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Understand how to optimize recruitment of healthy volunteers in phase 1

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UNDERSTAND HOW TO OPTIMIZE RECRUITMENT OF HEALTHY VOLUNTEERS IN PHASE 1

Mémoire présenté pour l'obtention
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Understand how to optimize recruitment of healthy volunteers in phase 1

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Abstract

Background: Phase 1 clinical trials in healthy volunteers (HVs) are a critical step in obtaining information about the safety of a product that is to be marketed. Recruiting HVs to participate in these phases is a challenging but important process. Threats and opportunities have emerged, particularly in the context of the new European Clinical Trials Regulation (EU CTR), which came into force in January 2022, and it is important to implement strategies to address these challenges. In the midst of all the debate on this topic, the question arises as to what can be done in terms of recruitment strategies to get as many HVs as possible into Phase 1 trials.

Objectives: The purpose of this work is to examine how HVs recruitment is optimized in real-world settings, how clinical research stakeholders deal with recruitment difficulties, and where it can be optimized.

Methods: After acquiring knowledges through the analysis of existing literature and the insights gained from the SWOT analysis, interviews were conducted with various professionals. Individuals were contacted through various channels, including the large database known as Clinicaltrial.gov, as well as contacts in the BAREC and Healexia communities. In all, 9 interviews were carried out. The qualitative nature of this study enabled us to compare what has been seen in the literature with the testimonies and real-life experiences of sponsors, CRAs and PIs, various stakeholders involved at different levels in the recruitment process.

Analysis: In general, experts confirm that there are recruitment problems to overcome in Phase 1. Depending on the type of respondent, disparities between answers were sometimes identified. This interesting finding shows that, depending on the position you occupy, you will not have the same ideas for improving the recruitment process. In addition, the EU CTR clearly has consequences for the work of professionals, which seems to have an indirect impact on recruitment in the end.

Conclusion: Failing to recruit HVs in the early stages can have serious consequences for the remaining research. But there is no one-size-fits-all solution: the field is constantly evolving, and every trial is different. Perhaps the strategies to be implemented will not be the same from one trial to the next? What is more, it is difficult to really assess the weight of the new EU CTR, as it is a new system that needs a transition period to be fully implemented and used with ease.

Keywords: Phase 1 trials, SWOT analysis, EU CTR, Recruitment strategies, Interviews.

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List of abbreviations

EMA – European Medicine Agency

ICH-GCP – Internal Council on Harmonization – Good Clinical Practice

EC – Ethics Committee

EU CTR – European Clinical Trial Regulation

EU CTD – European Clinical Trial Directive

MS – Member State

EU – European Union

CTA – Clinical Trial Application

CTIS – Clinical Trial Information System

RMS – Reporting Member State

CRU – Clinical Research Unit

SAEs – Serious Adverse Events

CRF – Case Report Form

PI – Principal Investigator

CRO – Clinical Research Organization

CRA – Clinical Research Associate

ICF – Informed Consent Form

IEC – Independent Ethics Committee

IRB – Institutional Review Boards

FAMHP – Federal Agency for Medicine and Health Product

SWOT – Strengths, Weaknesses, Opportunities and Threats

QRI – Quintet Recruitment Intervention

RCT – Randomized Clinical Trial

CTU – Clinical Trial Unit

GREET – Guidance to Recruitment Examining Experience at clinical Trials site

CTTI – Clinical Trials Transformation Initiative

OCEAN – Openness, Conscientiousness, Extraversion, Agreeableness and Neuroticism

TPB – Theory of Planned Behavior

BAPU – Belgian Association of Phase 1 Units

BAREC – Belgian Association of Research Ethics Committee

HVs – Healthy Volunteers

Eufemed – European Federation for Exploratory Medicine Development

GDPR – General Data Protection Regulation

Introduction

1. Clinical trials overview

1.1 Definition and conduct

As defined by the European Medicine Agency (EMA), a clinical trial is a study performed on human volunteers to investigate the safety or efficacy of a medicine (1). These studies are critical for the drug development in order to obtain a marketing authorization. This is a lengthy process which can take up to ten years. Clinical trials can be performed on human volunteers only after suitable non-clinical studies on animals (2,3). Clinical trials are divided into four different phases:

- Phase 1 is devoted to the determination of the safety and tolerability of the product on a small number of participants (10 to 100). The drug is administrated using a dose escalation in order to find the maximum tolerated dose. Indeed, the dose is increased from a reference dose calculated on the basis of data collected during animal experiments until it is tolerable, without any side effects. Usually, participants in phase 1 are healthy volunteers.

- Phase 2 involves a larger number of patients (more than 100) suffering from the related disease. Patients are exposed to different safe doses previously calculated in phase 1. Safety and side effects are still investigated during this phase.

- Phase 3 is the phase prior marketing authorization evaluating the therapeutic effect. Benefits are weighted against a small number of adverse events to ensure the safety and efficacy of the drug. A comparison of the experimental drug with an existing drug or with a placebo is performed. Increasingly, the use of placebo becomes unethical when there is an effective treatment already on the market. This phase includes more patients than previously, around 1000.

- Phase 4 is the post-marketing phase which aims to investigate the long-term efficacy of the drug in a real patient population. This phase allows a follow-up for side-effects occurring in patients (3–5).

1.2 Regulation

The International Council on Harmonization of technical requirements for registration of pharmaceuticals for human use (ICH) provide some international (for Europe, Japan and United-States) guidelines in order to well conduct a clinical trial, the Good Clinical Practice (GCP). The main objectives of this GCP are to protect the subjects enrolled in the trial and to guarantee the credibility of data generated during this one. Development of GCP guidelines derives from the Nuremberg code initially voted in 1947 to denounce clandestine experimentations occurred on human during the World War II in concentration camps. Declaration of Helsinki from 1964 is also part of the history of GCP. Finally, GCP has been inspired by the Belmont report written in 1979. The consent of participants is a key concept of the GCP as well as the review of the trial by an Ethic Committee (EC) (6).

In Europe, since January 31st, 2022, clinical trials conductance occurs under a new Regulation: the European Regulation on Clinical Trials No 536/2014 (EU CTR) which replaces the previous European Directive on Clinical Trials 2001/20/CE (EU CTD). The main objective of this new regulation was to provide a harmonization between all Member States (MS) of the European Union (EU) in terms of clinical trials application. Indeed, submission of Clinical Trial Application (CTA) by sponsors to authorities changed. Right now, submission of only one application dossier for all MS is possible through the Clinical Trials Information System (CTIS) online (7). This latter is divided into two parts. Part I is Europe-specific and contains all information about the study protocol, the technical requirements, etc. All those documents are gathered and assessed by a designated Reporting Member State (RMS) chosen by the sponsor among all member states of the EU. Part II is country-specific and contains information about more ethical concepts such as recruitment method, subject information, payment modalities, etc. Each MS concerned by the trial conducts the assessment of this second part and can accept or reject the decision of the first part. Those two different parts are submitted together but Part II is consecutive to Part I meaning that the second part is assessed only when part I has been fully reviewed (8).

When comparing this Regulation with previous Directive, changes are observed (9). In the EU CTR, new definitions arise, and they clarify the terms "clinical study" and "clinical trials", this latter being a kind of clinical study. The subject of the trial and its protection is one of the main focus in the new Regulation which remains almost the same as with the old Directive (9,10). And the new Regulation provides also more transparency (10).

The implementation of this new regulation required a transition period before to reach its full application. Indeed, from January 2022 sponsors had the choice to submit new trials trough the CTIS or with the old directive. But from January 2023, it is mandatory to submit new trial application under the EU CTR. Finally, it is only from 1st January 2025 that all clinical trials, even those already approved under the Directive, will be transitioned to the EU CTR and sponsors will provide information on the CTIS (7).

1.3 Situation in Belgium

In 2017, Belgium ranked second in Europe for clinical trials per capita. This strength is due to the good scientific and regulatory environment offered by the country in terms of available hospitals, universities and pharmaceutical companies. At that time, Phase 1 trials accounted for the vast majority of trials launched in Belgium, just behind Phase 3 trials (11) (12).

1.4 Healthy volunteers' studies

Phase 1 clinical trials occur on healthy volunteers, except for oncology trials enrolling patients. It allows the evaluation of tolerability, the determination of the therapeutic dose, the pharmacokinetics and the pharmacodynamics of the tested drug administrated in humans in the absence of any disease (13,14).
The course of a phase 1 clinical trial usually follows different steps: a pre-screening in the databases, a screening in the population of subjects who wish to enter the phase 1 after signature of the informed consent by both participant and investigator. This screening is based on medical examination performed during an outpatient visit to the Clinical Research Unit (CRU) to determine whether or not the participants meet the eligibility criteria (14). These eligibility criteria must be specified in the study protocol in order to assess individual's ability to

participate in the trial. As healthy volunteers, eligibility criteria often refer to the absence of clinical signs that are assessed during the medical examination. Based on baseline range, the results of the participant's medical examination will determine whether they can participate in the trial (15). Afterwards, volunteers go home and if eligibility criteria are met, they will be contacted by the CRU. They may then be admitted in the CRU where they will receive the drug and be observed for any possible effects. Finally, they can leave the CRU and follow-up is initiated (**Figure 1**)(14).

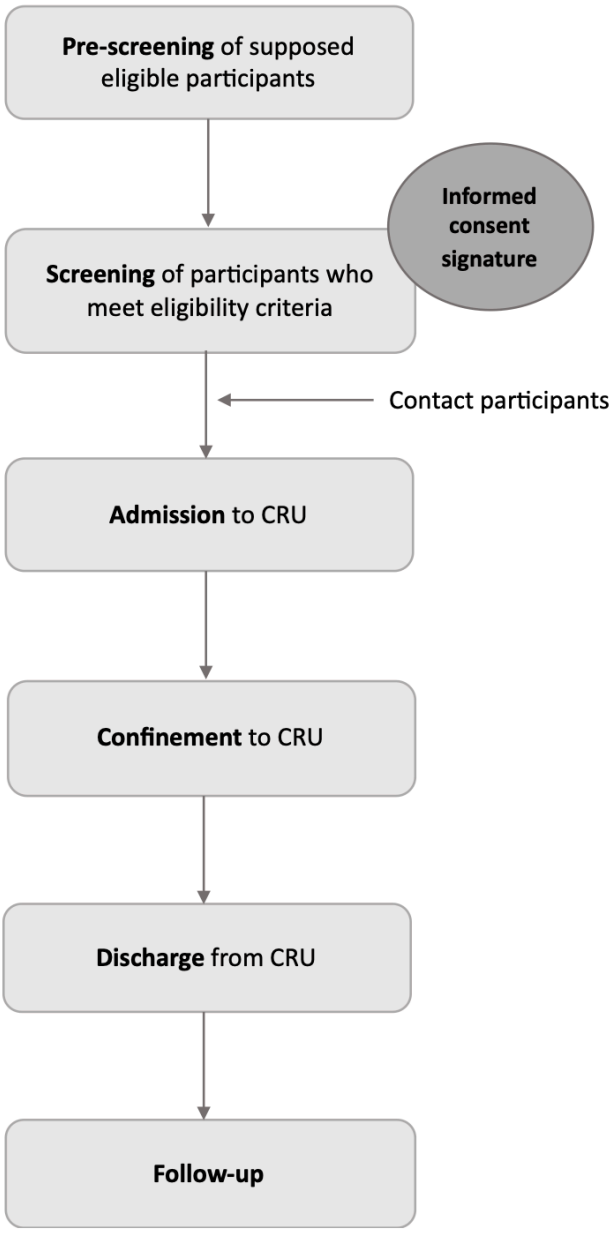

Figure 1 (adapted from Karakunnel JJ et al.): General design of healthy volunteer studies (14).

As Phase 1 trials are generally the first studies on humans, they are a highly controlled process to ensure safety and the least possible risk for the participant. The observation of Serious Adverse Events (SAEs) is rare (14). SAEs, as defined by the EMA, are those that can lead to death or those that are life-threatening and require hospitalization (16). In Phase 1, the risks are more likely to be short-term side effects and every precaution is taken as this particular phase is closely monitored in hospitals while participants are hospitalized in the CRU. Most of the

risks that the participant may face during this phase are mentioned in the consent form. This latter is intended to summarize information about the trial, including some information about potential risks, in order to inform the participant and help him or her make a decision about participating in the trial. Signing this document indicates the participant's agreement to participate in the trial (17).

Healthy volunteers enrolled in those early phases receive financial compensation for their participation. The confinement, particularly the time spent in the phase 1 unit, plays a role in determining the amount of this latter (13,17). Indeed, in most of phase 1 trials, a confinement period is required, participants must stay hospitalized during the time of the trial. Moreover, this requirement may be burdensome and inconvenient for participants and may cause them not to take part in the trial (18).

2. Stakeholders

2.1 Sponsors

Sponsors (which could be individuals or companies) are responsible for initiating and financing a clinical trial. One of their main responsibilities is to plan and design the trials. They are responsible for finding qualified investigators to ensure the recruitment and the medical follow-up of the trial, as well as other people qualified to carry out the trial, such as statisticians, managers, etc. When they launch the trial, they must submit their project to the competent authorities and the EC to obtain the authorization to start. All participant data collected during the trial must be recorded anonymously on the Case Report Form (CRF) by the principal investigator (PI). The CRF is the property of the sponsors, but completed by the PI, it acts as a link between these two stakeholders. Throughout the trial, the sponsor ensures that reports are drawn up, and may carry out internal audits to monitor compliance with the study protocol (19,20). The sponsor is also obliged to give a summary of the trials, whatever the results at the end, which will be available in the EU database (8).

Sponsors may delegate some tasks to a Contract Research Organization (CRO), which may be an academic institution or a pharmaceutical company, but even in this case, the primary responsibility remains with the sponsor. The responsibilities that sponsors may have throughout the trial are summarized in the ICH GCP (20,21). These CROs have Clinical Research Associates (CRA) who can monitor the trial on site and ensure that everything is going according to the protocol. CRA's reports are sent back to the sponsors (22).

2.2 Principal investigator

The principal investigator (PI) is a physician who has been chosen by the sponsor to conduct the trial on site. Most of the time, he has sub-investigator(s) capable of carrying out the tasks delegated to him. All PIs are qualified and trained to carry out their activities, and they also ensure the qualification and training of the people they employ.
The PI's responsibilities are manifold and consist of first and foremost in having participants sign the Informed Consent Form (ICF), after having informed them of the trial and its general objectives. This compulsory document indicates that participants have made the decision themselves, and that they are willingly participating to the study. In addition, PIs are responsible

for subject recruitment, general trial conduct and medical care, recording their activities and sending reports to sponsors. Audits and inspections are organized to monitor the investigator's activities (17,20,23,24).

The GCP guidelines contain a point summarizing all the aspects that the PI must have in mind to perform a trial. PIs must be in possession of their GCP certificate, which the sponsor is responsible for checking. This latter is valid for 3 years, after which it must be re-evaluated (25).

2.3 Ethics committee

According to the Belgian law on human experimentation passed in 2004, Ethics Committee (EC) must have a minimum of 8 and a maximum of 15 members, both men and women (26). Those Independent Ethics Committees (IEC), also known as the Institutional Review Boards (IRB), bring together a wide range of stakeholders from different backgrounds, not just scientists. They must be independent of the site and will examine everything to do with the trials, including all documents used in the trials, all strategies to communicate about the trials, but also the investigator's proper qualification. All this, before the trial begins, to guarantee the safety and rights of participants. In a way, they give the green light to get off to a good start (6,20).

2.4 Competent authorities

The competent national authorities are specific to each country. In Belgium, this is the Federal Agency for Medicines and Health Products (FAMHP), which is responsible for examining all trials carried out. Created in 2006, its role is to ensure the quality, safety and efficacy of medicines and health products (27).

2.5 Participants

In Phase 1 trials, participants are healthy volunteers. In this specific case, "healthy" means that those people do not suffer from a disease and will therefore not derive any therapeutic benefit from the trials (13).
Without them, there would be no trial at all. They are the backbone of the trial and must be properly recruited to ensure enough participants for the research results to be representative. It is important not only to recruit them, but also to retain them throughout the trial process.

