Implementing an IoT-based information system for the data recording in a phase I clinical center.

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List of Figures

1.1 Timeline of drug development. Source: Pharmaceutical Research and Manufacturers of America, Drug Discovery and Development: understanding the R&D Process, www.innovation.org 10
1.2 IoT for healthcare: a overall framework of embedding IOT technologies for personalised healthcare (Wan et al. 2018) 14

2.1 Description of the intial data workflow in a typical phase I clinical center 16

4.1 Schematic representation of the updated information system 27
4.2 Samples processing 28

5.1 Using a tablet at bedside. Source: youtube.com/watch?v=0X21BbY-7_c 35

8.1 Different team structures for change management. Source: Best Practice in Change Management, Prosci (2018) 48

List of Tables

5.1 Comparative table of selected barcode reader 32
5.2 Comparative table between cloud-based and on-premise servers. Pros of the two solutions 33

6.1 Cost of the solution, summary 41

8.1 Data Managers and Clinical Project Managers training sheet. 53
8.2 Nurses and Investigators training sheet. 54

Contents

I Introduction **7**

1 General background information **9**
1.1 Pharmaceutical R&D . . . 9
1.2 Clinical trials . . . 10
1.2.1 Roles and responsibilities of stakeholders in clinical trials . . . 11
1.3 Connected Devices and Internet Of Things . . . 12

II Development of the Research Question **15**

2 Organization of a Phase I Clinical Center **16**
2.1 Clinical procedures . . . 16
2.2 Data management . . . 18
2.3 Regulatory Environment . . . 18
2.4 Limitations of the current system . . . 19

3 Variables, Research Question and Method **21**
3.1 Variables . . . 21
3.1.1 Data Accuracy . . . 21
3.1.2 Time . . . 22
3.1.3 Cost . . . 22
3.1.4 Others . . . 22
3.2 Research Questions . . . 22
3.3 Method . . . 23
3.3.1 Study Case . . . 23
3.3.2 Variables . . . 23

III New Information system proposal **25**

4 General principle **26**

5 Technical description **29**
5.1 Measurement devices . . . 29
5.1.1 Type of data collected . . . 29
5.1.2 ECG . . . 30
5.1.3 Blood Pressure Monitors . . . 31

5.1.4 Label and wristband printers . . . 31
5.1.5 Barcode readers . . . 32
5.2 Server and database . . . 33
5.2.1 On-premise vs Cloud server comparison . . . 33
5.2.2 Database type . . . 34
5.3 Connectivity, languages and data exportation . . . 34
5.4 Computer infrastructure . . . 35
5.5 Clinical Trial Management System . . . 35

IV Expected results and consequences of the system implementation 37

6 Expected results 38
6.1 Impact on the clinical processes . . . 38
6.2 Data recording and samples handling . . . 38
6.3 Other data management . . . 39
6.4 Quality of data . . . 39
6.5 Time . . . 40
6.6 Expected Cost . . . 40
6.6.1 Expected cost of the solution . . . 40
6.6.2 Savings . . . 40

7 Opportunities 42
7.1 Patients Safety and fidelity . . . 42
7.2 Strategy . . . 42
7.3 Marketing . . . 43
7.4 Competitiveness and Positioning . . . 43

8 Challenges 45
8.1 Change Management . . . 45
8.1.1 Change Management Model . . . 45
8.1.2 Change analysis in the context of implementing a new information system 47
8.1.3 Sponsorship . . . 49
8.1.4 Role of managers . . . 49
8.1.5 Communication plan . . . 50
8.1.6 Managing resistances . . . 51
8.1.7 Training Plan . . . 52
8.2 General Data Protection Regulation . . . 52

V Conclusion 57

9 Conclusion 58
9.1 Conclusions . . . 58
9.2 Perspectives . . . 59

Part I

Introduction

Clinical trials as we have known are about to be completely disrupted. The rising running costs, the increasing conducting times and the commercial risks of failure are unsustainable. However, clinical studies constitute the most critical stage of a drug's development and are the result of years of research. Even though innovation is one of the keys in pharmaceutical development, incorporation of new technologies have bee slow. Recently, several disruptive technologies such as device connectivity and Internet of Things (Rosa et al., 2015), blockchain (Jahankhani et al., 2019), data analytics and artificial intelligence (Woo et al., 2019) have been cited as capable of transforming the clinical research landscape.

Connected devices and Internet of Things (IoT) have been used in care facilities for many years. An efficient information system based on this technology should be the first step to upgrade clinical centers and drive them into a progressive digitization. Data are still often measured manually, written on paper worksheets and then entered in an electronic capture report form (eCRF). This system, relying mainly on human intervention, contributes to errors and inaccuracies. Blood samples and investigational medicinal products (IMP) are often poorly tracked, leading to inversions and unusable results. IoT and connected devices offer the possibility to bypass these manual steps and processes by directly sending the collected data to a reliable electronic information system. As a result, the current system, widespread in clinical trials, will first be presented with its main issues, answering the question why clinical companies and units should consider making a change to novel technologies, using IoT and connected devices as a first step.

This work intends to present a simple and holistic, data management system that could be implemented in any clinical structure. The solution aims to simplify the workflow and increase data accuracy, in addition to decreasing processing times and costs. The general idea of the system will be presented, along with solutions that can be implemented to process clinical data more efficiently.

Then, the solution will be presented in more technical details, expending on practical information on how to implement the information system. References of the devices, types of technology, the data storage strategy and other technical aspects will be given.

After that, projections will be made on how the solution can address and improve the issues encountered in the current solution. Identified variables such as data accuracy, time, cost, company's image and competitiveness will therefore be discussed, in order to explore the viability of the proposed system regarding these factors.

Finally, the consequences of implementing such a system will be reviewed. Indeed, the solution can bring significant opportunities regarding both scientific and business-related matter: improvement of patient safety and monitoring, but also consequence in term of business strategy, marketing, competitiveness and positioning. As the proposed solution might be challenged by change management and compliance with GDPR, recommendations will be made to resolve the same.

Chapter 1

General background information

1.1 Pharmaceutical R&D

Developping new medicines is a critical challenge for any pharmaceutical company concerned with maintaining its growth, representing a huge investment. World's biggest companies spent from 18% to 31% of the budget on R&D in 2019, according to S&P Global Market Intelligence data (2019). Even though new treatment are getting more effective, development costs have increased exponentially; nowadays, 2,228 billions and 10 to 15 years would be necessary to market a new drug (Di Masi et al. 2016). In the following paragraphs, the main stages of drug development will be summarized.

Drug discovery and screening Thousands of chemically similar compounds are screened and tested in-vitro to select the best potential candidates. The selected molecules will advance to pre-clinical tests and for a very few of them, to clinical trials.

Pre-clinical development Pre-clinical studies give valuable information about the potential drug's behavior in human. They are essentially made on animals such as mouses and monkeys. The best candidates from pharmacodynamics, pharmacokinetics and toxicological studies are selected to be later tested on human, in clinical trials.

- Pharmacodynamics (PD): study of the biochemical, physiologic, and molecular effects of drugs on the body and involves receptor binding, postreceptor effects, and chemical interactions.
- Pharmacokinetics (PK): refers to the movement of drug into, through, and out of the body; the time course of its absorption, bioavailability, distribution, metabolism, and excretion.
- Toxicology: safety assessment of a compound.

Clinical trials The new treatments are tested on human, in different phases, as detailed in the next section.

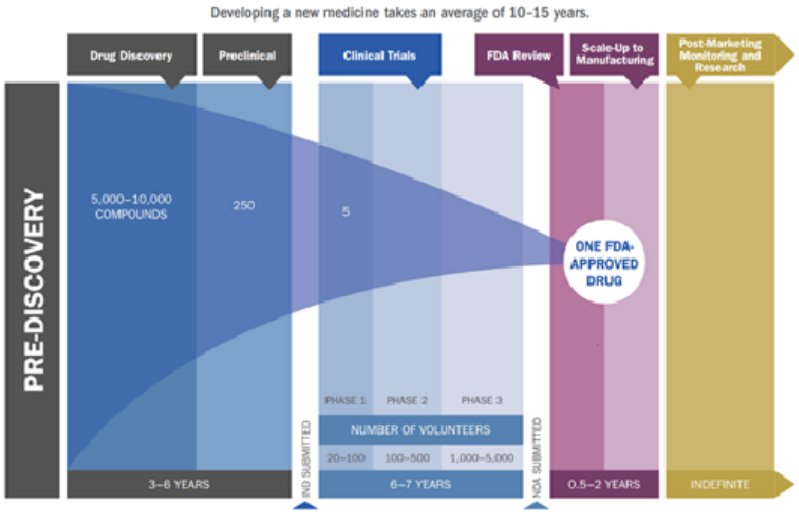

Figure 1.1: Timeline of drug development. Source: Pharmaceutical Research and Manufacturers of America, Drug Discovery and Development: understanding the R&D Process, www.innovation.org

1.2 Clinical trials

As shown in figure 1.1, clinical trials account for several years in drug development and are the result of many years of pre-clinical development. They are absolutely mandatory and allow the scientists to specify the drug's effect, efficacy and adverse events in human. They are 4 different phases in clinical trials:

- **Phase I** Also called "First-in-human" studies, they are conducted on healthy volunteers in authorized centers. These trials have 2 mains objectives. Firstly, ensure the safety results from pre-clinical studies are comparable to the ones obtained in human, so that the maximum tolerated dose can be determined. Secondly, measure the product's pharmacokinetics.
- **Phase II** It aims to determine the optimal dose in term of efficacy and tolerance on a limited amount of patients. Sometime, in order to accelerate the drug's progression to phase III, phases I and II can be conducted simultaneously.
- **Phase III** These are some larger-scale studies, involving thousands of patients in multiple countries, who represent the population for the disease the drug is intended for. The new drug is compared to existing treatments and sometimes a placebo. It is only after this phase that results can be presented to the competent authorities in order to get a marketing authorization.
- **Phase IV** Also called pharmacovigilance, they take place once the medicine has been marketed and intend to improve the knowledge on the treatment in real, non-clinical conditions.

Phase I studies, as a primary objective, generally aim to assess the safety and tolerability after a single or multiple escalating dose. As a secondary objective, they commonly aim to

determine pharmacokinetics (PK) parameters of the drug and its major metabolites, study the gender effect and sometimes, a few pharmacodynamics (PD) parameters. Subject are healthy volunteers. In this work, they will be called subjects, volunteers or patients, interchangeably. A clinical trial narrowly follows a written protocol, transmitted by the pharmaceutical company, called the Sponsor, in which all the study procedures are explained and detailed. In term of design, subjects are usually hospitalized during a certain period (going from 1 night to 14 or more), in which they are closely monitored. In a phase I study, multiple doses are tested on different groups of subjects. The first group receiving the lowest dose and the last one the highest dose. Doses are scheduled in the study protocol and the scheme is followed as long as the patients' safety is not at risk. The data generated by the safety assessments and the blood samples are transmitted to the Sponsor, who builds a clinical file that will later be submitted to the competent authorities.

1.2.1 Roles and responsibilities of stakeholders in clinical trials

For a better comprehension of this work, the main roles and stakeholders found in clinical trials, as outlined in the Good Clinical Practices (GCP) guidelines, should be briefly explained.

- **Sponsor**. It is the pharmaceutical company that is developing the new treatment and which decides to test the Investigational Product. It is the clinical center's customer. The Sponsor has the following responsibilities:
  - Organize the Data Monitoring.
  - QA and QC. The Sponsor is responsible for implementing and maintaining quality assurance and quality control systems to ensure that studies are conducted and documented in compliance with the protocol, GCP, and regulatory requirements.
  - Expertise to advise on clinical-related medical questions.
  - Designing the protocol.
  - Supervising the overall conduct of the study.
  - Managing and verifying the study data.
  - Ensuring the safety and rights of human participants.
  - Monitoring study performance.
  - Planning and conducting the statistical analysis.
  - Preparing study reports.
- **Investigator or delegates** (clinical center staff). The investigator or its designated delegates follow the Sponsor's protocol and takes care of the conduction of the trial, by recruiting, enrolling, collecting data and following the subjects' safety throughout the study. He has the following responsibilities:
  - Qualification and experience.
  - Care for participants.
  - Communication with the Review Board.

