledge of potential user needs and requirements within this area.

1.3 Problem statement and research questions

The primary research question is how a system for collecting clinical data remotely could be designed to comply with existing regulations and at the same time facilitate the work of the clinical trial staff. To answer this, the following research questions are used:

> ***RQ1:*** *What requirements does a digital system need to fulfill to allow clinical trial personnel to efficiently perform their work tasks in a decentralized clinical trial?*
>
> ***RQ2:*** *How can a digital system be designed to fulfill these requirements?*
>
> ***RQ3:*** *What regulatory, structural and societal aspects would need to be considered if the system was to be implemented?*

2 Theoretical background

In this section, the theoretical background needed to understand the project is presented. This includes information about clinical trials, RPM, clinical data, and Sony's DBD mSafety. The proposed system utilizing mSafety that works as a case study in this thesis is also explained.

2.1 Clinical trials

As described by the Swedish Research Council [3] a clinical trial generally consists of four phases. During the first three phases different interventions methods, such as introducing a new diet, testing a new procedure, or investigating a new medicine, are used [9]. The purpose of the first phase is to determine if the product is safe for human beings. This is done by investigating possible side effects, analyzing the substance's pharmacological properties and determining how the substance is broken down and excreted from the body. During this phase 20-80 healthy participants are normally used and are initially given a low dose of the medicine. The dosage is then steadily increased and before each increase a security evaluation is done. If the substance is deemed safe the clinical trial moves on to phase two.

The goal of the second phase is to get an approximation of the effectiveness of the medicine and determine what dosage might be suitable. Further information regarding the safeness of the medicine and possible side effects are also collected. For this phase a homogeneous participant group is desired and all the test subjects should have the disease the medicine is intended to treat. The number of participants is still fairly limited and the effect of the medicine is compared to similar treatments or placebo. The aim of the next phase, phase three, is to determine the effect of the medicine and discover possible side effects over a longer period of time. During this phase a large group of test subjects is used, between approximately 200 to 3000 persons. The study participants should be a good representation of the intended target group for the medicine regarding age, sex, weight to mention a few. If this phase is successful, the next step is to apply to have the treatment approved. The last phase, phase 4, is done after the product has entered the market. It consists of extensive studies to monitor the long term effect of the medicine, detect rare side effects and determine the optimal field of application [3].

A clinical trial needs to be designed and conducted in accordance with the principles in the Helsingfors declaration and Good clinical practice (GCP). The main purpose of these two documents is to protect the trial participants, ensure that correct research methods are being used, and that the process is documented sufficiently enough that the trial can be re-created [10]. Furthermore, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) compiles guidelines and requirements with the help of regulatory authorities and the pharmaceutical industry with the aim to attain greater harmonization [11].

There are two main parties involved in a clinical trial, the first one being the sponsor. This is often a pharmaceutical company that has the main responsibility for the clinical trial. Their responsibility includes planning the clinical trial, writing the test protocol, choosing the test sites, leading the project, supplying all materials, financing the clinical trial, and performing quality audits of the trial when needed. Ensuring that all necessary contracts are available before the clinical trial starts and obtaining a clearance for the trial from Swedish Medical Products Agency (SMPA) also falls under their responsibility. Lastly, they are also responsible for data processing, analyses and reporting. Due to the heavy workload some of these tasks are sometimes delegated to a Contract Research Organization (CRO). The main responsibility can not be delegated though, it always falls on the sponsor. The second party involved in the trial is the clinic. This is either a hospital clinic or a healthcare center that conducts the trial on behalf of the sponsor.

A clinical trial generally includes a multitude of people with different roles and responsibilities that all need to collaborate. A short description of the different roles vital to the trial are listed in the section below [10]. It should be mentioned though, that for trials conducted at a smaller company or within an academic research group the responsibilities from multiple roles may fall on the same person.

2.1.1 Roles at sponsor

- **International coordinating investigator:** If the trial is executed at multiple places and countries, this person is responsible for coordinating the trial.
- **Coordinator:** Responsible for the trial in one specific country.

- **Study team:** The people at the sponsor that have access to the anonymized participant data. Consists of:
  - **Project leader:** Have the main responsibility for a specific study. This includes, among other things, responsibility for the planning and making sure that the protocol, time plan, and budget is followed.
  - **Monitor:** An important link between the sponsor and the team working at the clinical site. Have the responsibility to verify that the trial is executed correctly and control the principal investigator's study documents. Tasks include quality control of the study and ensuring that possible problems are identified and solved.
  - **Medical writer:** Responsible for producing the report and trial protocol.
  - **Data manager:** Responsible for handling the participant data and producing a database for it.
  - **Biostatistician:** Responsible for analyzing data, creating tables and graphs. Sometimes also supports the medical writer.
  - **Programmer:** Works together with the biostatistician to create the needed tables and graphs.
  - **Clinical trial associate:** Is often a form of secretary that has the task of maintaining the Trial Master File (TMF).

2.1.2 Roles at clinic

- **Principal investigator:** A physician responsible for the execution of the trial. Allocates personnel and participants to the study. Can delegate tasks to coworkers with sufficient expertise but cannot delegate the overall responsibility.
- **Sub investigator:** Physician that works alongside the principal investigator. Can also make medical decisions.
- **Study nurse:** Nurse that works alongside the principal investigator. They often have the main participant contact and perform most of the practical tasks.
- **Pharmacists:** Not formally involved in the study but have a vital role regarding the medicine management.

2.1.3 Important documents

During a clinical trial a multitude of documentation is needed. Two binders that some of this information is stored in and that are vital to the trial are described here below.

- **Case Report Form (CRF):** Formulary where all data needed according to the protocol for each participant is collected. Is written by the clinic and then sent to the sponsor. All data in this document must match with the source data and all changes must be dated and signed.
- **Trial Master File:** Contains everything from planning, approvals, initiation, implementation and closure of the study. All the essential documents combined results are kept in the TMF.

2.2 Remote patient monitoring and decentralization

Remote patient monitoring is when medical devices and technology are used to gather patient data outside of conventional clinical settings [6, 7]. Some examples of measurements that are commonly taken during RPM are vital signs, weight, heart rate and blood pressure. RPM allows for medical data to be gathered no matter where the patient is located and gives the healthcare personnel the opportunity to check in on patients between visits and detect potential health issues earlier [12]. What techniques and equipment are used for the RPM vary depending on the purpose but all systems have some sort of sensor that takes measurements. There exist RPM devices that can collect, transmit, process, and store data and they can be in the form of anything from watches and smartphones to skin patches and shoes [13].

There already exist several systems for remote data monitoring, meaning that clinical personnel can access medical information from the clinical trial remotely [14, 15, 16, 17]. Pfizer used this method for example during the clinical trial for their COVID-19 vaccine [18]. A well established complete system that uses RPM during a clinical trial does not exist to the knowledge of the authors of this thesis. However, there exist some systems that have been used in a limited setting or are still being tested [19, 20].

Remote patient monitoring is a tool often used in decentralized or virtual clinical trials (VCT). DCTs or VCTs are two of the many paraphrases for trials using intervention methods which are not tied to the location of a specific study clinic [21]. DCTs can either be completely decentralized or only have

some decentralized components. This includes but is not limited to having digital technologies for recording participant information, collecting medical data, or creating the possibility for participants to communicate with clinical personnel on platforms and applications. While DCTs and VCT can be used to describe the same type of trial, VCTs are generally more focused on the digital part of the decentralization while DCT can also refer to the act of using local clinics to perform trial interventions [22, 23].

2.3 Clinical data

In the advancement of healthcare, clinical trial data (CTD) is a fundamental resource used to get further insight and develop new practices. CTD is important in the development of new systems and care processes, and is the key to understanding different therapies' effects on patients [24]. However, the use of CTD comes with privacy, security and ethical challenges as the data may contain sensitive and confidential information. It is therefore of utmost importance to protect the CTD. Generally the management of CTD involves having goals regarding security, privacy, safeguarding the confidentiality, the availability, and the integrity of the data. This means that the data should only be accessible to recognized personnel and that the data should always be available. Furthermore, it also means that the data can not be unlawfully erased or modified in any way and the data should not be exposed to any anticipated security threats [25]. The security and privacy of clinical data is regulated in Europe by the EU's General Data Protection Regulation, EU/2016/679 [26], which is enforced by local government agencies. In Sweden the regulation is supervised and enforced by the Swedish Authority for Privacy Protection [26].

2.4 Sony Network Communications and mSafety

Sony Network Communications Europe is a business unit within the Sony group with the purpose to drive the advancement of Internet of Things (IoT) products. The unit is creating intelligent, connected services for other companies and is only working business to business. One of their main services is the mHealth and safety solution, mSafety, which is produced by the Health Solution Division at SNCE. As described by SNCE, mSafety combines a user-friendly DBD with a trustworthy and safe back-end solution [27].

The mSafety DBD, which comes in the form of a digital watch, can both receive and send data. The transmissions are done with end-to-end encryp-

tion of the data using built-in security keys. The device is directly connected to the internet via Long-Term Evolution category M (LTE Cat-M), a global cellular connectivity technology. The LTE Cat-M is especially suited for eHealth and safety devices due to its reliable and continuous connection, and the low-power communication. Using LTE Cat-M, the data transfer is made without the need for an external mobile device. All data is uploaded automatically from the DBD directly to the mSafety cloud back-end. The mSafety cloud then creates the framework for secure interaction between Sony's customer's back-end servers and the DBD, without having access to the actual data. The mSafety cloud back-end uses an Application Programming Interface (API) for functions such as authentication, authorization, device management, data transfer and end-to-end security. The mSafety system comes with a Software Development Kit which contains API's for device features. This enables customization of the mSafety DBD and the ability to create one's own back-end and front-end solution, fit to a specific purpose [8].

One customization of the DBD is the use of external sensors, as the DBD has support for connection to external devices via Bluetooth. This includes external sensors for blood pressure, body weight, and glucose levels to mention a few. The DBD can also be modified to receive notifications and messages from a potential healthcare provider or receive reminders to complete predetermined health goals. Furthermore, the device also has the capability to send notifications to a potential healthcare provider, either by using the touchscreen or one of the three physical buttons on the sides, see figure 1. The touchscreen can be used to switch between different screens where for example the information from the sensors can be automatically displayed. The DBD also has multiple internal sensors and matching algorithms, these include for example a photoplethysmography (PPG) sensor to measure heart rate and an algorithm to calculate heart rate variability from this [8].

Figure 1: Sony's DBD called mSafety. Credit: mSafety, Sony.

2.5 The proposed system

The proposed system for this thesis consists of three different parts; data collection, data storage, and data analysis, as can be seen in figure 4. The first part, the data collection, implies medical examinations and testing typically done at the clinic in a traditional clinical trial. This could be, for example, blood analysis, screening of the participant, or palpation. Data collection will also include data from one or more DBD, thus creating medical data, such as heart rate and blood pressure, outside a clinical setting. Lastly, the data collection will include information entered by the participant. This could be participant diaries and surveys regarding general health and experienced symptoms for example. The data collected from the various data collection methods will be uploaded to and stored in a secure data cloud. Finally, the data is accessed and analyzed in an application created for personnel working in clinical trials. The intention of the application is to create a holistic solution which combines the data from the data collection and also provides access to other needed information such as the trial protocol. Furthermore, that the application can be used from start to finish in every part of the trial.

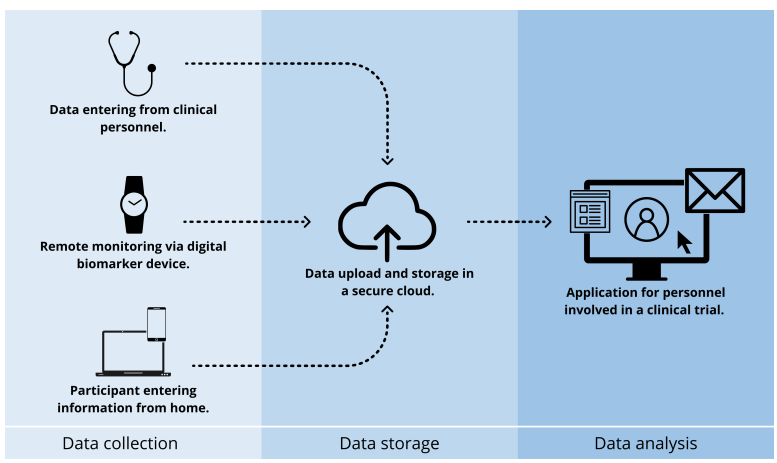


Figure 2: Show the DCT setup for the user case.

2.6 Design

When developing a system it is often useful to keep some design principles in mind. Some of the most commonly used design principles are the ones created by Donald Norman. Norman is one of the most eminent persons within the field of user centered design and human computer interaction. For designing any interface Norman proposes six key design principles to abide by. As described in the book *Interaction design: beyond human-computer interaction* [28] these are:

- **Visibility**: The user should without any effort see what their options are and understand how to access them.
- **Feedback**: The user should receive feedback from every action in the system to assure them that their action caused something to happen.
- **Affordance**: Should have a clear relationship between the appearance of something and how to use it.
- **Mapping**: Should have a clear relationship between the attributes of the object and its effect.
- **Constrains**: Restrictions placed on an interface that limits a specific user interaction with it.
- **Consistency**: Similar elements and operations should be used to achieve similar assignments.

These design principles can be seen as a general foundation and guide when creating an application. A system containing data regarding a person's health and well being should also consider specific designs to minimize potential safety issues. In a literature review by Zahabi et al. [29] the usability of electronic medical records (EMR) and electronic health records (EHR) was investigated. This review resulted in a design guideline with 9 design principles regarding EHR and EMR, listed below:

- **Naturalness**: The interface should provide a familiar workflow with a natural order of information to the user. The healthcare system's natural workflow should be followed and mirrored.
- **Consistency**: Similar elements and operations should be used to achieve similar assignments.
- **Prevent errors**: A system should prevent potential user errors, either by color coding, interactive interface, or automatic data entry.

- **Minimize cognitive overload**: The user should only be presented with relevant information for the present task. The interface should also avoid having multiple views of the same information.
- **Efficient interaction**: The interface should be effective to use, where more critical information is easier and faster to access. The user should also be presented with shortcuts to relevant functions and the amount of user interactions in the interface should be minimized.
- **Forgiveness and feedback**: The interface should include feedback to the user, for example alert them of potential errors or mistakes going forward.
- **Effective use of language**: The language and terminology in the interface should be appropriate, clear, and understandable for all users. Abbreviations and acronyms should only be used if they are recognized and deemed meaningful by the users.
- **Effective information presentation**: There should be good visibility, both in the whole system and in the interface. This means that actionable functions should be clearly distinguished as actionable. The interface should furthermore only include relevant information in potential templates.
- **Customizability/Flexibility**: The interface needs to be customizable, especially for expert users. The user should get a role-appropriate interface view and have the possibility to change information content after their own needs and wants.

3 Methods

In this section the used methods and workflow of this thesis is described.

3.1 Overview of the method

The method of this thesis can be divided into two parallel processes. The first process consists of the five steps: literature review, interviews, compiling needs, prototyping and evaluation. The first three of these steps aims to answer research question number one: *"What requirements does a digital system need to fulfill to allow clinical trial personnel to efficiently perform their work in a DCT"*. The last two steps of this process (prototyping and evaluation) aims to answer research question number two: *"How can a digital system be designed to fulfill the identified system and user requirements"*. The methods of this whole process can be read about in section 3.2 to 3.6. The second process consist of only one step, DCT considerations, and aims to answer research question number three: *"What regulatory, structural and societal aspects would need to be considered if the system was to be implemented"*. The method for this process can be read about in section 3.7. The overview of the complete workflow can be seen in figure 3 below.

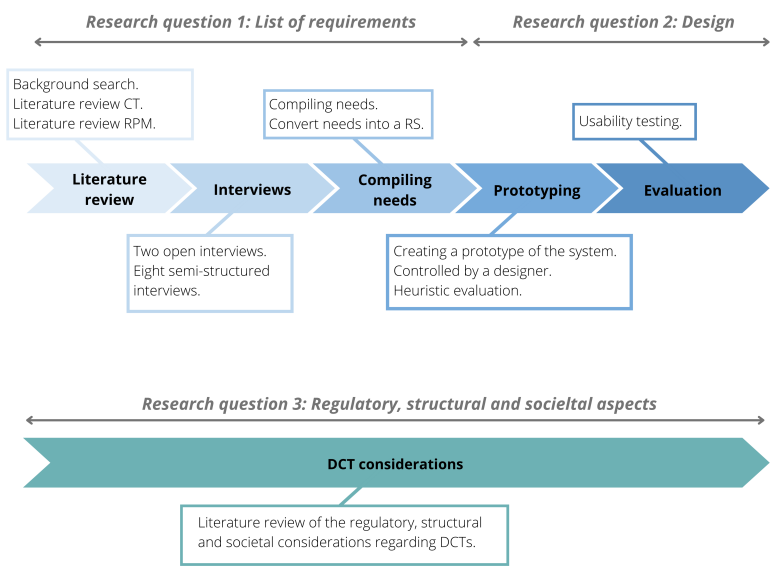


Figure 3: Workflow of the method.

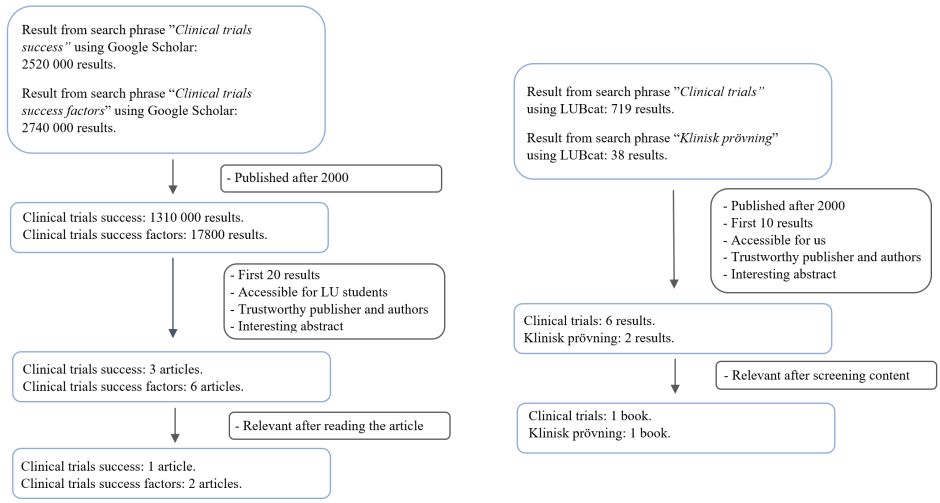
3.2 Literature review to identify needs

The literature review consisted of two parts. The aim of the first part was to gain a greater understanding of how clinical trials are conducted and what success factors and problem areas can be found regarding them. The aim of the second part was to gain a wider knowledge of RPM systems, and important aspects to have in mind when utilizing them.

3.2.1 Clinical trials

This part of the literature study was performed in two subparts. During the first subpart Google Scholar was used as the search engine with the search phrases *"clinical trials success"* and *"clinical trials success factors"*. Due to a limited amount of articles that fit this thesis purpose and since the process of clinical trials was deemed to not have changed much during the last decade, all articles written after 2000 were included in the search. The titles of the first 20 search results sorted on relevance were screened. If the title looked relevant and the publisher and author appeared trustworthy the abstract was read and the article skimmed through. The articles that still appeared promising after that were read and if they fit the aim of the study they were included. This whole process is described in the flowchart seen in figure 4a below.

The second subpart of this literature review was conducted with the aim to gain insight into the whole clinical trials process from start to finish. The previously found articles only described specific areas of improvement and a search for books describing the process as a whole and providing more extensive information were therefore made. The search engine Lubcat was used combined with the search phrase *"Clinical trials"* in English and in Swedish, *"klinisk prövning"*. The first ten titles were looked through and the ones that appeared interesting after reading the abstracts were included. This whole process is also described in the flowchart seen in figure 4b below.



(a) (b)

Figure 4: Flowchart of the clinical trial literature study. The left part (a) describes sub-part 1 and the right (b) sub-part 2.

3.2.2 Remote patient monitoring

The second part of the literature study was made to gain knowledge of both problems and opportunities with RPM systems. The use of RPM in clinical trials is still a limited area of research and therefore the search was conducted to be comprehensive of different uses of RPM systems. The search was done on the Google Scholar search engine with the search phrase *"remote patient monitoring system design"*, filtering on the last ten years. The search results were sorted based on relevance and the first 20 results were screened. Screening was performed by first evaluating the relevance of the title and the trustworthiness of the publisher and author(s). Thereafter the promising articles were evaluated by reading the abstract and skimming through the article. This was done due to RPMs many synonyms and paraphrases. The remaining articles were thereafter read and if still deemed suitable for the study, reviewed. The process of this literature study can be seen in figure 5 below.