3. Recruitment process

3.1 Its significance

Nayan Chaudhari *et al.* divided the recruitment process into different steps: finding participants that fulfill eligibility criteria, discussing the trial with participants, conducting a medical examination of the participants and finally enrolling the participants if they meet eligibility criteria (28). As the aim of a clinical trial, especially phase 1 trial, is to study the impact of a drug in development on the human body, the participants recruitment is the key to start those

first-in-human studies. But the task is not that easy and usually takes time for recruiters. Unfortunately, when there are recruitment issues, it generates delays in the drug development, and it has a cost. This is the reason why an optimized recruitment of healthy volunteers should be implemented in phase 1 units (13). Indeed, participants recruitment is both the most important part in launching a trial and the most difficult to accomplish in most trials (29).

3.2 SWOT analysis

To introduce the potential difficulties encountered in the recruitment process, a SWOT analysis could be performed. The SWOT analysis identifies the internal strengths (S) and weaknesses (W) as well as the external opportunities (O) and threats (T) that an organization or a process faces. It is kind of state of the art that can be used to conduct causal analysis to determine which practices should be continued or abandoned in order to improve the process (30). From a CRU or sponsors perspective, this SWOT analysis could determine the status of enrollment in phase 1 trials and whether trial initiation is feasible given the potential issues (29).

3.2.1 Weaknesses

First, internal issues, referred as weaknesses, represent the causes of recruitment failures encountered in phase 1 trials (**Table 1**). There are several reasons of recruitment problems that could be investigated in order to understand the way we could improve it. Five groups of causes linked to recruitment failures were identified in a three-countries study in Switzerland, Germany, and Canada. Funding-related causes are those associated with insufficient funding to cover all the trial over the time. Design-related causes are associated with unreachable eligibility criteria and a design too complex to be implemented in reality. Factors linked to the research environment reflect the fact that regulatory process and ethical concept are becoming more stringent, making recruitment more difficult, even if the basic idea is to better protect the subject. This last factor is a threat rather than a weakness because it is external. Trial team and recruiter-related causes result from a lack of collaboration within recruitment teams and a drop in motivation from the beginning to the end of the trial. Finally, participant factors include the time spent on visits, the feeling of being misunderstood, the distance with the investigators, etc. (31). Other participant-related causes, especially in healthy volunteers, are usually their age and gender that may prevent them from entering the phase, the fact that they participate more for the free medical examination than for the trial itself, but also because they try to negotiate the amount of their compensation and are not satisfied, so they refuse to take part in the trial. As with recruitment failures, retention failures can occur later in the course of the trial. Retention refers to the fact that participants stay and do not drop out for the duration of the trial. Retention failures are usually due to several factors such as a lack of communication between participant and researcher, the lack of time for the participant in the face of a lengthy trial, etc. (28).

3.2.2 Strengths

So, the importance of establishing a plan from the beginning by gathering all the aspects in favor of a recruitment failure is significant to overcome the problems and at least to prevent them (31). Many solutions have already been proposed to improve the recruitment process and build internal strengths in this process (**Table 1**).

3.2.2.1 Recruitment tools

Most of these tools have been developed to improve recruitment in all phases, but they could certainly be transposed to phase 1 trial. If they work for recruitment in all subsequent phases, they should work for phase 1 in particular.
First, the "Quintet Recruitment Intervention" (QRI) has been developed in order to simplify the participants recruitment in Randomized Controlled Trials (RCTs) by assessing and understanding the recruitment difficulties encountered during a trial (28,32). Indeed, QRI is a step that can be added to the trials to ensure more efficient recruitment or simply to assess why a trial should be stopped. The development of this tool required adjustments to the initial version and was tested in various trials. At the end, authors provided a plan of improvement based on these difficulties. The process of the QRI is divided into two phases. A first phase which aims to understand the recruitment followed by a second phase which aims to deal with the different actors implicated in the Clinical Trial Unit (CTU) in order to implement the tool to improve strategies recruitment. The use of this tools in 13 RCTs showed a real improvement in the management of the recruitment challenges (32).

The GREET project (Guidance to Recruitment Examining Experience at clinical Trials site) also aims to identify the main barriers at the recruitment sites in order to find solutions to avoid them. The project was initially developed thanks to barriers identified to interfere with well recruitment in a trial. These barriers were assess following a literature review and a survey of professionals involved in the conduct of clinical trials and potential participants. They considered the point of view of the potential participants or people who already participated in a clinical trial. Based on the survey results they created a guide containing 4 main themes. First of all, before starting the trial, site staff should determine its feasibility by assessing the recruitment capacities and local resources. Then, comes the "start-up" stage which must be carried out prior to recruitment in order to define everyone's responsibilities, obtain ethical approvals, and ensure that the budget allocated to the recruitment is sufficient. The next step is the recruitment method itself which is site-specific and includes advertising strategies. Finally, participants must be the priority of the trial and can therefore be part of the recruitment team (33).

The CTTI (Clinical Trials Transformation Initiative) has also proposed strategies for recruitment planning. Time spent on planning activities should not be neglected. In their study, they identified three areas to focus on in order to overcome the barriers to recruitment already discussed earlier in this work. The first recommendation is the trial design and protocol development domain, the second concerns the trial feasibility and site selection and the third one, the recruitment communication planning (**Figure 2**). All of these proposed frameworks must be put in place before the trial begins, otherwise it will be difficult to implement them once the trial is underway (34).

Figure 2: Three framework area for strategic recruitment planning proposed by CTTI (34).

3.2.2.2 Understanding participants

The term "understanding participants" refers to the idea of a targeted approach to the recruitment of healthy volunteers. By fully understanding participant's personal traits, motivations, peer influences, and fears, we could more easily attract them to trials and, at the same time, reduce the time wasted searching for people interested in participating in a phase 1 trial. This would likely improve recruitment and retention of participants.

The healthy volunteers in the Phase 1 trials appear to have certain typical character traits. Personal traits such as anxiety and depression play a role in the apprehension about participating in phase 1 trials. Indeed, one study found that people with anxiety, difficulties to have social interaction and with depressive tendencies are unlikely to participate in phase 1 trials (35). On the other hand, other character traits have been correlated with the willingness to participate. Based on the Big Five model (BIFI), also called OCEAN model, because it describes the five following personality traits: Openness, Conscientiousness, Extraversion, Agreeableness and Neuroticism, the characterization of participant's personality traits was performed through a questionnaire. The results show that participants, both patients and healthy volunteers, often experience personality trait such as openness, conscientiousness, extraversion and agreeableness but not that much neuroticism (36).

Since the healthy volunteers enrolled in phase 1 are not carriers of any disease, they do not have the same motivations as patients recruited in subsequent phases. Patients may find therapeutic benefits while healthy volunteers may not. Thus, one of the principal motivations in phase 1 is the financial compensation. In addition to these motivations, other factors may also influence

the participant's decision such as: altruism, curiosity, possibility of having access to health care while lack of time and risks taken may rather dissuade them from taking part (14,37). In a more recent study, they pointed out that in addition to the financial aspect, the willingness to contribute to research and help patients, the trust in the physician has also a significant impact on the decision to participate in phase 1 trial. Indeed, the 213 healthy volunteers surveyed in the study of Felix Bergmann *et al.* seem to agree more that trust in the doctor and contribution to scientific research influence their decision to participate rather than financial intensives they may receive in exchange for participating. 78% of participants (166 participants) are agree or strongly agree that their willingness to participate comes from the trust in their physician, compared with 56% (119 participants) who agree or strongly agree to participate in trials for financial reasons (**Figure 3**) (36).

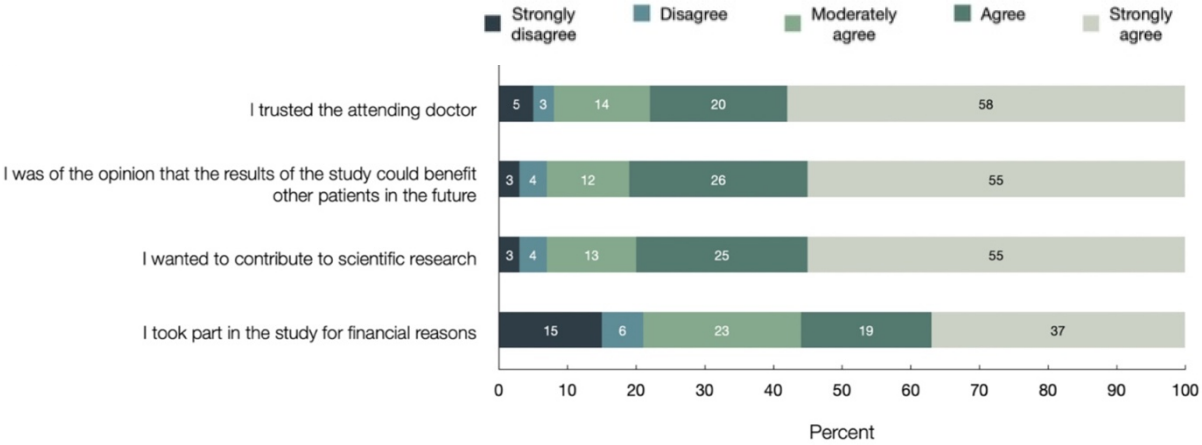

Figure 3 : Motivation of healthy volunteers. Responses to the question "What are your motives for participating in a study?" (36).

Understand the motivations of participants to enter in a trial as well as their personal characteristics can help recruitment and informed consent process. In a same way, understand why participants quit trials can also improve the retention process. Usually, reasons why people do not participate anymore to a clinical trial are adverse events, time of the trial, compelling medical procedures performed during the trial, etc. (28).

Beyond a behavior, there are intentions which are controlled by some beliefs. Three different categories of beliefs are mentioned: the attitude, the subjective norm, and the perceived control. This represents the Theory of Planned Behavior (TPB). The behavior, in this context, is the decision to take part in phase 1 trial. The qualitative study realized by Kerry J Manton *et al*. in 2019 highlights main themes influencing the decision-making by participants in the three beliefs' categories. Money remains the first motivation followed by altruism and the benefit of receiving medical check-up while the time spent, and potential side-effects are the main constraints to participate. The subjective norm is principally under control of family and friend that can influence the decision both in a positive or negative way. This TPB occurs unconsciously in everyone's head. This highlights the origin of participant's motivation (37).

Participants may be afraid to participate in a phase 1 trial. Even though the risk has been shown to be as low as possible thanks to strict monitoring in phase 1, some people are still scared off. The risk assessed by healthy volunteers, as well as their knowledge of the dose received, may deter them from participating in the trial. Although phase 1 trials are likely to cause only short-term effects, the occurrence of long-term effects is questionable and may also discourage participants from taking part in phase 1 trials (17).

3.2.2.3 Communication skills

Communication developed by the researchers is really the beginning of the recruitment process and the key to keep participants throughout the trial, to have good retention of the participants (38). The relationship established between investigator and the potential participant is a determining factor in the willingness to participate in a clinical trial. Indeed, as we previously explained, the trust placed in the physician can influence the participant's motivation. One of the main motivation of healthy volunteers is indeed their trust in the attending doctor (**Figure 3**) (36). Participants who are well monitored by the physician and for whom there is a comprehensive and appropriate communication tend to leave the trial less (28).

Basic methods of advertising are also part of the communication put in place to raise awareness of clinical trials and phase 1 trials. Vulgarization is important and represents a pillar in recruiting sufficient number of study participants. Advertising may include strategically placed flyers and newspaper advertisements in order to inform potential participants about the trials (28).

3.2.3 Threats

3.2.3.1 Research environment

It was pointed out that one of the causes of recruitment failures was linked to the research environment, which mainly includes the regulatory environment. Ethical approval procedures are becoming increasingly stringent in different countries, and can be an obstacle for recruitment sites, as they can delay the process (31).

3.2.3.2 Ethics with new EU CTR

Eugenijus Gafenas *et al.* explain that there is probably a marginalization of the Ethics Committees (ECs). As the submission of the application is divided in two parts, one part which is under control of the Europe and the other one which is country-specific, ethical aspects may be minimized in some countries (39). The main change in Belgium is the ethical evaluation process. The CT college has been set up to act as a link between the ECs and the FAMHP. This CT college selects the EC that will be responsible for evaluating the trial which is a big difference from the Directive, where the EC was part of one of the centers involved in the study (40).

3.2.4 Opportunities

3.2.4.1 More transparency with new EU CTR

In the literature, it is found that the EU CTR has an advantage that the EU CTD did not have: more transparency for phase 1 clinical trials. Indeed, the CTIS allows public to search information about clinical trials on the web. Even if the access to information of phase 1 trials is unusual for public research, it remains better compared to information retrieved about phase 1 in the EudraCT database where only information about mixed phase 1/ phase 2 trials were found. Thanks to the CTIS tools proposed with the new Regulation, there is more transparency for trials in phase 1 (41).

3.2.4.2 Social media

Today, the use of social media can expedite the recruitment process. EC approvals remains a requirement for such strategies (28). In 2017, we knew that 72% of adults in Belgium used social media, which highlights the fact that it can reach many people and inform them about the trials. Thus, using social media seems to be a good tool to recruit people. Social media used for the recruitment in clinical trials are mainly Facebook, Twitter, Youtube, Instagram, etc. However, Katja Reuter stated some challenges with them. First of all, guidelines need to be implemented to know how social media recruitment development should be done and to offer best practices on what we can or cannot do in terms of ethics. Indeed, social media could be used to target participants with the characteristics we seek, but in doing so, it is likely to violate the privacy of individuals. Despite these challenges, social media should be further exploited because there are potential benefits to using it in the recruitment process, at least in combination with basic methods (42). In fact, this was evident in the study by Elizabeth Mirekuwaa Darko *et al*., where half of the trials reviewed featured recruitment that combined social media with other recruitment methods. In practice, researchers can do targeted or untargeted advertising with social media. The review of several trials provided some recommendations that may be useful to overcome challenges encountered with social media recruitment such as the implementation of an authenticity process by researchers and a regular verification of the privacy policy of the social media in question (43). This was the aim of Elizabeth Flood-Grady *et al*.' study, which sought to provide a framework for using social media as a recruitment tool. Interestingly, in addition to being a tool for recruitment, social networks also serve as a platform for "information about health and science" which remains an important task in spreading the words about trials and, in the process, recruiting more participants interested in contributing to research (44).

It is reasonable to assume that all these communication strategies in place can increase participation rate in phase 1 trials if they are used appropriately. Since recruiting participants requires interaction with them, all channels are welcome and should be exploited. All of these new technologies have the potential to reach more people in a more targeted way, so they should be used as an opportunity for the Phase 1 recruitment process.

3.2.4.3 Participant involvement

Patients' involvement in clinical trials shows benefits. They are not only considered participants, but also collaborators. Because they already have participated in a study, they are familiar with the study process and can probably assist the researcher in developing the protocol. Indeed, taking patient's experiences and advice into account is seen as a valuable aid (45,46). Patients' involvement has been more developed in later phases, but participants involvement in the early phases is promising. Patients in the later phases and healthy volunteers in the initial phases of trials are the most legitimate people to know what is or is not good for them and what motivates them to participate in a trial. They could have a positive impact on potential participants' decision-making by persuading them and reassuring them through discussion (45). It makes perfect sense to involve patients, such as healthy volunteers, in research because they are the primary stakeholders in the research, reinforcing the concept: "Nothing About Us Without Us" (46).

Strengths - Tools helping recruitment process - Understanding participants - Communication strategies	**Opportunities** - EU CTR (transparency) - Social media technologies - Patients involvement parallel
Weaknesses - Funding-related failures - Design-related failures - Staff-related failures - Participant-related failures	**Threats** - Research environment-related failures - EU CTR (ethics)

Table 1: SWOT analysis of recruitment in Phase 1 summary

3.3 Optimization

Optimizing recruitment in Phase 1 trials means improving the quality and efficiency of recruitment, reducing the time spent, saving money and avoiding delays in subsequent phases. Optimizing recruitment also means selecting healthy volunteers who are willing to stay for the duration of the trial.
Optimizing recruitment in Belgium would enable us to maintain our second-place ranking in Europe, and keep sponsors happy so that they return to our country for phases 1.