  - Compliance with the Protocol.
  - Correct use of the IMP.
  - Randomization and blinding.
  - Obtaining Informed Consent.
  - Ensuring the accuracy, completeness, legibility, and timeliness of all study data that are reported to the Sponsor.
  - Providing all required reports to the Sponsor and regulatory authorities.

- **Clinical Research Associate** (CRA). Designated by the Sponsor, he ensures compliance with the clinical trial protocol, checks clinical site activities, makes on-site visits, reviews case report forms (CRFs), and communicates with both the Sponsor and the unit's Clinical Project Manager.

- **Data Management Department**. It is in charge of generating the eCRF and collecting the data from the clinical center. They prepare the data for the Sponsor.

- Analysis Laboratories. They handle the blood samples sent by the clinical center. They analyze the safety, PK and PD parameters. The safety results are sent back to the Investigator, while the PK and PD results are transmitted to the Sponsor.

- **Trial subjects**. In phase I, the subjects are paid to enroll a clinical and be administered the IMP. To do so, they have to sign a Informed Consent. They are the core of the trial, without them, no data can be generated. They have to comply with the protocol criteria and their data are collected anonymously.

1.3 Connected Devices and Internet Of Things

After years of steady uptake, the Internet Of Things (IoT) seems ready to become mainstream in business. According to McKinsey (2019), the number of businesses that use the IoT has increased from 13 percent in 2014, to reach 25 percent in 2019. The number of IoT devices was projected to almost threefold increase from 2018 to 2023. Indeed, the IoT has the potential to benefit businesses, from operational improvement to digital transformation (Blavier, 2020).

Gubbi et al. defines the Internet of Things as the *interconnection of sensing and actuating devices providing the ability to share information across platforms through a unified framework, developing a common operating picture for enabling innovative applications. This is achieved by seamless ubiquitous sensing, data analytics and information representation with Cloud computing as the unifying framework* (2013). An IoT system is compromised of 4 components:

1. Sensors: collect data from the environment surrounding the device.

2. Connectivity: successively the data is sent to the cloud (Wifi, bluetooth,...)

3. Data processing: once the data are stored, it can be processed (eg. check if the data are within certain range).

4. User interface: gives the results to the user, allow the user to interact with the system.

IoT is also becoming more dominant in healthcare. A Gartner survey amongst enterprise IT managers in 2019 revealed that 11% of those surveyed worked in healthcare enterprises, and 86% of those respondents reported having an IoT architecture in place for most lines of business. The survey of organizations with annual revenues of more than 100 million USD also revealed that 79% of the healthcare providers were already using IoT in their production processes.

Wan et al. (2018) describes the general structure of IoT-enabled healthcare, as illustrated in figure 1.2. The sensing layer transforms physical measurements into digital data, which are sent through the network. This network layer enables the secure data transmission to data process units. The data processing module is then responsible for collecting the valuable information measured by the sensors. Based on the 3 first layers, an application service can be developed allowing to extract as much as possible from the data collected.

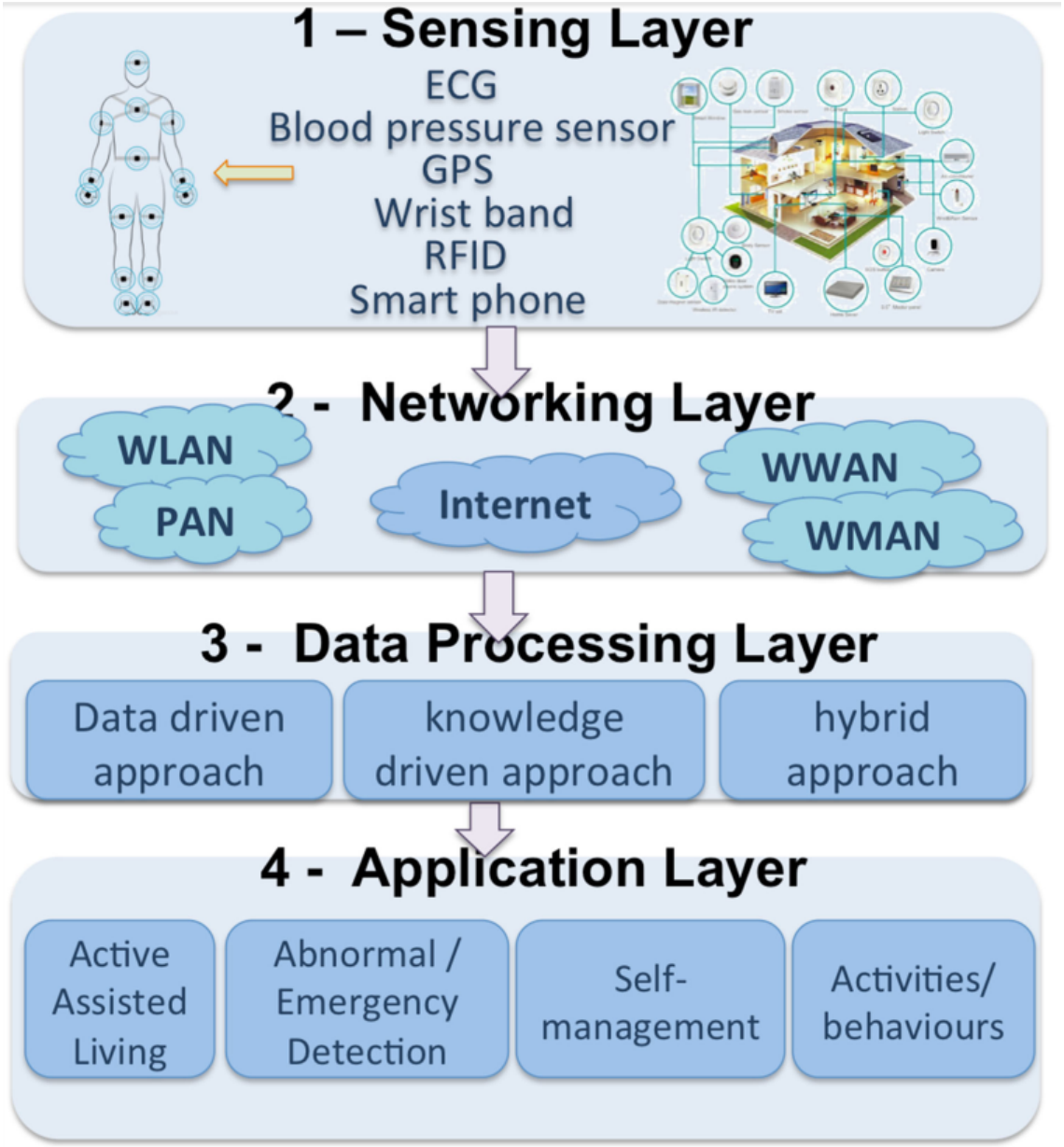

Figure 1.2: IoT for healthcare: a overall framework of embedding IOT technologies for personalised healthcare (Wan et al. 2018)

Part II

Development of the Research Question

Chapter 2

Organization of a Phase I Clinical Center

In this section, the current way of working in a typical clinical center will be described. It is important to explain how a clinical units actually works, in order to understand the main stakes of the data management in the specific sector of the clinical trials. Some regulatory aspects will also be discussed, as the the sector is tightly regulated by the federal and European authorities. The current information system mainly lies on the use of paper documents to collect the data. Data are written down by hand on the worksheets, which become the source documents.

2.1 Clinical procedures

Phase I clinical trials typically have some important processes and stages that can be found in most study designs. A summary of the data workflow can be found in figure 2.1 and will be explained in the following paragraphs.

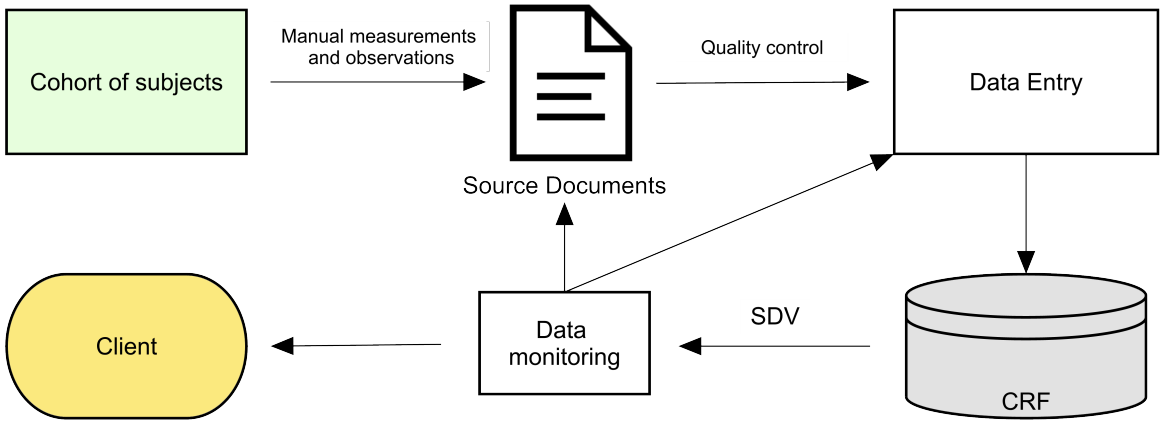

Figure 2.1: Description of the intial data workflow in a typical phase I clinical center

Screening Once the study has been officially launched, the first potential subjects can be screened in order to be potentially selected, in accordance with the protocol restrictions and requirements. Most of the time, a series of vital signs are measured, an hematology sample is

taken and the the investigator sees the subject in order to investigate about their medical history and their understanding of the study protocol. This screening procedure already creates a small set of data that will constitute a baseline for the ones collected later on during the study. Once the investigator has judged that the subject is eligible to be enrolled in the study, the collected data are shared with the Sponsor for a final approval. This means a Sponsor's representative has to come on site to verify the patients' data. Indeed, data are written into the patient's file, which cannot leave the premises.

Study enrollment Once the subject has been selected for the study, he's enrolled and can be administered the IMP on site. From this moment, a large volume of data are generated. In the current system, most of them are written down on worksheets by hand. These data can be for instance :

- Time of study drug administration + dose administered
- Time of PK samples
- Blood pressure + Heart rate
- ECG print-out
- Hematology print-out
- Adverse Events and Concomitant Medications
- etc.

Once a page is completed, a staff member, in charge of verifying the worksheets has been duly filled with the requested information, signs off with his initials and date, at the bottom of the page. This is an important step of quality control that can take the designated operator some time.

Clinical data processing Then, the page is sent to the Data Entry Officer, who will enter the data in the Sponsor's online platform, called the CRF (Case Report Form). This step allows the Sponsor to access the data, start working on the marketing approval and take strategic decisions based on them. In parallel, the investigator writes a "'Safety Report"' assessing the safety and tolerability of the dose tested. He therefore relies on the safety data recorded and needs to have an permanent access to them.

Laboratory procedures Once a blood sample is withdrawn for a PK or PD analysis, it is sent to the on-premise laboratory of the clinical center. It will be processed following the instructions from the clinical protocol. Often the samples are centrifuged to collect 3 aliquots of plasma or serum. These aliquots are sent by mail to the Sponsor's analysis lab. A complete listing of these sample should be sent with these aliquots, allowing to control all the samples have been properly collected and dispatched. Such a listing can be tedious to create manually on a spreadsheet, costing many hours of time and labor.

2.2 Data management

The medical data recorded in a clinical trial have two main purposes.

1. Monitoring the subject's safety. The clinical team has the responsibility to keep en eye on the patient well-being and react to any adverse event that could appear during the study. Protocols are designed to allow a sufficient surveillance of the subject's state. However, the Investigator can add as many examinations as he judges necessary to assess his patients' safety.

2. Collecting crucial data for the drug development. These raw data are transmitted to the Sponsor. They constitute the clinical center's core business.

Once collected, the data have to be entered in a Case Report Form (CRF), which is provided by the Sponsor or one of his independent partners. The good transcription of the source data into the CRF is extremely important and has to meet very high standards of quality, in order to meet the ICH E6 Good Clinical Practice's requirements of accuracy, completeness and verifiability from the source documents (ICH E6 R2 GCP, 2016). To avoid transcription errors, processes have been imagined by the industry. First, the clinical center can enter the source data twice, in parallel and by two different operators. Discrepancies between the two set of data can be easily cross-checked by a computer and transcription errors corrected. Then a external monitor is assigned to verify manually the source documents and the CRF. Both solutions can be extremely time-consuming and have a significant cost. The process of verifying the conformity of the CRF with the source data is called "Source Data Verification" (SDV). It ensures that the data collected are reliable and allow the reconstruction and evaluation of the trial. SDV up to 100% of all the data have been used to fulfill these requirements of quality.