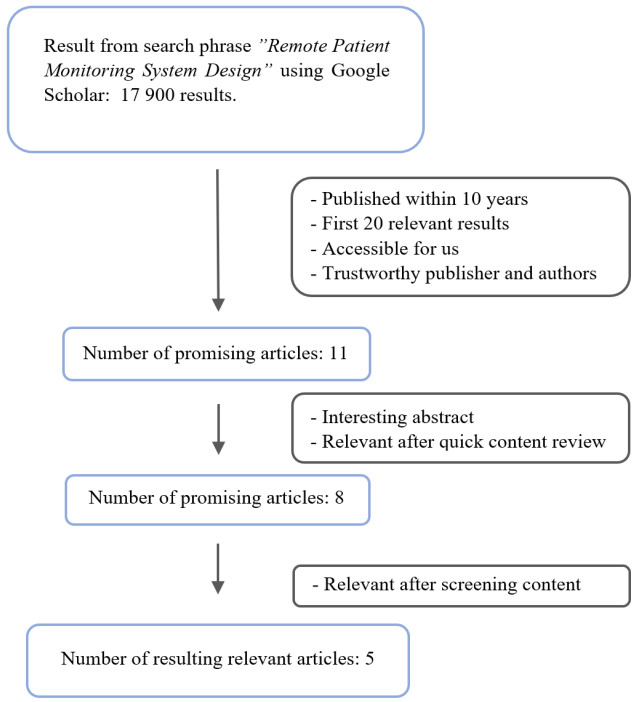


Figure 5: Flowchart of the RPM literature study.

3.2.3 Compiling the result from the literature review

After deciding which sources to include in the literature review, the material was examined and challenges and possible solutions were identified and compiled for both the clinical trial and RPM literature review. These were then translated into needs. The result from this can be seen in appendix 7.1. Lastly a summary of the most frequently mentioned and relevant needs was created.

3.3 Interviews

A series of interviews were performed to investigate the practical workflow of a clinical trial, gain knowledge of current digital methods, and identify areas of improvement. The ten interviewees were chosen to cover a multitude of aspects of a DCT. The interview process started with two longer open interviews of approximately two hours each. The aim of these longer interviews was to gain a deeper understanding of how clinical trials are conducted and

get an insight into the everyday tasks and needs of the different work roles. These interviews also provided inspiration for the interview protocol of the succeeding interviews. Thereafter an additional eight semi-structured interviews of 30-60 minutes each were performed. Semi-structured interviews were chosen as they were structured enough to allow comparison between the different participants' answers while at the same time being flexible enough to discover new information not thought to ask for [28, p. 234]. The interview questions explored four main areas but the time spent on each area was adapted depending on the interviewees area of expertise. The first area consisted of questions regarding the interviewee's general background within clinical trials. The second area focused on data management experiences, work responsibilities, and digital systems. The third area touched upon the possibilities and complications regarding DCT and the fourth area focused on data sharing.

To analyze the data gathered during the interviews, an affinity diagram was used [28, p. 292]. Observations from each interview were written down on digital sticky notes and these were thereafter grouped based on similarities. This method allows for individual observations from each interview to be organized into a hierarchy that displays general themes [28, p. 292]. Furthermore, the affinity diagram was seen as a beneficial method as it allows for a great deal of data to be organized into a compact result that made comparison with the result from the literature study easy. This in turn facilitated the process of compiling joint requirements based on the result from both the interviews and the literature study.

3.4 Compiling needs

All the identified needs from both the literature study and the interview were combined in a list. This was done to get an overview of the identified needs, be able to sort them, and remove duplicates. The 460 identified needs were first grouped together with similar needs to form categories. To create an implementable list, the needs were reduced in three rounds of iterations. In the first round needs that could not be implemented in a design prototype, such as aspects of data security, were removed. Needs related to the participant platform and the wearable were also removed.
In the second round a priority of the needs were created. Needs that were related to decentralized clinical trials and that had been mentioned more frequently were deemed more important and therefore given a higher priority. Needs where the level of detail were deemed insufficient and/or were

difficult to implement in the prototype were set as the lowest priority and once finished with the prioritizing process, removed. In the third round the needs were once again given a priority. The priorities were then based both on the importance of the need and the presumed time and effort of the implementation.

3.5 Prototyping

The prototyping involved combining the compiled needs with design methods to create a prototype in Microsoft PowerPoint. This was done with the aim to demonstrate a concept application which embodies the requirements posed by the users. In the prototyping, mSafety was used as an case study for the remote data collection functions.

3.5.1 Design principles and design methods

For the design of the prototype inspiration was taken from applications that most people recognize and use such as Microsoft Office, Zalando, Facebook, Google, among others. This was done to give the user a familiar feel, thus decreasing the time needed to learn the system. The design of the prototype was also created with regard to Donald Norman's design principles and the medical design principles, presented in section 2.6, to get an overall better system design. This was done by researching the design principles beforehand to get a good understanding of them, and then applying that knowledge in every step of the design process.

3.5.2 Design process

3.5.2.1 Limitations and Translation of needs

The prototype was limited in regards to three main aspects; the number of versions created, the program used to create the prototype and the number of implemented functions. While a customized version of the system would ideally be created for each role in a trial it was here decided to only create three user versions due to limited amount of time. These three versions were intended for a principal investigator, a study nurse, and lastly a monitor or project leader. These three roles were chosen due to two reasons. Firstly, they reflect the roles our interview subjects held which would both make our collected information and our evaluation more relevant. Secondly, these roles also represent the most likely users of the system.

Regarding the second aspect of limitations, MS PowerPoint was used to create the prototype. This meant that the design was also limited by the available applications. The third aspect of limitations, the number of implemented needs consisted of a selection of which functions to implement in the prototype. This had to be done due to the large amount of identified needs and the limited amount of time. The selection of needs to implement was based on the resulting list of needs described in section 3.4. The needs were translated into functions where the most vital and frequently requested functions were prioritized. It was also decided to focus on functions related to data collection and viewing since that is a central part of performing a DCT using a DBD. Functions which were based on a scant amount of collected data were deemed to be ambiguous and were thus excluded or implemented in a limited way. Further, functions that were easy to implement and made the system more credible were implemented. The functions were thereafter sorted into different views and windows. The various views with their respective identified functions were then presented to the project group involved in Sony´s clinical trial project. Lastly, an initial version of the prototype containing these views was created in MS PowerPoint.

3.5.2.2 First round of iteration

The initial version of the prototype was presented at a meeting with the project group at Sony. Feedback from this meeting included that the function to add new personnel to the trial should be restructured to reflect the hierarchy among them. Clarification of the different user views and how the homepage could be configured was also requested. Changes to the prototype were made based on this feedback.

3.5.2.3 Second round of iteration

After the first version of the prototype had been updated a second meeting was held with a designer working with designing digital systems at Sony. The new version of the prototype was presented and the designer provided feedback. This feedback included how the *create a new trial* part would expand when more information was added. Further, the possibility to reorganize the schedule and communication page was discussed as well as how it could be made clearer that the trial setup contained multiple sub steps. Based on the provided feedback the prototype was updated once again.

3.5.2.4 Third round of iteration

A joint meeting was held with the people from the first two meetings. The changes from the previous meetings were reviewed but no new feedback that could be implemented in the prototype was given.

3.5.2.5 Heuristic evaluation and other design principles

In the last round of iteration a heuristic evaluation was conducted. This evaluation method was chosen as it allows for identification of basic usability problems without the involvement of actual users. By fixing the problems identified with this method a more effective evaluation involving users could be performed later on. A heuristic evaluation utilizes a predetermined set of the best usability practices which brings structure to identifying problems that need to be fixed [30, p. 98]. For this project the ten usability heuristics created by Jakob Nielsen were used to evaluate the prototype [31]. To minimize the bias from each author the evaluation was first done independently and then the individual findings were combined. The prototype was thereafter also evaluated according to the design principles described in section *2.6 Design*. This was done by going though the listed design principles one at a time and examining if the prototype was in accordance with it. After the evaluation, improvements to the prototype were made in the identified problem areas. These changes included more options to cancel, adding an example of feedback when entering data, and making sure that the same icons were used throughout the whole prototype. The final prototype version was then saved and locked for further changes.

3.6 Evaluation

The prototype was evaluated by conducting interviews with five of the ten of previously interviewed people. During these interviews a usability test was performed. Usability testing is, as the name suggests, an evaluation method used to improve the usability of a system. It aims to do so by trying to identify which parts of the system that frequently confuse and frustrate users so that these problems may be fixed. During the evaluation testing the test subject was asked to perform a set of predetermined tasks in the prototype while the authors of this thesis observed. The test subject was asked to think aloud while going through the steps of the task which provided the authors with insight into their thought process. During the test the thesis authors documented errors, such as occasions when it took the test subject an unreasonable amount of time to complete the task or when

they expressed confusion.

As recommended in the book *Universal Methods of Design* [30, p. 194], the tasks were chosen to portray real situations that the end user would experience regularly using the interface. Moreover, the tasks were kept specific and concrete. Two different usability testing protocols consisting of two tasks each were made for this project. The first protocol was given to test subjects that had experience of working for the clinic, meaning people who had experience of being a study nurse or a principal investigator. The other protocol was given to test subjects that had experience of working for the sponsor as either a project leader or a monitor. The version of the prototype used in the testing was also chosen based on what clinical trial role the test subject had experience with. One of the tasks, Task 2, was kept the same for all test subjects to get a more credible result. The used test protocols and their respective tasks can be seen in table 1.

Table 1: Specification of usability test tasks.

Task number	**Task specification**
Task 1	You want to add new data regarding a blood drawn made during visit number three for the patient Mariam S. Afety, how do you do it?
Task 2	You want to look at new data regarding adverse effects to determine how many study participants have experienced a level two headache, what do you do?
Task 3	You want to create a new trial project and in that project you want to add a new study nurse and change the collection time for the Sony mSafety to 08:00, how do you do it?

After the usability testing the prototype was presented for the interviewee and they were asked to provide feedback. The following leading questions were thereafter asked:

- **Q1:** Would you like to work in a system like this one?
- **Q2:** Do you believe that you would be able to perform your work tasks in a system like this one?
- **Q3:** On a scale from 1-10, what would you rate the proposed concept?

3.7 Literature review of DCT considerations

A second literature review was conducted to gain insight into regulatory, structural and societal aspects to consider when conducting a DCT. First the search engine Google Scholar was used together with the search phrases *"Clinical trials decentralization aspect"* and *"Decentralized clinical trial regulation"*. The searches were made using a filter to only include articles from the last ten years and the search results were sorted based on relevance. The first 20 results in each search were first screened by evaluating the title, the credibility of the publisher and the author(s), and perceived relevance based on skimming the article. The articles that seemed promising were then read through and included in the study if deemed relevant. This process is also described in the flowchart seen below in figure 6.

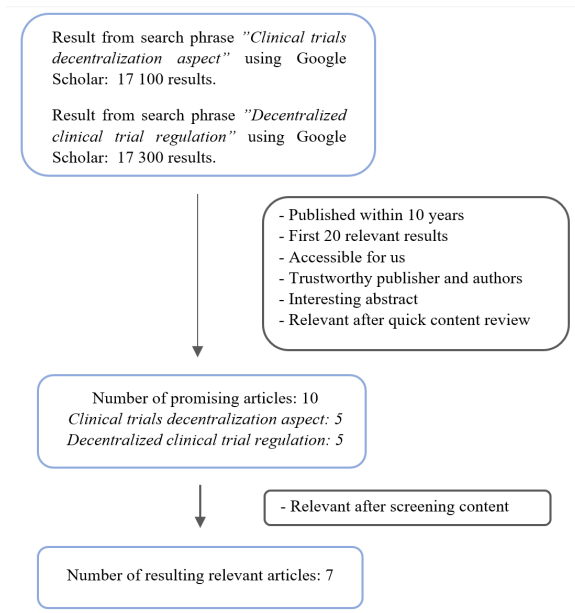


Figure 6: Flowchart of the literature review of DCT considerations.

To complement the resulting articles the official website of the SMPA [32] was used. The website navigation was done with the goal to find government information and regulations regarding DCTs. The resulting articles from the literature study, combined with relevant articles on the SMPA webpage, were reviewed and the information from these were compiled into eight different categories. The information in each category was then summarized.

4 Results

In this section the result from the literature review to identify needs and interviews is presented. The resulting prototype and the evaluation of it is also included. The section is concluded with the result of the literature review regarding consideration to have in mind when conducting a DCT.

4.1 Literature review to identify needs

The literature review resulted in a total of eight articles and two books. These can be seen in table 2 and 3 below.

Table 2: The resulting articles and books used in the literature study regarding clinical trials.

Part 1	**Title**
#1	Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review [33]
#2	The Process of Clinical Trials: A Model for Successful Clinical Trial Participation [4]
#3	Keys to success in clinical trials: A practical review [34]
Part 2	**Title**
#4	Fundamentals of Clinical Trials [35]
#5	Handbok i genomförande av en klinisk prövning: praktisk tillämpning av lagar och regler med fokus på monitorering (English title: Guide in conducting a clinical trial: practical application of laws and regulations with focus on monitoring) [10]

Table 3: The resulting articles used in the literature study regarding RPM.

Part 1	**Title**
#1	Effectiveness of Remote Patient Monitoring After Discharge of Hospitalized Patients With Heart Failure [36]
#2	Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): a randomized, controlled, parallel-group, unmasked trial [5]
#3	COVID-19 transforms health care through telemedicine: Evidence from the field [37]
#4	Smart Health Monitoring Systems: An Overview of Design and Modeling [38]
#5	Telehealth transformation: COVID-19 and the rise of virtual care [39]

From the literature review, 92 challenges and 114 related solutions were identified. Which challenges and solutions were mentioned in which article, and the needs they were translated into can be seen in the complete result found in appendix 7.1. A summary of the most frequently mentioned and relevant needs resulted in a total of 24 generalized needs that are presented in list 1 below. Many of the articles and books used in each part of the literature review mentioned similar challenges and solutions. There were also multiple similarities between the results from the clinical trial and RPM literature review part.

List 1: List of summarized needs from literature review to identify needs.

1. Possibility to view, sort, and analyze the collected data.
2. Possibility to annotate and correct data.
3. Possibility to verify data and lock it from further changes.
4. Possibility to change what data is collected and displayed for each trial.
5. Possibility for appropriate personnel to enter data into the system.
6. Possibility for participants to enter data into the system.
7. Data from sensors being transferred directly into the system.
8. Possibility for audit trail of activity and documentation.
   (a) Communication.
   (b) Data.
   (c) Data verification.
   (d) Study protocol updates.
   (e) User activity.
9. Possibility to access and change EMRs.
10. Possibility for notifications and reminders regarding data, tasks, and updates.
11. Possibility to send reminders to participants.
12. Design to be inclusive and intuitive to minimize the cognitive load and risk of user error.
13. Clear and updated instructions to the participants and personnel.
14. Possibility for communication between:
    (a) Trial personnel and participants.
    (b) Trial personnel and participants' regular physicians.
    (c) Trial personnel and trial personnel.
    (d) Trial personnel and pharmacy personnel
15. Possibility to schedule meetings.
16. Possibility to provide training and support to the personnel.
17. Possibility to have different user roles, tasks, responsibilities and access levels in the system.
18. Possibility to anonymize data from appropriate personnel.
19. Possibility to screen potential participants.
20. Data should be uploaded regularly.
21. Data security and participant privacy should be upheld.
22. Minimize the time participants need to spend on the trial.
23. Possibility to remove a participant and their data from the program.
24. Possibility for participants to view appropriate data.

4.2 Interview

A total of ten people were interviewed during the interview phase. Their respective roles and experience within the clinical trial field can be seen in table 4. The interviewees can be divided into groups with experience within four broad categories; the sponsor, the clinic, academic researchers using RPM and clinical trial advisories. Each category included at least two interviewees to reduce bias.

Table 4: Shows the title and work experience of all interview subjects.

Nbr	Title and work experience
1	Research nurse that has worked at the oncology and pediatrics department in Lund since the 2000, and is currently working in a research project with the pharmaceutical company Bayer.
2	Nurse that has worked on the sponsor side. Started in 1998 as a monitor, became a Clinical Research Manager (CRM) after a few years, and then worked as project manager from 2006. Have worked on the sponsor side for AstraZeneca and Ferring and since 2006 works for a CRO company.
3	Academic researcher working with DCTs.
4	PhD with long experience of working as a project leader within academic clinical trials. Have overseen multiple DCTs.
5	Clinical research manager that have worked at multiple companies and also as an independent consultant. Mainly worked at smaller companies where they have been involved in the whole clinical trials process.
6	PhD responsible for research and development at a department of clinical science at a university. Is a medial technology adviser and is also overseeing clinical research projects.
7	Regulatory expert at a clinical trial advice- and support group that aids other companies and the academia with their trials.
8	Started as a research nurse at AstraZeneca and then started working within private research. Worked thereafter as an inhouse clinical research assistant at a CRO company. The last six years have worked as clinical research assistant at Bayer on the behalf of the same CRO company.
9	Biomedical analytic with 20 years of experience in clinical trials. Have worked for AstraZeneca, different clinical trials units and is now working for an organization that provides support during clinical trials.
10	PhD working with procuring digital data collection system for AstraZeneca. Specialist in enabling transition from traditional to DCTs.

The detailed result of the affinity diagram created from the information obtained during the ten conducted interviews can be seen in appendix 7.2. The summary of the needs identified from the affinity diagram resulted in a total of 39 generalized needs which can be seen in list 2. There was a

large overlap between the identified needs from the literature review and the interviews. This can be seen as the first 21 needs in both lists 1 and 2 are the same.

List 2: List of summarized needs from interviews.

1 Possibility to view, sort, and analyze the collected data.

2 Possibility to annotate and correct data.

3 Possibility to verify data and lock it from further changes.

4 Possibility to change what data is collected and displayed for each trial.

5 Possibility for appropriate personnel to enter data into the system.

6 Possibility for participants to enter data into the system.

7 Data from sensors being transferred directly into the system.

8 Possibility for audit trail of activity and documentation.

- (a) Communication.
- (b) Data.
- (c) Data verification.
- (d) Study protocol updates.
- (e) User activity.

9 Possibility to access and change EMRs.

10 Possibility for notifications and reminders regarding data, tasks, and updates.

11 Possibility to send reminders to participants.

12 Design to be inclusive and intuitive to minimize the cognitive load and risk of user error.

13 Clear and updated instructions to the participants and personnel.

14 Possibility for communication between:

- (a) Trial personnel and participants.
- (b) Trial personnel and participants' regular physicians.
- (c) Trial personnel and trial personnel.
- (d) Trial personnel and pharmacy personnel

15 Possibility to schedule meetings.

16 Possibility to provide training and support to the personnel.

17 Possibility to have different user roles, tasks, responsibilities and access levels in the system.

18 Possibility to anonymize data from appropriate personnel.

19 Possibility to screen potential participants.

20 Data should be uploaded regularly.

21 Data security and participant privacy should be upheld.

22 Possibility for an offline-mode of functions and storage in the system.

23 Possibility to use appropriate authentication and security methods.

24 Possibility to have a seamless integration with another system.

25 Possibility for the system to encompass a broad variation of tasks and functions.

26 Possibility to work in multiple trials.

27 Possibility to create and change trial- and system setup.

28 Possibility to work in the system and add data directly in an efficient way.

29 Possibility for appropriate personnel to access the system from approved locations.

30 Possibility to conduct a randomized and anonymized trial.

31 Possibility to view and analyze adverse effects to monitor participant security.

32 Possibility to do source data verification and spot checks.

33 Possibility to monitor compliance.

34 Possibility to have information about participants.

35 Possibility to keep required information about trial personnel.

36 Possibility to view, add, update, and sign required documents.

37 Possibility to keep records of the DBDs.

38 The system should have a logical structure that is easy to follow.

39 Participant technology must be easily accessible and intuitive.

4.2.1 Opinions and beliefs

During the interviews the interviewees voiced some opinions and beliefs that could not be translated into direct implementable needs. These concerned mainly three areas: DCTs and the proposed system, business viability, and data sharing. When it came to concerns regarding DCTs most people were positive towards the proposed system and believed that it could reduce the amount of paperwork and increase compliance. They also believed that the participants could benefit from reduced travel and gain added value from the collected data. Most of the interviewees also advised that it is vital that the chosen technology is accessible and works as intended. Furthermore, they mentioned that the potential risks of a DCT needs to be considered and that not all trial interventions can be performed off-site.

When it came to business viability it was pointed out that the market is quite competitive and there exist multiple well established companies that creates CRF systems. Furthermore, there generally exists a resistance to learning new systems. The proposed system would therefore have to offer additional benefits to compete. It was suggested that it might be suitable to aim at a lower price range and larger volume in the beginning.