Objectives

The main objective of this work is to qualitatively analyze and evaluate the current situation with regard to the optimization of the recruitment process in phase 1. On this basis, we will be able to think about new strategies to implement, depending on what is feasible or not with trials on healthy volunteers.

The first part of the work was devoted to understanding what goes wrong in Phase 1 recruitment, but also to the methods that can be used to optimize it. Understanding root causes rather than superficial ones. The SWOT analysis, based on a literature review, answered this question and gave us an overview of the topic.

With the knowledge gained from this analysis, the aim of this second part of the work is to see what the various stakeholders in the field think about recruitment failures. It will provide an understanding of what strategies pharmaceutical companies, sites and investigators are using to improve recruitment of healthy volunteers.

So, on the basis of what has been done in the first part of the work, mainly the analysis of the literature on recruitment failures and strategies encountered during Phase 1 trials, the interviews with experts aim to give an overview of the situation in real contexts. Having examined the literature on recruitment difficulties and strategies, we can now compare it with the experiences of different people involved in clinical trials at different scales and see how they deal with recruitment difficulties in Phase 1.

Methods

1. Literature review

First of all, the methodology of this work included research in the literature in order to collect as much information as possible. The information collected includes recruitment challenges, EU CTR changes, existing recruitment tools and strategies already in place, enabling us to analyze the situation regarding recruitment failures and optimize these strategies. Advanced searches were carried out in various scientific databases, including PubMed, Scopus, Cochrane, BioMed Central and ScienceDirect. Official journals were consulted, such as the Official Journal of the European Union, Applied Clinical Trials, New England Journal of Medicine, JSTOR, as well as official websites, including those of the European Medicines Agency (EMA) and the Federal Agency for Medicines and Health Products (FAMHP).
This was made in order to provide sufficient information to be compared with the reality of the field through interviews.

2. Interviews

Next, the methodology included interviews. The qualitative nature of the interviews enabled us to obtain precise answers and information from the experts interviewed. In addition, the visual aspect offered by the video call interviews made it possible to strengthen the contact with the respondents, which is not the case with a questionnaire that is simply sent out. During the interviews, the possibility to travel in the discussion was easier and allowed a better interpretation of the answers and emotions of the interviewees.

2.1 Interview guide

In the light of a semi-directive approach, an interview guide has been developed and was modified according to the interview progress and with emergent idea as the work progresses. This guide was made up of several questions classified according to 6 different themes, the sentences in green simply served to contextualize the question asked (***see Annex 1***). For each theme, the first question was dichotomous, in order to minimize answers disparities and facilitate the analysis of the answers. Nevertheless, we noticed that our interviewees tended to respond in a more nuanced way. The following questions of each theme were open questions related to the first one in order to deepen the subject and understand what the professionals have experienced. The same questions were asked to both groups of people interviewed because the first two questions discriminate between people. In this way, it facilitated the analysis and made it more reliable without any biases. The other five themes of questions were built on the basis of this work. Since the main factors influencing the recruitment failures in phase 1 are participant-related and staff-related factors, as well as design-related factors, questions are focus on these themes and on the strategies to overcome the failures. The impact of the EU CTR is also part of the topic as well as the participant engagement in the recruitment team. As the interviews progressed, questions and discussions were added to what was originally planned in the interview guide.

2.2 Invitations to interview

How were people reaching out?
Reviewing the "clinicaltrials.gov" database enabled us to find PIs and sponsors using the advanced search, selecting only phase 1 trials taking place in Belgium and having completed or finished status, as we wanted to assess how the process went, but also those still in the recruitment phase, as it is interesting to understand failures and delays in recruitment. A total of 1,292 trials were found on September 2023.
In order to contact the sponsors, additional research was carried out to obtain their contact details, which were generally indicated on their web page, if they had one, and the invitation to the interview was sent to them by e-mail and varied according to whether it was an individual or a company that was contacted (***see Annex 2)***. It is important to note that, in some cases, no e-mail address or telephone number information was found, making it impossible to contact them. In addition, some companies were listed as permanently closed on the internet, meaning that no further contact information was available either. In the end, 276 sponsors were found and 198 were contacted.
Regarding contact with principal investigators, whose names were listed on clinicaltrials.gov, although sometimes no information about the principal investigator was provided, an invitation to contact those listed was sent via LinkedIn, accompanied by a short message of less than 300 characters (***see Annex 3)***. Then, if people agreed to connect with us, we sent them the full message inviting them to participate in the interview (***see Annex 4***) or gave them a brief phone call to explain the purpose of the contact. Some of them were also contacted directly by e-mail with the full invitation message if they didn't have a LinkedIn account. And sometimes, unfortunately, there was no contact information at all. A total of 235 PIs were found and 191 were contacted.

Next, the Belgian Association of Phase 1 Units (BAPU) was approached. As its name suggests, this is a Belgian organization of various members involved in clinical research, whose aim is to help conduct Phase 1 and provide training in this area. For 3 years now, BAPU has been part of the Healexia community, a group of Belgian professionals involved in all aspects of research and development (47). Contacting them via the e-mail address available on their web page gave us access to a large number of contacts for phase 1. This enabled us to carry out 2 interviews.

Finally, the website of the Belgian Association of Research Ethics Committees (BAREC) was consulted to find out about the various ethics committees in Belgium. This organization was created in 2016 to pool their powers to ensure the well-being of participants involved in clinical research. They often organize meetings to debate and discuss topics related to ethics in human research (48). The e-mail addresses of the ethics committees were found by further research on the websites of the various institutes and enabled us to contact them. They were invited to take part in the interview. Thirty-five Ethics Committees were contacted.

In addition, during the interviews we used a tree-based approach; we asked people to put us in touch with other experts they knew who could answer our questions.

2.3 People targeted

Who should be interviewed?
The experts interviewed here can be divided into different groups:

- Sponsors (pharmaceutic and academic) and Clinical Research Associate (CRA)
- Principal Investigators (PIs)
- Ethics committee (EC) members

Why those people?
They were representative of the main players involved in phase 1 trials. They were best placed to cover the three main areas of interest: safety and rights of participants, financial aspects and ethical considerations relating to the recruitment process.

2.4 Interview and analysis processing

All interviews were conducted via Teams (video call), which enabled us to easily record and transcribe the meeting afterwards (***see Annex 5***). Before starting the interviews, a brief reminder was given about the subject of this master's thesis.
The recording was only made with the permission of the persons concerned at the start of the interview. All transcriptions were made using the "Ubiqus IO" method. This is not an exactly word-for-word transcription, and eliminates repetitions and grammatical errors by rephrasing sentences (49). The transcript was made in the language in which the interview was conducted. The majority of interviews were conducted in English, but some were also conducted in French, depending on the preference of the interviewees. Transcribing the interviews did not require the use of any software or professional assistance. We chose to do it ourselves, in order to get a feel for the field we were working in, and to gain some perspective on what we would be analyzing later on. Transcribing 10 minutes interview took about 1 hour. All transcripts have been anonymized. No names of companies or institutes have been quoted in this paper.
The interviews were interpreted by reading all the transcripts and retaining the main information useful for answering the subject's question. This information was then compared with that already collected in the literature. The idea was really to integrate the experts' main opinions into the text, without repeating the exact phrases of what they said. Instead, we extrapolate what people have said, to avoid interpretation bias and out-of-context information.
This is a subjective method of working, which can potentially be a kind of limitation, but which is also the aim of the semi-qualitative approach.

Analysis

1. Answers to interviews' invitation

A total of 428 e-mails were sent to all the experts involved, details of which are given below, enabling us to carry out 9 interviews (**Figure 4**). After sending out the last invitations at the end of September, we gave people 3 weeks to respond, and the last interviews were scheduled. Subsequent responses were not taken into consideration and no more interviews were scheduled. The deadline for making the interview was the 31st of October. This was our out-of-time date arbitrary chosen to give the time for analysis.

1.1 From clinicaltrial.gov

Sponsors
Of the 198 invitations sent out, only 27 (13.64%) responded. Of these 27 respondents, only 4 interviews were carried out, as 23 replies were negative (**Figure 4**). Often, people did not have the time or felt unable to answer given the subject matter.

Principal Investigators
One hundred and ninety-one invitations were sent out and only 17 PIs responded, *i.e.,* 8.9%. Of these 17 responses, only 2 interviews were carried out (**Figure 4**). The reasons were the same as for the sponsors, some of whom felt unable to help given the subject matter. In general, they do not deal with healthy volunteers.

1.2 From BAPU - Healexia early phase

Thanks to the e-mail I sent them, they automatically forwarded my request to all their contacts, resulting in 2 interviews with PIs (**Figure 4**).

1.3 Tree-based approach

Thanks to our contacts with certain experts, and with only 3 invitations sent out, this technique enabled us to carry out 1 interview (**Figure 4)**.

1.4 From BAREC

Ethics Committees
Thanks to the BAREC list of ECs in Belgium, 35 were contacted, but only 5 responded (14,28%), even after re-launching them. Unfortunately, none of these replies were positive or were simply out-of-time, so it was not possible to conduct interviews with EC members (**Figure 4)**.

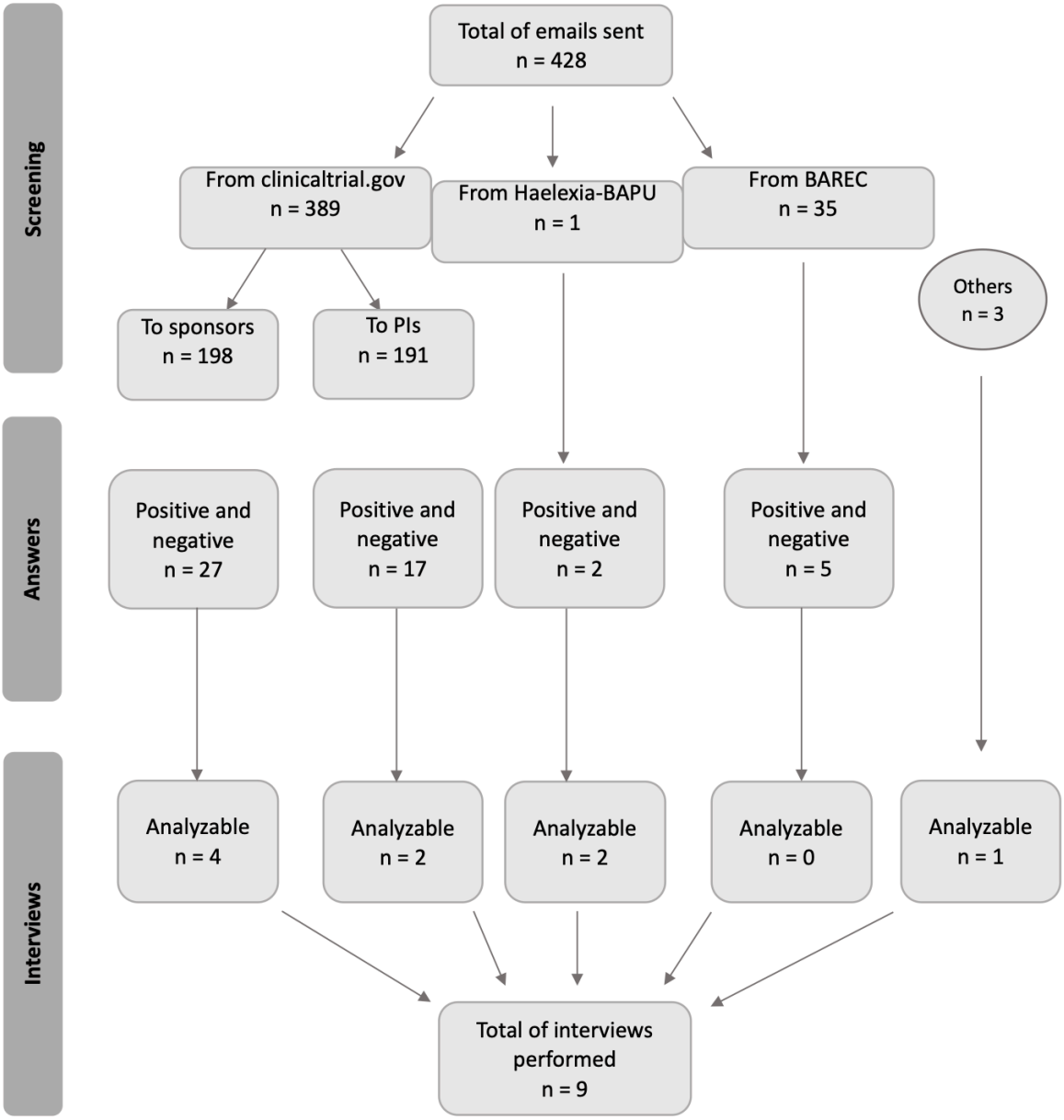

Figure 4 : Contact processing and response rate flowchart

2. Answers to interviews' questions

From a subjective point of view, we will see that the interviews and the answers given during them differed depending on whether the sponsor was an academic or a pharmaceutical company. Nor are the answers provided by site members or sponsors the same, as they have different points of view. One has direct contact with participants and is involved in recruitment, while the other provides the recruitment protocol, for example, but is not involved in the process itself. One of the PIs interviewed is involved in phase 1 oncology trials that do not include HV, but only patients. He has not been excluded from the analysis, as the information provided confirms the existence of a difference between phase 1 with healthy volunteers and patients. This indicates that it is important to investigate how to optimize the recruitment of HVs. And two of the PIs are working on vaccine trials, for which HVs are recruited.

The points presented here come from the responses analyzed after the interviews and bring together the information highlighted in the SWOT analysis in the introduction and discussed during the interview according to the interview guide developed earlier (which was sometimes slightly modified as a result of the discussion). The dichotomous nature of the first question of each theme illustrated in the questionnaire guide was intended to help identify similarities with sayings in the literature. However, during the interviews, the respondents gave more nuanced answers, which meant that we could not really take the dichotomous answers into account.

2.1 Recruitment failures factors (weaknesses)

2.1.1 Participants related factors

2.1.1.1 Time and money

A shared opinion by both sponsors and site staffs alike is that the main factors influencing recruitment are the duration of the study, which includes not only the hospitalization period, but also follow-up visits. Especially since follow-up visits are not as well remunerated as the hospitalization period. So, for a long-term trial with a long follow-up period, remuneration will be lower than for a long-term trial with a long hospitalization period. Similarly, the deprivation of doing something you enjoy because of the trial criteria will influence your recruitment rate. And this factor of such demanding trials is again linked to the length of the study, because the longer the study lasts, the more you will have to stop doing what you love, like exercising, going out with friends, having sex, etc. This represents a constraint for participants which can make them unwilling to participate.

Time and compensation fee are therefore the main factors to consider when dealing with healthy volunteers. Time includes the time they need to find to participate in the trial as part of their daily activities, but also the time you will give them to think about the participation proposal after the advertising process. They will probably talk to their family and friends about their potential participation before actually getting involved and signing the informed consent form. Finally, this notion of time is also important for them, as it is what is taken into account when calculating the remuneration they will receive for their participation, based primarily on the time they will spend in the unit.

2.1.1.2 Non-healthy

An important point made by a CRA interviewed is that recruitment failures are not only due to participants' lack of motivation, but sometimes to the fact that they are not as healthy as they think they are. Laboratory samples sometimes reveal an unexpected illness or health condition in the participant, preventing him or her from taking part in the trial. In general, this represents half of the candidates selected. This factor is being encountered more and more often as eligibility criteria become broader, such as larger age range. The more people you have of a certain age, the more likely you are to have people who are ill and therefore unable to recruit them.

2.1.1.3 Unawareness and fears

The fact that the public is unaware of the existence of clinical trials is also a weakness for recruitment. This appears to be a root cause of recruitment failures, as highlighted by several experts, particularly PIs. Making clinical trials as accessible as giving blood to the Red Cross would probably help to recruit more participants. There seems to be a need to popularize the subject.

Phase 1 is also more difficult, since the healthy volunteer only has access to animal experiments, and the drug has not yet been tested on humans. The point of a good explanation of the trial is to reassure the participant on this point, and to show him that phase 1 is also a well-controlled phase. Raising awareness of the control of these trials is important and must be really present in the mind of the PI when explaining the study and carrying out the ICF process.