2.3 Regulatory Environment

I n the past, medication for both adults and children were used without any, or insufficient prior testing for evidence concerning the efficacy and safety, leading to dramatic consequences. A clinical trial regulation was progressively set up, after having faced dire events in the past. The Nuremberg Code, a set of principles for human experimentation, was issued in 1947 as a result of the Nuremberg Trials and the human experimentation during World War II. Moreover, the Declaration of Geneva was written in 1948, as a declaration of the physicians to the humanitarian goals of medicine. The infamous Thalidomide (SOFTENON) crisis in the USA in 1960 also lead to updates of the regulation, by the Food and Drug Administration (FDA). Later, the declaration of Helsinki set the basis of current ethics principles in 1964. Finally, in 1996, the International Conference on Harmonization developed some extremely important guideline, still followed nowadays, the Good Clinical Practice (GCP). After that, the European Parliament issued the 2001/20/EC (Clinical Trials Directive) which was followed by an updated GCP directive in 2005. Both were later incorporated in the Clinical Trial Regulation on 2014. Finally, GDPR were issued in 2016, which will be discussed in a further section.

T he ICH E6 (R2) Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials that involve

the participation of human subject. The GCP are required by both the FDA and the European regulatory authorities (European Medical Agency, EMA). The GCP were developed to ensure that:

- Study subjects are protected
- Studies are based on sound science
- Study data have quality and are reliable
- Study procedures are undertaken and documented

These guidelines will be taken into consideration throughout this work, as they are now actually part of the European law.

T he Clinical Trial Regulation (CTR) (EU, 2014) contains laws covering every aspects of the clinical trials, from design, to conduction and follow-up. Some articles from the CTR will be especially relevant in the context of this work:

- The Art 3 concerns the right, safety, dignity and well-being of the subjects. A trial and its processes should be designed in order to generate reliable and robust data.
- The Art 29 emphasizes on the importance of Informed Consent Form, as detailed later.
- The Art 47, as explained earlier in this section specify the study must comply with the Study Protocol and the GCP.
- The Art 48 stipulates that the Sponsor should monitor the generated data and the conduct of the trial.
- The Art 56 details the recording, processing, handling and storage of clinical information.
- The Art 93 concerns the data protection and should be linked with the current GDPR regulation.

Not only the proposed solution must comply with the GCP and the CTR requirements, it should also be designed in a manner that upholds it to a higher degree of compliance.

2.4 Limitations of the current system

Taking into account the previous elements, some outstanding issues and limitations can be described in the data management, and overall, in the current manner of working.

Quality Due to an significant human impact in the way data are processed throughout the study, error are inevitable. However, the pharmaceutical R&D requires a close to perfect data accuracy and the current system seems imperfect regarding the quality of the data. Additional processes, such as "'crossed-data entry"' and source data verification, have allowed the clinical trials to reach higher standards in term of data accuracy, however the system is not perfect and needs to be improved. Indeed, Andersen et al. (2015) found out that the SDV, even performed at 100%, does not allow to reach a 0% of error rate and the use of complete SDV only offers a marginal 0.26% error rate reduction. Inversions in samples identification or treatments attribution lead to dramatic consequence in term of data accuracy. At best, these kind of inversions can be detected when analyzing the samples, creating gaps in the results; if not, the information will be definitely biased. Beside damaging the collected data, treatment inversions can have dangerous consequences for the subject's well-being.

Time The current data flow is slow. From the measurement to the actual processing of the data, it can take weeks to months. Ensuring the accuracy of the collected data takes time too. Pregelj et al.(2016) mentions that studies in 2009 had an average duration of 4 years, phase I accounting for 12 to 15 months alone. That study confirms the study lead by the *Tuft center for the study of drug development*, which mentions that the average total development and approval time for drugs in the US was around 7 years and 5 months, between 2007 and 2011.

Cost In order to minimize the impact of the 2 above issues, some new processes must be set. This consequently rises costs : increased working hours and a more complex verifications system. Quality control steps and handling of source documents keep a nurse busy for at least 1 hour a day. Manual entry needs a full-time Clinical Trial Assistant (CTA) or Data Entry Officer by study, costing the company 4219 EUR per month. At last, monitoring can take several days for a cohort of 8 to 12 subjects and can be very costly. Of course, a monitoring generates as well even more work for the CTA, as detected discrepancies and errors need to be investigated and corrected. For instance, Sertkaya et al. (2016) report that SDV can represent 15% of the study total cost in phase I. The delayed availability of the data also has an opportunity cost for both the center and the Sponsor.

Company's image, positioning and competitiveness The described system may seem archaic in a world more and more lead by technology. Hospital units have increasingly used new technologies and digitalization over this last few years. For example, electronic health record have overcome paper files and connected monitoring system have be used for many years in the intensive care units. The system used in clinical trials, compared to other sectors, seems totally out-dated and might become obsolete in a near future. This key factors should therefore be re-considered. Sticking to obsolete ways of working could hurt the clinical company's image an its positioning towards its competitors.

Chapter 3

Variables, Research Question and Method

3.1 Variables

The variables studied in this work will allow to assess the impact of the proposed information system. Some current limitations were described and are clearly linked to different variables and management parameters and indicators.

3.1.1 Data Accuracy

The data accuracy can be described as the number or errors entered in the CRF, compared to the total number of items to be entered in the CRF. Dictionary.com defines the term error as *the difference between the observed or approximately determined value and the true value of a quantity*. In this specific case, the true value is the true patient's condition. Different kind of errors can be identified in four categories, and for each of these categories an error rate can be calculated:

1. Measurement errors, due to the failure of a measurement device or an human mistake.

$$ER_{measurement} = \frac{\text{Number of measurement errors}}{\text{Number of total measurements}} * 100$$

2. Judgment errors, misinterpretation of the more subjective data;

$$ER_{judgment} = \frac{\text{Number of judgement errors}}{\text{Number of total data to be interpreted}} * 100$$

3. Error of transcription into the source worksheet, by the operator;

$$ER_{source\_transcription} = \frac{\text{Number of source transcription errors}}{\text{Number of total data collected}} * 100$$

4. Error of transcription from the source, into the CRF, by the data entry officer (Data entry errors).

$$ER_{crf\_transcription} = \frac{\text{Number of CRF transcription errors}}{\text{Number of total data collected}} * 100$$

These errors could also be classified in categories regarding the kind of data they refer to (time-related data, blood pressure data, ECG data, etc.), when relevant.

3.1.2 Time

The time needed for a task, an event or a whole project will be evaluated using real data. It can be measured in hours or days. A working day will be equivalent to 7.6 hours (or 7 hours and 36 minutes.) When talking about employees working time, the term Full-time Equivalent (FTE) can also be used. As defined by the US Goverment Accountability Office, it represents the number of total hours worked divided by the maximum number of compensable hours in a full-time schedule. For this work, we'll take consider a full-time schedule to be 38 hours per week, working all year long except during the legal holidays (4 weeks or 20 days in Belgium).

3.1.3 Cost

The cost in clinical trials can be of two different types : cost of the material and cost of the workforce. The costs will be evaluated in Euros (Eur) and material coming from countries using a different currency will be converted using the following rates: 1 Dollar = 0.89 Euros.

3.1.4 Others

Other parameters, such as Company's image or competitivity won't be assessed quantitatively. These are most subjective parameters and will be analyzed in a more qualitative way.

3.2 Research Questions

The previous section gave a general background allowing to specifically point out the different research questions and objectives of this work.

1. Proposal of a new information system, allowing to measure data from the patients participating to the trial. This new data management system should address the limitations discussed previously and should be though-out as a viable long term solution for any phase I clinical trial center.

2. Assessing and following the impact, either positive or negative, on the identified issues and variables.

3. Discussing some other consequences of the implementation of a new data management system, going over potential opportunities.

4. Giving recommendation on the way to implement the solution, addressing the challenges in term of change management and compliance with the GDPR.

3.3 Method

3.3.1 Study Case

To illustrate the impact on the variables, a small theoretical study case study has been be used as an example. It is based on standards phase I study designs, but is voluntarily simplified in term of study length and number of volunteers included. The following example is a 2-week extract of a typical multiple ascending dose, as commonly found in phase I studies. One cohort of 8 subjects is included for a hospitalization. The flowchart detailing the study can be found in the Annex 2.

An typical organization of a clinical unit was used, but should be adapted to any situation. The work intends to be a base for the implementation of the solution, but each organization should adapt it to its own specific processes, size, staff members, financial possibilities and ambitions.

3.3.2 Variables

S ome variables were defined in the previous section. However, their measurement could only be made once the system has been implemented. Their measurement should therefore be part of the reinforcement part of the change. A this stage, only assumptions and predictions can be made.

Devices The prices found for the presented devices are only indicative, as they come from different medical device websites in the USA or Europe, or the constructor themselves. Many of the measurement devices can be added additional equipments, such as trolleys. In order to more accurately compare the prices of these devices, a minimum equipment, similar in each device, was selected. For the definitive price, the brands' sell representative should be contacted, so they can adapt the offer to the center's size. In this work however, I will consider the indicative price found as definitive, so they can be compared.

Labor cost Taking into account that the average age of Belgian workers was 41,4 in 2018 (source: acerta) and that, at this age, a worker could have worked for 20 years, an average seniority of 20 years will be taken for the calculations. The salary scale used will be the "Commission paritaire 330", which is the one used in private hospitals. If an official salary scale cannot be found, an arbitrary estimation based on my personal experience and the website *www.glassdoor.com* will be used. To the gross salary, an additional cost of 37,52% for the belgian social security (ONSS) should be taken into consideration. Thus, the following cost rates will be used throughout this work:

- Nurse: 4520,28 Eur/month or 27,45 Eur/h.
- CTA = secretary: 4219Eur/month or 25,62 Eur/h.
- CRA 4755,44 Eur/month or 28,88Eur/h (estimated with glassdoor.be).

Part III

New Information system proposal

Chapter 4

General principle

The general idea of the updated information system is to reduce human intervention in the flow of data. Human intervention is still needed for orchestrating the measurement and verify the study protocol is well followed by the patients, but can be avoided for the data transcription, transfer and, to a certain extent, their analysis. Technology can also assist the operators for the data identification by tracking the samples and the medications, matching the sample with the patient using barcodes. Data were categorized into 3 subgroups regarding the type of processing they need, as shown in figure 4.1.

- Safety Data. These data do not need human intervention beside the measurement itself. The value are recorded and can directly be sent to the database.
- Written Assessments. These data are generated after human interpretation by the medical staff. They need a data entry interface to be added and typed into the study database.
- PK and PD samples. These are blood samples from the patients and need a additional processing by the site laboratory before being sent to the sponsor or his partners. The time of sampling and their identification should be directly recorded into the system.

Once the data are collected from the patients, they are sent to a database hosted on a server, using the implemented network. Once entered in the server's database, the data can be accessed by a user interface with specific access for the site staff or outside stakeholders if needed. Data are automatically sent to the client's eCRF, allowing them to quickly access the collected data. The user interface should also allow the exportation of data on other support (PDF, spreadsheets,...) and should allow the printing of certain documents. The user interface could also send automatic alert to the operator after having processed the recorded data, in order to assist him in detecting abnormal values. Written assessments are entered into the database by the operator, using the user interface and as soon as the observation is made. This information system is summarized in figure 4.1 in a more visual way.