The opinions regarding data sharing were more divided. Some believed that data, especially big data, could be useful and were positive towards sharing their own. A predominant part of the interview subjects were hesitant towards sharing data though and did not see the usefulness of getting access to other studies data. The high expenses of gathering the trial data, difficulties of comparing data between trials, and patient privacy were stated as major obstacles towards data sharing. It was also mentioned that the benefit of sharing data must be greater than the potential risk and if there is any ambiguity the company will not share the data. For more detailed opinions, see figure 33 in appendix 7.2.

4.3 Prototype

The final prototype of the system consists of three different versions intended for three different roles. These roles are principal investigator, study nurse and monitor/project leader. The version intended for the study nurse is mainly a limited version of the one intended for the principal investigator, where functions that a study nurse should not have access to, like trial administration, are not accessible. The difference between the principal

investigator's version and the one intended for the project leader is more significant. The most notable difference is that for the project leader all participant data is coded and the possibility to contact participants and add new data is removed. The project leader can unlike the other users though create a new trial. Below are a few examples of different views in the system presented.

Figure 7 below shows the homepage view, which is the first view that a user will see after having logged into the system and chosen a trial project. The purpose of this view is to give the user a good overview of the system and offer shortcuts to other pages. The view is intended to come in a widget format with the possibility to customize the page based on the user's wants and needs. This is therefore only an example of what a homepage could look like.

The green upper bar is fixed for every view in the system and shows the available pages. The white line on the bar indicates which page the user is currently at. At the top left corner the name of the project is displayed. The profile picture located to the right shows the user. The green circle located on top of the profile picture indicates that the user has received new notifications in other trials. By clicking on the profile picture the user can see which project the new notifications concerns and also access basic system functions such as program settings.

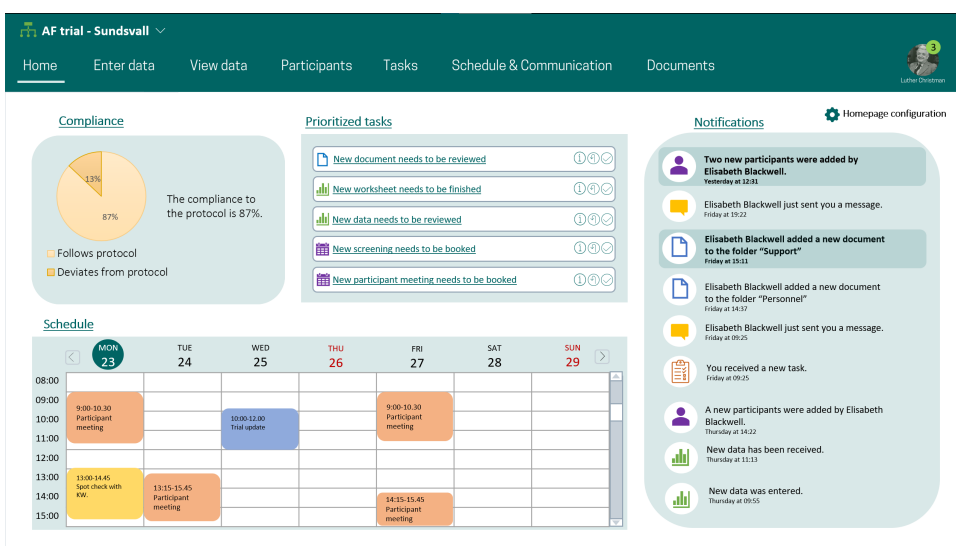


Figure 7: Shows the home view for a study nurse.

Figure 8 shows the personnel communication view where the user can communicate with personnel assigned to the project and schedule new meetings. The purpose of this view is to create an easy and secure way for the personnel to communicate, with all of their communication being saved directly to the trial documentation. At the sidebar to the left the user can switch between pages related to schedule and communication. The participant communication page gives the personnel the opportunity to communicate with participants. The *Schedule & Communication* part of the system is the same for all the prototype versions, except for the participant communication which only clinic personnel have access to.

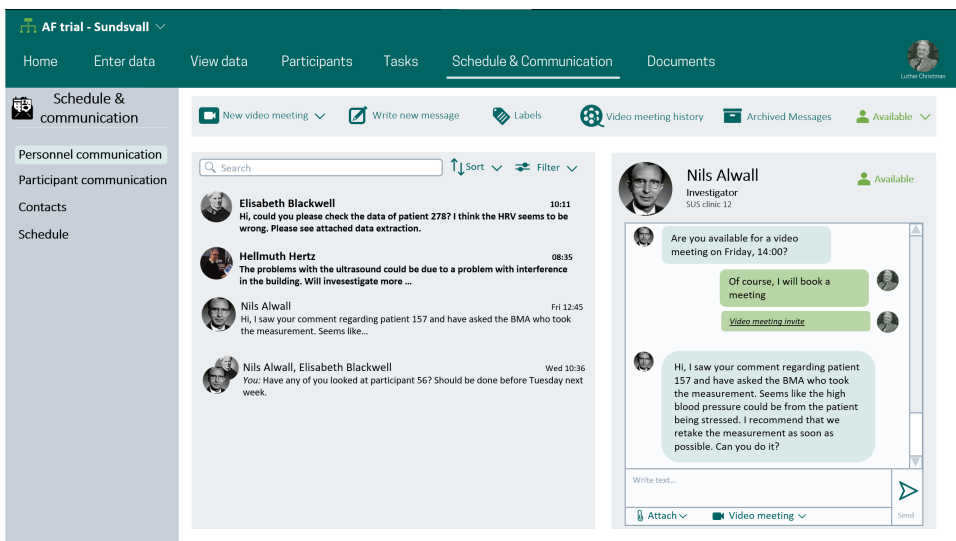


Figure 8: Show the communication view for a study nurse.

Figure 9 and 10 shows how data is manually entered in the participant's trial records. The overview of all worksheets seen in figure 9 is accessed by choosing the specific participant in a list of participants. The sidebar to the left lets the user navigate back to the list of participants if need be. The overview in figure 9 displays all the worksheets related to a specific participant, both those that have already been completed and the ones that still need to be filled out. These worksheets are templates of what data the trial personnel have to collect during the visits and an example of such a worksheet can be seen in figure 10. The view in figure 10 is accessed by choosing a specific worksheet from the list seen in figure 9. The worksheet has interactive boxes with helping text and units to avoid user error. The name of the participant is clearly stated at all times, along with the name

of the worksheet. Below the worksheet title a timeline is shown to illustrate the different steps in the workflow. The process of filling out the worksheet can be canceled or paused at any time. If paused the worksheet will be shown as having the status "Incomplete" on the worksheet overview page. When saving the information the user needs to control the added data and electronically sign, for example with BankID. *Enter data* and the associated views are only accessible for personnel with direct participant contact.

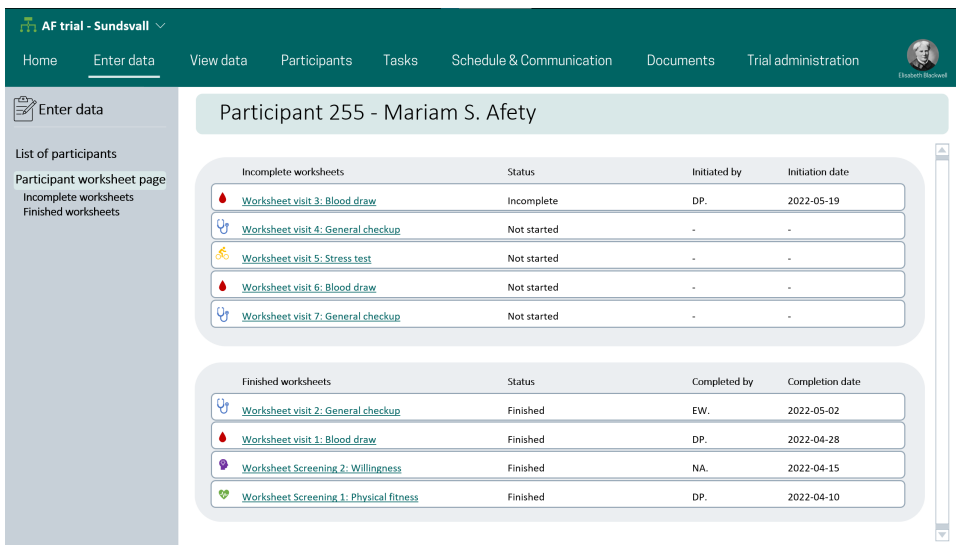


Figure 9: Show the overview of all worksheets for a specific participant for a principal investigator.

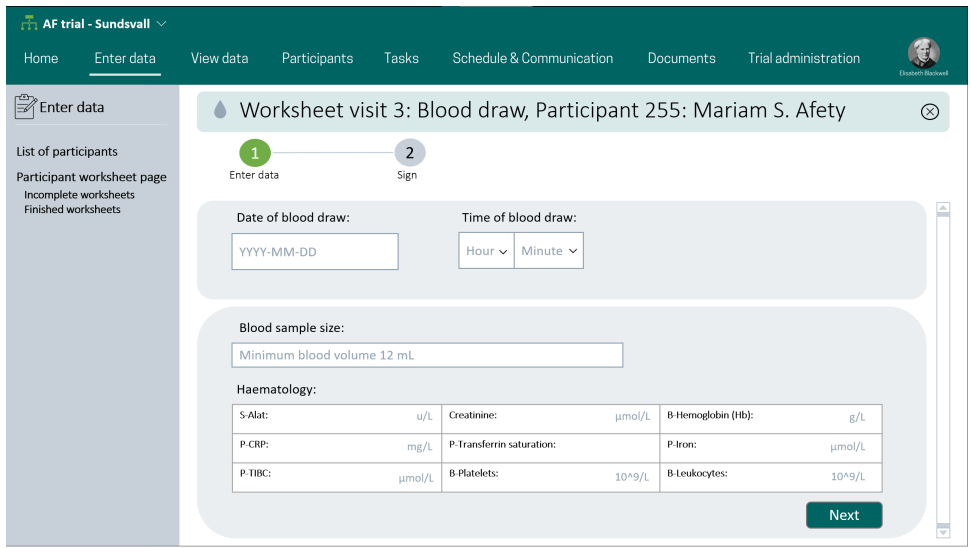


Figure 10: Show the worksheet view for a principal investigator.

The view seen in figure 11 and 12 are both examples of views found below the main section *View data*. In both example views a compilation of data from all the participants is shown. By selecting a single participant at "Select data" the data from a specific participant will instead be displayed. *View data* and all its subpages are available in all the prototype versions. The name of the participant is however not displayed for the sponsor side.

Figure 11 shows the view where data collected from a DBD can be seen. The purpose of this view is to allow the personnel to monitor the collected data and provide everything they need to draw conclusions from it. The possibility to comment on or edit data is accessed by right clicking on a point in the diagram. By left clicking on a point the exact values of that data point is displayed.

Figure 12 displays adverse effects experienced among the participants which allows the personnel to monitor the safety and effect of the treatment. At the top of the page all the reported effects are listed with the number of affected participants. The user may also see specifics about each and every effect when scrolling down on the page. The details provided in each section will be in a format deemed suitable according to current regulations.

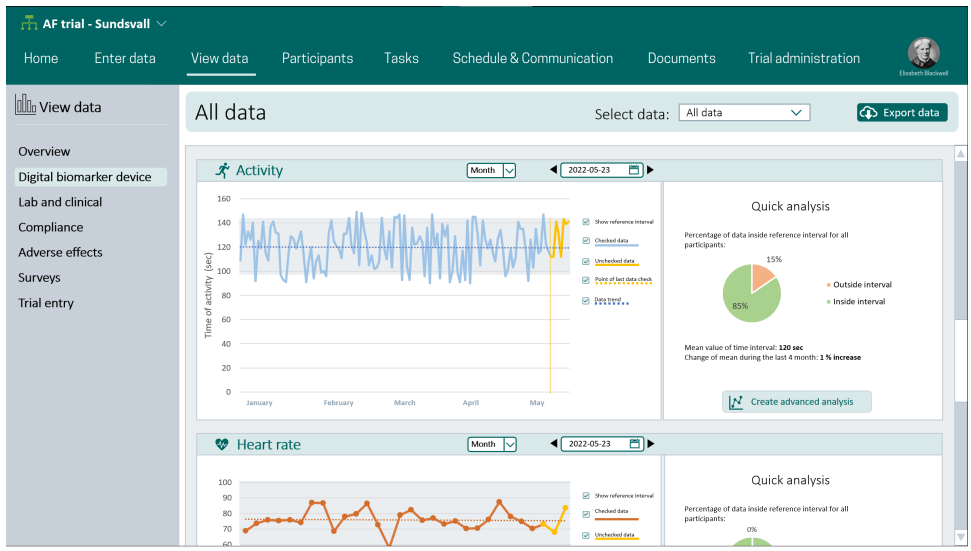


Figure 11: Show the DBD view for a principal investigator.

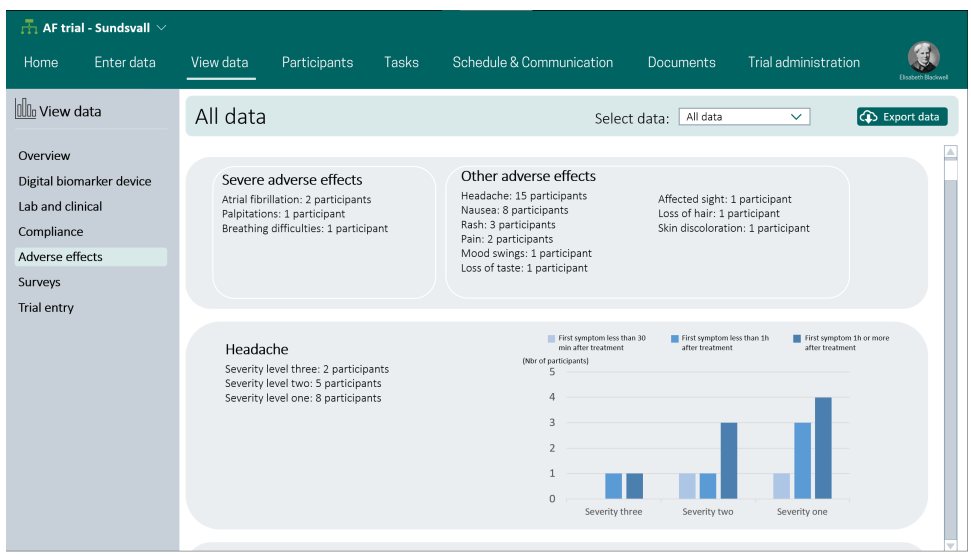


Figure 12: Show the adverse effects view for a principal investigator.

The view seen in figure 13 is intended to give the user a good overview over the assignments they need to complete and their upcoming meetings. A task can both be generated by a user or the system. A system task for a principal investigator could for example be to check a data value that has exceeded

a threshold and either correct it or proclaim it as missing data. Tasks can also have different levels of priority, vital tasks regarding the security of a participant will for example be prioritized. By clicking on each task the user will get more information about the task and can be redirected to the page where they may solve it.

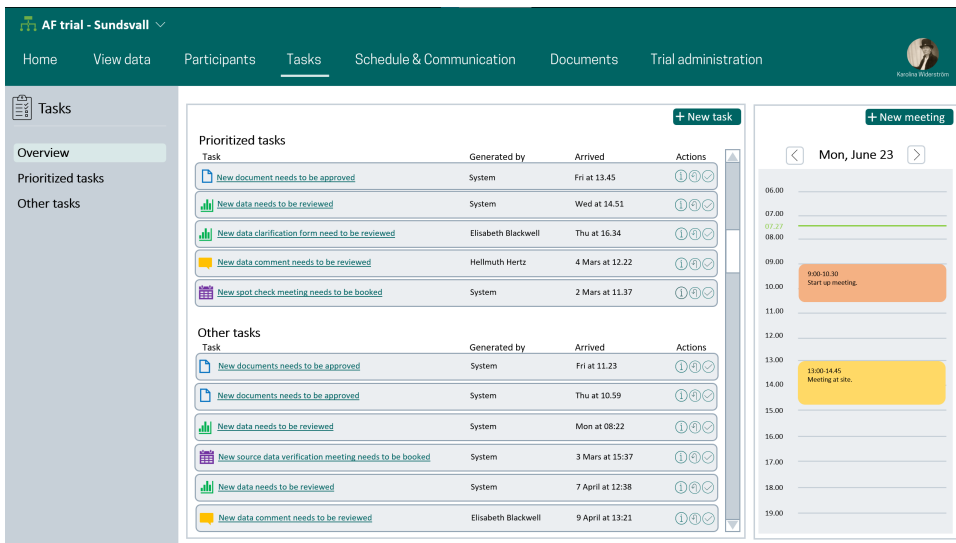


Figure 13: Show the task view of a project leader/monitor.

Figure 14 is one of many views seen when creating a new trial. When creating a trial the user is following a process of multiple steps, where each step is limited to a specific user task. The purpose of this is to avoid user error and cognitive overload. At the top of the page a timeline illustrates the whole process for the user. If a step consists of multiple substeps a smaller timeline is presented below the main timeline, as seen in the figure. The view seen in the figure is where personnel is added to a specific trial location. By clicking on the green plus next to the role you want to assign a new person to, a popup window will appear where more information will need to be added. The function to create a new trial is only available in the project leader version of the prototype.

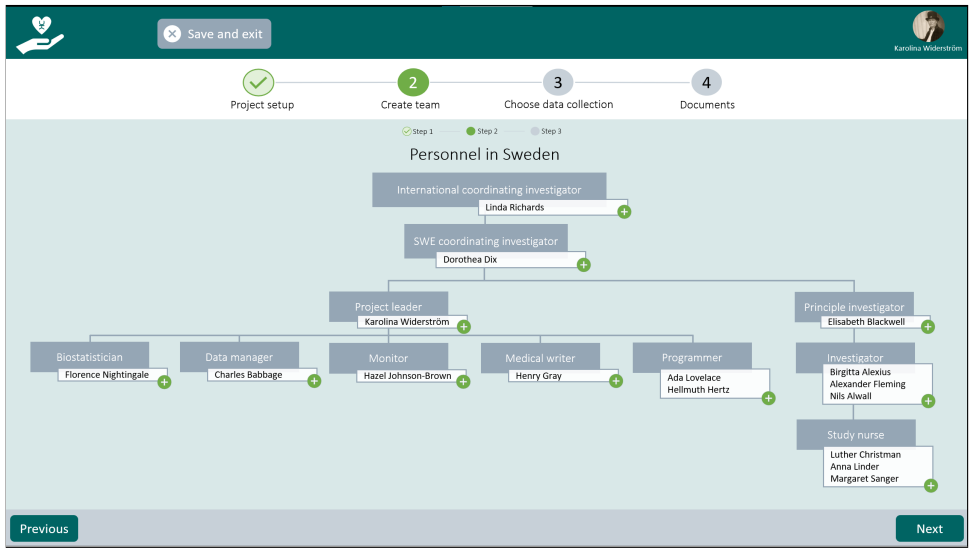


Figure 14: Show an example view of creating a new trial for a project leader/monitor.

4.4 Evaluation

Five of the ten people that were previously interviewed were used as test subjects for the evaluation. Which interviewees that participated and the respective test protocol and prototype version used on them can be seen in table 5 below.

Table 5: Shows interviewee number together with the used usability testing protocol and prototype version.

Interviewee	Protocol	Prototype version
1	Protocol 1	Study nurse.
2	Protocol 2	Monitor and project leader.
4	Protocol 1	Principal investigator.
5	Protocol 2	Monitor and project leader.
8	Protocol 2	Monitor and project leader.

4.4.1 Usability testing

The two interview subjects who were given task one, which consisted of entering new lab data for a trial participant, were able to complete the task as can be seen in figure 15. Interviewee one was able to complete the task without any problems. For interviewee four it took two tries before they came to the correct page. The interviewee first tried to click on the schedule on the homepage, when that did not work they moved on to click on the participants page. Lastly they clicked on the correct page, that is the enter data page. Initially they thought however that the enter data page was the same page as the participant page due to their similar layout. This is something that interviewee one also commented on. After figuring out that it was a new page interviewee four had no problem finishing the last steps of the task.

Task 2 was given to all interview subjects and consisted of finding information about adverse effects and interpreting the data correctly. All interviewees succeeded with this task directly without problem, which can be seen in the diagram in figure 15. The interview subjects seemed to easily understand that the compiled data was to be found under *View data*. When entering the overview, they immediately found the *Adverse effects* tab in the left panel. This took them to the correct view where they quickly were able to gather the information that was asked for.