2.1.2 Site related factors

2.1.2.1 "Unqualified" staff

The lack of qualified staff, probably due to a lack of resources, is another factor that has proved to be a weakness for recruitment, particularly in the case of university-funded studies. If there are not enough staff on hand to explain properly and take the time to answer participants' questions, recruitment is difficult because participants are not confident enough. It is often observed that a poorly explained trial leads to "withdrawal of consent", whereas around 80% of people will say "yes" to take part if they have been properly informed. Most site professionals surveyed agree that you really need a team working on communication and information transmission. Some have pointed out that this is probably more a threat linked to the lack of funding and resources available to academics compared to pharmaceutical companies. When the study is sponsored by the pharmaceutical industry, this weakness is easily overcome, as you will organize training for your employees to ensure they have good communication skills with participants.

2.1.2.2 Accessibility

Access to site facilities plays an important role in the recruitment rate, as one PI indicated during one of the interviews. Parking problems encountered during visits are generally a deterrent for participants. When you come for a visit and you cannot park your car, you feel like you are going home, and you will not come back for the next visit.

2.2 Impact of the EU CTR

The perception of the impact this new regulation could have is generally different for sponsors and PIs, according to the answers obtained during interviews. Generally speaking, it is felt that this regulation may be too recent to really measure its impact. At least, that is what people are hoping, that the impact they are feeling today is due solely to the new system and that, as with any new system, there is a period of adjustment. So, a reassessment may be necessary in the future.

2.2.1 Ethical review

The majority of PIs really perceive the impact of the EU CTR in terms of ethical approval, but it does not seem to have a direct impact on recruitment, it is more indirect as it causes delays and therefore gives less time for the recruitment procedure to be successful. The new EC chosen by the CT College has to be a different EC from the one at the trial site. It disrupts the process as it used to be easier and quicker to get some kind of pre-approval to already start the recruitment campaign when the study was not yet actually approved. The internal EC used to be more willing to modify recruitment material when the study was already underway, but the new external ECs are now stricter about this, and it is more difficult to modify recruitment material if necessary. The impact will therefore be greater if your recruitment strategies need to

be modified than if they are already prepared in advance and do not need to be changed for any reason. For example, one site reported that, under the Directive, when the EC was internal to its site, it was allowed to publish an advertisement with inclusion and exclusion criteria, which formed part of its recruitment material: potential participants were asked to answer a few questions about their age, BMI, etc. to prevent them from coming to the first visit "for nothing". A message simply informed them that they were unsuitable for the study and should therefore not attend the visit. But today, with the EU CTR, independent ECs generally refuse this type of strategy, as they consider it to be a kind of breach of privacy, since the participant has not yet signed the ICF at this stage.

Finally, arbitrarily chosen external ECs are sometimes less experienced and less trained than some on-site ECs. This can lead to delays in the process, as they will need more time to complete a task that the on-site EC could do, or perhaps because they ask more questions due to their lack of experience.

2.2.2 CTIS

On the sponsor side, and this is also felt by some PIs, the Clinical Trial Information System (CTIS) is the main challenge. Again, it has no direct impact on recruitment, but because of the time it takes and the delays it causes, it does have an indirect impact on recruitment. It takes time to integrate and familiarize oneself with a new system of this type. It really is a new way of working for sponsors, with cumbersome administrative procedures. Pharmaceutical sponsors may be better trained and have a bigger team to deal with it, while academics are not efficient enough and have fewer resources to submit the trial through this CTIS, which takes a long time to understand and whose platform does not seem to be the most user-friendly.

In addition, this portal makes the field of clinical trials more open, which can be seen as a threat, as competitors can see all the strategies you have used to carry out your trials and can perhaps draw inspiration from them. In a way, this may be a better way of checking submissions more easily and avoiding secrecy, as the pharmaceutical field is often regarded as secretive and murky, but it is also a good tool for competitors to steal your strategies or be dishonest.
On the other hand, this openness can be seen as an opportunity for recruitment. It provides greater transparency for participants, since it is a public platform, which can reassure some of them and, in a way, improve and facilitate their recruitment. Of course, the mandatory ICF process is already a good way of being transparent with them and is considered sufficient for some professionals.

2.2.3 Belgium place in Europe

Opinions are divided between those who think that Belgium remains the fastest and those who think that Belgium is probably diminishing a little its good capacity to run clinical trials in general. This variation is due to the fact that the system is new, and people do not really know if there is a big impact yet.
Belgium is still well placed in the field of clinical trials, according to most of the sponsors interviewed, as the CTIS process has more impact for the sponsors than for the site conducting the phase. This means that conducting the trial itself remains attractive, for example, to foreign sponsors wishing to launch a study in Belgium. One Danish sponsor said that Belgium was an interesting country in which to carry out clinical trials, like other European countries, because

communication and understanding are easier, we all have similar cultures and there is little or no time difference, which facilitates exchanges and easy travel.
Once the study has been launched and approved, the new regulations are not perceived as being very different from the directive; it is rather what happens upstream, such as managing the new EC requirements and the correct use of CTIS, that will be different and may cause delays. On the other hand, even if Belgium risks losing its leading position in Europe, pharmaceutical companies will still try to manage this situation, as will the units that are already trying to improve and take initiatives.

From the principal investigator's point of view, Belgium is probably reducing its ability to conduct clinical trials, but this is only a guess, given that this is a new regulation that only officially came into force this year. We may not be able to move forward as quickly because of the longer lead times involved in ethical review issues. They believe that the longer lead times may dissuade some sponsors from launching studies in Belgium because they do not want to waste time. Time is money, so they would prefer to turn to faster countries.

2.3 Strategies to improve recruitment (strengths and opportunities)

2.3.1 Recruitment tools

Most interviewees were unaware of the QRI, GREET and CTTI planning tools available in the literature to help plan the recruitment process. Sponsors already have their own internal strategies and are constantly questioning themselves. Sponsors develop the protocol and sites implement it, they work as a team. The PI is on site and has a good understanding of what is important to consider in terms of materials and recruitment protocol, for instance. Indeed, the sponsors develop this protocol and have the final decision, but they try to improve it by holding weekly or monthly meetings with the sites to share their problems and concerns. At any time during the trials, if the site encounters difficulties, it contacts the promoters, who then try to find a solution to overcome them.

Databases of healthy volunteers are important tools used in recruitment procedures. Sponsors use these databases to select the best candidate site for the trial. They present the trial and ask the site how many candidates they might have by simply consulting their database based on the study's eligibility criteria.

2.3.2 Participant-centered approach

Some sites think it is important to really look at the person in front of you, be aware of their age and understand what might prevent them from taking part in the trial. In general, the healthiest people are often the young. One idea is to replace telephone screening with digital screening. Young people generally do not like phone calls, or at least do not have the time to answer a call during office hours. This is why the idea has emerged to replace these calls with a simple e-mail - requiring a response - or a website questionnaire to schedule the first on-site screening visit. Perhaps young adults will be less resistant to this type of procedure and more interested in participating, because it is less burdensome for them.

The PIs and sponsors agree that the population likely to take part in the trial needs to be reached in a targeted way. Advertisements in gyms, cinemas, cafés, etc. can be a good way of attracting the interest of as many young people as possible.

2.3.3 Communication skills

It seems that confident staff and good communication with the PI can help recruitment. But some believe this applies more to participants already committed to the trial. If they feel more comfortable in the unit, they are more likely to stay. Training for recruitment staff could be useful. But at this stage, they are already involved in the trial. So perhaps it is the previous stage that needs to be optimized, to really draw them into the trial. The search for new participants, participants who are not yet in the databases for example. This may require an awareness campaign. Most people are unaware of the existence of clinical trials. This is where targeted advertising comes in. Expanding site databases thanks to this advertising will facilitate recruitment. The use of social media is also a good way of disseminating information about clinical trials and publicizing studies for which recruitment is underway, as young people are generally avid users of these technologies. However, some researchers warn against using such tools, as they believe that people are likely to be put under pressure if they see that they can be paid to take part in trials in this type of advertising. Pressure can be exerted by the fact that they need money, which will encourage them in their choice to participate.

Communication also involves the creation of a well-structured website. The websites developed by the sites are the interface where participants or potential participants can find information about ongoing trials. Some sites have also created a “FAQ” window to answer common questions that participants may have. Of course, these are only general questions, as study-specific questions concerning an effect, or the drug administered are dealt with during the visit with the principal investigator.

Finally, professionals, especially investigators, feel that the general public is unaware of the existence of clinical trials. A publicity campaign could help to promote clinical trials by explaining that without the participation of healthy volunteers, there will ultimately be no new treatment. It is also necessary to reassure the public about the way the trial is controlled. PIs are genuinely interested in the well-being of participants and are responsible for their safety.

2.3.4 Healthy volunteers’ involvement

Regarding the concept of involving healthy volunteers in addition to patients, opinions are divided between the pros and the cons. PIs seemed more supportive of the concept than sponsors, finding it more interesting than the latter.
When we raised the possibility of involving healthy volunteers, such as patients, respondents distinguished between different subtleties: involvement in the EC, involvement through their feedback and involvement through the creation of a community of participants.

2.3.4.1 In the EC

The majority think it is not necessary to put them on the EC to help with recruitment. The site is really the place where participants will be useful in helping to raise awareness, which is not the case by being on the EC. In addition, we already have patients represented on the EC and they are more willing to give up their time to help with protocol design and review the various documents to see if they are understandable, compared to Healthy Volunteers (HVs). The need for additional participants has not been proven.
What is more, HVs are not the "final target". The patient is, because the drug tested will ultimately be used by patients if the trial is successful. So, the aim is really to look after patients, sick patients. Even if the HVs really help us during the first phase, the focus is on the patients at the end, and it is only the patients who can know what the drug will do for them, not the HVs,

who cannot answer those kinds of questions and probably do not belong in the EC for that reason.

2.3.4.2 Feedback

That kind of participants involvement can be useful for raising awareness of clinical trials among the general population. Feedbacks can be collected via online surveys after participation, or perhaps via a recorded and filmed interview to be broadcast on the site or elsewhere.
Some sites have already set this up and ask participants to give their views on how they felt in the trial. Some turned this into a video available on their website, which can also make a good advertising campaign. This type of publicity, which comes from the HVs itself and not the staff, is probably preferable because HVs are ordinary people, like everyone else, and it can perhaps reach many more people than if it were the staff trying to explain what a trial is and how participants are welcome on the unit. It is always best if a trial participant's story is explained by participants themselves.
Healthy volunteers can also be the best ambassadors, sharing their positive experiences with potential candidates. By establishing a bond of trust between old and new participants, this can reassure them, and they may no longer hesitate to take part in the trial.
In addition, online feedback via surveys that the site sends to the participant enables future trials to be properly adapted. Sites ask for advice and feedbacks on their stay in the unit to ensure that the participant feels comfortable thereafter. They inform the sponsor if any comments suggest that a design adaptation is needed for future trials. It is also important to better understand what motivates participants, so that recruitment materials can be adapted accordingly. This is an advantage for the pharmaceutical industry, as there are likely to be fewer rejections if participants' opinions have been taken into account for future campaigns.

2.3.4.3 Participants communities

If you are faced with potential participants who are reluctant to take part because of the potential risk, pointing them in the direction of a community of participants could help. The creation of such a community, sharing their positive experience, may reduce their anxiety and increase their willingness to participate.
However, if you create such an organization of like-minded people, if we take into account that the people who participate may be those on low incomes, you will always have, or at least a lot more low-income people in your trials and you probably will not have much diversity in your selection. So, this may not be what we want, as it could introduce a bias.
In addition, the PIs fear that it will be more difficult to create an organization of HVs than of patients. From a practical point of view, it may be more difficult to group together HVs with no common interest than patients, since the latter all have the same motivation, namely the disease in common.

A general problem felt by professionals is that, since we have HVs and not patients, they may be less interested in spending time on feedback, reviewing documents or belonging to a community of participants. And one of the PI also pointed out that if they are paid for such involvement, there may be an ethical issue and the authenticity of the participants themselves may be lost, as they may only do it for the remuneration and not be sincere in their testimonies. It is therefore necessary to have independent, voluntary HVs.

2.3.5 Professional HV

The question may arise as to whether or not healthy volunteers can make a living out of it. All the professionals interviewed seem to agree that this field is fortunately well regulated.
No one wants to have this type of participant, as it can compromise both their safety and the integrity of the data. HVs must be in good health to avoid interference with the drug.
A washout period is required before participation in a new trial. In general, the HVs cannot participate in a trial if they participated in a trial in the course of three previous months. Registries exist gathering information on the participants who have already taken part in such or such study and at what time, in order to control this information.
Moreover, what reassures the experts is that it is not a constant salary they receive, sometimes it seems like a nice sum of money but given that you may only be participating in 2 or 3 clinical trials a year, it cannot replace a real living wage.
So, in Belgium at least, this factor is actually monitored and verified through existing registers, so that participants cannot make it their job.

Conclusion

1. Summary and opinions

When it comes to optimization, it is necessary to examine failures, weaknesses and threats in order to remedy them by developing strategies to improve recruitment or, at least, to understand how to use opportunities in the best possible way. All these aspects identified in the literature were compared with the experience of professionals. That is what we have done in this work.

The recruitment failures highlighted due to participant-related factors or staff-related factors in the literature (28,31) seem to be the same as those encountered by professionals. But perhaps it is more subtle, and participant factors are actually staff factors. Participants' time needs to be taken into consideration if they agree to take part, but this time needs to be managed by the staff and those designing the trial. Fears related to participation that may deter participants must be addressed by the principal investigator by reassuring them.
Other design flaws do not appear to be a problem, especially in the context of a trial sponsored by a pharmaceutical company, as opposed to an academic trial. Problems can be overcome more easily because of the funding available. This view is shared by Snezana Djurisic *et al.* in the review about barriers to the conduct of randomized clinical trials. The difficulty in finding funding for academic trials can lead to an inability to recruit properly. Academics depend on public funding and have to present a structured project in order to be considered important for funding. Industrial trials do not face this scenario (50).

The EU CTR seems to have an indirect impact on recruitment due to the delays caused by this new system, which requires an external EC to review the trial and the use of the CTIS for the submission. In their article on the main changes brought about by the new regulation, E. Tenti *et al.* already indicated in 2018, before the regulation was implemented, that it would require a high level of human resources and more technical skills (9). An effort that may have more impact on university-sponsored trials than on industry-sponsored trials, as the human resources and time required to acquire new technical skills certainly require funding.
Overall, then, it is hard to say whether this new regulation is more of a threat than an opportunity when analyzing the responses from professionals, or at least they do not really see the benefits yet. But perhaps this will change as people will become more familiar with the regulation over the coming years. As with any new system, we need a transition period, and perhaps sentiment towards this new regulation will be different in the years to come, and we will need to reassess the situation at this stage. Moreover, this impact is perceived differently depending on the sponsor's or site's point of view. One seems more affected by the changes brought about by the CTIS, the other by the constraints imposed by the EC. This is also the reason why they do not feel the same way about the threat to Belgium's top spot. The sponsors do not think it will have a major impact, while the sites are more worried. In this case, the feeling of the sponsors is perhaps the most interesting to hear, as they are the ones who launch the trials and select the place(s) where the trial will be conducted. They are more in line with the statement of the authors about the attractive position of Europe thanks to the harmonization (9).

In terms of strategies to be implemented, communication skills seem to be more of a site concern when we analyze the various interview responses. But in a way, the sponsors are also involved since they have the funds to possibly train the staff on site. As they are responsible for site selection (28). In general, there is no one single solution as each trial is really different, this area is dynamic, but for each different scenario, site and sponsors must be creative to

overcome difficulties in the best way. The kind of person you need will also differ from one trial to another which makes the process also “challenging” because depending on the person you have in front of you, you will not catch them the same way. This is in line with the targeted approach described at the beginning. Knowing your potential participants, their motivations, fears and age will help you to find the best way to attract them to your study. This will enable you to implement appropriate advertising strategies, such as using social media, making videos for television or putting up posters in strategic locations. It will also enable you to consider the possibility of avoiding telephone calls to young people, rather than older people, during the pre-screening phase. This point was also confirmed by authors Nayan Chaudhari *et al.* in their article on recruitment challenges and solutions: these types of recruitment strategies can facilitate the recruitment process. All these strategies used must be examined and approved by the ECs (28).