Regarding the tracking of the blood samples, the idea is to use a barcode identification system, allowing to pair subjects' samples with their right owner. As seen in figure 4.2, an identification barcode must be generated on a wristband which will be sealed around the patient's wrist. In parallel, tubes are identified with a unique barcode, labeled before the study starts. When a nurse has to withdraws some blood from the volunteer, she scans the subject's wristband and

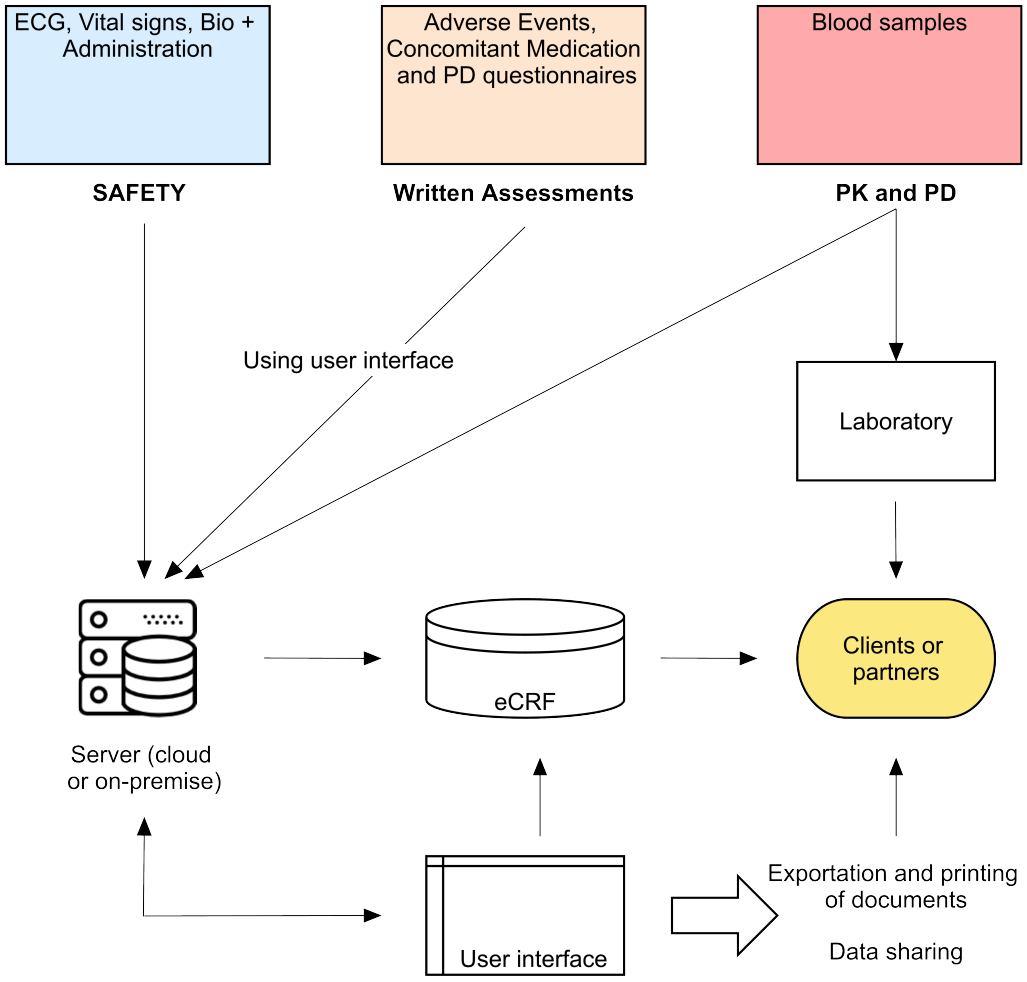

Figure 4.1: Schematic representation of the updated information system

then scans the tube, allowing the system to match both identification numbers and accurately track the sample. The system can record the exact time of sampling and send it into the database. Then the identified tube is sent to the site's laboratory for further treatments. There, technicians extract serum or plasma from the samples and transfer it to smaller tubes (aliquots, often 3 per sample). These smaller tubes will have to be correctly labeled with unique barcodes, so that the lab technician can scan both tubes and easily track the patient's sample from initial tube to the aliquot tubes, avoiding the risk of misidentification. After that, the properly identified aliquot tubes can be stored and then sent to the client or his partners.

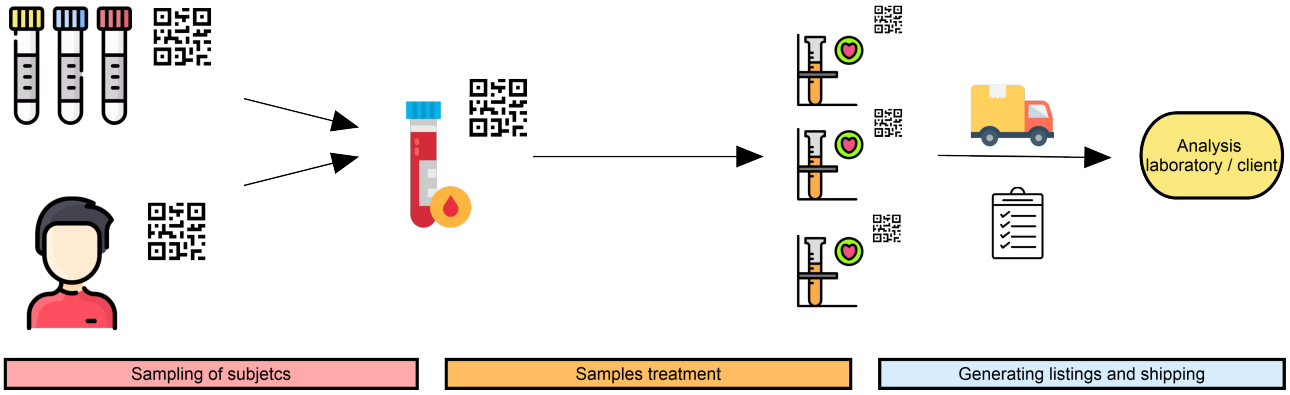

Figure 4.2: Samples processing

The new system could allow to properly track the administration of the investigational product as well. When prepared by the designated pharmacist, IMP should be labeled with a unique identification barcode containing at least the following information : type of treatment, dose and more importantly, the patient's identification. When administering the IMP to the subjects, the nurse or doctor will scan the subject's wristband and the IMP to verify the drug goes to the right subject. Of course, labeling should still be compliant with the GCP guidelines by being readable by the operators and containing in written letters all the necessary information to allow a human control.

Chapter 5

Technical description

5.1 Measurement devices

5.1.1 Type of data collected

The type and the frequency of the data collected in clinical trials can vary quite largely from studies to studies. However, all phase I trials have at least two common objectives. Firstly, assessing the safety and tolerance of the product and secondly, measuring his pharmacokinetics by taking multiple blood samples after administration. This means most of the clinical trials require some basic vital signs measurements, ECG measurements, hematology and a precise transcription of the possible adverse events and concomitant medications. These safety data are therefore supplemented by frequent blood samples, intending to investigate the evolution of the concentration in the blood of the IMP and its main metabolites.

For all these data, an accurate tracking of the subject identification, time and date has to be recorded. Ideally, the identification should follow the existing hospitals standards by using barcodes on the subjects' wrist. The devices that are compatible with this technology will consequently be favored. The following parameters are the most common raw data required in phase I clinical trials.

- Subject's identification;
- Time and date of the measurement or the sample;
- Tracking of the IMP administration: type of treatment, date and time;
- The concentration of the IMP and his metabolites in blood (PK);
- The concentration of the IMP and his metabolites in urine (ūrinalysis);
- Electrocardiogram trace (ECG);
- Heart Rate (HR);
- Standing and lying Blood Pressure (BP);
- Evolution of a series of blood markers, for the safety purpose;

- Study of the biochemical and physiologic effects of drugs (PD);
- Continuous monitoring of Adverse Events and Concomitant Medication;

These data can be measured, analyzed or observed and will be detailed in the following sections. A specific device or method of processing will be proposed as well.

5.1.2 ECG

An ECG device allows to monitor the cardiac condition of the subject. Several measurements are taken throughout the study in order to detect a significant change in the patient's cardiac trace compared to his own baseline. This measurement requires a staff member to correctly set up the electrodes and start the measurement.

Selection criteria

When analyzing the different solutions on the market, the following basic eligibility criteria were applied, in order to be compatible with the system and make a pre-selection:

- Professional precision and accuracy, meeting of the standards of the industry and the authorities' recommendations. As a consequence, only 12-lead ECG were considered.
- Possibilities of connectivity to the system (LAN, WIFI, bluetooth, etc.).
- Possibilities of an extensive data exportation in a commonly used language (XML, JSON, etc.).
- Sufficient product information (detailed brochure, available technical characteristics).

Initially, wearable devices were also considered. However, the eligibility criteria "Wearable and mobile" had to be removed because none of these devices could meet the requirement of precision and accuracy. So devices such as the Apple Watch or the AliveCor's KardiaMobile 6L-ECG had unfortunately to be removed from the selection, despite their high potential. The resulting ECG devices were then compared using the following parameters : type of connectivity, language used in data exportation, price, possibility to connect a barcode scanner and other relevant technical specification.The list of the considered devices can be found in Annex 1.

Discussion and recommendations

Many ECG are available at a price range varying from 3000 to 5400 Eur. Most of the ECG found had WLAN and LAN connectivity, could be connected to a barcode reader and had the same level of professional accuracy. The main differences mainly lied in the design and the interface. The *Welch Allyn ELI 250c* appeared to be the cheapest of all, however, the user interface is very simple and needs to be connected to a computer. This solution could be the best in the case the clinical site have already some computers that could be used for that purpose, but does not seem to be the most convenient. The *Phillips PageWritter TC30*, at a similar price as the *GE MAC 2000* or *Schiller AT-10* had a computer interface and a barcode reader included and seemed to be a very good choice too. Overall, among the selected ECG in the Annex 1, each of them could very well suit the system and could be selected according to preferences and price conditions offered by the brands' sale representative.

5.1.3 Blood Pressure Monitors

The Patients' blood pressure is tightly monitored during the study, several times a day. Most of the protocol designs require standing and lying measurements, which means an operator has to make sure the two measurements are correctly done in these two positions.

Selection criteria

When analyzing the different solutions on the market, the following basic eligibility criteria were applied, in order to be compatible with the system and make a pre-selection:

- Professional precision and accuracy.
- Possibilities of connectivity to the system (LAN, WIFI, bluetooth, etc.).
- Possibilities of an extensive data exportation in a commonly used language.
- Sufficient product information (detailed brochure, available technical characteristics).

After extended research, it appeared that connectable blood pressure monitors are not common, unless for the ones that are used in the intensive cares, which seem excessive for the clinical trial use. As a result, only a few names came out of the research, matching the aboved mentioned criteria. The three resulting BP monitors are presented in the Annex 1.

Discussion and recommendations

Even if the two Rossmax Devices did meet the basic requirements, their connectivity demands additional human intervention by having to connect the device to a computer and manually transfer the information. Despite their cheap price, they are not so convenient and only seem to offer a part of the solution in term of global connectivity. Consequently, the *Welch Allyn PROBP 3400* seems to be alone in his category. As described in the manufacturer's brochure, it offers some very convenient characteristics such as :

- Handy pocket-format and possibilities to be carried attached to a trolley.
- Quick measurements, only 15 seconds.
- Compatible with many armbands.
- On battery, 100 measurements per charge.
- Fully connectable, using bluetooth.

5.1.4 Label and wristband printers

Investing in a label printer is part of the subjects' identification system. Because the device is not as crucial as the measurement system, only a few suggestions from the main constructors will be given.

Model	Price	Specifications
Honeywell Xenon 1952h	750 Eur	Wi-Fi
Zebra Symbol CS4070-HC Companion Scanner	715 Eur	Bluetooth 2.1, pocket format
Zebra DS8100-HC	720 Eur	Bluetooth, Wi-Fi
Datalogic RIDA DBT6400	600 Eur	Compact Size, can be sold without the charger, Bluetooth

Table 5.1: Comparative table of selected barcode reader

Selection Criteria

When analyzing the different available printers, only the criterion of connectivity was considered. Many office printers are available and have similar characteristics. The Dymo brand was often brought out by specialized websites and was used to represent the small-sized and more office-oriented type of printer. Other printer brands offered printers for a more specific laboratory use or a more industrial scale. The selection used for the comparison is displayed in table **??**.

Discussion and recommendations

The *Brother TD-2130NHC*, despite being quite expensive, has unique advantages that could not be found in other printers : an included label creation software and the possibility to print wristband as well. Added to the fact that the printing speed is more than decent, that it is compatible with several label formats and it is small and mobile, this printer seemed versatile and would perfectly suit the system.

5.1.5 Barcode readers

Selection Criteria

Only barcode readers for healthcare purpose were considered, so that IV bags, foil med-packs and other competitive scanners usually struggle with, could be easily scanned. These devices are also equipped with disinfectant ready and antimicrobial enclosures which makes it ideal for bedside point-of-care applications. 3 main brands of barcode reader maker were analyzed. Only wireless scanners were selected and the 4 outstanding readers are shown in table 5.1.