Task 3 was given to interview subjects from the sponsor side. It consisted of creating a new trial where a study nurse should be added and the start time for data collection was to be changed. Interview subject two and eight understood the instructions and completed the task without problems. Interview subject three had some problem understanding the initial task and project view, and thus needed one try before finding the correct function at the start. They first tried to click on the list of projects, meant to illustrate active projects already in progress. They then saw the button titled "New project" which took them to the next correct step. When inside the task of creating a new trial, subject 3 had no further problems with completing the given tasks.

	Interviewee 1	Interviewee 2	Interviewee 4	Interviewee 5	Interviewee 8
Task 1	Succeeded		Succeeded after 2 tries		
Task 2	Succeeded	Succeeded	Succeeded	Succeeded	Succeeded
Task 3		Succeeded		Succeeded after 1 try	Succeeded

Figure 15: Shows the outcome of different tasks performed in the usability testing.

4.4.2 Feedback

The feedback on the prototype as a whole was very positive, multiple interviewees described the system as easy to use and navigate. They also thought that the system looked good and liked that no instructions or course was needed to start using the system.

One topic that was discussed during all three interviews with people representing the sponsor side was who should have access to what data. Two interviewees suggested for example that it would be good if all clinics could see how many participants the other clinics had enrolled to get motivated to try to enroll more. It was also said that sometimes the clinics choose to cooperate and then it would be good if they could access each other's worksheets in the system. Furthermore, in addition to seeing the adverse effects from a specific person and clinic, the possibility to see all data from a specific country was requested.

Another function that multiple interviewees requested was the possibility to get a notification from the system in their regular mail when not logged in. They wanted this function to ensure that no vital information was missed due to not logging in frequently enough.

Something that all interviewees except the one working within the academia commented on was the naming of different functions. For example one person's company used the word *"adverse events"* instead of *"adverse effects"*, *"multicenter"* instead of *"multiple center"* and *"serious adverse events"* in-

stead of *"severe adverse effects"*. They also commented that the expressions varied between different companies and it would therefore be good if each company could change the names to their preference.

Another topic that was brought up during three of the interviewees were differences between who is technically responsible to do something and who does it in real life. An example is that the clinics are technically responsible for creating the worksheets but in reality it is almost always the sponsor who ends up doing them. This could potentially create complications regarding access and assigning tasks in the system which would need to be looked into further.

Interviewee one, that is the study nurse, came with practical feedback regarding multiple functions. For example they commented that adverse effects should be sorted in alphabetical order, more participant statuses are needed and that it would be good to see the participant's social security number in the participant list. Furthermore, functions for management of medicines, handling and storage of biological samples, delivery of samples to a lab and possibility to order transportation were missing.

4.4.3 Interview questions

As can be seen in table 6 the response to the three questions asked during the evaluation interviews were overall positive. All interviewees answered yes to questions one *"Would you like to work in a system like this one"* and all but one also to question two *"Do you believe that you would be able to perform your work tasks in a system like this one"*. The answer to question three *"On a scale from 1-10, what would you rate the proposed concept as?"* resulted in a mean of eight.

Table 6: Shows the answers to the three evaluation questions asked to every interview subject.

Question	Interviewee 1	Interviewee 2	Interviewee 4	Interviewee 5	Interviewee 8
#1	Yes	Yes[1]	Yes[2]	Yes	Yes
#2	No [3]	Yes	Yes	Yes	Yes[4]
#3	8	8	8	8	8

[1] Yes, with small adjustments.

[2] Yes, if it was a complex clinical trial.

[3] No, are missing some functions like the management of pharmaceuticals and biological samples.

[4] Yes, except to directly access participant health records.

4.5 Literature review of DCT considerations

The literature review of DCT considerations resulted in a total of nine articles, these are presented below in table 7.

Table 7: The resulting articles used in the literature review of DCT considerations. Part one consists of articles found through the search on Google Scholar. Part two consists of articles by the SMPA.

Part 1	**Title**
#1	Rethinking Cancer Clinical Trial Conduct Induced by COVID-19: An Academic Center, Industry, Government, and Regulatory Agency Perspective [40]
#2	Stakeholder Perspectives on Barriers and Facilitators for the Adoption of Virtual Clinical Trials: Qualitative Study [41]
#3	Digital technologies for medicines: shaping a framework for success [42]
#4	Accelerating Adoption of Patient-Facing Technologies in Clinical Trials: A Pharmaceutical Industry Perspective on Opportunities and Challenges [43]
#5	Legal, Regulatory, and Practical Issues to Consider When Adopting Decentralized Clinical Trials: Recommendations From the Clinical Trials Transformation Initiative [44]
#6	Decentralized Clinical Trials: The Future of Medical Product Development? [45]
#7	Report of National Brain Tumor Society roundtable workshop on innovating brain tumor clinical trials: building on lessons learned from COVID-19 experience [46]
Part 2	**Title**
#8	Regulatory framework for clinical trials on medicinal products for human use [47]
#9	Decentralized and virtual interventional clinical trials [48]

From the articles presented in table 7 above, considerations regarding a DCT were identified. These considerations were grouped into eight main themes and sometimes also related sub-themes. An overview over all of these themes can be seen in figure 16 below. In section 4.5.1-4.5.8, a summary of the considerations belonging to each theme is presented. The themes in the text are presented in the same order as in figure 16.

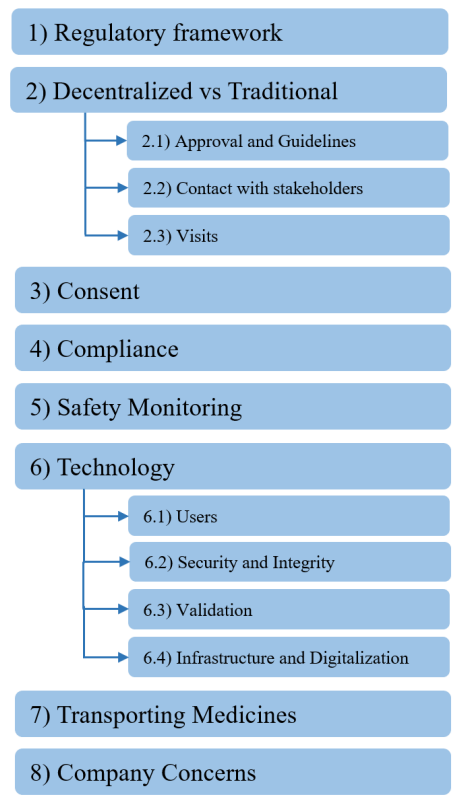


Figure 16: Shows the identified themes and their sub-themes.

4.5.1 Theme 1: Regulatory frameworks

As described by the SMPA [47], the regulatory framework surrounding clinical trials in Sweden is extensive and includes a multitude of laws and regulations. The regulatory framework covers, among other things, Swedish laws, regulations published by SMPA, and other regulations regarding public health, medical products and social services. Furthermore, EU regulations and directives also need to be followed. On the SMPA website there are

approximately 30 laws and regulations mentioned and they are not to be considered the complete regulatory framework. One of the most central laws is the (EU) No 536/214, called *European Clinical Trials Regulation*. It came into effect on the January 31 in 2022 and all member states in the European Economic Area must adhere to it regardless of if the trial is commercial or academic [47].

As a limited number of DCTs have been conducted and they require additional regulatory aspects to be considered, the regulatory element of a DCT can be complicated to say the least. When analyzing established practices, guidelines, and regulatory frameworks, the SMPA concluded that there were no legal obstacles prohibiting DCTs. SMPA have also previously approved decentralized elements in clinical trials and have published an article with a discussion around five different trials where decentralized elements have been used. This includes, among other things, visits performed remotely, participants collecting samples in their home, and the usage of remote electronic consent [48].

A country that has made great headway when it comes to DCTs is the United States (US). The regulating agency there, the Food and Drug Administration (FDA), have created multiple guidance documents to support decentralized elements. These include guidance documents on the use of electronic health record (EHR) data, electronic consent and remote monitoring using electronic source data such as imaging or laboratory data. Furthermore, FDA is collaborating with external stakeholders to further adapt the frameworks to include additional aspects of DCTs [40].

4.5.2 Theme 2: Decentralized vs Traditional

DCTs and decentralized intervention methods (DIMs) are used in numerous validation and pilot studies. These studies are creating the groundwork for the understanding and use case of DCTs. Before choosing to conduct a DCT it would therefore be beneficial to investigate already proven DIMs in previous work and determine which data collection methods that are deemed reliable by regulators [41]. The planning of a DCT should start early to allow for potential regulatory and structural obstacles to be solved before starting the trial and thus avoiding possible delays [44]. When planning a DCT it is important to adjust the traditional clinical trial study protocol to comprehensively describe the DIMs in detail with each method's motivation and potential risks defined [48]. The protocol should cover the different digi-

tal technologies used and how they are classified according to medical device regulations. This includes if the technologies are a stand-alone intervention or used with a medical product, and a description of the primary function of the digital product [42]. It is also important that the planning involves discussion around the type of trial and trial design.

It is prudent to also have a discussion about the suitability of conducting a DCT, having both the population of the potential trial participants and the risk-benefits in mind. If the trial is including the use of an investigational medical product (IMP), its characteristics should also be considered [48]. Furthermore, areas such as the implementation of communication, the flow of data, and storage of data and documentation should be discussed and decided at the beginning of the planning. For a DCT it can also be beneficial to define terms related to DIMs and DCTs, and to increase training and other safety procedures to ensure compliance to the protocol [44].

The decision to conduct a DCT must always be well thought through, based on scientific knowledge, and have proper motivations not relating to trial costs [48]. Therefore, the DIMs should be motivated with an explanation on whether the intention of the DIM is to measure something new or replace a traditional intervention method. Moreover, the benefits of the DIM should also be described in the motivation [42]. For example, a DIM using mobile technology could potentially produce clinical data during the participants daily life, thus enabling a more objective view on their health compared to a more traditional intervention method. Depending on the technology and the trial, the DIMs may either complement other methods or replace them completely. In both cases the comparability of the different methods should be validated [44]. Nevertheless, some intervention methods are hard to replace with digital DIMs, such as in-person examinations or monitoring of an IMP with an unknown safety profile, and some medical devices may require extensive training and experience before being effective [46]. It is therefore important to consider the IMP's safety profile, choose a trial design fit-for-purpose, and determine which interventions should be decentralized and in what way when choosing DIMs [44]. Determining if decentralization of a clinical trial and its intervention methods is suitable is central to conduct a safe DCT. In addition to the previously mentioned considerations, the type of trial and the phase of the trial must be considered. Trials in a later phase or with a more open question, such as the general health of the participants, are often more appropriate to decentralize, as are trials with established infrastructure [44, 46].

4.5.2.1 Sub-theme 2.1: Approval and Guidelines

A key barrier when it comes to DCTs mentioned in multiple articles [41, 43, 44], is a potentially low acceptance level by regulatory agencies, partially due to the fact that DCT evaluation methods are not deemed to be sufficiently established [41]. Another mentioned barrier is the lack of regulations and guidelines regarding DCTs [41, 43, 44]. While COVID-19 might have sped up the process, guidelines were still described as mainly missing or incomplete. Furthermore, the few that exist were said to be vague and abstract, or lacking clarity and specification which complicated the process of assessing if a DCT would be approved [41, 44].

Another major regulatory challenge is the geographical variation of regulations, interpretations and guidelines. These inconsistencies exist both between whole countries and between states, such as within the US. The variation of regulations and guidelines are said to limit large scale implementation [43, 44]. Suggested solutions for this problem include implementing standardized laws, or clarifying and keeping records of the different laws in an accessible database [44].

4.5.2.2 Sub-theme 2.2: Contact with stakeholders

Before creating a DCT application, it is beneficial to seek out external knowledge and guidance [48]. External guidance can for instance be found at the appropriate regulatory agency and could help instill acceptance for the project at the beginning [41, 42]. It would also help with the identification and involvement of needed experts for assessment of the application, thus increasing the possibility for the applicant to be approved [42]. It is useful to meet with regulatory agencies as early as possible in the process to receive guidance in both trial design and planning [44]. Furthermore, early regulatory contact could reduce the risk of inadequate or invalid data collection and generation in digital technology [42]. It is also beneficial to have meetings early in the process with other stakeholders and potential collaborators such as research organizations, other pharmaceutical companies, and potential clinics [41, 44]. Furthermore, special knowledge regarding the technology, telemedicine, and participant perspectives should be obtained by finding experienced partners and using a patient-centered approach [44]. Finding experienced partners could be facilitated by an application or website with different trial options and potential partners [46].

4.5.2.3 Sub-theme 2.3: Visits

While many visits to collect data could be replaced by the participant wearing a DBD and doing testing on their own, some trial moments, such as giving consent or injecting drugs intravenously, have to be done in the presence of trained personnel [46, 48]. That does not necessarily mean that the participant has to do a traditional visit at the study site as there are many different options available. These include digital visits, visiting other health centers than the trial site, and visits in the participant's home [46, 48]. All of these options can be defined as remote visits and are allowed by the SMPA if the safety of the participants are not threatened and an acceptable scientific reason for the remote visit can be provided. The sponsor also has to demonstrate that the data collection conditions regarding efficacy and safety are unchanged compared to a traditional visit. The same regulations that apply to traditional visits also apply to remote visits and the principal investigator is still responsible for ensuring that the visits are conducted correctly. Close contact with and supervision of external healthcare providers are therefore important [48].

Conducting visits at other healthcare centers comes with a new set of challenges. One such challenge is to identify reliable and competent personnel at healthcare centers that are located in a suitable place, and then also train the personnel remotely if needed. Obtaining permission to use this personnel staff might also result in additional regulatory challenges. Furthermore, barriers such as not having a common transmission method of data, variance in data quality and interpretation of results, and uncertainties regarding external personnel adherence to the protocol complicates the process further. This combined with the need to control the quality of the used technology could also result in additional costs and added time [46]. It is therefore of utmost importance to find reliable partners and clinics and it would be beneficial to have a system to safely transfer data between different healthcare centers. The use of telemedicine to monitor external personnel, only delegating responsibility to qualified personnel, and expanding the trial to more sites were also suggested as potential solutions [44, 46].

Conducting visits in the home of a participant also comes with its own set of challenges. In the SMPA article [48] a sponsor expressed for example that home visits require quite extensive planning and that it can be more complicated to handle the needed equipment in other places than the clinic [48]. Furthermore, as visits have traditionally been conducted in person, switch-

ing to digital visits might also cause logistical problems. Suggested solutions included continuing to try and improve telemedicine and examine the effects of telemedicine visits compared to physical visits. To improve remote visits in general, collecting input from all parties included in the trial and designing more patient orientated trials was suggested. Lastly, the possibility to exclude some visits by collecting data remotely was proposed as a solution [46].

Another important aspect to keep in mind when using external personnel is who to accredit [46]. While it is the sponsor's responsibility to decide who should be accredited, the task of identifying external expertise and resources in the community falls upon the principal investigator. Local providers and experts must therefore be assessed and if deemed to contribute substantially to the trial they may be added to the protocol (or if in the US, form-1572) [44, 46]. This could require additional clearance and training, which is why it might not be justifiable depending on the extra cost. For the decision of whether the local partners should be added to the protocol/form-1572, the interventions methods they may perform and what complexity and expertise are needed should be considered. [46]. It could be prudent to consult the applicable regulatory agency and their regulations when deciding this [44]. The principal investigator always has the utmost responsibility in the trial, even when interventions take place at other locations and the possibility to assure that external personnel do their job correctly is therefore vital [48].

4.5.3 Theme 3: Consent

To conduct a fully decentralized trial, participant consent would have to be collected remotely. The SMPA allows electronic consent if the correct requirements are fulfilled. This includes following relevant regulations and both justify the use of remote consent and describe how the consent will be obtained in the protocol. Informing the participants of the trial and providing them with opportunity to ask questions according to ICH GCP(R2) is also necessary. The only option to do this remotely is by video meeting as other forms of contact are not recognized as satisfactory. Once the consent has been given it must be documented in the participant's medical record and an encrypted copy of the consent should be sent to the participant. This could be done through a link with a password for example [48].

The system used to collect the consent must be appropriate and validated for the objective. Out of the five trials described in SMPA's article about DCTs, three used electronic consent. All three of these used a platform and

Swedish BankID for the participants to sign. In the article, the advantage of compatibility between the consent system and other existing health systems was highlighted [48].

The US also allows electronic consent and FDA has published guidelines regarding the subject [40, 46]. Lee et al. stress in their report the necessity of an appropriate and secure system to collect the consent. The system must for example store the consent, make audit possible and comply with relevant demands for electronic signatures and records. It is the clinic's responsibility to ensure that the system is up to standard and validate that it works correctly. It is also vital that the main elements of the trial are communicated to the participants and to ensure that the participant understood them [46].

A potential challenge with remote consent is to confirm that the participants are appropriately informed of the trial and understand what they are signing up for. Another is confirming the identity of the participant and protecting their privacy [44]. Establishing procedures and creating a system fit to collect electronic consent that guarantees a truly informed consent was suggested as a possible solution [46].

4.5.4 Theme 4: Compliance

As mentioned in multiple articles [41, 43, 44, 48] compliance and adherence is an important key barrier for DCTs. Compliance, that is how well the trial protocol is followed, is a recurring problem during traditional trials [41]. Whether DCTs will increase or decrease compliance is still a question, Polhemus et al. believe it will increase while Coert et al. think it will decrease compliance [41, 43]. A potential benefit mentioned by Polhemus et al. [43] was that no matter what the answer is, the DCT could at least generate knowledge about non adherence which would provide the opportunity to increase it. Potential challenges raised in the articles include ensuring that activities are carried out according to the protocol when using personnel from multiple clinics with varying knowledge levels and medical qualifications [44]. Furthermore, the limited in-person contact could have a negative impact on the compliance as the possibility to stand next to the participant and control that the protocol is followed vanishes when performing a DCT. Another recurrently mentioned challenge is how to monitor if a drug has been taken, or if the DBD is worn by the participant and not someone else [41]. A potential benefit that was mentioned with DCT is that it could generate knowledge about non-adherence [43].

A clinical trial discussed in SMPA's DCT article [48] shows an example of how adherence can be monitored in a DCT. In the article, all trial participants were given a medicine bottle that recorded every time the lid was opened. If the opening frequency deviated from the protocol the investigator got notified which allowed them to contact the participant and by doing so potentially increase the compliance. The participants were positive towards being contacted in those cases [48].

4.5.5 Theme 5: Safety Monitoring

The importance of ensuring that safety monitoring is maintained during a DCT is something that both Apostolaros et al. [44] and SMPA [48] highlights. To comply with the regulatory demands a detailed description of the safety monitoring procedure is needed and the clinical trial personnel should be well trained in the decentralized elements of the trial [44, 48]. A protocol specific plan for all communication and safety monitoring for the people involved in the trial should be developed and records should be kept to ensure compliance [44].

During a DCT the clinical personnel should be able to report in the same way as during a normal trial [44, 48]. This means that a risk-based approach should be used to monitor the collected data. Routines must be established for analyzing the collected data according to patient safety requirements and ICH GCP(R2) and these routines need to be clearly stated in the study protocol [48]. The collected data should be analyzed continuously and means to intervene over a distance if necessary should be in place [44, 48].

4.5.6 Theme 6: Technology

4.5.6.1 Sub-theme 6.1: Users

When introducing digital systems in a DCT it is important to consider the impact on both the participants and the clinical personnel. Implementations of technical aspects should be done with the goal to increase participant engagement, provide better experience and care, and remove barriers for participation [43]. To achieve this the systems should be user-friendly, fit for the participant population, and convenient to use for both participants and the clinic [41]. Moreover, measures to avoid user-error must be implemented in the technology and trial design. A possible way to do this is by recording the collected data in several ways, one example being that the participant

documents a medical value both by taking notes and by photographing it [48]. As the participants must become active users of the technology it is important to involve both the participants and the clinics when evaluating the technology and its design. This patient-centered approach needs to include feedback both before and during the trial from both participants and clinics. It should also include measures for technical support and training for all users [43, 44]. Through feedback about the trial design and choice of technology, the technology impact could be better understood and thus be better suited for its purposes [43].

A patient-centered trial approach also minimizes the many barriers the participants face when participating in trials. This enables the recruitment of participants from a wider geographical area and those with limited time and economic means [46]. While this aspect of the technology may increase the willingness for patients to enter the trial there are several other factors which could affect the participant adherence and willingness. The most observed one is the participants' age and technology experience, where younger or more technology experienced people have proved more willing to participate. Other possible factors are the severity of the participants' disease, how often the digital interventions are planned, the increased burden of the technology, and opinions of privacy. Moreover, people have proven to be more willing to participate if they think the technology can add scientific value or help them with their overall health [43]. To succeed with a DCT the concerns and willingness of the clinic must also be considered. The willingness of the clinic could be affected by the additional workload of learning multiple systems for various sponsors. For each new device or system, they must manage and remember passwords or other security measures. Additionally, these systems may differ between different healthcare specialties and geographical areas, and sometimes only being accessible in certain languages. All these complications and problems reduce the willingness of the clinic to use new digital systems. Polhemus et al [43] mentions that clinics are often open for the implementation of technology when they feel that it is beneficial to their work and provides added value to the participants. The new method would also need to be an improvement of the traditional way of performing the tasks [43]. It is therefore important that the technology is easy to use, has a positive impact, and is reliable [43, 48]. Furthermore, factors such as scalability and standardization of the technology and good technical support can increase clinics willingness for digital systems [43].