As many of the PIs interviewed feel that the general population is not sufficiently aware of clinical trials, developing strategies to bridge this gap could make a significant contribution to recruitment. If people simply don't know about clinical trials, how can they be interested in taking part? Advertising on television could reach a large number of people and raise their awareness of the topic. The sponsors do not feel the same way, or at least they did not mention it in the interviews, perhaps because they are more aware of the financial aspects and what is and is not feasible in terms of the budget devoted to recruitment strategies and advertising. We can imagine that television advertising requires a lot of funds.

The sponsors do not seem to be very familiar with the recruitment tools presented at the beginning of this work, stating that they already have their own strategies and that they are sometimes overwhelmed by the new methods. So, they say they do not need them, but perhaps this is a gap in their knowledge. If they had the knowledge and used these external tools, recruitment and the other stages of the study might be easier and quicker.

However, one of the most useful tools, an opinion shared by the principal investigators and sponsors, is the use of databases. These databases are very useful because they help the sites, during pre-selection, to find participants who meet the study's eligibility criteria. But these databases are also the determining factor in whether or not the sponsors select the sites, depending on the number of candidates they can offer for each specific trial.

Although there is no literature available on the involvement of healthy volunteers, the professionals interviewed showed an interest in the subject. As the involvement of patients and the public is currently practiced in the field of clinical trials (45,46), it was legitimate to wonder whether healthy volunteers could also be involved. As part of the GREET project, participants involvement was described as a key element in improving and accelerating recruitment (33) which shows the importance of trying to include healthy volunteers to improve recruitment in phase 1. This is also a subject that the Eufemed (European Federation for Exploratory Medicines Development) attempted to explore during its webinar on "Subject Centricity in Phase 1". It seems that professionals are thinking about implementing this in the near future. The interviews identified three main areas in which healthy volunteers can be involved: in EC, through feedback and by creating a community of participants to enable them to tell their story. But the most interesting part is the development of a survey questionnaire to get feedback from participants. This can be useful to improve the recruitment process. It appears that PIs are more favourable to the idea of involving healthy volunteers than sponsors. Especially because they have already implemented feedback surveys. Perhaps this is more of a site issue, as they can involve participants to a greater extent. The sponsors will not ask the participants directly for feedback, but the PI will.

In the context of healthy volunteers' recruitment, where there are recruitment failures, the question seems to be straightforward. Since the main motivation for participating is financial compensation, increasing fees could increase the recruitment rate. But the answer is not so simple. Behind this are ethical, safety and regulatory considerations. These considerations are well controlled, and always with the aim of protecting the participants themselves, as taking part in too many trials, in order to gain the maximum, could jeopardize their safety. In addition, the risk of interference between products, as well as being dangerous for the participants themselves, can distort the results of the study. Ultimately, this could compromise the safety of the general population using the product based on a biased study. The risk is therefore twofold. Fortunately, it seems that the ECs and sponsors have taken steps to avoid this kind of scenario. The ECs are responsible for approving the amount that participants can receive, which is initially proposed by the sponsors or sites. This amount is calculated according to the constraints that participants may face, such as the length of their stay in the unit. The ECs assess whether the amount is appropriate given the constraints of the trial.
In addition, as we have already explained, there are databases that can be consulted to check whether a participant has already taken part in a trial within three months and to prevent them from doing so again. These healthy volunteers' registries allow a certain wash-out period to be respected and avoid bias (28,51).

So, this is all a question of balance, between ethics, the financial aspect and, above all, the safety of participants. Communication between all stakeholders, particularly sites and sponsors, is important at this stage, as sponsors manage the funding and design of the trial, while sites are in contact with participants and can sense their feelings about their stay in the unit and ultimately provide feedback to sponsors (52).

2. Limitations

First of all, although this personal account provides a nuanced and in-depth understanding of the subject, it can also be perceived as a subjective work because it was carried out from A to Z by ourselves. This personal involvement may be seen as an asset for some or a source of bias for others.

Secondly, recruiting professionals to conduct interviews was no easy task. This is illustrated by the percentage of respondents who agreed to take part in the interviews. Even when they were contacted again, some did not respond, while others just said no. Either they did not feel comfortable enough with the topic to answer the questions, or it was more a question of confidentiality, for fear of divulging their strategies. And perhaps the participants were not totally transparent and open in explaining all the actual strategies they put in place because of this confidentiality factor. So, the response rate was not really high, which is also probably due to the lack of time available to them, given that they are all professionals with many responsibilities. In the end, this led to a limited number of interviews.
Of those who responded positively and were interviewed, the majority were PIs and a minority were sponsors (6 *versus* 3). This may have an impact on the responses. They are not motivated in the same way and do not do the same things in the clinical trial setting. None of the ECs contacted responded positively. It would have been interesting to have the ethical point of view in this work.

Then, the literature on phase 1 clinical trials is a niche. There is very little information on phase 1 in the literature, which means we have had to transpose the tools used and information on other phases to phase 1. But the fact is, phase 1s are totally different. It is therefore possible that we were not as precise as we should have been when it came to the tools and strategies outlined.

Finally, time constraints prevented us from hearing from the participants themselves. The idea would have been to contact them to get their views on what motivates them to take part in clinical trials and understand what, from their point of view, could be improved. But the reality is that interviewing professionals has already taken up a lot of time. There was also a confidentiality issue in accessing HV's databases to contact them. Indeed, there is a European regulation concerning the protection of individuals' data: the General Data Protection Regulation (GDPR), which states that you cannot do and share whatever you want with personal data (53). As HVs databases could contain personal information, access to which is restricted. But since time was short, and recruiting professionals was already difficult, we ultimately had to focus solely on the professionals' point of view for the purposes of this work.

3. Perspectives

Further investigations should be carried out to better understand what can be done to optimize recruitment in phase 1.
First of all, as already mentioned, the opinions of healthy volunteers should be obtained. For instance, a questionnaire could be prepared in advance, sent to a site which could in turn send it to its database of healthy volunteers through e-mail. The volunteers would answer online, return the form to the site and the anonymous answers would then be forwarded to us. With this type of survey, the confidentiality of participants' data is guaranteed, in accordance with the GDPR.

Secondly, the economic aspect might be interesting to keep in mind when talking about strategies and tools to help with recruitment. They can better know what is feasible given the economic notions they have, and perhaps for Belgium, but also for all other European countries. The idea of advertising the opportunity to participate in Phase 1 trials on television may be feasible, but is it really financially viable? Such a campaign could probably overcome the problem of public awareness by reaching people in a simple way, for example when they are sitting comfortably in their living room.

Finally, as the field of clinical trials is constantly evolving and dynamic, this type of work should be reassessed. In particular, if we consider the impact of EU CTR on recruitment, it should be reassessed in the coming years, when this new process will be more familiar to professionals. But also, you do not face the same hurdles when it comes to a vaccine or drug trial, so perhaps we should consider a customized strategy for each specific trial.

To answer the question of how to optimize Phase 1 recruitment, we need to consider these three main factors: the safety and well-being of participants, funding, and the ethical aspect. And this is never the end of the story - the answer will evolve with any opportunities or threats that arise in the years to come. Also, it seems like there are gaps between the things we would like to do and the things we can do.

This is a really interesting topic to explore further, because the success of a clinical trial is ultimately determined by the success in recruiting and retaining participants (28). And this is particularly interesting for the first phase, as the success of the first phase will allow you to move on to the other phases.

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ANNEXES

Annex 1

<u>Interview guide</u>: in green, simple explanations of the question.

Person's background

-What is your role in clinical trials (phase 1)? Does your role in clinical trials involve recruiting healthy volunteers in phase 1?

Impact EU CTR, opportunities and threats for recruitment

-Do you think the new EU CTR had an impact (positive or negative) on the recruitment in phase 1 trials?

-Why? And how could you explain this impact of the EU CTR on the recruitment?

-Especially when we compared to others European countries, do you think that Belgium decreases his good capacity of conducting clinical trials?

Recruitment failures in phase 1, weaknesses of the recruitment process

In the literature, they talk about factors that are linked to recruitment failures in phase 1 trials including participant-related factors such as the time they can spend at the CRU, lack of trust with the physician and their sometimes-insufficient motivations to take part in the trial. Staff-related factors also lead to lower recruitment due to a lack of communication with the participant and a lack of motivation to enroll them.

-Do you think these are real weaknesses in the recruitment process?

-Would you explain your proper experience?

-What is for you the main weaknesses identified in the recruitment process in Phase 1?

Strategies to overcomes recruitment failures, strengths of the recruitment process (Part 1):

Strategies to overcome these participant-related recruitment failures include to understand the participants, their motivations, their fears and to build a communication channel with them in order to catch them in the study.

-Do you think we can actually recruit participants by knowing their traits and targeting them in recruitment strategies?

-Do you think that by establishing a trusting relationship with them, recruitment is better?

-Could you explain your experience with this "targeted approach"?

Strategies to overcomes recruitment failures, strengths of the recruitment process (Part 2):

Another important factor in the recruitment failure is related to the design phase.

-Did you already heard about or used tools to improve phase 1 recruitment (QRI, Greet Project, CTTI planning)?

-Which ones?

-Would you explain your experience with the tools?

-Did you see a real improvement with the tools used?

Perspectives and potential of participants engagement:

Patients' involvement in CT conduct is increasingly practiced. From this point of view, engaging healthy volunteers could really be the key to improve the recruitment strategies, as they know exactly how people like them might be interesting in participating.

-Do you think that subjects who have already participated in phase 1 should be included in the team responsible for improving recruitment strategies?

-Do you think it could be feasible? Or maybe did you already experience it?

-Moreover, will you not be afraid that healthy volunteers can make it their job and become professional healthy volunteers?

Annex 2

<u>Interview invitation:</u> sent to sponsors.

Dear Sir, Dear Madam,

I am Mathilde Rasier, student in the second year of a master's degree in biomedical sciences with a specialization in clinical research at the University of Namur. I am currently working on my master thesis entitled: "**Optimization of recruitment and communication strategy in phase 1 trials on healthy volunteers**", supervised by Benjamin Boinem and co-supervised by the Professor Régis Radermecker.

I am contacting you today because, as your company is listed as a sponsor for the phase 1 studies, you seem interesting in helping me for the purpose of my master thesis. Indeed, I would like to compare the information I have found in the literature on recruitment failures encountered in phase 1 trials with the reality of the field through interviews with experts. In this way, I will be able to better understand and evaluate the strategies implemented to optimize the recruitment process and, at the same time, I hope to find new strategies.

Would you or someone in your community be willing to participate in the interview? As the interview will follow a questionnaire consisting of 6 main questions, I'd say it can last around 30 minutes.

I thank you in advance for your attention and your valuable time.

Kind Regards,

Mathilde Rasier

Annex 3

<u>LinkedIn connection message:</u> sent to Principal Investigators.

Working on my master thesis entitled "Optimization of recruitment and communication strategy in phase 1 trials on healthy volunteers".
I'm looking for a PI to interview to help me with my work, that's why I'm trying to contact you.

Thank you in advance.

Annex 4

<u>Interview invitation:</u> sent to Principal Investigators.

Dear xxxx,

I am Mathilde Rasier, student in the second year of a master's degree in biomedical sciences with a specialization in clinical research at the University of Namur. I am currently working on my master thesis entitled: "**Optimization of recruitment and communication strategy in phase 1 trials on healthy volunteers**", supervised by Benjamin Boinem and co-supervised by the Professor Régis Radermecker.

I got your contact information from clinicaltrials.gov. I am contacting you today because, given your experience in the field of clinical research as a PI, your profile seems interesting in helping me for the purpose of my master thesis. Indeed, I would like to compare the information I have found in the literature on recruitment failures encountered in phase 1 trials with the reality of the field through interviews with experts. In this way, I will be able to better understand and evaluate the strategies implemented to optimize the recruitment process and, at the same time, I hope to find new strategies.

Would you be willing to participate in the interview? As the interview will follow a questionnaire consisting of 6 main questions, I'd say it can last around 30 minutes.

I thank you in advance for your attention and your valuable time.

Kind Regards,

Mathilde Rasier

Annex 5

<u>Interview transcripts</u>: in blue, the interviewees' answers.

Interview 1 – 04/07/23 – Sponsor side

Quel-est exactement votre rôle dans les essais cliniques de phase 1 ?

J'ai un rôle mixte, je suis à la fois le CRA (Clinical Research Associate) mais aussi le CTM (Clinical Trial Manager). Le rôle du CTM est un peu différent partout mais, au fond, c'est un « Project manager ». Je suis avec un collègue qui travaille également pour les phases 1 uniquement et on alterne pour chaque étude. Pour une étude il est le CTM et moi le CRA et pour la suivante c'est l'inverse. Et quand nous allons en vacances, nous sommes le back-up de l'autre.

Êtes-vous vraiment impliquée dans l'équipe de recrutement ? Ou faites-vous plutôt partie du côté du sponsor ?

Non, toutes les études se font [redacted] qui se trouve à côté de l'hôpital universitaire de [redacted]. Ce sont eux qui s'occupent du recrutement en tant que tel. Mais si ce recrutement vient à être difficile, ce qui peut arriver, nous donnons des conseils et solutions pour trouver d'autres participants. Mais la plupart du travail de recrutement est réalisé par eux et pas par nous.

Est-ce que vous pensez que la nouvelle régulation européenne a eu un impact, aussi bien positif que négatif, sur le recrutement en phase 1 ?

Non, pas du tout. Le seul problème, c'est qu'avant on avait une très bonne fonction législative en Belgique. Ça marchait très bien, l'approbation (ou pas) était donnée après 15 jours alors que maintenant, suite à la nouvelle soumission européenne, ce délai a été retardé. Par exemple, la première étude que nous avons réalisée avec ces nouvelles méthodes a pris 56 jours alors que normalement c'est moins d'1 mois. Mais pour le recrutement en tant que tel, c'est égal. Les participants ne le savent pas, il n'y a aucune conséquence pour eux.

Qu'en est-il par rapport aux autres pays d'Europe ?

C'est le début, aujourd'hui on soumet seulement la troisième étude sur volontaires sains en Belgique de [redacted] Mais, ce qu'on a constaté et j'ai également participé à une conférence avec le gouvernement (AFMPS) et ils ont promis d'être plus rapide que possible. Et j'ai vraiment vu qu'ils faisaient tout ce qu'ils pouvaient dans cet environnement. En effet, la Belgique a une très belle image, particulièrement pour les phases 1 sur volontaires sains. En Europe, le Danemark et la Belgique sont les pays qui ont le plus d'études en phase 1 (insiste sur le fait que ce sont des volontaires sains et pas des patients comme c'est le cas pour les essais oncologiques) à « leur compteur ».
Je connais seulement les Pays-Bas, car je travaille également pour eux, et ils se sont vraiment adaptés à leur manière de soumission européenne et ils sont aussi très rapides.
En ce qui concerne l'Allemagne aussi, la première étude a pris 126 jours, ce qui est beaucoup trop long pour une phase 1. Ça doit avancer vite car on attend les résultats des phases 1 pour pouvoir démarrer les études sur les patients.
Pour les autres pays je ne sais pas.

Pensez-vous réellement qu'il y a en effet des faiblesses dans ce processus de recrutement liées aux participants ou au staff ?

Oui. Le plus important pour le participant, c'est la longueur de l'étude, pas uniquement le fait de rester dans la clinique mais aussi les visites de follow-up. En effet, beaucoup de participants s'engagent dans l'étude principalement pour l'argent. Mais attention, ils ne peuvent participer que 4 fois par an.
J'ai eu le cas, par exemple, d'une étude qui durait presque 6 mois, et nous avons constaté un recrutement très faible parce que les gens ne veulent pas participer, c'est trop long. En plus de cela, ils veulent gagner de l'argent et les visites de follow-up sont rémunérées également mais dans une moindre mesure comparée à la durée du confinement. C'est donc la plus grande faiblesse que nous avons expérimentée, la longueur de l'étude.