Discussion and recommendations

The different brands analyzed for this work offered approximately the same characteristics for a price range from 600 Eur to 750 Eur. The main decision criteria should be the design and handling as the prices are quite similar. However, the *Datalogic RIDA DBT6400* seemed to offer the same kind of specifications for a slightly lower price and could therefore be favored amongst the others.

5.2 Server and database

5.2.1 On-premise vs Cloud server comparison

A server provides functionality for other programs or devices, called "clients" and can store the data. The question that should be addressed first is what kind of server should be used. The two main solutions are a cloud storage service or an on-premise server. They should be compared in order to select the best solution for the storage of these valuable clinical data. On-premise server are physically located on site. The machine has to be stored in a safe environment, set up and managed on site too. A cloud-based server is a virtual server hosted through cloud computing. Cloud computing often provides web-based software and computing resources on demand, giving access only to the resources the user needs. Both solution have their advantages and characteristics, summarized in table 5.2.

	On-premise	Cloud
Cost	- Lower total cost for a long-term solution	- Monthly or annual fees - Does not requires any upfront investment - No hidden costs
Data accessibility and security	- Confidential data stay on-site and are not share to a third party - Physical control on the data - Not reliant on an internet connection	- No potential hardware failures - Reliable back-ups - Data security (better expertise), vendor's responsibility - Easy remote accessibility to the data on a broad range of devices - Data privacy experts
Integration, flexibility	- Better flexibility, integration and customization	- No software, hardware or upgrades - Does not require and IT-support on site, easy maintenance - "Infinite" scalability

Table 5.2: Comparative table between cloud-based and on-premise servers. Pros of the two solutions

Even though both solution are technically feasible and would suit the information system, cloud computing seems to have the edge over an on-premise solution. From a price point of view, considering the investment that the whole information system would represent, a "pay-as-you-go" service could allow to slightly alleviate the total upfront costs of the solution. Data security and integrity is crucial in clinical trials and must be taken very seriously. Not only the patients' private data must be protected, but also the clinical data constitute confidential and critical data for the clients. The main cloud service providers have the proper expertise to keep these data away from being lost or stolen. Cloud-based structures are not subject to hardware failures and allow to constantly back up data. Moreover, a cloud-based structure would open new possibilities in term of study design. Data could be recorded and accessed from anywhere, allowing the staff member to easily work from home for example, the partners to easily access certain types of data when authorized and the patients to participate to the study from home,

when possible. In term of integration and flexibility, everything would be easier to implement. With cloud-based services come infrastructures (IaaS), platforms (PaaS), software (SaaS) and even analytics (AaaS) if needed. It offers a large flexibility and scalability. It has also to be noted that a cloud solution does not require any IT support on site and this kind of service is included in the renting price. Finally, from a perspectives point of view, when wearable will be ready for accurate data measurements in clinical trials, a fully operational cloud system seems to constitute a way better base for their implementation.

The three main generic IoT cloud platforms are Amazon Web Service (AWS), Microsoft Azure and Google Cloud, all three offering similar solutions. However, specific knowledge is needed to develop on these platforms and an IT specialist would be absolutely necessary to build the solution. An easier alternative would be using a specific cloud-based clinical trial data management service, probably more expensive but easier to install and use. These alternative will be discussed in a further section.

5.2.2 Database type

In term of database, two approaches can be identified: the relational approach (SQL) and and the non-rational approach (noSQL) (Ali et al 2019, Birgen 2014, Vanroose and Thillo 2014). To select the database that would suit the system, one must take a deeper look at the type of data generated. Clinical trials generates very structured data that can fit table based database and they are quite simple by nature. Their integrity and validity is paramount. In this proposed system, measurement are taken at specific time points and the generated data do not need to be handled continuously and in real-time. Even if noSQL could be privileged in complex IoT system when tons of data must be stored simultaneously, a standard SQL data base should be sufficient for this kind of simpler infrastructure. Bell (2016) describes in details how to implement a mySQL database in an IoT system and corroborates the choice of using a traditional SQL database. In a cloud solution, the database would be included and managed by the cloud service supplier.

5.3 Connectivity, languages and data exportation

The devices must be connected to the network and communicate through it, sending queries to the server and the database. ECG's are connected to the network by LAN or WLAN. Once the measurements have been made, the data can be exported using a XML file. The XML data are stored into the database by being converted into the mySQL database. The BP pressure monitor connects via bluetooth to a computer and use XLM for the exportation. The Brother TD-2130NHC label printer could be simply connected using USB if the label a printed in an office. However, Bluetooth and WIFI could be used if a tablet was used at the patient's bedside for example. The selected barcode scanner connects through bluetooth, other with a similar price connect through Wi-Fi. Both solution could be used, again, depending on the chosen infrastructure.

5.4 Computer infrastructure

Most of the devices needs a computer interface to fully benefit from their connectivity. A computer with all the compatible software and the user interface installed on it would be used to export the data stored on the BP monitors and the ECG, depending on their specification. A tablet could be used for bedside care, observation of Adverse Event, PD questionaires and observations, etc. The user interface would therefore also be available on the tablet so the printer(s) and barcode scanners can be connected using bluetooth, as illustrated in figure 5.1.

Figure 5.1: Using a tablet at bedside. Source: youtube.com/watch?v=0X21BbY-7_c

5.5 Clinical Trial Management System

At last, a final component is absolutely essential to complete the solution: a all-rounder platform, capable of connecting the devices, the database and the users. In clinical trials, such a platform is called a Clinical Trial Management System (CTMS) or Electronic Data Capture depending on the included functionality. In this case, the EDC becomes the eCRF and vice versa. To be compatible with the presented solution, the platform or software should have the following characteristics :

- Communication with the medical devices,
- User interface accessible on computer or mobile, by the authorized staff members,
- Communication with the cloud database,

- Manual data entry and editing,
- Internal and external monitoring possibilities,
- Forms customization, in order to adapt to the study design.
- Additionally, some data analysis capacities would be a plus, at least for example, to generate alerts when data seem odd or out-of-range.

Direct entry into the CRF is allowed per GCP, but it must be mentioned in the study protocol. Indeed, even if the solution is based on the recording of data from the measurement devices, data like Adverse Events, PD questionnaires or observations will still be directly entered by the staff, using a computer or a mobile interface,without the intermediate of a paper source.

Many EDC solutions exist on the market, relying on a cloud database and a standard Software as a Service (Saas) solution when it comes to pricing. The core EDC price is based on the number of studies and their duration. Taking into consideration the anonymous price proposition I gathered from some of them, such a service can cost up to 1700 Eur per month, including as many sites, users, forms, subjects, data as required.

Part IV

Expected results and consequences of the system implementation

Chapter 6

Expected results

6.1 Impact on the clinical processes

Before the inclusion of the subjects, all the study material must be prepared and labeled. In term of work quantity for the staff, the new solution would approximately take the same time as before. Printing and sticking labels on the blood tubes and the IMP's is something that was done before, o nly the type of label and information they contain has changed. Wristband have to be printed as well. Previous wristband was created using standard paper wristband and by sticking a label on it, which took slightly more time to make.

6.2 Data recording and samples handling

The volunteers are included on D-2, a physical examination is performed by the Investigator, as well as a Drug and Alcohol test. The subjects are identified and will have to wear barcode identification wristbands for the whole hospitalization duration. The investigator can easily enter his findings in the CTMS. Then The D1 is the first administration day. Many data are collected on this day, in term of safety, PK and PD. Same things for the D7 and D14. These 3 days, called "PK days", request a lot of labor to collect all the data. On D15 to D18 subject are only monitored while the concentration of the study drug in their body is decreasing.

Blood samples The same nurse withdraw blood, filling multiples tube, one subject after the others. So she scans the patient, scans the empty tubes and start to fill them. The scanning time is recorded by the system. These tube will be used for different purposes: PK, PD and safety. Biochemistry and hematology samples (safety) are sent to an external analysis laboratory. It means the identification system must also comply with their own way of working. The new information system allow to use a fully electronic identification, provided that the analysis laboratory is able to use a similar solution. Samples should be sent as soon as possible, clearly identified. Both structures' system could be very well compatible and communicate with each other, but such a compatibility should be determined and implemented on a case-by-case basis and could not be anticipated. If not compatible, the old identification should be of course maintained. The PK and PD samples are sent to the lab for a potential post-treatment. As they are identified by a barcode, the lab technician scan the filled tube so it is well registered and properly identified.

ECG The selected device allows the nurse to identify the patient by scanning the subject before recording the ECG. She places the electrodes, launch the recording and move on to the next subject. Once all the subjects have been recorded at a specific time point and once the Investigator approved them, she can export the data to the system. There is also no point anymore to print the report for archiving purpose, everything will be stored in the database.

Vital signs The new device not only allows to make the required measurements in 15 seconds, but also save the results in its memory. The nurse can go from subjects to subjects more quickly, selecting him into the device and exporting the timed data to the system.

Urine sample for PK The subject's urine is collected in identified containers. The urine are sent to the lab, scanned on arrival and processed if necessary. The scan allow to exactly time and identify the sample.

IMP administration The identified treatments and the receiving subjects are scanned, so potential inversions could be detected and tracking of the drug administered can be easily done.

Investigator and nurses can easily record any change in the subjects condition, by reporting Adverse Event and Concomitant Medication using the CTMS device interface.

6.3 Other data management

Most of the data can be directly sent into the system's database. However, some specific data can always be manually entered into it. However, everything should be set in a way that the operator can directly enter the data into the system, using a tablet or a computer that would be in the subjects' room, for instance. The purpose being avoiding any pointless and additional steps of data re-transcriptions, that could lead to errors and time losses.

6.4 Quality of data

The system ensures the integrity of data, by reducing the risk of human error in the data handling. Losses of data are also avoided: for instance, the nurse can no longer forget to transcript her measurement, as it is automatically saved. Samples will be unequivocally and electronically identified. Moreover, when the sample listings have to be created for the sending of the samples, the system can just export the list of the samples taken, classifying them by subject, by timepoint, etc. Also, the system allow to bypass the usual data entry process into the eCRF, which is usually manual and can lead to mistakes. Referring to the type of errors that were identified earlier, the measurement errors should remain approximately constant, as an operator is still needed for the measurements. Judgment errors could be decreased providing the system could create alerts for out-of-range parameters. The most impacted errors are the transcription errors. The number of transcription errors into the source and from the source to the CRF should be close to zero, the process becoming automatically done by the system.

6.5 Time

While the quality of data is improved, many time-consuming tasks are also avoided. That is probably the most important improvement in the workflow that the updated system can bring. While the measurement and observation steps will take approximately the same time as before, a lot of precious time can be gained in the data processing. Stages of quality control of the source documents and a significant part of the data entry can be removed from the center's processes. Then this is less work for the CRA when monitoring the entered data in the eCRF. More accurate data means less findings by the CRA and less data to correct after his monitoring. While SDV monitoring allows to meet a more or less acceptable accuracy rate, the CRA has to monitor all the data to get close to a perfect accuracy rate. This step takes several days, increasing the time of data accessibility for the client. As a conclusion, no much time will be gained in the subjects' room, when measuring the data. However once the data are measured, the whole process becomes more instantaneous and the client can have access to accurate data way more quickly than before, as less verification steps are needed.

The new identification system adds a lot of value to the data. Indeed, there is no point measuring accurate data if they are not attributed to the correct subject. Sometimes, when analyzing the samples, doubts can be expressed about potential subjects inversion. Even though it is possible to detect when the inversion takes place between an active and a placebo subject, most of the time, it is impossible to detect. Finally, such inversion suspicions are always embarrassing and show a lack of professionalism in the data management, coming from an experienced Investigator and its team.

6.6 Expected Cost

In this section, two financial aspects should be taken into consideration. Of course, the cost of the solution itself, taking into account the devices and the licenses that need to be purchased, for instance. But also the savings the solution can bring, considering the gain of accuracy and time.

6.6.1 Expected cost of the solution

The costs are summarized in table 6.1. The number of devices per type of measure should be adapted to the bed capacity of the center. In this example, 1 device for 8 subjects is used, which, even if realistic, should be adapted to the needs of each study.