To ensure that both the clinic and the intended participant population is both willing and able to participate, the sponsor should consider some societal aspects when designing the trial. The participant demographics should be evaluated to assess the possibility for implementation of digital elements. Aspects beyond age and geographical area could be the access to technology and transmission methods, the acceptability of the technology in the society, and the access to information and help with the technology. It is also important to not digitize or remove all interactions for the participant with the clinic but instead use the technology as a complement to other interventions [43].

Another safety aspect to consider is the participants ability to report adverse events. When participants report adverse events through mobile technology it is imperative to educate and train the participants to do it correctly. It is also necessary to consider that an adverse event such as blurred vision for example could create difficulties for the participant to use a tablet or computer. It is therefore important to contemplate what sort of technology to use when reporting the adverse effects remotely [44]. Reporting adverse events through mobile technology may also require the participants to have greater technological skills and more active engagement, meaning that once again the participants technological capabilities are important to consider. A suggested way to ensure sufficient technological capabilities was to add it as an inclusion/exclusion criteria [44].

To facilitate the DCT process, easily understandable instructions and to assist the participants when needed are considered essential. Compared to a traditional trial, participants in DCTs often need additional technical support, for example on how to use the DBD. Providing the needed support and training is extremely important to assure the quality of the data by getting the participants to use the DBD correctly. To improve compliance and to ensure that participants understand their tasks, proper instructions and a clear protocol are needed [41]. It is necessary to consider that conducting participant training and providing assistance could potentially increase the burden on the clinic [43]. As mentioned before, the potential risk of some participant groups experiencing additional issues when it comes to DCTs and therefore needing more assistance have to be considered. This could for example be older people that might not have the necessary technology experience for the study such as how to use the internet. It is important to find solutions that still include these participant groups as excluding them might result in biased data and consequently inaccurate conclusions. A suggested

solution to ensure that all participants understand the technology was to provide additional support to these groups through a help desk for example [41]. In one of the trials mentioned in SMPAs article [48] a sponsor commented that questions regarding the trial and treatment often are brought up at the same time as technical questions and it is therefore important to still have clinical personnel available to answer those questions.

4.5.6.2 Sub-theme 6.2: Security and integrity

When decentralizing an intervention method by using technology, it is necessary to plan for training, technical support, and data integrity compliance [44]. If the purpose of the intervention method is to measure biological values it is also required to certify that it can produce reliable, repeatable, and accurate measurements. This should be documented on a detailed level but with room for minor changes in the technology, such as small software updates [42]. Furthermore, a risk assessment should also be performed and needs to cover both potential changes in the technology and the data capturing, processing and analysis [42, 44]. The collection and processing of data is especially important with continuous monitoring as the amount of transmitted data from a DBD is far greater than the amount collected at a clinical appointment [44]. If the intervention method is instead decentralized by using a remote team or clinic, it is necessary to assure the quality of the data from the local equipment and the adherence to the protocol in those teams. The obtained data from the remote teams must also be compatible with the record system used at the trial location, which can easily be ensured by using the same or a compatible digital system at both the trial and the remote location [46].

Regulatory aspects also include the integrity and reliability of the data. When starting a DCT it is therefore prudent to address how the data should be stored, how verification of the data will be done, and map the flow of the data and the user access controls [44]. The collected data may be transferred or stored at different locations which is why it is important that all parties who are handling the data can oversee the data flow through control and management. This also includes assurance of data security [41, 44]. In a traditional clinical trial the CTD is often secure behind firewalls as it is stored and managed locally. In a DCT however, the data can be collected at different providers or from DBDs, depending on the trial design. Thus, a system with reliable cybersecurity is required. One way to assure the integrity and security of the data may be blockchain technology. Blockchain,

which is used for Bitcoins for example, is a decentralized data management technology which allows the data to be stored at different nodes. This increases the security as an attack would have to breach every single node to access all the data [45]. To summarize, the risks around data management and storage must be minimized. It is therefore important that every system is implementing procedures to safeguard the data privacy, the confidentiality, the management, the access, the data transfer and the overall security of the data [43, 44].

A potential barrier to achieving this is that the current regulations regarding data security and privacy are considered to be inconsistent and unclear. These inconsistencies regarding storage, data privacy, variation in different countries transfer regulations and ethics committees ruling among other things, were reported to negatively impact the implementation of DCT. Furthermore, a participant wearing or using a medical device in public was lifted as a potential privacy violation and something that an ethics committee might oppose [43].

With some DBDs, concerns were also raised regarding the accessibility to the proprietary data. If the DBD manufacturer views the data as their own, they may have access to the source data while the clinical research personnel do not. This poses dilemmas regarding both the validation and integrity of the data. Furthermore, the data is sometimes processed with algorithms which are seen as proprietary information. With fast-paced development of new technology and DBDs, the processed data can not be compared to other methods and thus become outdated and unusable. To ensure that all used technologies and devices in DCTs are generating value in a secure and accurate way that guarantees quality data Coert et al. believes that standards and policies regarding this needs to be created [41]. This is supported by the results from the article by Polhemus et al. [43].

4.5.6.3 Sub-theme 6.3: Validation

Conducting a DCT using digital systems for remote data collection and management comes with additional challenges. One of the main ones is the validation of both the technology and the produced or collected data [41, 43]. The validation of the system is done depending on the intended use of the collected data and the associated risks, and it is the sponsor's responsibility that this is done correctly [48]. The digital systems are also required to adhere to health guidelines from local health authorities and any system

used for a medical purpose must be classified and approved as a medical device [43]. The technology which is collecting medical data, such as blood pressure, must be accurate and comparable with other methods. To ensure this the device must be clinically validated which can be done with a "fit-for-purpose validation". This validation method is conducted as a trial and includes clinical and analytical validation, and verification of the device [41]. According to Coert et al. [41] there is a great need for validated devices, especially DBDs.

4.5.6.4 Sub-theme 6.4: Infrastructure and digitalization

Potential barriers when conducting a DCT with digital elements include limited infrastructure and technology. This could be immature or too complex digital systems, limited alternatives to telemedicine and telehealth services, insufficient infrastructure for transmission methods (for example poor number of cellular towers in a certain area), and local regulations and restrictions [45, 46]. To conduct a safe trial the sponsor must provide the clinics the support and the tools needed to conduct these DIMs in several different communities in different jurisdictions if needed [44]. If the DCT is spread over several geographical areas, it is prudent that the sponsor provides the clinic with a secure telemedicine function and clear written information to the participants [46]. Furthermore, the technology can be difficult to manage and to use, thus being vulnerable to potential attacks, technology failures, or user errors. One solution is to create a good back-up system, provide accessible technical management and support to the clinic and participants [43, 45]. Lastly, it is also important to have in mind that there might exist differences and access problems between different systems that cause complications [46].

4.5.7 Theme 7: Transporting Medicines

A major challenge with DCTs is the medicine distribution. Transporting the medicines to numerous locations and letting multiple receivers that potentially lack medical training manage them introduces new risks and increases the complexity of the trial [45]. Distributing the medicine to multiple locations could for example result in missing or delayed doses, create problems with drug accountability, or cause protocol deviations [46].

The SMPA allows for IMP to be transported to a participant's home if it is compatible with the trial setup concerning route of administration, storage requirement and safety. To get approval, all shipping of the IMP must be ini-

tiated by the investigator and the distribution process needs to be specified in the application. Furthermore, routines for the management of the IMP are needed and the process needs to be well documented and traceable. It is also important that the identity of the participants remains unknown to the sponsor. The delivery of the medication must therefore be arranged by the clinic or a pharmacy [48]. Compared to the Swedish and European regulations regarding transportation of medicine, the regulations within the US are far more complicated. Not all states allow for transportation of medicines to the participant and the regulations are often unclear and may also vary depending on the medicines status with the FDA [44, 45]. To improve the situation, more extensive guidance documents regarding transportation of medicines were requested [44] and the importance of describing the distribution and administration process thoroughly in the protocol was highlighted [44, 46]. Stating the responsible party at every step in the supply chain and documenting the complete process was said to be crucial [44].

An important challenge mentioned in both American [44, 45, 46] and Swedish articles [48] is ensuring that the correct person receives the right quantity of the right drug. In Sweden it is required to deliver the drug directly to the person and not leave it in a mailbox which ensures that the correct person receives the medicine. SMPA suggests that the security can be improved further by a follow up phone call after the delivery to make sure that the participant has received the correct drug [48]. Other suggestions mentioned in the articles was to create a system to track drug accountability and compliance [44, 46] and using standard operating procedures connected to the protocol to establish who is responsible at every step of the supply chain [46].

It is also important for the sponsor to contemplate how the participant shall manage the drug after it has been delivered, for example controlling that the medicine has not been tampered with and that it is stored correctly [44, 45]. They also need to consider what the participant should do with leftover medicine and who they should get in touch with regarding questions or if problems arise [44].

Another key challenge mentioned in multiple articles [44, 45, 46, 48] is the storage and administration of the drug. To distribute the medicine securely to the participants home, suitable methods for storage with temperature tracking must be available throughout the whole supply chain and a guarantee of drug stability is needed [45, 48]. The risk of unauthorized access must be minimized and methods to determine if the medicine has been tampered

with should be implemented.

Before deciding to ship the drug to the participant it is important to consider that not all drugs are suitable to be transported to a participant's home due to the nature of the product, such as stability and life expectancy [44]. Furthermore, the route of administration might be a problem, for example if the drug is to be injected intravenously [44, 46]. A discussed solution for that particular problem is that previously approved drugs could be injected at local clinics or in the participant's home by trained medical personnel [46].

4.5.8 Theme 8: Company concerns

Another aspect to have in mind when considering DCTs is the company's willingness and competency. In their article Polhemus et al. [43] mentions multiple organizational barriers towards implementing DCTs. One such barrier was risk-averse corporate culture due to burdensome regulations. This combined with an inadequate internal expertise and limited communications, especially regarding learning from pilot studies, was said to restrict the progression of DCTs. Companies focus on the near future and aversion to collaborations was also cited as barriers. Furthermore, the absence of a corporate strategy and supporting leadership was mentioned, as was lacking internal structure and processes [43].

The article also discussed business challenges where trial cost was mentioned as the main barrier towards DCTs. The uncertainty regarding the return of investment and the limited maturity of the technology were also stated as important challenges. Furthermore, the potential negative effect on the trial timeline and often increased trial cost were said to make sponsors hesitant to choose to conduct a DCT [43].

5 Discussion

5.1 Results on literature review to identify needs

The literature study established a solid foundation for the complete collection of identified needs. The used search method was deemed successful in the regard that a relatively large number of relevant articles and books were found. This in turn resulted in the identification of a considerable number of relevant needs, which was the aim of the literature review. Further, the relevance of the identified needs were supported by the fact that many of the books and articles mentioned the same challenges and solutions. Nonetheless, the search could most likely have been made more efficient with more relevant search terms such as "decentralized clinical trial" or "virtual clinical trial". These terms were however not known to the thesis authors until the second literature review regarding DCT considerations and were therefore not used in the first literature review. A limitation of the literature review result worth mentioning is that the review focuses on Sweden and the USA, and the result might therefore not be applicable to other countries. On the other hand, the fact that articles from both of these countries mentioned similar challenges makes it a reasonable assumption that our findings may still be relevant in other parts of the world.

The choice of focusing on Sweden was due to three main aspects. Sweden was chosen as it is a familiar country to the thesis authors and also where the mSafety Sony team is located. Furthermore, Sweden is regulated by the international EU directives, meaning that other countries who also are members of the EU are subjected to similar regulations [47]. The USA was chosen as it is a driving force in biomedical technology with a large supply of research institutions and clinical trials. Due to this, a great quantity of relevant research articles are written by researches in the US.

5.2 Results on interviews

The ten interview subjects were chosen from a wide variety of backgrounds and expertise areas to cover the many different roles involved in clinical trials. The selection, which formed four main areas, was however slightly uneven regarding how many that represented each area. Of the ten interviewees, four represented a sponsor, and the remaining six were evenly divided among the other three areas. While this may have created a bias towards the sponsor side it is also worth noting that the work of the academics are more closely

related to the work of the clinic. Additionally, there is a greater diversity among the work process and needs of the different roles at the sponsor. The chosen interviewee selection therefore contributed to a good distribution of identified needs and allowed for detailed information to be compiled from a multitude of relevant areas. Furthermore, it made it possible to gain information about the different topics from multiple angles.

When creating the interview protocol it was decided that it would be adapted depending on the interviewee to utilize their knowledge to the fullest. It is possible that this could have increased the bias of the result as it reduced the number of interviewees that answered the same questions, but the fact that at least two people always got the same question will hopefully have reduced it somewhat. Furthermore, the interview subjects' experiences and knowledge are so varied that even if the same questions were asked to everyone it is doubtful that they would have been able to answer them all.

In total, ten people were interviewed for this thesis. While it is always beneficial to get the opinion of more people, this number was deemed high enough considering the scale of this thesis and the quality of the received answers. In a future development of this work, it would however be prudent to have a larger selection of interview subjects. As can be seen in the summarized list 2, a large number of the needs were identified from the interviews, and over half of the summarized needs overlapped with the ones identified from the first literature study. While this overlap supports the relevance of them, it is possible that the overlap is partially due to the fact that the interview protocol was influenced by the result of the first literature review.

Regarding the interviewees opinion of the proposed system, most people were positive. It must be considered though that all the interviewees had an interest or special knowledge regarding the subject of the thesis before the interview and if they had opposed the subject they might not have chosen to participate. Furthermore, some people might feel uncomfortable giving negative feedback. An area that all interviewees were asked questions about was data sharing. The results received from this indicated divided opinions, where people working for bigger pharmaceutical companies were in general more negative towards the idea of it. Most of these people agreed that an incentive to share the data would be needed and that privacy was a major concern. Data sharing is a fascinating area and something that the European Medicines Agency is promoting. From our result it is clear though that there are many obstacles left to overcome before it becomes the new standard.

5.3 Results on the prototype

The prototype was mainly intended to work as a visualization of the identified needs to make an evaluation possible. The interaction of the prototype was therefore kept quite limited and instead the focus was kept on displaying the main concepts. It became quickly clear in the prototyping process that more detailed information were needed when creating the concept for complex functions. Many views were therefore only meant as an example of what a user could do in the fully developed system. An example is the *View data* function where it was clear what categories of data that the user would need access to, such as adverse effects and lab values. However, the details in every specific category, such as the data format and the presentation, were unknown. The design for those views was therefore arbitrary. The prototype was further limited by the program it was constructed in. It was known beforehand that MS PowerPoint has quite limited functions. Despite this, the decision to still use that program was made as it has a short start up time and is reliable.

5.4 Results on the evaluation

The result from the evaluation was in general positive. Regarding the usability tasks, all participants were able to perform the tasks, although some people made some errors along the way. In task one, interviewee four had problems with finding the correct page to enter data for a participant. There were also some confusion regarding if the participant page and enter data page was the same page due to the fact that they look very similar. The interviewee's thought process was very logical and it would make sense to enter new data on a participant profile. Similar looking pages with different purposes should also be avoided when possible. A potential solution to the problem could therefore be to allow enter data to be a sub-page to the participant page.

The result of task 2 was deemed to be a success. All the interviewees seemed to easily complete the task which indicates that this part of the prototype is straight forward and following good usability principles. In task 3 the interviewee 3 had some problems completing the initial task which could be related to how the task and program were introduced. As the usability protocol was not tested before the usability interviews the explanation may have been insufficient. This could have been improved by walking through the evaluation protocol with a person not involved in the project. Intervie-

wee 3 was the first interview subject which was presented with this task, which allowed for a slightly better explanation to interviewee 2 and 8. This might contribute to the reduced problems in the later interviews regarding task 3.

In general, the feedback were positive and most of the proposed changes concerned small adjustments such as changing a name or removing the possibility to add more than one monitor for example. The one feedback that would require major reorganization to fix would be trying to remove the list of participants that exist at the views *Enter data*, *View data* and *Participants*. This could be improved by merging enter data and the participant page into one category for example. During the evaluation the participants also gave feedback on additional functions they would like in the system. The majority of these were functions that had been identified during the data collection process but had been down prioritized and not included during the prototyping phase. In total, the received feedback shows that the foundation of the system is there and additional iterations could make sure that the needs of the users are fulfilled.

The three questions asked during the evaluations interviews were meant to summarize the interviewees general opinions of the proposed system. All interviewees answered that they would like to work in a similar system to the proposed one and four out of five believed that they could perform their tasks in the system is definitely a positive result. The one that did not believe that they could perform all of their work tasks in the system was a study nurse. During the evaluation it became clear that the study nurse version lacked multiple vital functions such as management of pharmaceuticals and biological samples. These are functions that could easily be added to a worksheet though, which means that with small adjustments the system could cater to these needs as well. Further, keeping records of what economical compensation the participants are entitled to, which is another function that the study nurse requested, could be managed with a survey that the participants have to fill out. It would therefore appear that only minor adjustments would be needed to ensure that also a study nurse could perform all of their work tasks in the system which is overall a good result. That the proposed system was given a mean rating of 8/10 also has to be considered a success. Based on this, it would appear that the design of the prototype fulfills the most vital requirements identified during this thesis.

When studying the evaluation there are several aspects and additional limitations to consider. The most obvious one is perhaps that only a fraction of the result from this thesis was evaluated. There are several identified needs that have not been evaluated and the same goes for the literature review regarding DCT considerations. To be able to evaluate these, a whole complete system would have to be implemented which was not possible within the frame of this thesis. Another important aspect to mention regarding the evaluation is that only five people were interviewed and for task one and task three only two respectively three people performed them. This means that each interviewee had a significant influence on the result. Furthermore, the evaluation interviewees had contributed to the identified needs through the previously conducted interviews. This could potentially have caused bias, as the prototype is constructed from their requests which may mean that they are more positive towards the prototype than the general user. It is also possible that the test subjects have a more positive attitude towards DCT systems in general as they all volunteered to participate.

The prototype had limited functions that were not interactive which may have made it easier for the test subject to conduct the tasks correctly. On the other hand, the limited interactions may have reduced the level of understanding of how the system is meant to work which would have made it harder for them to perform the tasks. It should also be mentioned that the level of understanding of the prototype might have been reduced by the fact that all test subjects' native language is Swedish while the prototype was in English. Some of the usability interviews were also performed online which further limited the interviewees interaction with the prototype. In those cases the interviewee were told to direct the thesis authors on where to click, which may have affected the experience. Lastly, the prototype shows an example of what a large trial testing a new pharmaceutical might look like, it could therefore make it less relevant for the test subjects that have worked in smaller trials or within the academia where drugs might not have been used.

5.5 Results on the DCT considerations

The literature review on DCT considerations was successful in the regard that a large number of successfactors and potential problems areas were identified. These addressed a wide variety of areas which enabled a diverse analysis. Many of the identified obstacles concern uncertainties related to the fact that DCTs are still a relatively new area. Once the practice of DCT

becomes more established it is possible that some of these obstacles may disappear and new benefits could emerge instead. As many of the mentioned aspects can not be implemented in a digital system a full implementation of a DCT would be needed to determine the relevance of the identified aspects.

5.6 Future work and applications

In this thesis, the number of iterations of the prototype was limited and the changes made to it were mainly based on the opinions of a small group of people. While these people had knowledge within similar areas they were not the intended users of the system. To improve the prototype more iterations with potential users and the involvement of other stakeholders would therefore be beneficial. They could potentially provide answers to questions regarding design details, such as how to ideally present the data, which the test group used during the iterations could not. Before doing this a first logical step to improve the prototype would be to revise it based on the results from the usability testing.

During the design process many comments have been given, both by Sony and the interviewees, regarding the integration of other services and applications with the system. An example of this is the desire to get a notification to one´s regular email account when getting a notification in the program. Similarly, the ability to export or import iCalendar files to and from the schedule has been mentioned as a potential future function in the prototype. A mapping of all potential services and applications relevant for the prototype would therefore be a sensible next step in the process.