À côté de cela, il y a aussi le fait que l'étude requiert d'arrêter de faire de l'exercice physique (aller à la gym, faire du football, etc). Alors quand c'est pour une durée de 4 semaines, c'est encore acceptable pour les participants sportifs mais si cela doit durer 6 mois alors cela devient plus difficile pour eux. De la même manière, l'emploi d'un préservatif pour éviter que la femme ne tombe enceinte pendant l'étude peut gêner certains. Si cela dure pendant 1 mois, c'est encore acceptable. Car il faut savoir qu'après la dernière visite, il faut encore attendre 30 jours avant de pouvoir le retirer. Donc si l'étude dure 6 mois et qu'il faut encore attendre 30 jours avant de pouvoir ravoir des rapports non protégés avec son partenaire, cela leur semble trop contraignant. Ce sont des choses pratiques et l'argent qui sont des barrières au recrutement.

Par rapport à l'argent justement, nous travaillons avec une « fair market value », ce qui veut dire que un sponsor ne va pas pouvoir payer plus qu'un autre, la somme donnée devra être égale. Cela dépend de combien de jours le participant va devoir rester à l'hôpital, combien de jours il va devoir revenir, la durée du screening, si il doit y avoir un « re-check » ou pas. Mais le taux d'une visite est le même ou presque pour tous les sponsors. De plus, toutes les études sont soumises à un comité d'éthique et si une étude paye 2 fois plus ses participants qu'une autre, ce n'est pas accepté.

Le taux de motivation du staff est aussi très important pour le recrutement. L'IC, quand le participant est sur le site, est la première chose qu'il voit, qu'il entend et qui lui est expliqué. Il n'est pas simplement donné au participant mais il est lu et expliqué ensemble avec le participant et le médecin. Si on le donnait simplement, le participant le lirait dans une salle à part et après il devrait poser un tas de questions donc ça ne marche pas comme ça.

Pour rebondir là-dessus, peut-être avez-vous déjà expérimenté le fait que certains PI n'ont pas fait cette démarche correctement en donnant simplement le document sans trop d'explications ?

Oui. Et on voit alors dans ce cas plus de participants qui font ce que l'on appelle le « withdraw consent » et ne signent donc pas l'IC.
Et alors il faut savoir aussi et c'est partout le cas, on observe que sur un total de 100 participants, seulement la moitié peuvent participer. Mais ce n'est pas à cause de leur motivations, c'est parfois juste parce qu'ils ne sont pas en bonne santé, on voit quelque chose au laboratoire dont l'ECG ou autre chose qui confirme une maladie ou parce qu'ils prennent des médicaments qui vont les empêcher de participer.
Cela représente aussi une faiblesse, qui est indépendante de la volonté de chacun.
Tout dépend de l'étude en réalité, maintenant on fait des études qui permettent à des gens entre 18 et 65 ans de participer. Mais alors dans ce genre d'études, on a plus de gens qui ne peuvent

pas participer parce qu'ils ont des maladies ou qu'ils prennent des médicaments qui sont en contradiction avec les critères d'éligibilité de l'étude. ON a également des études qui vont jusqu'à 40 ans et alors dans ces études, on a moins de « drop-out ».
Quand on élargit la tranche d'âge, il y a plus de participants mais ils sont plus à risque d'être en mauvaise santé ce qui fait qu'il y a moins de participants qui peuvent rentrer dans l'étude.
Et donc on fait ça, élargir le groupe de volontaires, mais on voit que ça ne fonctionne pas vraiment (surtout le groupe de 18 ans à 65 ans) .

Est-ce que vous pensez que ces stratégies centrées les participants et le fait de les comprendre sont des bonnes stratégies de recrutement ?

Vous voulez dire avant qu'ils arrivent au centre, par des publicité ou après donc dans le centre ? Ou les 2 ?

Les 2, avant de les recruter pour qu'ils viennent au centre mais aussi une fois qu'ils sont au centre pour vraiment les garder.

On emploie beaucoup « d'advertisments » ici et surtout dans les locaux pour étudiants, on est lié à l'université, ainsi que dans les clubs de fitness et dans les cinémas. En effet, les jeunes gens vont au cinéma, au fitness et particulièrement au fitness, ce sont des gens en bonne santé généralement. On doit faire connaissance (se faire connaitre par ?) avec tous les groupes de personnes susceptibles de participer. Ça c'est vraiment le début.

Et alors je suppose que pour après, lorsqu'il y a une certaine confiance qui s'installe entre le participant et le PI, le recrutement est meilleur ?

Oui mais aussi et surtout entre les volontaires, parce que ce sont souvent des gens qui reviennent et téléphonent à leurs amis en disant « est-ce que tu reviens pour cette étude ? » et ça, ça marche bien aussi.

De plus, l'environnement du centre joue un rôle. SGS il y a quelques années étaient installés dans des vieux bâtiments mais maintenant tout est nouveau et cela attire plus de recrue. C'est plus moderne. Il y a un parking également, cela semble être un détail mais ce sont des choses très importantes. La mobilité est une chose importante pour aider dans le recrutement.

Avez-vous déjà entendu parler des outils que l'on peut mettre en place pour améliorer les défauts de recrutement dû à des problèmes de design (QRI, GREET project, CTTI planning) ?

Non, ça ne me dit rien. Peut-être que je connais sous un autre nom, pouvez-vous m'expliquer ?

The QuinteT Recruitment Intervention (QRI) permet d'évaluer et de comprendre les difficultés et de traiter avec les acteurs de l'unité de recherche. The Guidance to Recruitment Examining Experience at clinical Trials site (GREET) vise à identifier les obstacles et à trouver des solutions. Le Clinical Trials Transformation Initiative (CTTI) vous fournit un plan pour le processus de recrutement. Tous ces outils sont vraiment conçus de manière à ce que, si vous rencontrez des problèmes, ils puissent vous aider à concevoir et à planifier le recrutement et les différentes tâches que vous devez accomplir pour aider au recrutement.

Oui, par rapport au dernier outil que vous citez, es protocoles sont écrits par les investigateurs en collaboration avec nous. Cela signifie qu'ils maitrisent les méthodes pour attirer et recruter un maximum de participants et ils ont de l'expérience là-dedans. Et nous de l'autre côté, on travaille ensemble et ça se passe très bien. Et quand le projet est en cours, chaque semaine on fait des meetings via teams avec les PI pour voir comment se passe le recrutement, ce qu'on peut améliorer, etc. Par exemple, nous avions une étude où les critères de l'âge allaient jusque 50 ans et on a décidé d'élargir cette tranche d'âge jusqu'à 65 ans. Un autre exemple, on a du limiter le temps d'hospitalisation d'une étude. On s'est rendu compte que ce n'était pas nécessaire de prendre 5 jours, que cela pouvait être fait en 3 jours. Donc de temps en temps, on revoit tout cela et on améliore le recrutement. Mais c'est vraiment un travail ensemble. Le protocole ce n'est pas quelque chose de fixe, non, ça change.

Et vous voyez vraiment une réelle amélioration quand vous changez le protocole ?

Oui. Ou alors de temps en temps, ce n'est malheureusement pas une amélioration. Par exemple, on a eu une étude où le taux d'IMP dans le sang ne restait pas 5 jours comme prévu mais 105 jours ce qui veut dire que les participants doivent rester plus longtemps dans l'étude. Ce n'est pas optimal pour le recrutement mais c'est comme ça mais le protocole doit changer pour des raisons médicales dans ce cas et pour la sécurité des participants. La sécurité du participants est toujours le grand but recherché, on ne veut pas des malades ni des décès dans une étude clinique pour des volontaires sains.

Est-ce que l'on pourrait envisager d'intégrer le principe du « patient involvement » dans les phases 1 ? Est-ce que des personnes ayant déjà participé à des phases 1 pourraient être impliquées dans les équipes responsables du recrutement ?

Non, pas pour le moment. Je pense que ce n'est pas facile car ils ne sont pas malades. Leurs motivations n'est pas de guérir ni d'avoir un médicament qui peut les aider à guérir. Pour les volontaires sains c'est soit l'idéalisme, soit l'argent. Et par exemple, l'unité de recherche SGS a des bases de données avec des milliers de participants possibles. Mais ce serait trop difficile. De plus, les protocoles des phases 1 sont très techniques. Parce qu'on a pas encore eu de tests sur les humains. On fait souvent des First-in-Human et donc pour la plupart des études on a seulement des résultats qui ont été obtenus sur des animaux. Ce n'est donc pas facile pour une personne de lire ça et de se dire qu'il va avoir quelque chose qui a seulement été testée à des rats et des petits chiens. Contrairement aux patients qui connaissent leur maladie, qui sont bien informés à propose de leur maladie, les volontaires sains c'est autre chose. Et en plus, toutes les études se font toujours avec des nouvelles molécules. De temps en temps, on a une « single rising dose » et puis un « multiple rising dose » mais après cela c'est fini et on reprend de nouveau une nouvelle molécule.

Et puis finalement, je sais qu'il y a des patients et des avocats dans les comités d'éthique et on emploie les mêmes comités d'éthiques que pour les autres sortes d'études cliniques.

Oui donc il y a quand même l'aspect du patient dedans ?

Oui mais les volontaires sains ne sont pas des patients. Et d'ailleurs au sein de ces comités, on ne parle pas de patients mais de sujets.

Mais ce qui est intéressant et comme vous le disiez plus tôt quelqu'un qui a déjà participer va téléphoner à son ami et dire « tu serais intéressé de participer toi aussi ? », on pourrait quand même « utiliser » cet aspect de communication ?

Oui, établir une petite communité c'est possible. Et « l'advertisment » se retrouve aussi dans Instagram, Facebook, etc. On emploie beaucoup cela. Et une personne qui tombe dessus, l'envoie à son ami en disant « tu as-vu ça ? ».
Mais pour les volontaires sains ce n'est pas important l'indication de la molécule en tant que telle. Pour certains oui si par exemple quelqu'un de leur famille ou entourage est atteint de telle ou telle maladie mais à priori ce n'est pas ce qui importe pour eux.

Et est-ce que vous avez déjà pensé à organiser des témoignages de volontaires sains comme publicité ?

Non.

Pensez-vous que cela serait intéressant ?

Oui mais peut-être plus pour les phases 1.

Interview 2 – 24/07/23 – Site side

What is your role in clinical trials phase 1?

I am the medical director of the clinical pharmacology unit of [redacted] We have a unit of 1 hundred beds for mostly heathy volunteers' trials, mostly phases 1. We do some patients trials but mostly it is based on healthy volunteers. My role is mainly the medical oversight and I'm responsible for the medical team, we have 10 positions working at our facility performing trials, *BPI of trials* and things like that and I'm responsible for that team and also for things like consultancy from external partners towards us basically.

And so, are you really involved in the recruitment of healthy volunteers or just in the management maybe?

Well, we have a recruitment department of a total of six people working on recruitment itself so really recruiting the ones who are already on database and two who are trying to find people who want to be in our database so not study specific but find people who want to do clinical trials and six people actually for trial specific recruitment. So, we don't call the participants itself as positions but of course we always see them help with recruitment strategy for trials we help with reviewing of advertisement and things like that.

Does [redacted] is a CRO?

It is actually a quite large company for inspection testing and things like this but also in industry in harbours and things outside of clinical research. Within our specific department we did have a site where we performed trial this where I'm working and next to that we indeed have a CRO as well with their money focused on the late phase and things like that but for the early phase in recruitment is purely our clinical pharmacology unit.

We know that there is a new clinical trial regulation, and I was wondering if you think that this new one had a positive or negative impact on the recruitment in phase 1?

Yes, it is a greatly negative influence in my experience. Because, in the past everything with recruitment was discussed with our own ethical committee who was located in the [redacted]
And we, for instance, also had some pre-proofs templates that we could use to already start recruitment before we had actual approval of the trial so with just some generic information, non-trial specific information so that would allow us to get some recruitment done and we knew of course when their hearings will be there and we would have the results so the next day we could start screening.
Now this is not possible anymore or just very difficulty possible because you know now there are ethical committees reviewing it and you have to wait for your approval to start recruitment which means that you lose about two or three weeks before you can actually perform your first screening in comparison to the directive. And in early phase when we talk about well mostly winning one week it's already very important for clients the fact that it turn out two or three weeks later for your start as a great impact on the willingness of clients who come to Belgium.

If we compare the Belgium with other European countries, do you think that Belgium decreases his good capacity of conducting clinical trial because of the new regulation or not?

At this moment, for what I understand and what I can see from other units as well is that we're still the fastest in the timelines which still helps that we can still be the first one to start recruiting and start clinical trials but it's already way worse than it was on the directive and you notice that countries around us are really trying to catch up, for instance the pre-approval is something that in Netherlands now exists already so they can start recruiting before they have approval in the entire Netherlands. In England they're also trying to have faster approvals, Germany also started saying that they want to do it in 26 days. So, we feel the hot breath of the surrounding countries at our next. At this moment we're still the fastest but I do not know if this will stay the same in the future.

We identified some weaknesses in the recruitment process in phase 1 and in the literature, they talk about factors that are linked to the recruitment failures including participant-related factors such as the time they can spend in the unit, the lack of trust with the physician or sometimes insufficient motivation to take part and also some staff-related factors that can lead to a lower recruitment process. Do you think that these could be real weaknesses in the recruitment process, and do you have any explanation about that based on your own experience?

I think these are all important factors, but I think the silver most important factor for healthy volunteers are indeed the amount of time they have to be in the trial and the fee that they will get for it, that's still the major cost. We noticed one or two years ago recruitment was going very bad not only *diversity* but everywhere and it was mainly due to the fact that there were a lot of more trials after COVID. We saw that during COVID less trials were there and after that people tried to catch up. We saw in Belgium normally there were like 45 to 50 trials a year running and two years ago it was 90 trials and you see that all around Europe that there were a lot of more trials which means people can really pick and choose the type of trials that they want to do and the only ones that getting recruit easily are the ones that were a short period with a decent amount of fee. So, the trials for typical biological trials let's say so the ones with 1/2 year follow up with only three days in the house so less money and longer in a trial were very difficult to recruit.
So, I do agree the basic for people have to be that they trust the staff there that's all true but still the most important thing for people is to make money. And we know the trials that are still recruiting well are the ones that, or indeed have a lot of money in a short time, or for specific populations let's say trials for people with the age from 55 to 65 they of course have a lot of trials they cannot participate in because they're a little bit older so they can be *less picky* so they will still join the trials. For us in a moment we had difficulty recruiting in some trials we increase the age from 55 to 65 and recently noticed a lot of increasing in recruitment so that's important about what is possible for the participant itself to do.

Strategies do exist and constitute the strengths of recruitment process. We saw that understand the participant, their character traits, their motivations, their fears and build a good communication between them and the staff is important to increase the recruitment. Do you think that by targeting these particular traits could be a good recruitment strategy?

That helps. For instance we recently had a trial for healthy volunteers but only without a gallbladder because we knew that the medication could give them bold stones and we specifically targeted in our advertisements "Do you not have a gallbladder, you can join the trial", it was not like that it was a little bit more ethical but basically like that and what I notice indeed is that we had an increase of participants joining our database because of that because they feel attracted to that part in recruitment and they feel needs we have specific characterization which other people don't have and they feel attracted to that to say read it and

they sooner subscribing in the trial. For general approval it is of course difficult but for some specific characteristics that can indeed help.

Do you also think that establish a trusting relationship between the staff and the participant could help for the recruitment?

Yes, at the start because people who want to do the first trial are indeed very afraid of their safety and how it's going to be in everything like that so for that indeed I think it's important to help them and have a confident staff of people explaining to them what it's all about and why they don't have to be afraid for their health. So, at the start, yes, I do agree on that to be in a database in the first trial. But of course, when people have done two or three trials already, they know everything and then the impact of the staff itself will get less and indeed they're more looking towards the fees they're gonna get. So, I think for the first trial indeed the staff is very important, but it decreases overtime, well the fee they going to get will be more important over time.

We know that another important factor in the recruitment failures is related to the design phase. Did you already heard about or maybe used some tools to improve phase 1 recruitment such as QRI, GREET project, CTTI planning?

For those, I've never heard.
But what are they doing? They look at your project and design the recruitment plan or do you mean recruitments related to design of the protocol?

These tools are built in a way that if you meet some problems, they can help you to design and plan the recruitment and the different tasks you have to do to help you to have the good recruitment rate.