The cost of an independent tracking application is unknown and should be investigated by requesting a customized offer to the CTMS provider or an any other SaaS provider.

6.6.2 Savings

For one study, one Data Entry Officer is usually assigned. This staff member will not be needed anymore, however a Data Manager should be hire or trained to handle the technical aspects of the solution and manage the generated data. Even if a Data Manager would be probably paid more, only one is needed for a many different studies, reducing the labor cost.

Use	Item	Price (Eur)
ECG	Phillips PageWritter TC30	5130
BP-HR	Welch Allyn PROBP 3400	840
Labeling	Brother TD-2130NHC	639
Barcode reader	Datalogic DBT6400	600
Data capture and tracking	EDC	1700/month
Tracking	Azure, Google or AWS	Unknown

Table 6.1: Cost of the solution, summary

The quality control of the document is often done by the Clinical Trial Manager or a Study Nurse. This task can take several hours per day, at the CTM or Nurse salary rate.

CRA are paid to monitor the data, taking several days for a group of 14 days of data. Removing this important cost allows to reduce the price for the client, while meeting the usual standard of quality.

When sending the PK and PD samples to the client or its partner, the center's laboratory has to list then to track which sample are sent in the package. Making the listings, is a tedious task, as thousands of samples can be sent over the trial course. With the new system, all the samples are identified and listing can be exported in one click. Days useless of labor can be avoided.

Chapter 7

Opportunities

7.1 Patients Safety and fidelity

From a medical point of view, improvement in data collection and accuracy can only means that there will be an better follow-up of the subjects. Volunteers feeling safer are more likely to come back for other studies, reinforcing the fidelity.

7.2 Strategy

Implementing an Iot-based information system could be the first step of a longer-term strategy, involving more and more digitization. This could be part of the company's vision to progressively establish itself as being on the cutting edge of the digital innovation in clinical trials. It seems that an increasing number of pharmaceutical companies are heading toward a deeper digitization in their process and in that scope, they would probably be more incline to choose a clinical center in phase with their vision. Of course, such a change can only take time and needs progressive improvements. Mindsets inside the company should also be changed progressively. This change should be executed in parallel with reviewing the current company's strategy, which itself should be based on the company's values and mission. On the other side, digitalization could also be the consequence of a change of direction in the business' strategy.

Clinical trial units, by following the GCP, should already have some common values of *Subject's safety* and *Data quality*. Other values like *Innovation*, *Efficiency*, *Continuous improvement*, *Embracing change*, *Customer satisfaction*, *Reliability*, *Transparency*, *Flexibility* and *Exceeding expectation* could, for example, be considered as well. The mission, based on the values, could also be modified if needed. As described by Crutzen (2020), it should be one sentence answering the 3 following questions: What, For whom and why.

In term of global strategy, a new service would be proposed on the existing markets, following one of the four big strategy directions from the Ansoff's Matrix.

7.3 Marketing

In term of marketing, Laurence Dessart (2018) covers some important aspect of a company's marketing that should be briefly raised. First of all, customer orientation should be at the core of the marketing strategy. Meet customers' requests, surpass expectations and remove frictions are some of the most important aspects of it. The developed solution improves these three aspects:

1. It meets the expected standards of quality of the current clients. It also potentially meets the standards of other and perhaps more demanding customers, which would not have considered the center before.

2. It improves the quality, decrease the processing time without increasing the cost. So it can surpass current customers expectation.

3. As seen before, the current system is full of frictions and inefficiencies, which would be solved.

A defaqto research shows that 55% of clients would be ready pay more for the guaranty of a good service. That statement should be confirm in the clinical trials sector, but this is potentially a way to increase earnings too (Dessart, 2018).

The number one objective of marketing should be creating value. The perceived value can be increased by increasing the perceived benefits while reducing the perceived cost. The product, here represented by the data sent to the Sponsor, would be of a better quality. The service would be better perceived giving the fact that the data would flow more easily, faster and without any friction to the sponsor. Then, the solution also gives a image of technological innovation and professionalism. Altogether, the benefits are increased by these 3 elements. On the other side, it was showed that money, time, energy cost for the customer were decreased, mitigating the perception of costs.

In the marketing approach, a deeper analysis of the clinical market and the global demand for the solution should be made. Macro-environment should be studied and an internal analysis of the clinical center should be performed as well.

7.4 Competitiveness and Positioning

Porter (1979) describes some generic strategies for a good positioning on the market. One of them is to differentiate from the other competitors. This solution could be a way to offer a unique solution in term of product (data) and service (data management), offering more value than the competitors. The solution would improve the company's image and the new way of working would definitely be more practical for the Sponsors. Investing in it would allow to differentiate from the competitors and improve the global competitiveness of the clinical center. For instance, centers located in the Eastern Europe have the price leadership and their rates are very difficult to match. Western Europe centers have therefore to add value to justify the price difference. Accelerating digitization and offering innovative services that would significantly

improve the way trials can be conducted, may be a solution, and adopting such an information system may be a way to take a more favorable position on the global market.

Chapter 8

Challenges

8.1 Change Management

8.1.1 Change Management Model

In order to make sure a solution generates the expected return on investment, a solid change management plan has to be developed prior to his actual implementation. Grimolizzi-Jensen (2018) defined change management as a structured approach to ensure the changes are thoroughly and smoothly implemented for achieving lasting benefits of change. Daryl Conner (1993) emphasizes how important it is to shift individual attitudes and behaviors to bring the new solution to life. The human aspect is one critical component of the strategic execution of a new project. People are the engine of change and drive its implementation. While it is vital that the new solution is properly developed and delivered, it must also be adapted and efficiently used by the staff members. By planning the change, the portion of return on investment linked to the good use can be protected. Jenifer et al (2002), reports that the change management project that use the best change management practices bring more value. Prosci (2018) shows that an effective change management increases probability to reach the initial objectives, to follow the budget and meet the deadlines.

To build this change management plan, the *Prosci*'s ADKAR model will be followed. ADKAR is the abreviation of 5 words (Awareness, Desire, Knowledge, Ability, Reinforcement), representing 5 important steps of change. This model will be used by also having in mind Kotter's 8-step change model (Kotter, 1995).

Awareness

It represents the understanding of the nature of the change. Why making a change, what are the risk of not changing ? Information about the internal and extenal drivers leading to that need for change must be given to the stakeholders. It is supposed to help answering the question "What's in it for me ?" (WIIFM). Awareness is not to be aware that a change is happening, it is the awareness of the **need** to change. To build *Awareness*, the nature of the change must be shared as well as the reason **why** the change is necessary. A communication plan should therefore be carefully conceived, as detailed further. The executive sponsor of the change is the best person to communicate the why and the risks of not changing. Finally, Managers should also be able to coach the employees during this change.

Desire

Once the first step of awareness could be established, the next one for an individual is to make a personal decision to participate to the change. The *Desire* represents the willingness to support and engage the change. It is influenced by the nature of the change and personal circumstances. Multiple factors influence a person' level of desire. The nature of change, how the change is going to impact the individual and what's in it for him (WIIFM) should be addressed. Individual experiences change in the context of their own perception of the organization (culture, history, etc.). Employees' personal situations and values should be taken into consideration as well: family status, financial security, career aspirations, relationship at home and at work, etc. A reaction to change that appears excessive or counterintuitive might therefore be due to personal matters and not to the change itself. Building *Desire* may be the trickiest part. Sponsorship is one of the keys to create that engagement. Employees also look to their immediate supervisors about how to respond to change. Risk assessment and resistance anticipation should also be included in the plan. It is also important to involve the employees in the change process. Increased engagement of impacted employees in a change initiative translates directly into increased likelihood of the initiative achieving its desired results. Employees' behavior during change are driven by how they are measured and rewarded. As a result, an incentive program should be planned as well.

Knowledge

Once a individual has the awareness of the need to change and the desire to support it, building knowledge is the next block in the *Prosci* ADKAR model. *Knowledge* represents the information, training and education needed to know how to change. It includes behaviors and skills, processes, tools and systems, roles and responsibilities. Different factors can influence the successful achievement of knowledge, such as its the current level, the capacity to learn and the resources available for appropriate training. Some of the following tactics should be considered in order to create or reinforce knowledge. Training programs should be scheduled, using readings, lectures, video programs, webinars, etc. Some kind of knowledge-building content should be available, allowing employees to remember ideas, even long after their initial training. One-on-one coaching should also be considered to fill emerging gaps that were not well covered by the training. Learning groups and platform should also be encouraged.

Ability

Ability turns Knowledge into action, by applying intellectual understanding to the a real-world environment. The concept is based on the fact that there is a difference between knowing how to do something and actually being able to do it. Employees must receive sufficient time and tools to develop their own abilities. Like in the previous steps, day-to-day involvement of managers can have a significant impact on the change. Experts on the subject can be valuable resources to foster ability. The training should include hands-on exercises to allow employees to test their knowledge.

Reinforcement

Once the change has been implemented, every effort should be made to sustain it over the long term. Some tactics known to build reinforcement should be applied, such as celebrations and recognition, rewards, favoring feedback from employee and following the performance using management dashboards.

Thus, in this section, some recommendations will be suggested, following the good change management practices. The project characteristics in term of change management will be detailed, the groups impacted will be explained, recommendations for the project's sponsor and for the managers will be issued. Then, a communication plan will be proposed as well as recommendations for managing resistances and finally a training plan.

8.1.2 Change analysis in the context of implementing a new information system

As a starting point, the project to implement should be analyzed in the context of a phase I clinical center, in order to adapt the change management plan to the context.

Key roles attribution

According to Conner (1993), the following roles should be identified within the organization : sponsors, change agents, targets and advocates.

Sponsors The sponsors are the people who have the power to lead or legitimate the change, by allocating the sufficient resources to it. They could be the general managers, CEO or even higher managers who would have similar power. These job titles are not specific to the clinical sector but are well applicable to it.

Change agent The change agents are the people designated by the sponsor to plan and implement the change. They could be internal or external to the organization but should have the skills to plan this change. The change agent will be responsible to create the change management plan and make sure it is well followed. The following sections are therefore addressed to the change manager and are intended to help him in his task.

Targets The people concerned by the change. In a clinical unit, they are :

- Data Entry Officer and Clinical Trials Assistants
- Nurses
- Clinical Project Managers
- Investigators
- Pharmacists
- Laboratory Technicians

Advocates Individual or group of individuals who would like to achieve the change but who do not have the power to lead it. They need to be specifically identified because they are huge allies in the road of change, as it will be detailed further in the resistances management.

Type of change

This change could be labeled as a "transition", as defined by Ackerman and Anderson (2010). Indeed, the change happens in a context where there is a need of improvement, by implementing a new way of working. It is a transition towards a quite clearly definite state which should resolves some of current identified issues. The current way of working must be abandoned to set up the new information system. Moreover, the new system does not absolutely need a change of values, only a transition to using new tools and a good adaptation to it from the company's workers.

Change team structure

The structure of the team must be slightly adjusted as the change manager has to be included, in order to get the best results possible. The four possibilities presented by *Prosci* (2018) are shown in figure 8.1.

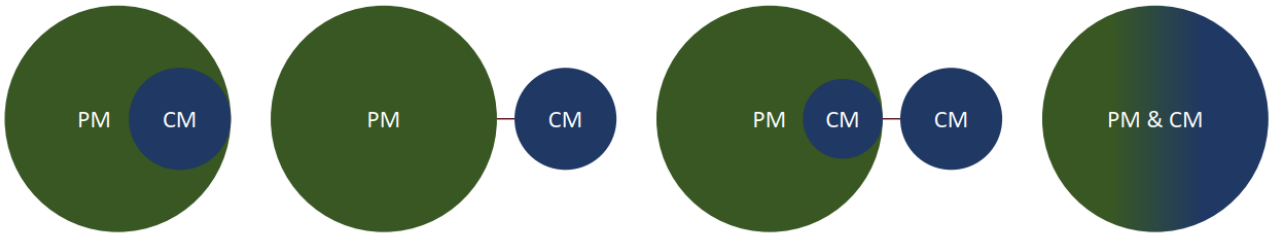

Figure 8.1: Different team structures for change management. Source: Best Practice in Change Management, Prosci (2018)

1. The change manager (CM) integrates the Project (PM) team.
2. The CM stays out of the PM team.
3. The CM team is split into the two above solutions.
4. The CM is also the project manager.