A next step in developing a DCT system would entail building a fully functioning prototype where all the identified needs would be implemented. This includes needs regarding data transmission, security, and other software related needs. The created design concept in this thesis could then be used as a basis for the design of the application. Moreover, the identified needs and DCT considerations could be used as a baseline for the system's software and user requirements specifications. As with the created prototype in this thesis, the fully functioning prototype would have to undergo usability testing or other equivalent evaluation methods. Lastly, the system and proposed concept would have to be evaluated based on its business feasibility. To do this, market research is needed to judge the need on the market for this type of system and which area of the market to target when introducing the product.

5.7 Ethics

The process of testing potentially dangerous treatments on people gives rise to a mountain of ethical challenges, and by adding a decentralized aspect even more may emerge. As this project aims to facilitate the implementation of DCTs it is important to consider ethical aspects that can appear as decentralized elements are introduced.

When decentralizing an clinical trial element it is important to consider if it is done for the good of the participant or for the benefit of the sponsor. All parts of a DCT must be adapted to fit the participants' needs and the sole purpose cannot be to save money or time. In some cases, decentralization can lead to delayed treatment and inventions methods, as DCTs are more dependent on novel technology than traditional clinical trials. This could in turn affect some peoples access to the optimal treatment.

A related aspect to consider is that remote monitoring might not be as efficient or accurate as traditional methods. Depending on the purpose this may be problematic. For example, if a DBD is used to collect heart rate data to detect dangerous arrhythmia's, a potential error in use or the technology could result in inconclusive data, thus leading to incorrect treatment. To ensure that the participants are safe, the potential DIMs must therefore be evaluated on their intended use and risk-benefits. It is also important to consider that monitoring of the participants may infringe on the participants integrity, especially if the trials intervention methods include continuous monitoring or monitoring of location.

Lastly, the decentralization of clinical trials may place an additional burden on the participant, as they are the ones who uses the data collection systems. Participants with inadequate technology experience may be negatively affected by this. On the other side, the advancement to more digital or decentralized elements may give the participant more freedom and autonomy in both their lives and the trial participation.

The ethical aspects of starting a clinical trial are as mentioned many and it is therefore important to review the risk-benefits. This is one of the reasons that it is mandatory to get the approval of an ethics committee before the beginning of the trial [35]. All of the above mentioned aspects and risk should therefore already have been deemed acceptable before trial initiation.

6 Conclusion

The aim of this thesis was to investigate how a system collecting clinical data remotely could be designed to comply with existing regulations and at the same time facilitate the work of the clinical staff. To determine this, a large collection of needs were compiled from a literature review and ten interviews. The needs covered a multitude of areas and similar needs were found in multiple sources. Based on a selection of these needs a conceptualization of a system to be used by the clinical personnel was created. During the usability testing of the system the interviewees were able to complete all tasks. When asked, all interviewees also replied that they would like to work in a system similar to the proposed one and gave it a rating of 8/10 on average. Thus, the evaluation indicates that the prototype fulfilled the most important requirements. To get a notion of how viable a potential realization of the system would be, the project was finalized with an analysis of obstacles and aspects to consider when implementing the system. These considerations were sorted into eight main themes and the result from this could be used as a foundation when considering performing a DCT. The result from this thesis will hopefully have shed light on the possibilities of DCTs and provided a foundation for creating similar systems. Further, it aspires to act as an inspiration for further development within clinical trials.

Authors' Contributions

Both authors have contributed an equally amount to the writing and reviewing of this report. All tables, figures and diagram are created by both authors. In the first literature review, Klara Indebetou was responsible for the review regarding clinical trials and Caroline Zander was responsible for the review regarding remote patient monitoring. All other parts were done in collaboration.

References

[1] Wouters OJ, McKee M, Luyten J. Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. JAMA. 2020; 323(9): 844–853.

[2] Karolinska institutet. Fakta om klinisk forskning [Internet]. Stockholm: Karolinska institutet; [updated 2021-06-02; cited 2022-02-08]. Available from: `https://ki.se/forskning/fakta-om-klinisk-forskning`,.

[3] Vetenskapsrådet. Den kliniska studiens olika faser [Internet]. Göteborg: Vetenskapsrådet; 2017-03-21 [updated 2020-12-11; cited 2022-02-08]. Available from: `https://www.kliniskastudier.se/for-dig-som-forskar/den-kliniska-studiens-olika-faser.html`,.

[4] Lengacher CA, Gonzalez LL, Giuliano R, Bennett MP, Cox CE, Reintgen DS. The Process of Clinical Trials: A Model for Successful Clinical Trial Participation. Oncology Nursing Forum. 2001; 28 (7) :1115-1120.

[5] Koehler F, Koehler K, Deckwart O, Prescher S, Wegscheider K, Kirwan BA, et al. Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): a randomised, controlled, parallel-group, unmasked trial. Lancet. 2018 Sep; 392(10152): 1047-1057.

[6] Careinnovations. What Is Telehealth? What Is Remote Patient Monitoring? How Are They Different?[Internet]. Careinnovations. [cited 2022-04-25]. Available from: `https://news.careinnovations.com/blog/what-is-telehealth-what-is-remote-patient-monitoring-how-are-they-different`.

[7] Wikipedia. Remote patient monitoring [Internet]. Wikipedia; [updated 2022-02-01; cited 2022-02-08]. Available from: `https://en.wikipedia.org/wiki/Remote_patient_monitoring`,.

[8] Sony Network Communication Europe. The technology behind mSafety: Open remote monitoring platform with always-connected wearable device. Sony Network Communication Europe; 2022 [cited 2022-02-17]. Available from: `https://www.sonynetworkcom.com/msafety/technology`.

[9] ClinicalTrials.gov. Learn about clinical studies [Internet]. ClinicalTrials.gov: National Library of Medicine (US); 2019. [cited 2022-05-23].

Available from: https://clinicaltrials.gov/ct2/about-studies/learn.

[10] Öman A, Lindberg N, Lomberg H. Handbok i genomförande av en klinisk prövning. 1:1. Lund: Studentlitteratur; 2012.

[11] ICH. Home [Internet]. ICH. [cited 2022-02-08]. Available from: https://www.ich.org/,.

[12] DelVecchio A. Remote patient monitoring (RPM) [Internet]. Tech target [updated 2019-04, cited 2022-04-25]. Available from: https://www.techtarget.com/searchhealthit/definition/remote-patient-monitoring-RPM.

[13] Noah B, Keller MS, Mosadeghi S, Stein L, Johl S, Delshad S, et al. Impact of remote patient monitoring on clinical outcomes: an updated meta-analysis of randomized controlled trials. NPJ Digit Med. 2018 Jan; 1(17).

[14] Florence Healthcare. Remotely Monitor Study Sites by Deploying and Connecting to Electronic Investigator Site Files [Internet]. Atlanta USA: Florence Healthcare; 2022 [cited 2022-04-25]. Available from: https://florencehc.com/workflows/remotemonitoring/.

[15] Veeva Systems. Going Digital with Remote Monitoring: Key Considerations [Internet]. Burks B; 2020 [cited 2022-04-25]. Available from: https://sites.veeva.com/resources/going-digital-with-remote-monitoring-key-considerations/.

[16] SureClinical. The Future of Clinical Trials: Going Digital With Remote Monitoring [Internet]. SureClinical; 2021 [cited 2022-04-25]. Available from: https://sureclinical.com/2021/05/14/clinical-trial-remote-monitoring/.

[17] Quanticate Commercial team. Remote Monitoring During Clinical Trials - COVID-19 Update [Internet]. Quanticate Commerical team; 2011 [updated 2022-05-03; cited 2022-04-25]. Available from: https://www.quanticate.com/blog/bid/70489/remote-monitoring-during-clinical-trials-a-risk-based-approach,.

[18] Fink JLW. Is Remote Clinical Trial Monitoring Here to Stay? [Internet]. Pfizer; 2021 [cited 2022-04-25]. Available from: https://www.pfizer.com/news/hot-topics/is_remote_clinical_trial_monitoring_here_to_stay.

[19] Leiwert. Transforming clinical trials [Internet]. Leiwert [cited 2022-04-25]. Avialable from: https://www.leitwert.ch/solutions/clinical-trials/.

[20] ObvioHealth. Virtual Clinical trials deliver better data [Internet]. New York, USA: Obvio Health [cited 2022-04-25]. Available from: https://www.obviohealth.com/virtual-clinical-trials-deliver-better-data.

[21] Van Norman GA. Decentralized Clinical Trials: The Future of Medical Product Development?. JACC Basic Transl Sci. 2021 Apr; 6(4): 384–387.

[22] Khozin S, Coravos A. Decentralized Trials in the Age of Real-World Evidence and Inclusivity in Clinical Investigations. CPT. 2019; 106(1): 25–27.

[23] Agrawal G, Xue J, Moss R, Raschke R, Wurzer S. No place like home? Stepping up the decentralization of clinical trials. McKinsey Company; 2021 [cited 2022-02-23]. Available from: https://www.mckinsey.com/industries/life-sciences/our-insights/no-place-like-home-stepping-up-the-decentralization-of-clinical-trials.

[24] Institute of Medicine (US) Roundtable on Value Science-Driven Health Care. Clinical Data as the Basic Staple of Health Learning: Creating and Protecting a Public Good: Workshop Summary [Internet]. Washington (DC): National Academies Press (US); 2010. Summary. Available from: https://www.ncbi.nlm.nih.gov/books/NBK54290/.

[25] Puppala M, He T, Yu X, Chen S, Ogunti R, Wong STC. Data security and privacy management in healthcare applications and clinical data warehouse environment. IEEE-EMBS International Conference on Biomedical and Health Informatics (BHI). 2016 Feb; 5-8.

[26] IMY. Our mission [Internet]. IMY; 2021 [updated 2021-12-17; cited 2022-04-25]. Available from: https://www.imy.se/en/about-us/swedish-authority-for-privacy-protections-assignment/.

[27] Sony Network Communications Europe. About us. Sony Network Communications Europe; 2022 [cited 2022-02-17]. Available from: https://www.sonynetworkcom.com/about-snce.

[28] Preece J,Rogers Y, Sharp H. Interaction Design: beyond human-computer interaction. 4th. Chichester, West Sussex, United kingdom: John Wiley Sons Ltd; 2015.

[29] Zahabi M, Kaber DB, Swangnetr M. Usability and Safety in Electronic Medical Records Interface Design: A Review of Recent Literature and Guideline Formulation. Hum Factors. 2015 Aug; 57(5): 805-34.

[30] Martin B, Hanington B. Universal Methods of Design [Internet]. Digital edition published in 2012. Beverly: Rockport Publishers; 2012. [cited 2022-04-25].

[31] Nielsen J. 10 Usability Heuristics for User Interface Design [Internet]. Nielsen Norman Group; 1994 [updated 2020-11-15; cited 2022-02-09]. Available from: https://www.nngroup.com/articles/ten-usability-heuristics/,.

[32] Swedish Medical Products Agency. Clinical trial: Medicinal product for human use. Swedish Medical Product Agency; Jan 17 2022 [cited 2022-02-22]. Available from: https://www.lakemedelsverket.se/sv/tillstand-godkannande-och-kontroll/klinisk-provning.

[33] Fogel DB. Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review. Contemp Clin Trials Commun. 2018 Aug ;11:156-164.

[34] Butryn T, Cornejo K, Wojda TR, Papadimos TJ, Gerlach AT, Deb L, et al. Keys to success in clinical trials: A practical review. Int J Acad Med. 2016; 2(2): 203-216.

[35] Friedman LM, Furberg CD, DeMets DL, Reboussin DM, Granger CB. Fundamentals of Clinical Trials [Internet]. Fifth edition. Switzerland: Springer International Publishing; 2015. [cited 2022-04-25]. Available from: https://link.springer.com/content/pdf/10.1007/978-3-319-18539-2.pdf.

[36] Ong MK, Romano PS, Edgington S, Aronow HU, Auerbach AD, Black TJ, et al. Effectiveness of Remote Patient Monitoring After Discharge of Hospitalized Patients With Heart Failure: The Better Effectiveness After Transition–Heart Failure (BEAT-HF) Randomized Clinical Trial.JAMA Intern Med. 2016; 176(3): 310–318.

[37] Mann DM, Chen J, Chunara R, Testa PA, Nov O. COVID-19 transforms health care through telemedicine: Evidence from the field. J Am Med Inform Assoc. 2020 Jul; 27(7): 1132-1135.

[38] Baig MM, Gholamhosseini H. Smart Health Monitoring Systems: An Overview of Design and Modeling. J Med Syst. 2013; 37.

[39] Wosik J, Fudim M, Cameron B, Gellad ZF, Cho A, Phinney D, et al. Telehealth transformation: COVID-19 and the rise of virtual care. J Am Med Inform Assoc. 2020 Jun; 27(6): 957-962.

[40] Flaherty KT, Doroshow JH, Galbraith S, Ribas A, Kluetz PG, Pazdur R, Theoret MR. Rethinking Cancer Clinical Trial Conduct Induced by COVID-19: An Academic Center, Industry, Government, and Regulatory Agency Perspective. Cancer Discov 2021 Aug; 11(8): 1881–1885.

[41] Coert RMH, Timmis JK, Boorsma A, Pasman WJ. Stakeholder Perspectives on Barriers and Facilitators for the Adoption of Virtual Clinical Trials: Qualitative Study. J Med Internet Res. 2021; 23(7): e26813.

[42] Cerreta F, Ritzhaupt A, Metcalfe T, Askin S, Duarte J, Berntgen M, et al. Digital technologies for medicines: shaping a framework for success. Nat. Rev. Drug Discov. 2020 May; 19: 573-574.

[43] Polhemus AM, Kadhim H, Barnes S, Zebrowski SE, Simmonds A, Masand SN, et al. Accelerating Adoption of Patient-Facing Technologies in Clinical Trials: A Pharmaceutical Industry Perspective on Opportunities and Challenges. Ther Innov Regul Sci. 2019; 53(1): 8-24.

[44] Apostolaros M, Babaian D, Corneli A, Forrest A, Hamre G, Hewett J, et al. Legal, Regulatory, and Practical Issues to Consider When Adopting Decentralized Clinical Trials: Recommendations From the Clinical Trials Transformation Initiative. Ther Innov Regul Sci. 2020; 54: 779-787.

[45] Van Norman GA, et al. Decentralized Clinical Trials: The future of medical product development?.J Am Coll Cardiol Basic Trans Science. 2021 Apr; 6(4): 384-387.

[46] Lee EQ, Selig W, Meehan C, Bacha J, Barone A, Bloomquist E, et al. Report of National Brain Tumor Society roundtable workshop on innovating brain tumor clinical trials: building on lessons learned from COVID-19 experience. J Neurooncol. 2021 Aug; 23(8): 1252-1260.

[47] Läkemedelsverket. Regelverk för klinisk läkemedelsprövning på människa [Internet]. Läkemedelsverket; 2019 [updated 2021-02-21; cited 2022-04-25]. Available from: https://www.lakemedelsverket.se/sv/tillstand-godkannande-och-kontroll/klinisk-provning/lakemedel-for-manniskor/regelverk-for-klinisk-provning.

[48] Läkemedelsverket. Decentraliserade och virtuella kliniska läkemedelsprövningar[Internet] . Läkemedelsverket; 2021 [updated 2022-01-17; cited 2022-04-25]. Available from: https://www.lakemedelsverket.se/sv/tillstand-godkannande-och-kontroll/klinisk-provning/lakemedel-for-manniskor/decentraliserade-och-virtuella-kliniska-lakemedelsprovningar.

7 Appendix

7.1 Literature review to identify needs

7.1.1 Clinical trials

Problem nbr	Challenge	Article nbr	Solution	Need
1	Deciding if there is merit in continuing the trial or if it should be terminated.	1	At all stages be able to study the result so far.	1) Possibility to get an overview over the collected data. 2) Possibility to get summary of the result.
2	Determine if it is safe to move on to the next phase.			
3	Taking appropriate measurements.	1 & 3	Control the collected data to determine if appropriate measurements are taken.	
4	Demonstrate trial safety.	1 & 3 & 5	Warnings when participants measured value are outside of reference interval or have changed very drastically.	1) Notification if a participant's value deviates from reference interval. 2) Notification if a value drastically changes. 3) Possibility to set reference intervals and limits.
5	Missing data.	1 & 3 & 5	Deal with the missing data correctly.	1) Notification when data is missing. 2) Possibility to mark and comment on missing data. 3) Possibilityto notify appropriate person of missing data. 4) All changes need to be saved and a protocol needs to be created of what changes were made, why and by whom. 5) Possibility to show version history.
6	Incorrect data.	1 & 3 & 5	Deal with the incorrect data correctly.	1) Notification when data appears to be incorrect. 2) Possibility to mark and comment on incorrect data. 3) Possibility to notify appropriate person of incorrect data. 4) All changes need to be saved and a protocol needs to be created of what changes were made, why and by whom. 5) Possibility to show version history.
7	Incorrect data is entered into the system.	3 & 5	Minimize the risk of incorrect data being added.	1) Clear and well organized data entry fields. 2) Logical sequence of questions. 3) Design to minimize missing data, by for example not being able to move on until mandatory questions have been answered. 4) On questions regarding present conditions, yes, no or unknown checkboxes should be used. 5) Avoid write-in answers. 6) Only include necessary questions. 7) Follow the data entry categories presented by Cook and DeMets.
			Enter data directly to the program or have it transferred automatically.	1) Possibility to work in the system and add data directly in an efficient way. 2) Data from sensors being transferred directly into the system. 3) Possibility to verify and approve the data before it is saved.
			Control dates and times.	1) Possibility that suggest dates and times. 2) Possibility to get overview of dates and times.
			Control if values have changed unreasonably much.	1) Possibility with warnings if value deviates unreasonably much. 2) Possibility to set limits. 3) Possibility see what the values were the last time.
			Control extrema laboratory values.	1) Possibility with warnings if a value is unreasonable. 2) Possibility to set limits for how much that is.

Figure 17: Part one of table of identified challenges, solutions and needs from literature review regarding clinical trials.

8	Unnecessary data is collected.	2 & 3 & 4 & 5	Only collect necessary data.	1) Possibility to decide what data to collect that can be modified for each trial.
9	Verifying the data regularly.	3 & 4	Data needs to be actively verified more regularly.	1) Reminders to verify data. 2) Possibility verify data. 3) Records of data verification.
10	Store data for appropriate period.	5	Store data from trial for at least 10 years.	1) Possibility to download all data or save the whole file.
11	Participant data that are going to be transferred to the sponsor needs to be coded.	5	Possibility to code/anonymize data.	1) Possibility to code/anonymize data. 2) Access to the code key at the clinical trial site.
12	Keep record of which data has been cleaned.	5	Be able to close data against changes and mark it as finished or "clean".	1) Possibility to mark data as clean and then also block further changes. 2) Possibility to mark deviation and comment on how they will be solved in the analysis work.
13	Delay in submission of data.	3	Remind the participants to submit their data.	1) Possibility to send reminders to participant to send in data if it has not been done. 2) Possibility to see history of reminders.
14	Protocol deviations.	1 & 3 & 5	Clear and easily available protocol instructions for the personnel.	1) Instructions how data should be collected available in the system. 2) Possibility to go through how the visit should be carried out.
		1 & 3	Clear and easily available instructions for the participants.	1) Possibility to send reminders to participants regarding instructions. 2) Possibility to communicate with participants and see if they handle the equipment and data collection correctly. 3) Possibility for participant to contact personnel and ask for help.
15	Different level of blindness in different studies.	3	Able to perform both single, dubbel and triple blinded studies.	1) Possibility to anonymize data from some personnel. 2) Possibility to have different access depending on who the user is.
16	Different units are used in different trials.	3 & 5	Use the same units/standard units when possible.	1) Possibility to change units. 2) Display of units when need to enter or interpret data.

Figure 18: Part two of table of identified challenges, solutions and needs from literature review regarding clinical trials.

17	Traceability.	5	See who have added, changed or removed what information. The original data needs to be saved.	1) Possibility to keep records of who have added, changed or removed what information. 2) Possibility to access the untouched original data.
		5	Track when data manager ask questions to the principle investigator.	1) Possibility for communication between these two people and possibility to comment on data. 2) Possibility to keep records all that communication.
18	Study protocol is not audited often enough.	4 & 3	Study protocol needs to audited more regularly.	1) Reminders to control study protocol. 2) Record of when study protocol has been controlled.
19	Not all adverse events are reported.	1 & 3 & 5	Make it easy to report adverse events and remind participants of the importance to report adverse events, even those that are mild.	1) Possibility to report adverse effects. 2) Should be reported according to which category of serious adverse events, general adverse events and adverse events of special interest belongs to. 3) Should use common terminology according to (MedDRA). 4) Overview of how many reports are made. 5) Possibility to send reminders to participants to report any adverse effects.
20	Assessment of harm.	3	Personnel needs to have a clear view over contributions to assessment of harm.	1) Page with overview over different contributions to assessment for harm. 2) Possibility to show dropout rates due to adverse events. 3) Possibility to show adverse events. 4) Possibility to for each adverse event be able to report severity, time of onset and duration. 5) Possibility to show number of participants that had their dose reduced. 6) Possibility to show number of participants that continued with treatment protocol despite adverse events.
21	When adverse events occurred and when medication was given needs to be connected in the CRF.	5	Need to be able to see when adverse event occurred and when medication was taken.	1) Possibility to add time when report adverse events. 2) Possibility to record when medications are taken.
22	Exclusion/inclusion criterions might be too high or too low which impacts the number and quality of study participants.	1 & 3	Clear inclusion/exclusion criteria that everyone that needs them can access and the possibility to change them throughout the process.	1) Possibility to show the current inclusion/exclusion criteria. 2) Possibility to change inclusion/exclusion criteria. 3) Possibility to send notice to personnel when criterias are updated.
		1	Need to know how many of the screened participants that enroll to know if they need to change exclusion/inclusion criteria.	1) Possibility to show enrollment fraction.