So far as I know we don't use that because we have quite a standardised start of recruitment like database that we're going to use, we have 14,000 participants in our database so a lot of trials will already get filled purely on that, so you do not need a lot of additional recruitments on that. For the difficult trials so the special populations indeed we look specifically towards social media, sometimes in the gym we have advertisements or in the cinemas. So, we have some standardised methods that we use so far we didn't have to use programmes like that but I think it might be interesting in the future indeed if you notice some difficulties maybe main for some smaller sites because they don't have a large database and they have to find people new every time and then I can think that it might indeed be beneficial.

You may know about the patients' involvement in some clinical trials increasingly practiced. From this point of view, I was wondering if it was possible to engage healthy volunteers to improve the recruitment?

That's a very good topic, you have to listen to our webinar we're going to give the 15th of September because together with some colleagues from EUFEMED, EUFEMED is the federation in Europe for early development, we're performing a questionnaire throughout Europe for healthy volunteers to see for one side to the preference: why do you do clinical trials, what is important for you and things like that but also partially are you willing to be part of the review of documents so this is one of them but also informed consent that we ask healthy volunteers are interested to review informed consent. We want to see if it's really layman's

terms or not maybe to review the layman summary at the end of the trial which now mandated since the clinical trial regulation.
So have indeed the healthy volunteer participation the same as you have the patient involvement, we need working on the project in that in all Europe at the moment. So I totally agree on that, I think it's very important to do that because a lot of people have great insights about the things they really want to do so I think it can indeed surprises but like you said there's nothing of literature on that yes that's that's still a big gap so that's why we did have started with you from it last year to start it up and hopefully have the results of that somewhere in September October and we have word in our the 15th of September about this specific topic as well so it's well it's good thought of you as well they said I think it can greatly help.

And do you think it could be feasible?

Yes, I think it could be feasible because we have in Belgium a quite large group of participants who do trials in all the units, it's a job let's say it like that, they're very invested in it. For instance, we also have one of our participants who's part of the ethical committee of our local hospital to help reviewing and things like that so there a lot of them who are quite interested to help maybe for some fee that can be possible of course but it's something you have to work out. So, I think it's in detail as a benefit for them and there's a willingness for them on one side and also on the other side the pharmaceutical companies at this moment not really know if they're interested or not, but I think in the future they will see the benefits of it as well. If they have them reviewing information you have less chance of rejections of your protocols and can start soon and things like that, so I think in time we have to convince them maybe a little, but I think also for the pharmaceutical companies it's a big benefit if you have healthy volunteer involvement in your documentation.

Yes, for the pharmaceutical company but for the participant himself we could think there is no benefit compared to a patient who can really have benefits because of the disease they want to overcome while the healthy volunteers do not have any disease and so maybe they are not interested.

Yeah, I don't think it will help for the participants who might do one trial for three years, they're not interested in that they just want to do a trial make some money and go home. But I think the ones that are really doing 3,4,5 trials a year like I said this is like a job for them, they might be interested. And the things that you going to ask to them is not indeed what kind of medication do you need for your disease or anything like that but for instance discussion we are having at the moment is how long to keep people in house it has to be ethically possible. But let's say you have a trial that's in house for four or five days you know if you can extend it with two more days you have a lot more money so you get tricked more people but they had to stay in house two days longer maybe for just one or two PK samples so not something big we do that because we think the fee will increase and it's more interesting but maybe the participants say OK I rather stay in house later *less* because I can stay home more. So, it's difficult for those kinds of details to find out what is interesting for them or not. And therefore, they can have the influences on the type of trial set that we can offer them, and they can participate in.
So it's indeed not the disease itself, they're not interested in if it's for breast cancer, for coronary disease, that's they're not interested about but rather in the design of the trial, where they gonna make from it, the time they have to invest in it, restrictions during trousers because also very important we notice recruitment fails due to the fact that people cannot drink alcohol during the entire trial and they say OK I cannot drink alcohol in unit but I want to drink one glass of wine a week afterwards, that can be a deal breaking improvement as well.

So, those are things that may be healthy volunteers' involvement can greatly help and I think we have participants that might be interested in that as well.

You talked about participants who participate in 2 or more trials a year, don't you think it could become a job for them and do you think it is a good thing?

This is always ethically difficult to say if it's good or not. For the general health, as long as all the restrictions are being held which means that they can't do participate in trials at the same time and they really respect the washout period, I don't think there's an issue in that. People need to realise only that it is not a job because for a job you know at the start of the month what you're gonna earn at the end of the month and you have the 12 months a year. For this OK you have the first specific trial for instance we have now a trial where the half-life was longer than expected so people have to stay in the trial for two months longer than expected which means they cannot do another trial. That's it could happen, it's exploratory medicine there's no issue, they're informed about this but it can happen. But, of course, then they cannot start a trial two months earlier and they miss money because of that. So, if it's really a job for them that can be difficult when things like that unexpectedly happen *or if you have some period that are less trials they cannot participate at any.* So, I think really seeing it as a job is quite dangerous but the fact that they wanna do multiple trials a year just to have some extra cash I don't think that's an issue as long as the correct wash-out periods have been followed.

Yes, because safety must never be compromised.

Correct. As I know in the surrounding countries there are some rules about that. I think in in England you can only do three trials a year max, in France, I think you can earn max €4500 not that everything is going to *tax* so people do not left out there as well.
So, there are some protection mechanisms around us. To my opinion, it's a bit too conservative I think the way we describe it and volunteer himself the right to decide if they want to do it or not. But our job is just to make sure that it's safe for them.
We need to make sure that all those factors like washouts periods being respected but if they want to do more trials it's their responsibility, they are informed, they know it so they can choose what they want to do.

Interview 3 – 25/07/23 – Site side

What is your role in phase 1 clinical trials and are you really involved in the recruitment of healthy volunteers?

My role here at [redacted] is business operations manager, I am in charge of the recruitment of healthy volunteers together with my team of five people. So, they are responsible to set up the communication campaigns, to send out direct mailings to our database, to do pre-screening through telephone with healthy volunteers, to fill the screening cohorts with healthy volunteers, etc and so I'm in charge of that. Next to that I'm also in charge of everything that has to do with human resources of temporary staff here at the unit and also a little bit of finance.

There is a new European Clinical Trials Regulation, do you think this had a positive or negative impact on the recruitment in phase 1?

Well, it will have definitely an impact and the recruitment of healthy volunteers will become more challenging. Why is that? Before the new CTR regulation we were able to start already digital campaigns before we received an approval of the study. But now, we have to submit everything, also recruitment campaign material, and so we have to wait with the recruiting of healthy volunteers until we receive the approval of the whole study which means that in some cases, we will have only like 7 days or 10 days' time to recruit new healthy volunteers.
And if you know a little bit about marketing, to convince people to buy something, to participate something, to do something, it needs more time. You do that to retargeting, to create first awareness about a product or about a clinical trial and afterwards by retargeting the person with different messages, the potential candidate will consider to participate. And after consideration, he or she will take action. But that takes a long time. Of course, we have a database of healthy volunteers, people who already participated at our clinical trials or news so that's also a channel that we can use to contact possible or potential candidates and that makes it a little bit easier for us. But for attract new healthy volunteers in our database a period of seven days is too short.

If we compare with other European countries, do you think that Belgium decreases his good capacity of conducting clinical trials recruitment due to this new regulation?

I don't have any idea about that. I hear messages or other voices within pharma industry. They indeed say that it will decrease our top position of clinical trials in Europe and in in the world, but I don't know exactly how reglementations in other European countries are at this moment. But I think the pharma industry will take actions to see how we can handle this new regulation. And in the meantime, a as a clinical pharmacology unit, we try to take new initiatives to solve, to handle those challenges like for instance if we cannot start a campaign we maybe can start already kind of campaign to making list of people who are interested. So that is what we are doing now and then if the study is approved then we can immediately contact those people who are interested, and we will mention their name on that list. So, those are the creative solutions today we are trying out.

We know that recruitment failures in phase 1 do exist, in the literature they talk about some factors that are linked to these recruitment failures including the participants-related factors such as the time they can spend in the unit, the lack of trust they may have with the physician and sometimes the insufficient motivation they have to take part. Next to that we also have some staff-related factors who can lead to a lower recruitment sometimes due to a lack of

communication with the participants. Do you think that those factors are real weaknesses for the recruitment process in phase 1?

I would rather say that there are not really hard weaknesses for the recruitment phase because those things you just summed up, you can solve easily through training of your employees through communication training, through fine tuning internal processes procedures and communication towards volunteers, so I don't see their huge difficulties. For instance, we tried first of all to communicate very well on our website, that's the hub of all information you can find as a volunteer or as a potential candidate all information on our website: how do you subscribe for study, how does your stay looks like at the unit, when do you get paid, all those frequently asked questions you can find the answers of them all our website. Secondly, our team of five motivated people they are also trained to have quality phone calls which means we just not asking or recruiting people and making appointments, we are explaining very well the restrictions they have to follow for the screening, we explain them very well what's the calendar of the study etc. And before they come to the units, a day before screening, they also receive reminder through SMS etc. And then during the screening, we have stewards, physicians, psychologists, who are trained to explain the expectations, the assessments, the duration, the possible risks, etc of study. As a matter of fact, it's obliged. We are obliged to do that because they sign an informed consent and so we, as a pharma company, have to make sure that we explain the study and its risks in and language that volunteer understands and that is not too scientific but that gives also kind of trust.

What is for you the main weaknesses identified, based on your proper experience, in the recruitment process in phase 1?

I think a future challenge that might happen is digital advertising about clinical trials because for Google and Facebook and those big tech companies, clinical trials is something sensitive to communicate about and it's also a special ad category which means you cannot select only the advertising to be shown at women for instance or at men because that could be interpreted as discrimination. So you have to advertise to a broad public, while the inclusion and exclusion criteria of a study protocol are very specific so you I don't need people above let's say 65 age or under 18 years old, and sometimes for some studies you only need men, for some studies you only need people of certain skin type, etc. So, I think advertising can be that limited that it will be a challenge to find the right candidates.
At the other hands, now with the new regulation, we have to submit also all campaign material together with protocol, etc for submission and it gives us less flexibility on creating and setting up digital campaigns because every text, every single picture has to be the same as in submission while before we could use templates for all our campaigns, we could say these are the kind of pictures we are going to use, these are the kind of messages we are going to publish and depending on study we tweak here and there a little word but that's it now it has to be the same as in the submission and that gives also a lot of limitations.

We found in the literature some strategies to overcome these participants-related recruitment failures by using a targeted-approach: understand them, their motivations, theirs fears and build a good communication channel. You already mentioned it previously. So, do you have some experiences with these targeted approaches?

The biggest motivation is still the financial compensation. We can say whatever we want, that’s the final and most decisive motivation, the fee. However, we, as a pharma company, cannot use

- and it's also an internal policy of [redacted] that - this as the biggest trigger to attract potential candidates because then people would feel not really free to participate and then you are really selling something and that's our policy we don't want to do that. So what we do is, we have like in our campaigns if you look on our website, on our digital campaigns, the key messages is "you participate in a clinical trial to help somebody else", to help the mother of your friend, to help the sister of your colleague, etc. So that is the key message that we use in our promotion, in our digital campaigns: you participate because you want to help somebody and without you we can't deliver a drug medication, we can't help make people better. So that is the key message, but the key motivation still stays the financial compensation which is of course approved by Ethics Committee.
About the trust and fear and risks, that is something that needs to be solved by our research physicians, they are responsible of the clinical trial as a principle investigator and the assistant physician during screening, for instance, or the principle investigator during participation at the study, he or she needs to be able to answer on all their questions about safety, about the possible effects, about the adverse events they feel, etc. How do we communicate about safe and trust, we have also information on that on our website that is something people really want to dig in when they considered to participate. At first, they are aware of clinical trials, they see a publication on digital media and they think "maybe it's something for me", "maybe I want to help somebody", "maybe I want to do something for society" and "oh yes interesting, I can earn something by participating at the study, let's have a look on the website". When they have a look on the website, they realised that it asks a certain engagement, it asked that they're willing to take risks, it asks that they have to follow a certain diet, a certain minimum stay to unit, etc. And then, during that consideration, I guess they will search for safety-related questions. That kind of information can be found on our website. Of course, non-study specific information but general safety information. Study-specific safety-related information must be told by the research physician, that's according to the Good Clinical Practices.
We try to communicate during all kind of touch points with our volunteers which means not only online through our website but also through telephone, SMS, direct mailing, here life on our site. At every stage we try to have a straightforward, honest and open transparent communication. Like, for instance, it's also possible to get feedback through surveys and volunteers can fill in a survey at any moment, they can give feedback at people working here at unit.

We also identified that recruitment failures may be due to the design phase and some tools exist to improve the design. Did you already heard about those tools: the QRI, the GREET project and the CTTI planning?

No.

So, what are the tools you used to have a better recruitment when this one failed due to a design-related cause.

What do you mean by "design"?

For instance, if the eligibility criteria are too complex.

As recruitment team, we cannot change anything about inclusion or exclusion criteria but of course, before we plan a study we also have like an internal feasibility meeting with all partners where we can express our concerns about, for instance, finding the right candidates according

to these or these inclusion an exclusion criteria so that study sponsors are then already informed about possible difficulties to find the right candidates.
At this point we once had like a study where the recruitment was a big failure and it was because the financial compensation was rather low and we could only recruit men between 18 and 45 years old and there were also a lot of other studies at that moment at unit that make the competition of other better bait studies quite high because people will also choose the study with the biggest fee and less involvement. Then we had to do some calling, so we had to do we really selected group of possible candidates in our database and started to call themselves and say "hey are you not interested to participate?".
But based on very special criteria, there were once a study - it was not one with healthy volunteers but more patient – where study patients must be depressed but not yet receive any drug medication of their psychologist or psychiatrist and then it was quite difficult. Let's say that my team of volunteer recruiting officers they do the first selection, the preselection, the selection by telephone but in the end, it will be research physician who decides if the person can participate. So, I think create being creative to find the right people is important and what we then do was contact some doctors in the region because maybe they had or they were aware of some patients and that they could send to us.
But we don't have one big solution for specific recruiting difficulties, it's always being creative.

You may know about patients' involvement in clinical trials which is increasingly practiced. From this point of view, I was wondering if you think it is possible to engage healthy volunteers in order to improve the recruitment strategies and things like that?

Well by asking them feedback through surveys, I guess that's a possible way. Or like today, we had a debate with the volunteers that stay at this moment in house because we wanted to know how they find our website, how they use our website, how the experience there stay here because if they have a good experience, they might be coming back next time for another clinical trial. Yes, of course there's patient centricity but there's also healthy volunteers' centricity, you want to make it as comfortable as you want and as you can so that he or she can come back.
I don't have the impression that a lot of healthy volunteers quit in the middle of the study, most of them engaged until the end. It depends also on the age, for instance, for certain vaccine studies we often need elderly people, people starting from the age of 50 years old and older. And we know that because the amount of studies where elderly people are needed are pretty low, those kind of volunteers are happy to participate when there is one available and so they have a huge engagement, they're very loyal, they don't forget their screening dates, they respect restrictions for screening, etc. So, engagement depends also a little bit on what kind of people you are dealing with or what kind audience you're targeting.

Are you not afraid that some people that participate make it as a job?

To be honest we have like small group of volunteers for who it is a job. They are unemployed, or they have debts, or they have a too small income from their job so they need money. And then we see them coming back regularly, not only here but also in other CROs. We have like kind of system: the VCT check for Verified Clinical Trials, I don't know if you are aware of that but that's actually an international organisation where we can check if somebody is still participating at another study before participating at the new study. Because you cannot participate at a new study if you're last dose has only been 10 days ago, you need a kind of wash-out period. So, there is an international system between, I think, the Netherlands, Belgium

and Luxembourg called Verified Clinical Trials, where we can see if the volunteer who has a screening's appointment is really allowed to participate at a new study.

Yes, really to guarantee the safety.

Yes, the safety and also the data. Data integrity is also very important because if he has been dosed with other molecules or compounds, it can influence our data.

Interview 4 – 18/08/23 – Site side

What is your role in phase one clinical trials exactly?

I am the head of departments of the centre for vaccinology, which is a dedicated vaccine research and evaluation centre at [redacted], and I am PI of many phases 1, 2 and 3 vaccine trials.