Often, clinical trials last months and it is very likely that at the date of the official launch of the project, it will not be possible to apply it to several ongoing studies, already started using the old system. Making a transition while a study is running would have many procedural complications, such as amending the protocol, and would probably not be beneficial for the quality of the data. However, every new studies starting from the launch should be implemented with the new information system. Choosing a team structure is very situation-dependent. If there is only one study to be started in the following few months, the Clinical Project Manager (CPM) could also be the Change Manager, providing he has the abilities or the experience to

do so. However, it might be preferable to dissociate the two roles, while including the CM in the project team. If multiple studies had to be launched in a short period of time though, it would probably better to assign one external Change Manager who would coach the different CPM of these studies.

8.1.3 Sponsorship

Jennifer et al. (2002) emphasize on the importance of Sponsorship in the course of change. Change must come from the higher levels of the structure and sponsors have therefore an important role in leading the way. As recommended by Conner (1993), a single linear sponsorship organization will be used, with the the change agent being the intermediate between the sponsors and the target. In this case, the company's CEO and the higher managers should form a coalition of sponsors, to meet some important characteristics such as power, expertise, credibility and leadership. The sponsorship as important role in most steps of the ADKAR method. Here are the main actions the sponsors should take or be involved in :

1. Taking part to an initial meeting where the change manager inform the coalition of sponsors about their crucial role as change leader.

2. Being trained following a coaching plan.

3. Organize an official project launch meeting. Present the business reasons behind the change. The first step is to communicate awareness. The sponsor should follow a communication plan, as detailed further.

4. Convey the vision.

5. Staying visible and active throughout the the entire change process, not only at the official launch of the project. Direct communication to the employees should also be used, increasing adoption. Senior leaders have a lot of influence and need to be present and interact at a personal level with the employees. Sponsors who disengage, will clearly communicate that the change is not that important to them.

6. Allocating sufficient resources to make the change happen.

7. Inviting Clinical Project Managers to team leading workshops as well as inviting the employees to training workshops, as detailed later.

8.1.4 Role of managers

Change agents also include managers. They should understand the current state weaknesses, understand the expected final state, be able to identify the impact of the change on the structure and the processes, determine the level and the type of sponsorship required and manage the people impacted by the project. Manager can also be a barrier to change, without necessarily realizing it. They can lack communication change management skills, they can have a hard time managing the project's timeline, misunderstand their role and or even having difficulties to properly understand the change. Managers must be prepared to help individual to make sense of the change. They are supposed to clearly articulate both negative and positive impacts

of the change. For managers, there are two main steps: the preparation to lead the change and effectively lead collaborators through it. The preparation step therefore includes understanding the change and their role in that change, having the support of the hierarchy and being trained to change management. This preparation would therefore involve the following plan:

1. Managers workshop: the CM provides the team leader/managers with the necessary concept.
2. Individual interview between the CM and the managers
3. The managers prepare their staff
4. Monitoring and follow-up by the CM.

8.1.5 Communication plan

Presenting the WHY

The reason behind this whole project was detailed earlier in the work. This new way of working aims to improve data quality by increasing their accuracy, save time in data transmission to the client and reduce cost related to this two previous points. It also needs to be explain that company's image is at stake, as well as improving competitiveness and adjusting its positioning on the market. The current way of working is still relevant, but will probably not be sustainable in the long term. Change must be anticipated and should begin as soon as possible.

What's In It For Me [WIIFM]

This reflection should be made individually. However, to present some guidelines, it will be approached for each groups of targer, as detailed before.

Data managers Data Entry Officers are the most impacted in this change project. Their day-to-day task will change drastically. The staff in charge of entering the source data into the eCRF will become completely obsolete without a tasks restructuring. However, they will go from a boring data entry job to a more rewarding and complex data management. They will still have some data to enter manually but the amount will be much reduced and their job will be more diversified. They will acquire new knowledge and great experience.

Nurses Nurse will have more time to actually take care of the patients. They can focus more on what the results mean in term of safety and less in term of data management (like ensuring it is accurate, well transcribed, etc.). The overall workflow will be more straight forward, and for nurses having an experience in the standard care, the job will get cloer to the one they would have had in an regular hospital unit.

Clinical Project Managers and Clinical Trial Assistants A dimension of data management will be added to their job description, adding variety and valuable knowledge. The initial preparation of studies will change as the transition from paper to electronic worksheet must be implemented. That could be an opportunities to evolve and diversify their work as well as to take up a new challenge.

Investigators This group is probably the least impacted in term of day-to-day way of working. However, being responsible of the whole clinical activity, this change can only benefit them and they could be valuable change advocates.

Pharmacists The new barcode system will only slightly impact their work. This system, however, allow them to track more accurately which drug is allocated to which subject and so allow them to control more effectively the administered dose. This hugely improve the quality to their work, without impacting a lot their habits.

Lab technician The barcode system significantly benefits them as it automatically tracks the blood samples, reducing their error rate and the chance of subjects inversions. Exporting the tube listings before sending the samples to an analysis laboratory will be instantaneous and accurate. This task was done manually and could take several hours to days to complete, depending of the number of samples. It would give the lab technician more time for other tasks in which they can input human value.

8.1.6 Managing resistances

Prevention

The best and simplest way to avoid resistance is to follow the good change practices, as explained above, regarding sponsorship, efficient communication, manager engagement, active implication, etc.

Pro-active resistance management

Some resistance could be anticipated in the different impacted groups or category of employees. Here are exemples of possible resistances that could appear on the way. Resistances linked to a lack of knowledge or ability can be solved by applying the training plan and will not be included in the following list.

- The data entry officer: could be afraid of losing his job with the new solution. The sponsor and the managers must explain him how his job is supposed to evolve, insist on the fact he will still be needed, even if it is in a different way.
- The nurse: could continue to rely on the old devices, by bypassing the information system and preferring encoding manually the measurements. She might be blocked at different stage. If awareness is the issue, make sure she understood the need for change. A lack of *Desire* would be more complex to handle. In this case, investigate on personal matters and make sure she understood the "WIIFM". Knowledge and abilities should be the easiest steps to overcome with sufficient trainings and coaching. Individual coaching should be privileged, with the Head Nurse or the Clinical Project Manager for example.
- The clinical Project Manager: does not engage the change and continues to work like he used to, bringing down the whole clinical team with him. They are absolutely crucial for the change and they are the most important people to make the change happen. He has to be the first person to understand the reason behind the change, and how the whole

team can benefit from it. The is a change leader and has to be aware of it. A particular attention should therefore be paid to them as soon as the change project starts.

- The Investigator: continues to make hand-written notes instead of entering them into the system. This resistance has a smaller impact but is also easy to fix. Investigator may be older than the rest of the staff, may have strongly established habits and could find the technology part a bit daunting. Training and follow-up is important from his close collaborators, such as an other investigator or the Clinical Project Manager.

- The Lab Technician: does not read the barcode and manually identify the sample. This would annihilate the whole process at the last step of the sample journey. As the technology is quite easy to use, it probably means he did not understand de change and should be individually coached by the managers. Other collegues may have a great impact on them, so indirect communication could be a way to fix it as well.

Reactive resistance management

A close follow-up and monitoring on how the solution in being implemented by the staff is crucial to detect resistance as early as possible. The best tool for the change manager to handle resistances is an active listening to the employees. It means listening without interrupting, reformulating and confirm what we heard. Piedboeuf (2018-2019) some examples of actions to manage resistances: inviting the collaborators to participate to the HOW of the solution, removng barriers, bringing hope, showing tangible results and asking for help.

8.1.7 Training Plan

A training plan sheet designed by Lamarsh et al. (2004) will be used, containing the following elements. Knowledge or Skill required, Needed by, When, How and Assessment. The training sheets are presented in the following tables, table 8.1, 8.2. The other members should be trained by this two initial groups, depending on their field. Barcode scanner are quite straight-forward to learn and would do not need any specific training from the manufacturer, for example.

8.2 General Data Protection Regulation

The European Union's General Data Protection Regulation (GDPR) entered into application on 25 May 2018 (GDPR, art 99) and made a lot of noise. Changes of data policy had to be made in many sectors and the clinical trial sector did not make an exception. A good understanding of GDPR and regulations are required to appropriately implement an information system, as many subjects' data will lie at the heart of the solution. One one hand, EU data protection strives to facilitate the free flow of personal data; on the other hand, it makes the free flow of data subject to conformity with legal requirements. The GDPR retains many elements from the previous 1995's regulation and add some outstanding elements such as a more severe sanctioning regime, the right to be forgotten and the mandatory assignment of a Data Protection Officer. The GDPR introduces the principle of accountability, it means entities are invited to be proactive and holistic in term of compliance and should be able to prove they have taken all the necessary steps to be in compliance with the GDPR.

Data Managers and Clinical Project Managers training sheet	
Knowledge required	Exhaustive knowledge about the devices and how to export data. They need to be able to support the staff on technical questions and being pro-active in the research of information. They should be the person who would contact the manufacturer and be able to understand the instructions. Extensive knowledge about the data management platform.
Needed by	They should be trained prior to the project launch, as soon as the devices are ready and connected. Data manager should be able to run tests in order to adapt the change plan, if needed.
When	As soon as the material is available.
How	A training by the device's manufacturer should be negotiated at the purchase. Same thing for the data management platform and possibly the cloud supplier. These kind of trainings are often organized in group, but only a handful of employee's should be attending it (the data managers and the clinical projects manager dedicated to the change project). The initial trainings should be organized inside the clinical center and should be both theorical and practical. Hands-on exercises must be foreseen as well. The devices' documentation should be easily available.
Assessment	As the first staff members to be trained, they should auto-evaluate and be independent regarding their level of knowledge. The first test before the start of the project should help them to assess their level of knowledge of expertise and should allow them to fill their weak points.

Table 8.1: Data Managers and Clinical Project Managers training sheet.

Nurses and Investigators training sheet	
Knowledge required	Exhaustive knowledge about the devices. More specifically, how to use it on patients and record accurate data. They need to be trained to the medical aspect of the device. They also need to learn how to directly enter data to platform, for the data that cannot be captured by measurement devices.
Needed by	The start of the project
When	At the same time as DM and CPM for the part regarding the medical part.
How	A training by the device's manufacturer should be negotiated at the purchase. These kind of trainings are often organized in group, but only a handful of employee's should be attending it (the head nurse and the most regular nurses). The initial trainings should be organized inside the clinical center and should be both theorical and practical. Hands-on exercises must be foreseen as well. The devices' documentation should be easily available.
Assessment	As the first staff members to be trained on the medical part, they should auto-evaluate and be independent regarding their level of knowledge. CPM and DM could help challenging their knowledge as well. The first test before the start of the project should help them to assess their level of knowledge of expertise and should allow them to fill their weak points.

Table 8.2: Nurses and Investigators training sheet.

The GDPR use 4 distinct categories to make sense of the notion of personal data, each of which have legal obligations in the processing of these data (Monschein et al., 2019). The "personal data" category such as names, location, address, phone number, bank account number, etc. is widely used in a phase I clinical center for practical and safety aspects. "Sensitives data" are also collected and are used for a clinical research purpose: racial or ethnic origin, genetic data, health data, sex life, etc. For example, if it is recorded that a subject do not eat certain kind of food, it should be considered as a sensitive data, giving that religious beliefs can be inferred from it. Once the subject has enrolled into the trial, all his data are pseudonymised. In the regard of GDPR, it means that personal data are altered so that the data subject cannot be directly identified without having access to further information stored separately (GDPR, Art 4). Typically, a screening or a randomization number is allocated to the subjects and throughout the study, data are identified using this number and not the subject's real name. The center keeps privately the conversion table and is the only entity to be able to personally identify the collected data. That process allow to share the data with the Sponsor without linking them to a specific, named, individual. As a consequence, once the data arrive to the Sponsor, they can be considered as Anonymous and GDPR do not apply anymore. Nevertheless, it means that the center is responsible for the non-spreading of the information and is the "data controller", as defined by the GDPR. Thus, the center is responsible for the lawful processing of the data, as described in Article 5 of GDPR.