Figure 19: Part three of table of identified challenges, solutions and needs from literature review regarding clinical trials.

23	It is hard to recruit enough study participants and make them stay.	1 & 2 & 3	Promote participant enrollment motivators such as supporting participant belief that: - They have opportunity to receive better treatment. - The result can help others. - Their health is improving.	1) Possibility to show the values and results to the participant in a participant mode perhaps? 2) Possibility to send out result of study to participants once the trial is finished.
		1 & 2 & 3 & 4	Staff should: - appear available and interested. - not give the participants too high expectations. - provide appropriate empathy for participants that suffer during the trial. - have clear and open communication with the participants - be aware of how the participants feel. - keep participants informed. - be trustworthy. - make sure that participant concerns are addressed.	1) Possibility to facilitate communication between participant and personnel.
		1	Participants should be allowed to meet the same personnel each time if possible. They should also be allowed to request change of personnel.	1) Possibility to assign one personnel to each participant.
		1 & 3	Analyze data regarding why participants decide to leave a trial.	1) Possibility to show statistics on dropouts 2) Possibility to show why a participant dropped out according to the subcategories: dropout due to adverse events, dropouts for lack of efficacy and dropouts for administrative reasons.
		1 & 2	The trial process should be as effective as possible to minimize the time and cost it takes to participate.	1) Want to minimize the time participant have to dedicate to the trial.
		2 & 3	Participants regular physician do not recommend that the participant participate in the trial.	1) Possibility to communicate with participants regular physician.
		2 & 3	Do not enroll participants that have doubts.	1) Possibility to screen participants before trial. 2) Overview of screening result.
		1 & 2	Personnel should try and minimize the stress and burden for the participants.	1) Want to minimize the number of test and tasks the participant have to do.
		2	Participants need to know that their privacy is upheld.	1) Possibility to anonymize data.
		1	Participants should not have to wait at their appointments when possible.	1) Possibility to schedule participants and see when their next appointment is.

Figure 20: Part four of table of identified challenges, solutions and needs from literature review regarding clinical trials.

24	Participants have a hard time understanding scientific literacy.	1	Keep language that participants see as simple as possible.	1) Keep language that participants see as simple as possible.
25	Participants do not come to their appointments.	1 & 2 & 4	Send reminders to the participants and make it easy for them to reschedule.	1) Possibility to reschedule 2) Possibility to send reminders for appointments to participants.
26	Lack of long term follow up.	1	Need to be able to easily follow up participants after the trial.	1) Possibility to follow up participants.
27	Do not consider the participants needs and level of illness when make arrangement for visits.	2 & 4	Need to know participants needs and level of illness.	1) Possibility to show a summary of participant information.
28	Ineffective process of identifying potential study participants, reporting adverse events and finding information about the participants.	3 & 4	Need access to Electronic medical records.	1) Possibility to access or import data from electronic medical records.
29	Need to know how much is reasonably to financially compensate the participants with.	4	Need to know how much time the participants have spent on the study.	1) Possibility to record all participant meetings. 2) Information page about the participant.
30	Must know what the baseline for each participant was to see the effect of the study.	3	Need to have clear and available baseline information.	1) Possibility to show and add baseline information about participant.
31	Want similar distribution of baseline factors in each study group.	3	Need to examine the baseline data of a group.	1) Possibility to calculate and display mean, median, std etc. of the baseline data in different categories.

Figure 21: Part five of table of identified challenges, solutions and needs from literature review regarding clinical trials.

32	Participants do not adhere to their medicine instructions.	3	Send reminders to participants when they need to take their medicine.	1) Possibility to send reminders to participant when they need to take their medicine.
		3	Need to check how many pills are left in the bottle.	1) Possibility to enter how well the participant adhere to the medicine regime. 2) Possibility to sign when participant have been given the medicine. 3) Show the code number for the bottle on the participant page.
33	Making the participants adhere to the protocol.	3	Nurture a warm and friendly relationship between participants and the clinical personnel.	1) Possibility to facilitate communication between participants and personnel.
		3	Make sure that participants feel safe.	1) Possibility to show the values and result to the participant. 2) Possibility to send out result of study to participants once the trial is finished. 3) Possibility to keep participant updated when collected data have been reviewed.
34	Participants drop out of the study.	5	Possibility to remove participant and choosen parts of their collected data from the study.	1) Possibility to remove a participant from the program. 2) Possibility to remove specific parts of the data.
35	Personnel preform tasks that do not allow them to utilize their abilities to the maximum.	4 & 5	Assign specific rolls to personnel that allow them to utilize their abilities to the maximum.	1) Possibility to assign different roles. 2) Possibility to assign tasks. 3) Possibility to see who is responsible for what. 4) Possibility to keep records of who is assigned what.
36	No standardized communication process between clinical personnel.	4	Need standardized and effect tool for communication and feedback.	1) Possibility for communication between personnel. 2) Possibility see when internal meetings are scheduled. 3) Possibility to comment on data or assign task to someone.
37	Pharmacy professionals are not as well integrated in the trial as they should be.	4	Need to communicate and utilize the expertise that pharmacy professionals possess.	1) Possibility to communicate with pharmacy professionals. 2) Possibility to allow pharmacy professionals limited access to the system.
38	Clinical trials requires good collaboration between multiple parties.	5	Multiple people have to be able to work in the same program but have different access.	1) Possibility to assign rolls. 2) Allow different access levels to different functions in every trial.

Figure 22: Part six of table of identified challenges, solutions and needs from literature review regarding clinical trials.

7.1.2 Remote patient monitoring

Challenge. No.	Challenges	Solution	Article No.	Need
1	Expensive with physical meetings.	Possibility for the participant to communicate with clinical personnel and take measurements from home.	1 & 2 & 3 & 5	1) Possibility to facilitate communication between participants and personnel. 2) Possibility to view the collected data.
2	Participants don't want personnel to visit them at home.			
3	High number of hospital visits.			
4	Trial visits are done in a metropolitan area, thus making it harder to recruit participants from rural areas and other metropolis.			
5	Participant is unable to attend physical meeting due to being affected by potential infectious disease or being immunocompromised.			
6	Physical visits is time-inefficient, thus making it harder to recruit participants and making them adhere to the intervention.			
7	Low communication adherence, not enabling functionable feedback.	Use of a communication device/application which is easy and intuitive for the participant and clinical personnel to use.	1 & 2 & 4	1) Clear instructions easily available for the personnel and participants. 2) Possibility for participants to ask for help. 3) Possibility to facilitate communication between participants and personnel. 4) Communication can be made by text, phone calls or video calls.
8	Participants feel the contact is impersonal due to having different nurses all the time and inefficient due to having explaining their medical history, thus being unnecessarily uncomfortable and time wasting.	Each participant is assigned a care manager nurse to handle all scheduled contact.	1	1) Include participant contact information on their participant page. 2) Possibility to assign one personnel to each participant.
		The same nurse(s) are handling all scheduled contact with the participant. The nurses have access to participants medical record and history.	1	
9	Transition of care between usual care and trial care is not effective, leading to potential miscommunication and delay in treatment of the participant.	Involvement of participants usual healthcare practitioners (specialists and general). Direct communication between clinical trial personnel, participants and participants usual healthcare practitioners.	1 & 2	1) Possibility to facilitate communication between trial personnel and participants usual healthcare practitioners.
10	Integration of trial intervention in participants in usual healthcare.			
11	Physical visits is time-inefficient, thus making it harder to involve disease specialist and other clinicians.			
12	An intensive and instantaneous management of the disease is needed.	Create a study-specific electronic participant file to give participants' usual healthcare practitioners access to participants health data and thus manage the participants disease(s).	1&2	1) Possibility to share a electronic participant file with participants usual healthcare practitioners.
13	Participants' usual healthcare practitioners are not informed on participants' treatments.			
14	Participant is experiences symptoms and want more information or assurance.	Participant is able to initiate communication, is able to find answers to standard questions, and use self-service tools such as easy symptom reporting and help function.	1 & 2 & 3 & 4 & 5	1) Possibility to facilitate direct communication between participants and personnel. 2) Possibility to list standard questions. 3) Help function or guide. 4) Possibility to report symptoms and symptom severity.
15	Communication between participants and clinical personnel is lacking, leading to missed symptoms, delayed treatment change, among other things.			

Figure 23: Part one of table of identified challenges, solutions and needs from literature review regarding remote patient monitoring.

16	Communication shall be as inclusive as possible	Communication includes different alternatives to be as inclusive as possible for all ages, disabilities, and socioeconomic status.	5	1) Possibility to facilitate different alternatives to communication, e.g. via text, voice or video.
17	Creating satisfactory trial protocol and making sure that it is followed.	Trial designed, implemented, and overseen by an independent steering committee.	2	1) Possibility to read trial protocol. 2) Notification if changes are made to the protocol.
18	Participant adherence to protocol.	Information to participant on the trial.	1	1) Clear and easily available instructions for the participants. 2) Possibility to facilitate communication between participants and personnel. 3) Easy to follow participant guide on RPM equipment. 4) Clear and easily protocol instructions for the personnel.
		Participant education on; - The disease. - RPM equipment. - Importance of adherence to trial, medicine. - Importance of adherence to RPM protocol (importance of collected data).	1 & 2	
		Apply "teach-back"-method for participant education.	1 & 5	
		All calls reinforced participant education and participant are also given the information to look at home.	1 & 2	
		Participants can access to their medical and health data to be better informed.	3 & 5	1) Possibility for the participants to see their own data.
19	Hard to achieve full compliance in data transfer from the participants.	Contact participant within 24 h of missing data transmission.	2	1) Possibility to send reminders to participants. 2) Possibility to facilitate communication between the participant and clinical personnel.
		Use monitoring system which has as little effect on participants daily life as possible.	2	1) Want to minimize the time participant have to dedicate to the trial. 2) Only include necessary questions. 3) Use of monitoring devices which are unobtrusive to participants daily life.
20	Stopped transmission from participant	Contact with participant within 24 h - to investigate cause for transmission stop - to encourage participant resume transmission	1	1) Possibility to send reminders to participants. 2) Possibility to facilitate communication between the participant and clinical personnel.
21	Participant is experiences information overload which may contribute to the participant getting confused on where and how they shall get information again and make contact if needed. This can in turn lead to decreased participant adherence.	Participant can access all different services and participant tools through an application. The application is using standard application interface and allows the participant to request contact, answer questions, etc..	3 & 4 & 5	1) Possibility to facilitate direct communication between participants and personnel. 2) Possibility to list standard questions. 3) Help function or guide for the participant.
22	Participants of higher age feel uncomfortable with the technology.	1. Participant education on all technology. 2. Guide on the technology. 3. User friendly interface, made to be inclusive with good visibility, clear purpose of functions, etc.	3 & 4	1) Help function or guide for the participant. 2) Possibility to list standard questions. 3) Possibility to print guide. 4) Aspect: Inclusive interface design. 5) Possibility to show instructive teaching guide for the clinical personnel.
23	Users (clinicians and participants) have trouble using the monitoring system devices.	1. Both system hardware and software follow usability design principles to avoid user error. 2. Clinical personnel may be educated on both participant and personnel devices to ensure that they can help the participants. Information booklet for personnel and participants are available online. 3. Participants is educated on home monitoring devices and software by clinical personnel. Booklet with information for participant is available online.	4 & 5	1) Aspect: Inclusive system design. 2) Aspect: Usability design principles followed in both software and hardware. 3) Possibility to show information guide(s). 4) Possibility to list standard questions. 5) Possibility to print guide(s). 6) Possibility to show instructive teaching guide for the clinical personnel.
24	Users (clinicians and participants) have trouble understanding the manual instructions for system devices.			

Figure 24: Part two of table of identified challenges, solutions and needs from literature review regarding remote patient monitoring.

25	Low adherence rate to trial	Treating and seeing the whole person.	1	1) Possibility to rate general wellbeing. 2) Possibility to show summary of patient information.
		Engaging participant before discharge	1	1) Possibility to facilitate communication with participant.
26	Risk of participant withdrawal from clinical trial: - Before trial start (but after given consent). - Prematurely (after trial start but before end).	Study population should be well defined before recruiting participants to ensure their suitability and willingness.	2	1) Possibility to screen patient before trial. 2) Possibility to show current inclusion/exclusion criterions. 3) Possibility to create risk profile for each participant.
		Screening of participants mental health and energy to ensure their ability to adhere to trial protocol.	2	
		Conducting interviews with participant to ensure participants satisfaction with care, quality of life, and use of intervention.	1	
27	Participants' experience symptoms without alarming the clinicians	Regularly scheduled contact for interviews	1 & 2	1) Possibility to schedule regular contact with participant. 2) Possibility to facilitate direct communication between participant and clinical personnel.
28	Participant have trouble identify symptoms and establish their severity.	Include information regarding symptoms and their severity in participant education.	1	1) Provide clear examples on severity of symptoms. 2) Function with list of known symptoms and their severity. 3) Possibility to choose symptom and severity. 4) Possibility to add new symptoms not in the list.
29	Achieve equity in participant care and management.	Help participant manage potential comorbidities.	2	1) Possibility to rate general wellbeing. 2) Possibility to facilitate communication between trial personnel and participants usual healthcare practitioners.
30	Participants' comorbidities is overlooked or forgotten.	Tailored participant care/support/management with individual participant specific risk profiles (created by taking recorded monitoring data, baseline data and biomarker data, and analyse it, eg. with an analysis software).	2	1) Possibility to create risk profile for each participant. 2) Possibility to screen patient before trial. 3) Possibility to see monitoring data. 4) Possibility to see biomarker data from lab results. 5) Possibility to analyse participant data. 6) Possibility to update risk profile. 7) Possibility to sort participants based on risk profiles. 8) Possibility to assign one personnel to each participant.
31	Participants general health places them at a higher risk for lower protocol adherence.			
32	Difficulties to evaluate and treat each participant with the perfect amount of care that they need during the whole trial, and difficulties to prioritise participants and their need.			
33	Difficulties to evaluate each participants current physical and mental health.	Do an assessment of the participant using predetermined parameters collected through monitoring and interviews.	2	1) Possibility to facilitate regular scheduled contact with participate. 2) Possibility to create predetermined parameters.
34	Unknown cause of concerning or acute symptom(s) reported by the participant.	Contact with participant - to investigate cause for alarming symptoms. - to encourage participant to come in/contact healthcare provider.	1	1) Possibility to facilitate direct communication with participants. 2) Possibility to notify clinical personnel of alarming symptoms. 3) Possibility for participant to report symptoms. 4) Possibility to schedule physical visit for the participant.
35	Unknown cause of value outside predetermined threshold interval/value.	Contact with participant to investigate cause when threshold value/interval exceeded.	1	1) Possibility to facilitate direct communication with participants. 2) Possibility to notify clinical personnel of value outside predetermined interval. 3) Possibility to schedule physical visit for the participant.
36	Physical exam of participants may be lacking.	Trial should be designed to monitor physical parameters both by home monitoring and by visitation to clinic if needed. Participants should be recommended to visit clinic or other healthcare if needed.	5	1) Possibility to facilitate communication with participant. 2) Possibility to schedule physical visits for the participant. 3) Possibility to view collected data. 4) Possibility to list answers to standard questions.

Figure 25: Part three of table of identified challenges, solutions and needs from literature review regarding remote patient monitoring.

37	Clinical personnel is cognitive load is too great due too alarms (both true and false). The interruption of alarms leading to the personnel having less time and energy for other tasks. great.	Avoid creating alarms for non-acute actions. Promote the use of notices instead.	4	1) Possibility to only create notice for non-acute actions. 2) Possibility to see notice history. 3) Possibility to choose the number of notices.
		Minimize the possibility of having false alarms.	4	1) Use of rigorously tested system. 2) Use of analysis software to avoid false alarms.
38	Monitoring system is generating false alarms/exceeded thresholds because of faulty sensor contact, system failure or faulty internet connection.	1. Use monitoring system which is tested and proven to generate as few false exceeded thresholds as possible. 2. Use monitoring software capable of distinguish between false and true values outside predetermined interval. 3. Only generate alarms for acute values to minimize cognitive load.	4	1) Possibility to only create notice for non-acute actions. 2) Possibility to see notice history. 3) Possibility to choose the amount of notices. 4) Use of rigorously tested system. 5) Use of analysis software to avoid false alarms.
39	Clinicians make wrong assessment of changes in the medical data.	Software support for assessment. E.g. in the form of predetermined threshold values, risk profiles, etc.	4	1) Possibility to create predetermined threshold values/intervals. 2) Possibility to create risk profile for each participant. 3) Possibility to receive notifications regarding exceeded thresholds.
		Participant diary giving context to the data	4	1) Possibility to view participant diary. 2) Possibility for participant to create or upload diary.
40	Server get overloaded with the amount of activity from different participants and contact between participant and clinical personnel.	Stable servers with enough capacity for all the participants and clinical personnel.	3	1) Aspect: Use stable servers with enough capacity. 2) Possibility to backup all data to secure server.
41	The quality of the data from the monitoring devices.	Use of medical classified monitoring devices, clear for recording medical and health data.	4	1) Aspect: Use of medical monitoring devices.
42	The stability of the monitoring system, from monitoring devices to the server and the applications, is not stable enough.	Use of medical classified monitoring devices, which has gone through stability testing.	4	1) Use monitoring system which has been stability tested. 2) Possibility to backup all data to secure server. 3) Use of security protocol for transmission and servers.
		Use of transmitting and server protocols for improving of the stability.	4	
43	Transmission is delayed due to the processing of real-time data and/or wireless data transmission.	The time of the measurement is saved with the measurement. No visual of real-time measurement is essential for the analysis of the monitoring data.	4	1) Possibility to save time of measurement of data. 2) Possibility to view time of measurement of data. 3) Aspect: No real-time monitoring data.
44	Participant has lost monitoring device.	Device can be localized.	4	1) Possibility for participant to localize monitoring device.
45	Safety data is not reviewed or is following the correct regulations.	A review of safety data is done by an independent data safety monitoring board on an ongoing basis.	2	1) Possibility to show when data safety was lastly reviewed.
46	Ensure the safety of participants medical data.	Data is sent to a secure server.	1 & 2 & 4	1) Aspects: Follow data security regulations.
		Data transmission is done in compliance with international and local data protection regulations.	1 & 2 & 4	
47	Unauthorised access to participants data.	Only authorised personnel have access to participant file.	1 & 2 & 4 & 5	1) Implement different authorisation levels. 2) Possibility to see viewing history of participant data. 3) Implement medical access authentication log-in. 4) Aspect: Follow data security regulations.
48	Participants identification is known/can be determined.	All data is anonymised or coded.	4	1) Possibility to anonymize or code participant data.
49	Monitoring system is generating great amounts of data	Server is dimensioned for containing large amounts of data and is backed-up regularly.	5	1) Possibility to back-up data to secure server regularly. 2) Aspect: Use of server dimensioned for large quantities of data storage.

Figure 26: Part four of table of identified challenges, solutions and needs from literature review regarding remote patient monitoring.

50	To collect data securely and regularly.	Data is transmitted automatically to server for review by clinical personnel.	1 & 2	1) Possibility to review data. 2) Possibility to show new data since last review. 3) Possibility to show time of upload of data.
		Data is transmitted daily	1 & 2	1) Possibility to show time of upload of data. 2) Data should be uploaded regularly. 3) Notification to participants if data could not be uploaded. 4) If data upload was not possible, data will be uploaded as soon as issue no longer remains.
51	Transmission and/or sensors draw too much energy from the device leading to poor battery life, thus creating instability in transmissions.	Use of low power technology to increase battery time.	4	1) Aspect: Use low power network transmission. 2) Aspect: Use low power sensors.
		Notify device user of low battery.	4	1) Notification of low battery.
52	Monitoring devices have a limited signal coverage, thus creating a constraint for the participant in movement.	Only use wearable/implantable devices for continuous monitoring.	4	1) Aspect: Chose non-obtrusive continuous monitoring device. 2) Function: Reminder to take measurements. 3) Possibility to display when measurements were taken.
53	Participant is not able to continue monitoring outside home/is forced to bring large health monitoring devices with them everywhere they go.	Schedule measurements from larger, non-wearable devices at a convenient time for the participants.	1 & 2	
54	Monitoring devices is not comfortable for the participants to wear. Devices may also be restricting or irritating.	Use monitoring devices designed to be comfortable on the human body meaning it is lightweight and small, and can comfortable unobtrusively be placed on the body.	4	1) Aspect: Use of unobtrusive and comfortable monitoring device.

Figure 27: Part five of table of identified challenges, solutions and needs from literature review regarding remote patient monitoring.

7.2 Interviews

Interviewee	Interviewee role
1	Study Nurse
2	Project manager/Clinical research manager
3	Researcher
4	Researcher
5	Clinical research manager
6	Technical adviser
7	Regulatory adviser
8	Clinical research assistant/study nurse
9	Biomedical analytic
10	Digital data collection system specialist at sponsor

Figure 28: Color coding of the interviewees used in the affinity diagrams.

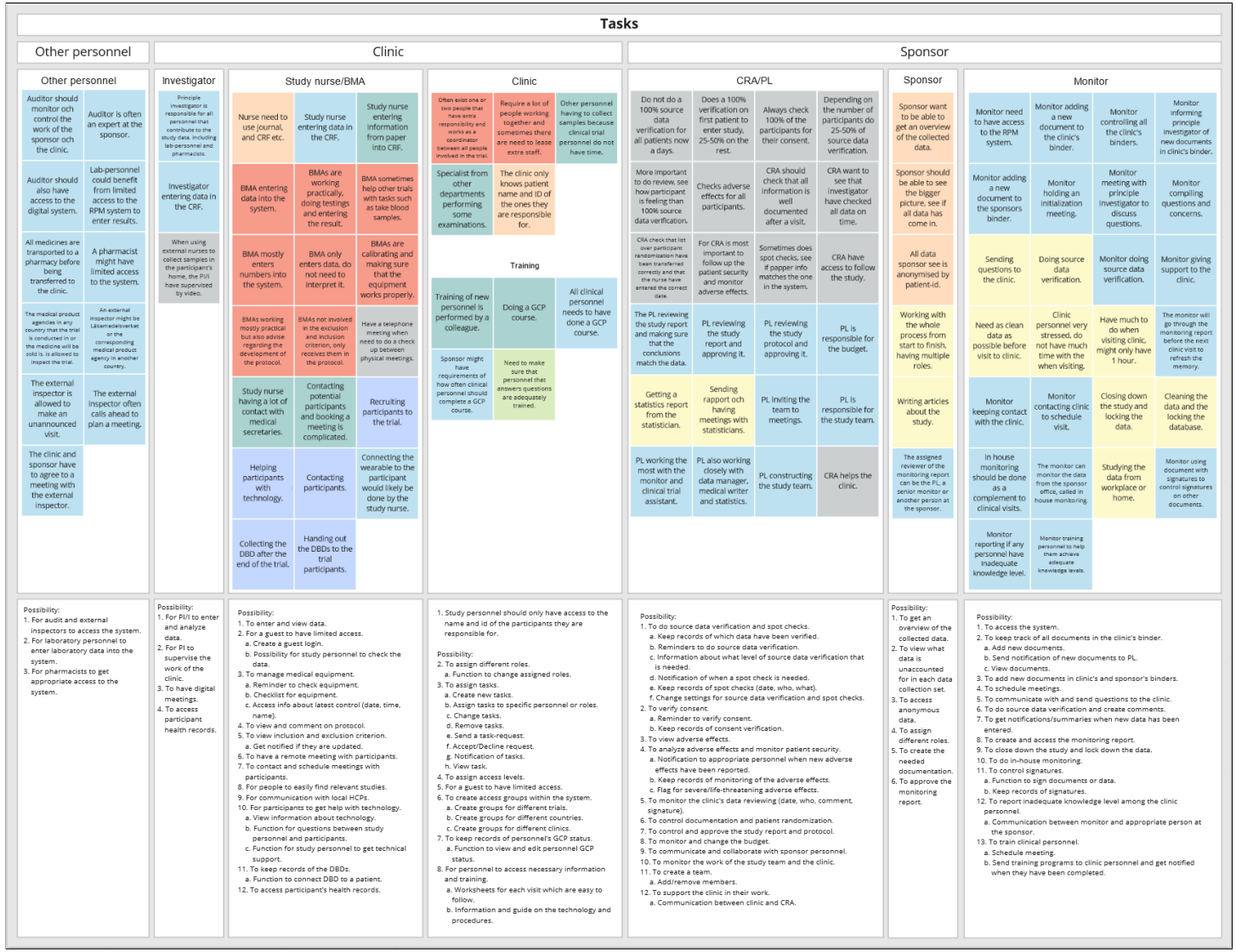


Figure 29: The resulting data gathered from the interviews and the associated needs, regarding tasks of the personnel.

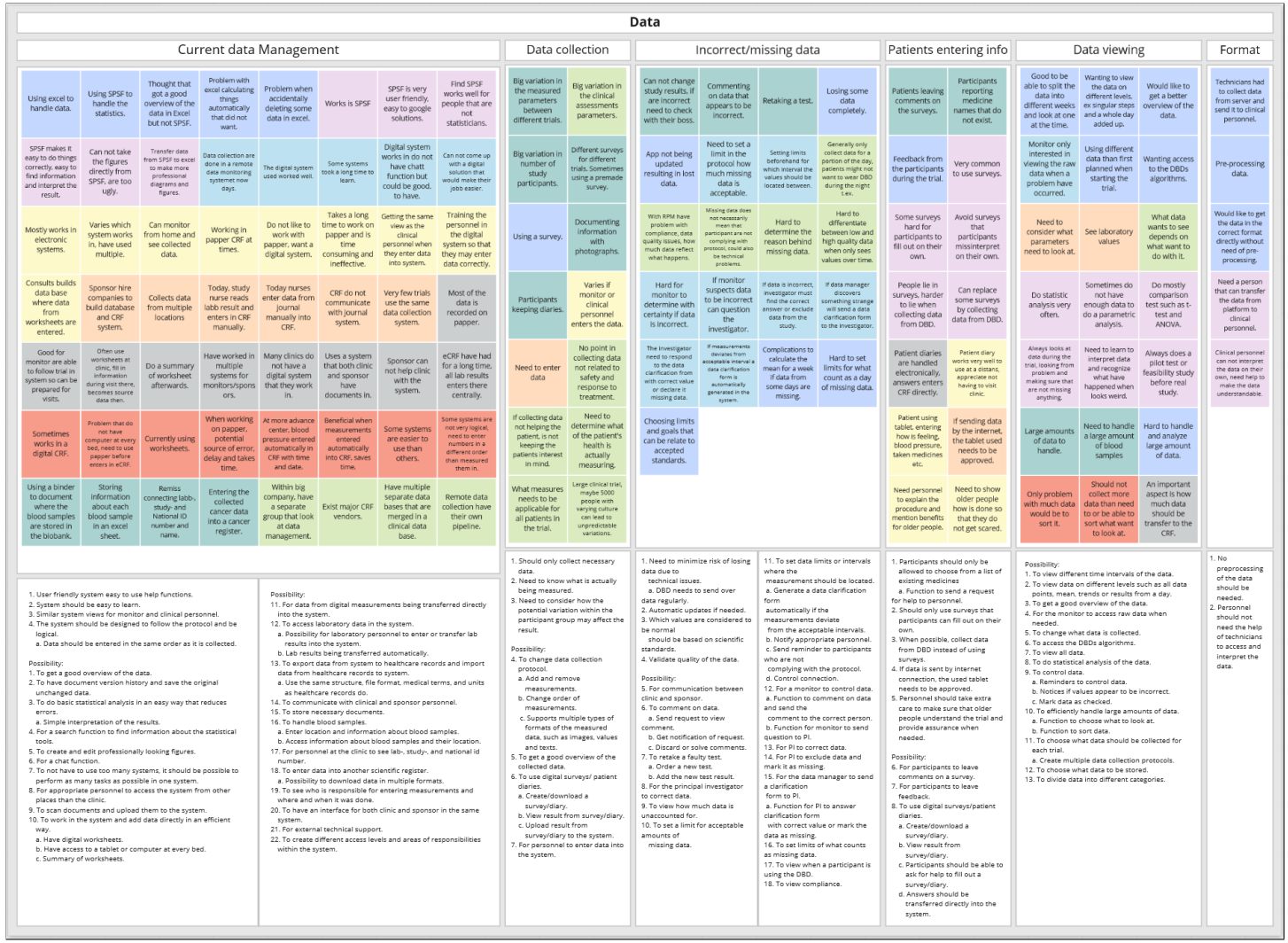


Figure 30: The resulting data gathered from the interviews and the associated needs, regarding data.

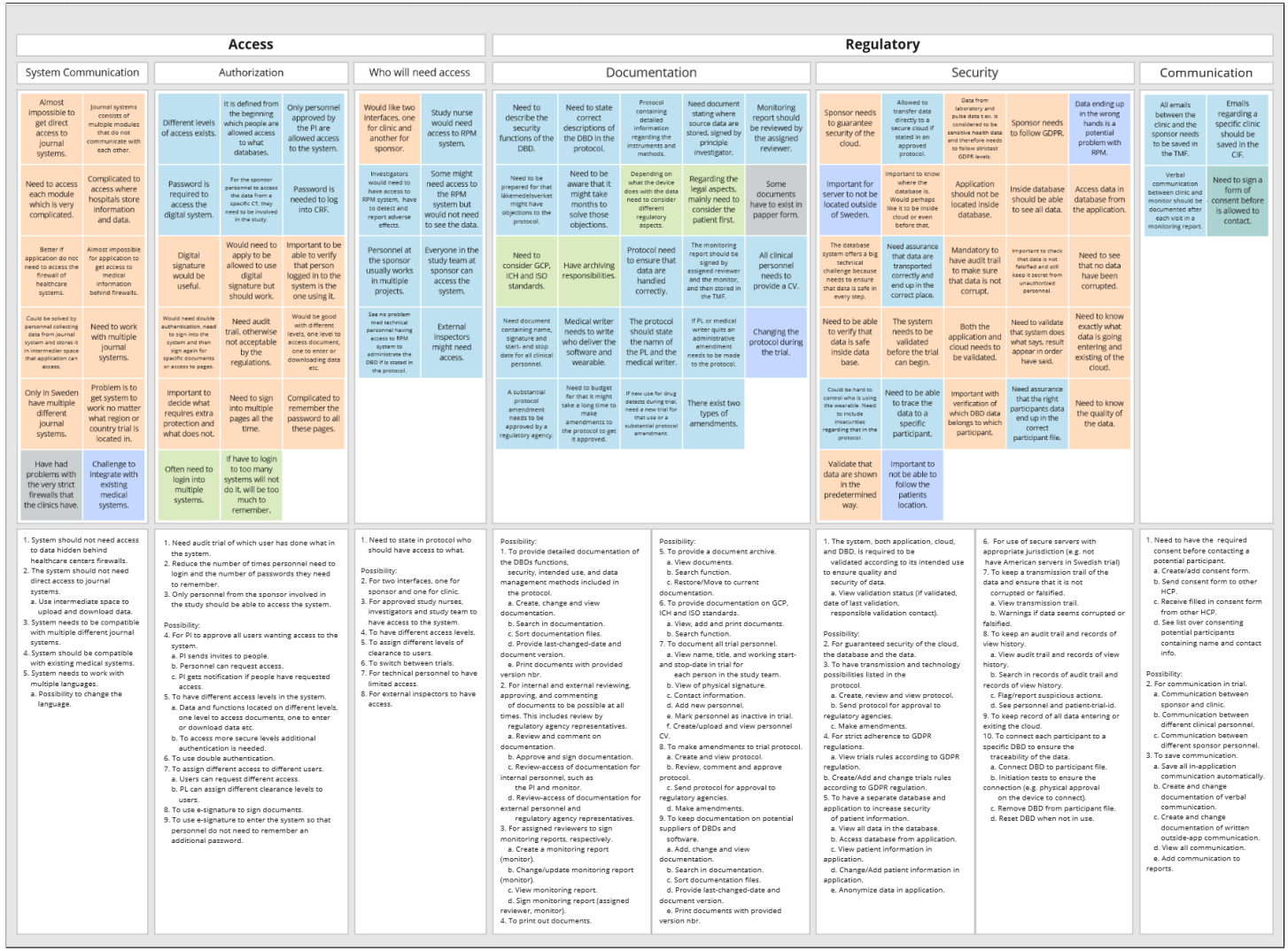


Figure 31: The resulting data gathered from the interviews and the associated needs, regarding system access and regulatory concerns.

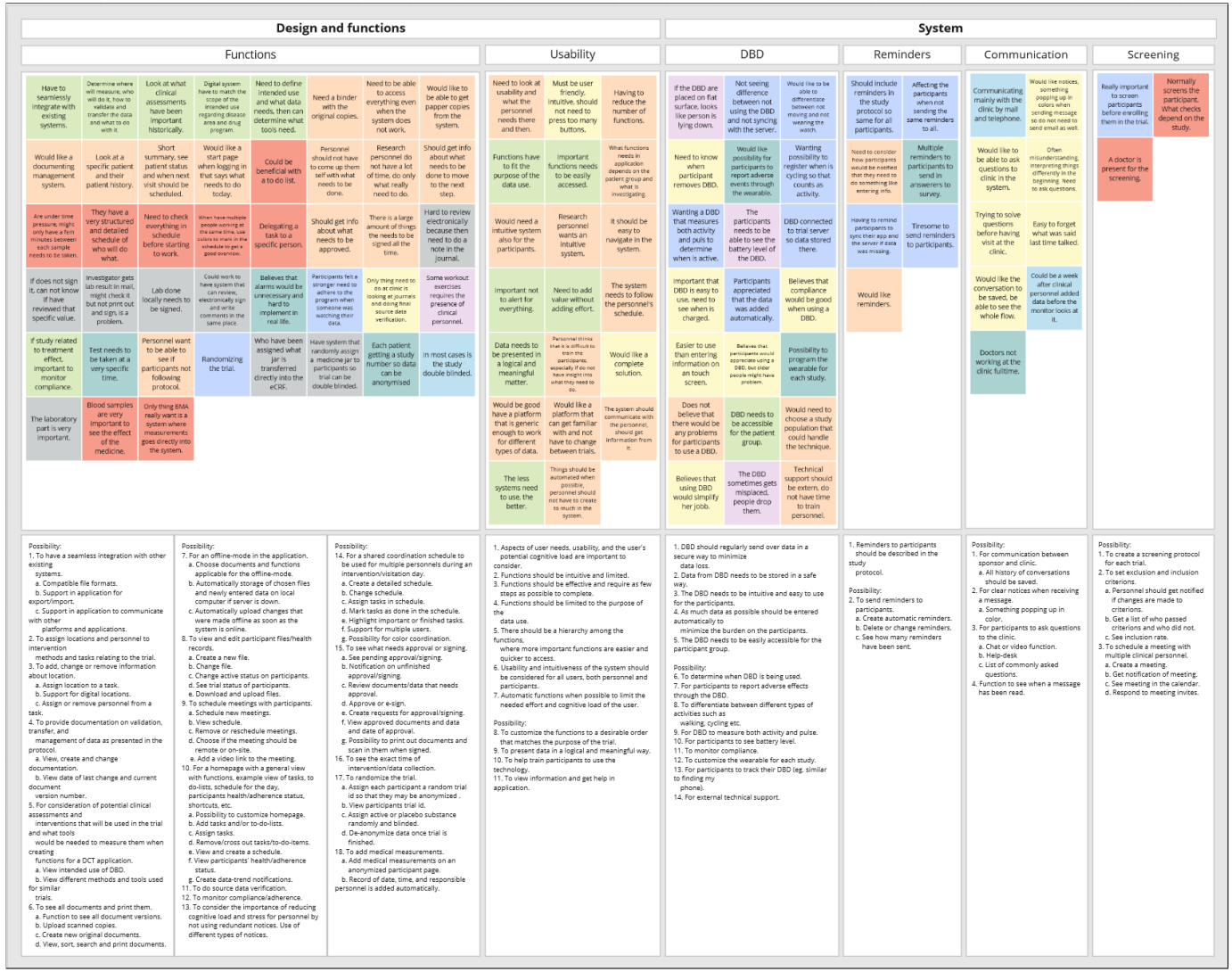


Figure 32: The resulting data gathered from the interviews and the associated needs, regarding system design and potential functions in an application.

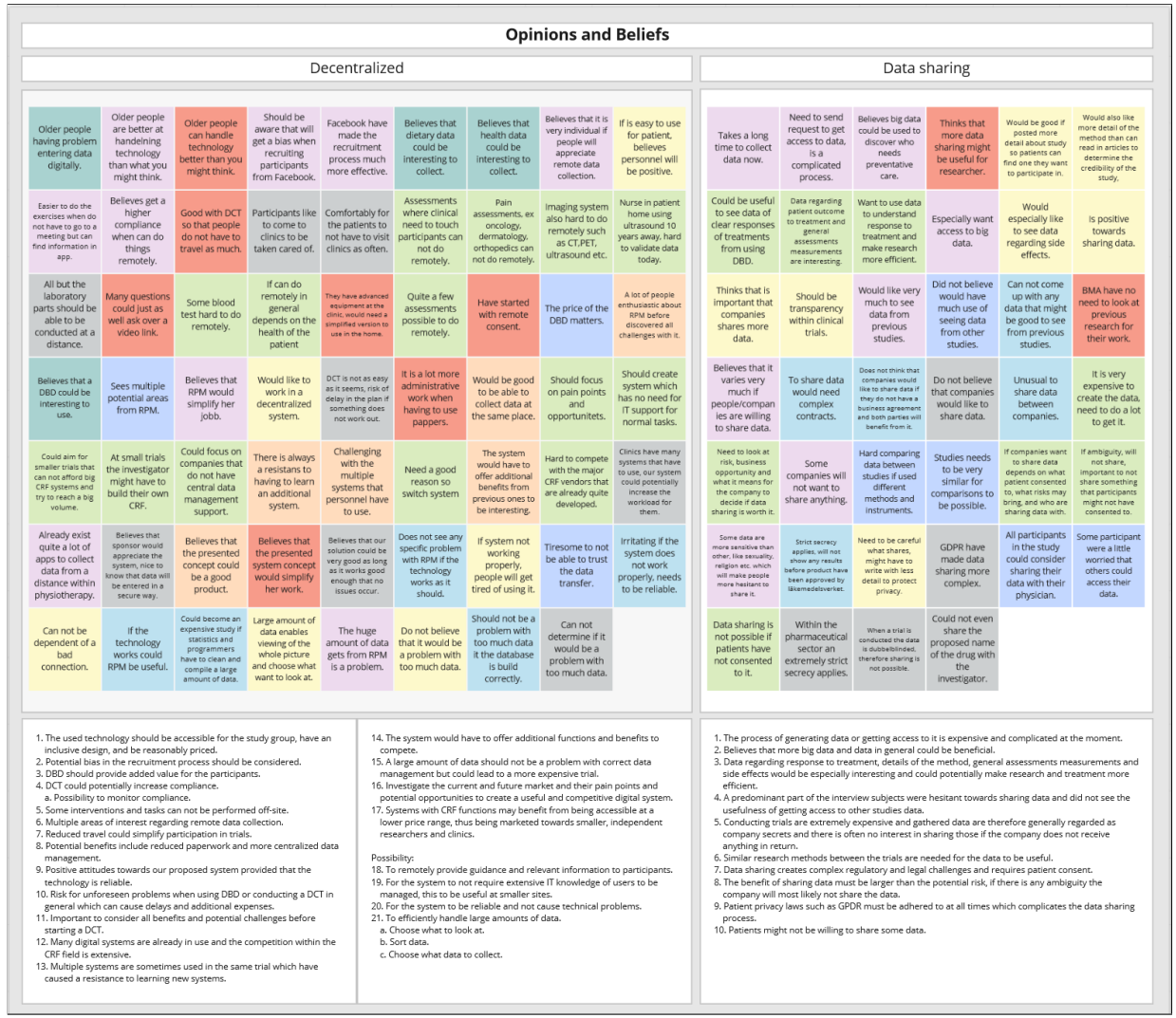


Figure 33: The resulting data gathered from the interviews and the associated needs, regarding the interviewees opinions and beliefs.

LUND
UNIVERSITY

Department of Biomedical Engineering
Faculty of Engineering LTH, Lund University
SE Lund, Sweden
www.lth.se