In order to be able to process personal data in a lawful manner, the controller (the investigator's clinical center) should specify a legal basis, as described in Art 6 of GDPR. In the context of clinical trials, the consent is already widely used as it is a mandatory step for a subject to be enrolled. However, differences between informed consent within the meaning of the Clinical Trial Regulation (CTR) and consent within the meaning of the GDPR (European Commission, 2019) can be outlined. The inform consent required by the CTR serves as an ethical standard and procedural obligation. It is a fundamental condition to sign a consent in order to be included in a clinical study. Besides, it was not conceived as a way to control data processing. Both type of consent should be therefore signed by the volunteer. According to GDPR, the consent should be freely given, specific and informed. To prove that the consent was lawfully obtained, good documentation and archiving of the consent forms are absolutely required. Since sensitive data are processed during a trial, the GDPR requires explicit consent of the subject (GDPR, Art 9), which means a stronger affirmative action is required. A explicit signed and written statement should therefore be added to the consent form by the subject.

Regarding the technical solution described in this work, the GDPR claims to take a technological-neutral approach and should not be influenced by the techniques used (GDPR, Recital 10). It means GDPR should be applied in the same way it has always been with the previous system. However, data integrity and safety process must be taken into consideration when implementing the new solution. In many ways, a secure digital system with encrypted data should allow to increase data integrity and security, as well as improve accuracy, as per GDPR requirements. The new system does not really impact the personal information used for practical purposes, such as taking appointment and contacting the subject during the study. Regarding the process of the clinical data, namely the pseudonymised data, they will be first stored on the device, then sent to a secure cloud storage, made available for consultation or modification by the

authorized stakeholders and sent to the Sponsor. In practice, some basic requirements should be respected:

- Inform the subject on the extracted data and the way they will be processed, using a Inform Consent Form compliant with both CTR and GDPR requirement
- Comply with the concept of data minimization. Even if devices can potentially gather tons of information, only the information required by the protocol should be stored. This recommendation is in line with the choice of not using monitoring devices, capable of recording vital signs 24/7, if not required per protocol.
- Appoint a Data Protection Officer prior to the study, as required per GDPR. This advisor will also make sure the system is compliant with the current regulation.
- Protect the non-pseudonymized data from the whole system. If stored in a digital way, the information should be encrypted, and only accessible to the clinical staff.
- Ensure there is a way to delete all digital and non-digital personal data, in case a subject requests it. For example, if the data are stored on the cloud with regular back-ups, it must be possible to definitively delete all of a subject's information, even on the backed-up files.
- Of course, the data should only be shared with the authorized stakeholders. CRA and auditors have the legal right to access the non-pseudonymized data, to audit the Inform Consent Form for example, as they are bound to professional secrecy.

Part V

Conclusion

Chapter 9

Conclusion

9.1 Conclusions

In this work, an IoT-based information system for the phase I clinical trials was presented, involving connected devices and automatic handling of the patient's data. The technical description of the solution, including references of devices and indicative pricing, can be used to facilitate clinical units to implement and adapt the technology to suit their needs. ECG devices, a blood pressure monitor and tracking material such as barcode readers and printers were therefore suggested. An IT environment was also described, embedding the whole system in using a cloud-based platform, database and user interface.

Potential benefits of the solution were also presented. The information system aims to decrease the cthe duration of the clinical trials by significantly improving the time of data availability, therefore allowing the pharmaceutical companies to start analyzing them sooner. More importantly, the solution improves data accuracy and integrity without increasing cost. Although involving significant upfront investments, the solution could diminish costs in the longer term: the data entry costs would be significantly decreased and the information system has the potential to reach a close to 100% data accuracy, making the very expensive step of monitoring almost obsolete.

Implementing an IoT-based information system could be the first step of a longer-term business strategy, involving more digitization. The mid and long-term strategy of the clinical company should therefore be reviewed in order to match the solution's philosophy. Regarding the marketing strategy, the solution meets the current customers' standard of quality, has the potential to surpass expectations, removes inefficiency and obstacles, while creating significant value. The solution can also be used to improve the positioning of the company on the global market, differentiating from competitors worldwide.

Being implemented in a highly regulated environment, the compliance with the GCP and GDPR were verified. Overall, it can be asserted that the solution complies with the GDPR. It is also expected that higher standards of GCP guidelines will be met.

Finally, good practices and guidelines regarding Change Management were also proposed, as the system must be adopted by both the managers and the employees to work effectively and generate the expected return on investment. The five steps of Prosci ADKAR model were used and applied to the organization of a clinical unit. Conner's key roles of change (1993) were attributed, the type of change was defined as a "transition" according to Ackerman and Anderson (2010) and propositions of team structures were given. Then , the crucial roles of the project's sponsor and managers were emphasized and recommendation were given to these Changes' stakeholders. A communication plan was also proposed, highlighting the reason why the system should be implemented and the "WIIFM" of the different groups. Recommendations to manage resistances were given. Finally, a training plan for the two most important groups of employees was outlined.

In conclusion, the upgraded information system, based on connected devices and IoT, can definitely lead the way to a technological disruption within the clinical trials sector. Adopting an IoT-based information system in clinical trials should be the first step to embrace the digital transformation the sector needs. Nowadays, decreasing financial and time costs has become one of the main priorities in drug development, and shifting to newly available technologies such as the IoT and connected measurement devices has a great potential to alleviate these costs and increase the sector's global efficiency. For clinical centers, the proposed information system is an opportunity to pave the way to digitalized clinical trials, setting new standards for the industry.

9.2 Perspectives

This work opens new perspectives for the clinical trials sector and should only be the first step to a larger-scaled digital change. This change should be the first of many more, progressively adopting the technological revolution of medical devices and infrastructures in healthcare. Wearables are on the verge of being ready for more accurate and complex vital signs measurements (Izmailova et al., 2018); therefore, the whole system was thought-out in order to adopt them as soon as the technology becomes available. Wearable are therefore the main future perspective of this work, and an eye should be kept on their progress on the healthcare market. In this work, the solution was applied to a fictive phase I clinical center and a fictive phase I study. However, the solution could very well be applied to phase III clical trials. Third phase studies are often ambulatory trials and could do well with such a system based on connected measurement wearables (watches, patches, wristband...).

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Annex 1

COMPARATIVE TABLE OF ECG

Eligibility criteria :

- **Professional precision and accuracy, meeting of the standards of the industry and the authorities' recommendations. It means that only 12-lead ECG had to considered.**
- **Possibilities of connectivity to the system (LAN, WIFI, Bluetooth, etc.)**
- **Possibilities of an extensive data exportation in a commonly used language (XML, JSON, etc.)**
- **Sufficient product information (detailed brochure, available technical characteristics)**

NAME	Specifications	Connectivity / communication	Average estimated price	PRO (+) / CONS (-)
GE MAC 2000	12-lead ECG On-site only	LAN - WIFI XML - PDF	**5130** Eur	- Barcode reader optional (price?)
Schiller Cardiovit AT-102 G2	12-lead ECG On-site only	LAN - WIFI XML?- PDF Dicom & HL7	**4055** Eur	- Barcode reader optional (650 Eur) - Minimalistic design
Schiller Cardiovit AT-10	12-lead ECG On-site only	LAN - WIFI XML – PDF Dicom	**5348** Eur	- Barcode reader optional (price?)
Schiller Cardiovit FT-1	12-lead ECG On-site only	LAN (ethernet 1Gb) WIFI XML - PDF Standards HL7 and dicom	**3108** Eur	+ or - Tablet format “mobile” + Extentisive connectivity possibilities - But no trolley available
Philips PageWriter TC30	12-lead ECG On-site only	WIFI XML - PDF Dicom	**5130** Eur	+ barcode scanner included
Welch Allyn ELI 250c	12-lead ECG On-site only	WIFI LAN XML PDF DICOM HL7	**3570** Eur	+ barcode included + the cheapest + Extensive connectivity possibilities - Minimalist Screen display and design - No computer included

COMPARATIVE TABLE OF BLOOD PRESSURE MONITORS

Eligibility criteria :

- **Professional precision and accuracy**
- **Possibilities of connectivity to the system (LAN, WIFI, Bluetooth, etc.)**
- **Possibilities of an extensive data exportation in a commonly used language**
- **Sufficient product information (detailed brochure, available technical characteristics)**

Only a few names came out of the research. Connectable blood pressure monitors are not common, unless for the ones that are used in the intensive cares, which seem excessive for the clinical trial use.

NAME	Specifications	Connectivity / communication	Average estimated price	PRO (+) / CONS (-)
Rossmax Professional X9	Atrial Fibrillation Premature contraction	USB cable and software	**155** Eur	+ Cheap - Limited connectivity - Few technical information about the product - No obvious exportation possibilities beside a manual connection to a pc software : exportation capabilities of the software ??
Rossmax Professional X5	Atrial Fibrillation Premature contraction	Bluetooth (via an mobile app) USB cable	**120** Eur	+ Cheap - Limited connectivity - Few technical information about the product - No obvious exportation possibilities beside a manual connection to a pc software : exportation capabilities of the software ??
Welch Allyn PROBP 3400	Measuring time: 15 seconds	Bluetooth Can connect to any hospital information system XML via Welch Allyn Service Tool	**840** Eur	+ Extensive connectivity + Professional accuracy + Trolley available - Expensive

Annex 2: Example of study Flowchart

Time	Study Days								
	D-1	D1	D2 to D6	D7	D8 to D13	D14	D15	D16	D17 and D18
Hospitalization	←	—	—	—	—	—	—	—	→
Physical examination	X							X	
Biochemistry, haematology, and urinalysis (external lab)		X[1]		X[1]		X[1]	X		
Urinary drug screen & alcohol breath test	X								
Study drugs administration		X[2]	X[2]	X[2]	X[2]	X[2]			
(Standing and lying) Vital signs (BP, HR)		X[3]	X[4]	X[3]	X[4]	X[3]	X[5]	X[5]	X
ECG		X[3]	X[4]	X[3]	X[4]	X[3]	X[5]	X[5]	X
PK blood sampling		X[7]	X[1]	X[7]	X[1]	X[7]	X[5]	X[5]	X[8]
PK urine collection		X[9]				X[9]	X[10]	X[10]	X[10]
PD blood sampling		X[11]		X[11]		X[11]			
PD test (with dedicated device)		X[6]		X[1]		X[6]	X[6]		
Adverse Event and CM monitoring	←	—	—	—	—	—	—	—	→

1. Predose
2. Administration of IMP every morning
3. Predose, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 7.0, 8.0, 10.0, 12.0, 13.0, 14.0, 16.0 h post-morning dose
4. Predose and 1h post dose
5. 24, 36 and 48h post D14 dose
6. Predose, 1.0, 4.0 and 8.0h post dose
7. Pre morning dose, then, 0.16, 0.33, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 12.16, 12.33, 12.5, 13.0, 14.0, 16.0 and 20.0 h post-morning dose
8. 72.0 and 96.0h post D14 dose
9. 0-24h collection of urine postdose
10. 24-48, 48-72 and 72-96h postdose collection
11. Predose, 2.0, 8.0 postdose

Implementing an IoT-based information system for the data recording in a phase I clinical center

PORTELANGE Nicolas

Abstract

Clinical trials are facing many efficiency challenges. The clinical development of a new drug represents a huge investment for pharmaceutical companies, takes several years and demands very high standards of data accuracy and integrity. Amongst other disruptive technologies, the Internet of Things has been cited as capable of transforming the clinical research landscape. Implementing an information system based on this technology should therefore be the first step to drive clinical centers into digitalization. An information system based on connected devices is discussed, as well as suggestions of devices and their connectivity. The general computer infrastructure is also mentioned, including the choice of a cloud-based data management platform and server. The solution is expected to revolutionize the way clinical trials are conducted, significantly increasing the data quality, simplifying processes and saving time, while driving down the costs. For example, the manual data entry of the parameters and the Source Data Verification would become partly irrelevant, as the data are supposed to be directly transferred from the measurement devices to the study database, untouched. The system would also allow the study Sponsor to access to accurate data nearly instantaneously. Such an implementation involves new strategic and marketing opportunities, as well as improving competitiveness and positioning on the clinical trials market. Moreover, with such a project, the human aspect should be approached and a plan of Change Management is therefore proposed, based on the Prosci's ADKAR model. Furthermore, the compliance with the GDPR is verified and explained. Finally, it should be noted that the solution was designed in order to be potentially applicable to any clinical unit and should be adapted to a center's specific needs.

Keywords: Clinical trials, Internet Of Things, connected medical devices, data management, change management.