So, are you really involved in the recruitment of healthy volunteers?

Let's say I'm indirectly involved in a way that I often give inputs in designing recruitment messages. When recruitment is difficult, I participate in meetings where we brainstorm on novel strategies. Sometimes we have Instagram live sessions, Facebook lives or we post on Facebook small videos and very often I'm the person presenting those messages. When we contact the press, journalists for example if we think the study might be of interest to a broader public, I will also be the one responding to the questions of journalists in the written press or also on television.

I wanted to know if you really think there is a need for optimising the recruitment process in phase one. And if yes, why?

We invest a lot of time in looking for the right volunteers. Personally, I think with our team at [redacted], it's mainly the nurses that do a lot of phone calls and also some administrative *assistance job students*. But at least for the nurses I think it's a *pity* that we are investing so much time in recruitment. It would be better if that could be done by other profiles or if that process could be optimised so that the nurses can be performing more of clinical visits and assessments vaccinations blood *draws* and so on. So yep, very often we are limited in the number of volunteers we can enrol because recruitment takes so much time.

Yes, so from what I hear, there is indeed a need to optimise that time.

There is a need to optimise I think the awareness among the general public that it's safe to participate in trials, that it's something you can do. For example, a lot of people give blood to the Red Cross and donations. And that [clinical trial], this is also another way of helping science, helping medicine to progress. So, creating that awareness then finding a way to register for a trial, I think every individual centre or unit does a lot of efforts, but if we could bundle those efforts may be to a regional or a national initiative, that could also make our lives much easier, I think. We have thought about this a lot already and there are examples, for example in in Denmark I don't know if you've heard of "trial nation". It's, at least from what I've heard, one of the main reasons why Denmark is actually in Europe country number one with regards to clinical trials. So, the number of clinical trials per capita is highest in Denmark as compared to other European countries and from what I've heard this is also because it is very well organised, there is a national platform website for sponsors as well as for candidate participants or patients where they can sign up and then be informed about which studies are ongoing where. And I think if we, as Belgium, are also performing quite well in Europe, I think we are number 3 if I'm not mistaken, two or three after Denmark and Estonia. I think, if we want to maintain that position and even strengthen it, that an initiative like that to optimise recruitment would really be helpful.
Have you seen the pharma.be report on Belgium as a lead country with the plot demonstrating the attractiveness of the Belgium as a clinical trial country? I think in the most recent report of

2023, we have mailed pharma.be to get the full report because we only have a slide set summarising the main results. But one of these let's say pillars in the plot or elements is recruitment where we used to be very good. You see variation actually from year to year and with the trends of reduced recruitment efficiency. Of course, COVID has also had an impact with accelerated timelines for COVID trials but really other trials being put on hold so of course 2021 is not a representative year. Anyway, as Belgium we have lost our advantage of quick starting up timelines because of the CTR, the new regulation and I think we have to compensate for that loss. We used to be very quick, but we can't anymore as all European countries have the same set up timelines. I think we have to compensate for that lost advantage by improving for example recruitment efficiency.

Do you think the new EU CTR had an impact (positive or negative) on the recruitment in phase 1 trials?

I don't think it has a major impact on recruitment. On the other hand, the fact that we used to be able to submit at our local Ethics Committee and for example if you adapt the recruitment message, you have a new recruitment message you can more easily submit that to your local EC and get a rapid response as opposed to the current regulation and the current process via CTIS and the college and so on. So, I do think that in some cases if you have all your messages prepared and you don't need to apply any alternative recruitment strategy, I don't think it has an impact but if, for example, you forgot to submit a message you need to change strategies then it's a disadvantage the new procedure. At overall, I think the major disadvantage or impact is a slower timeline.

And so, when comparing to other European countries, you think that Belgium decreases that good capacity of conducting clinical trials because of that regulation?

Yes, I do think so. And also, because the fact is that we have noticed an impact because our clinical trials are not reviewed by our own Ethics Committee, they can be evaluated by an Ethics Committee of a hospital which is less experienced in vaccine trials leading to a whole series of redundant or unnecessary questions. We have that experience already now where we see that some ethics committees don't have this experience and they ask all types of questions, and it takes time to answer all these or certain additional data they're requiring. We have had a recent experience with the study being reviewed in US as well as in Belgium, the American FDA ask two or three questions and in Belgium I think almost 20 questions were raised. We have had situations where a sponsor receives all these questions and says this is too much effort, some of these questions are not really relevant, we don't want to invest time in answering them or collecting additional data so let's stop in Belgium and we just continue in US. Because the FDA requires that, I think, at least 25% of the subjects have to be enrolled in the US so that means that sponsors start up a trial and - I'm particularly talking about phase three now - but sponsors are starting up trials in the US anyway. So, if then it becomes more difficult to start up a trial in Europe, and in Belgium in particular, they might just say well let's stop this effort and just do the study in the US.

In the literature, they talk about factors that are linked to recruitment failures in phase 1 trials including participant-related factors such as the time they can spend at the CRU, lack of trust with the physician and their sometimes-insufficient motivations to take part in the trial. Staff-related factors also lead to lower recruitment due to a lack of communication with the participant and a lack of motivation to enroll them. Do you think those factors are real weaknesses in the recruitment process?

Subject related factors, the ones you named like lack of trust and so on, it's really not an issue. Staff related issues; I don't really think so. We have the advantage that we have a very stable team of very experienced staff, and a new staff member has a quite long period of training. We have a very rigorous quality system describing all steps of training and before we hand over a subject to an investigator or study nurse, they have to have all these training requirements fulfilled. We really monitor that so yeah.
One of issues we have is access ability of the hospital campus. We are based in a separate building but on a hospital campus which is very busy and with parking problems for example. Accessibility is an issue. Especially because we do quite a lot of studies in older adults, we stimulate people to come by tram, by public transport but still a lot of people come by car and find encounter difficulties to find a parking space and then sometimes they call us from the car and say "sorry I'm not going to come from my visits I'm already half an hour late because I unable to find parking space", I think that's one of our barriers, the main one.

Some strategies are already put in place to overcome those factors and I read an article talking about really understand the participant itself, their motivations, their fears and to build a communication channel with them to really target what they want to catch them in the study and so I was wondering if you do so maybe or if you have proper strategies including those sort of targeted approach?

What we do is that we have like a questionnaire at the end of the study to ask each subject about how happy they were, about their participation, their experience, if they have any tips for us on how to improve the services we provide, the way they have been welcomed, the waiting time, and so on. So, we evaluate all of these aspects of their participation and then have an open comment field like anything else you would advise us and we monitor the general level of satisfaction and where we can improve we really try to implement these suggestions if possible. We have any important comments with regards to recruitment. *For instance*, we have a database of 12,000 volunteers. When we start a new study, an e-mail is sent to that database very often targeted: we can say only send e-mail to people of this or this age and so on, that are not currently enrolled in a trial and most of the time, this e-mail is sufficient to get enough candidates. But then the process is that person will register so they get a link in the e-mail they will register and then we get an e-mail in our inbox and that e-mail is actually printed out, we do phone script to give some explanation about studying and evaluated the main in- and exclusion criteria before we actually make an appointment for screening visits. So, it's like a pre-screening procedure but that pre-screening procedure takes some time, it's a phone call of 20 to 30 minutes and we often notice especially young people they don't have a lot of time, they don't like to answer phones. They're the digital generation which prefers communication via e-mail messages and so on, so that's why we recently implemented a strategy of pre-screening via a form so we don't have to bother people when they're going to classes or working (because we can only call during daytime it's not that we're calling in the evening). So, optimization is certainly this digital form although for example older adults prefer personal conversation to give some explanation, they like to hear somebody on the phone, they like to talk and ask questions. So, I think you need to optimise that according to your target group. Have a digital form or call people or maybe have them when they register allowing them the choice: do you want to be contacted by phone or would you prefer to have a digital form/ Maybe give this option to both options, so I think that's already something we have started and are further optimising and implementing.

Another important factor that we found in the literature about the recruitment failure was related to the design phase and at this point we also found that there were some tools that were proposed

to improve those factors. So, there are some design phase failures, maybe it's too complex and so some tools can be put in place to better organise the design phase and the three tools we found in the literature were: the QRI (QuinteT Recruitment Intervention) project, the GREET project and the CTTI (Clinical Trials Transformation Initiative) planning but I don't know if you have ever heard about it?

No, I've never heard about it.

Ok, interesting because these are tools that we found in the literature but of course these maybe are not really used by the sites.

What is the CTTI you said?

They give you a plan to conduct the recruitment process.

Okay, never heard of it.
And the other one QRI was what?

They try to assess and understand the difficulties of the recruitment process and they will deal with the actors of the clinical trial unit to implement the good strategies.

Okay, it's all new concept.
Is there a way of reading your master thesis or getting a copy of it afterward?

Yes, I can send you a copy of my final work in January.

Let's move to my last question. As a perspective of my master thesis, we know that patient's involvement in clinical trials is increasingly practiced and from this point of view I was wondering if we could engage healthy volunteers maybe in the ethics committee and if it could help to improve the recruitment process. We didn't see any information about that in the literature. What do you think about it, and do you think it is feasible?

Involving patients in ethics committees and in quality boards of hospitals is becoming more and more common practised, it's also something which here in the University Hospital has only recently been adopted. But of course, these are patients with one specific disease that have enough time to spend and look at informed consent forms for example, see if they are easily understandable and so on. For recruitment, because that's I think your question, if involvement of healthy volunteers, they're not patients, could be feasible. I don't I don't think by putting them in Ethics Committee that will help recruitment. That's good to evaluate the documents are clear enough and so on. I do think and I do believe in the in the power of influencers maybe to increase the awareness of clinical trials phase 1, you can help science, you can contribute as a citizen and there's several ways of contributing as I said in the beginning. Donation of blood is something which is really well known but participating clinical trials much less or often has this connotation of being a Guinea pig in a lab. People have this very weird images of what being having to undergo painful experiments and so on, they don't want to be Guinea pig.
Especially among young people, I'm a mentor of a group of medical students and I remember asking them the question "have you ever participated in a clinical trial", you know an informal small group of people being medical students so with an interest and it was funny to see that they were something, they often did not know, they were bachelor students they did not know it existed, they didn't have any idea about what it really involved, what was going to be done

with them. The fact that you get a reimbursement often increases feelings of distrust so if you get money for it must be dangerous. So, I have a feeling, even in this group of highly educated medical students, that this is not known enough and maybe influencers in some way or another could help.

Yes, so vulgarization seems to be important here?

Yes. And we have tried to make the process clear by making two videos which you can find on our website, but the fact is you have to find our website, and then enter the specific page, and then Scroll down and there you see the video you can click on. I don't think we have a way of monitoring the number of views, but we've spent quite some budget making these two videos, I think almost 10,000 euros but we should still I think optimise it, get some feedback or optimise the accessibility of the videos and get some feedback "is this helpful", "does this really make the process clear"? I can send you the link if you want to have an idea, but we've done it's not really with an influencer, but we involved a couple of volunteers from various age groups. So, people could, like an older adult and a younger person, a man and a woman, explaining why they participated, what are their experiences.

My last question will be about the fact that maybe some volunteers make trials their job. Is it not too dangerous to have professional healthy volunteers? What is your point?

I think it is the case for drug trials because these are short studies, often with overnight stays and with significant amounts of subject fees being paid. In vaccine trials, there are long studies, there's ambulatory visits which are much less paid it's like 50-60€ per visits and maybe 8 visits over a year so it's amounts of 400-500€ maybe sometimes €1000 (but then it's a study of two years). So, you see you cannot live from that, so we don't have any professional volunteers in vaccine trials.
Of course, the CHIM studies, is Controlled Human Infection Model, these could be studies with antivirals, with vaccines where volunteers are vaccinated for example in phase one and then they are challenged with the virus or the bacterium to see if they're protected or not. Small groups of very healthy young people and this is a very specific type of study with overnight stay, people are quarantined actually until they have cleared the virus or the infection, they're documented negative. So, these are studies which are very well paid obviously but we do not do that type studies. The sites doing those in Belgium are SGS then the site in Antwerp Vaccino Police. But it's a very recently constructed facility, so the site exists for long time it's a site of Pierre van Damme but the facility to perform CHIM studies, it's a 30 beds facility, is new. And from what I've heard from Pierre, there is certainly during the whole covid's pandemic there was a lot of debates whether it would be ethically acceptable or not to do CHIM studies with new COVID vaccines. But anyway, there's a large database of volunteers internationally wanting to participate in that type of studies. I don't know, I think it's a combination probably the remuneration plus the fact that you can really make science advance quicker because if you see that type of experiment that vaccine is not protective at all you don't have to go through all the hassle of setting up a phase three study. It will cut the timelines, but it will not, in the current regulatory landscape, it is not accepted as a surrogate, as replacement of a phase 3 study. So it's additional and some companies do it, some don't. It's especially useful if you don't really know what mediates protection and what you're looking for and so on. It's expensive but phase three studies are obviously also very expensive. So, if it can avoid a full phase three and 10,000 or more participants, it's good.

Interview 5 – 02/10/23 – Sponsor side

I was impressed that you found me I am not very visible on social medias or anything. My name is [redacted], I'm a pharmacist by training I graduated in 97 so it's quite some years ago and ever since graduating the majority of my time I have spent on the sponsor side and mainly within early clinical development, so phase one but I've also done phase two and phase three. But you can say maybe I spent 60% of my time to invest one so I could be kind of an expert, I don't like to say that I'm an expert, I think you should be very ample, and things are changing constantly regulations is changing. It is a very dynamic environment, and whenever you think it's *smooth sailing* then you have COVID or something else coming in changing the whole settings so there's not no such thing as an easy trial. All trials will once you go into them be more or less you can say challenging - challenging is a positive word - but it's just never the same melody and you cannot just repeat what you did, you have to look at the environment and to figure out what will be the challenge here the devil is in the details so we can go back to different trials at some point where I could tell you about my challenges and my way of overcoming different barriers. But before we even start, I would say whenever I do phase one, I actually normally say that recruitment is kind of simple because you say 18 to 50, you say healthy volunteers. The majority of people would be between 18 and 50 and be healthy. So, usually recruitment is more predictable, more less of an issue and much simpler when you do phase one. Phase one is the easy trial that's always where you don't have recruitment issues and then you do phase two, you start in patients you may not even giving them anything but placebo and there you have all the challenge. Because then you have a patient, you have the mindset of the patient but in healthy volunteers it's feed and breed, so you give them money you give them food and you want their blood, it's a very fair straightforward transaction where there's a benefit for the person which may be gone in the later stage of the trials. And that's why I was a bit confused when you say to overcome various because I would say you pick the area where there's the highest predictability where is the least problems, so you may have found a non-existent problem. I don't know but we can go through your interview it's just to warn you that I was a little surprised when I read what you sent which I appreciated because I'm the person who likes to be prepared maybe I had my observations, or you can say comments.

Okay, interesting. I understand your point of view, but I think here one of the main difficulties encountered and maybe just in Belgium I don't know, is the awareness of the population about phase 1 clinical trials. Most of the time when you ask somebody in the street "Do you know the existence of phase 1 trials", they just don't. So, I really think the main challenge here is to make people aware about phase 1. Because as you said, indeed, it is very simple to recruit participant if we think about the financial compensation they can receive and so on. It seems to be the easiest recruitment process compared to all other phases; I agree but maybe what I observed is that people just don't know about it.

But then I think it's a fair comment and I can say now you looked at a trial we're doing in Belgium it's called [redacted] and whenever we look at these phase one units we really go into that database: how many potential healthy volunteers do they have and you could say, I believe there are 10,000 in their database, you could say you want women, you want men, you want both, you want them with their coloured skin, you want them with a special diet or whatever. You can find them in their database, they have a lot of information on their sockets who have volunteered to be in this directory and then they can tell you whenever you say I need - there's always something special you need - you may say they should be whatever and just then they can cut their numbers and then they would tell us that it's OK we can reach out to let's say 500 or 1000. Usually in the phase one you don't need that many, you need maybe 50 or 100 so if they have

like 10,000, you are never close to the end and then well all these has turn it several times. If they have done it more than once, you know if they are compliant with all these come to the visit, you have to give blood on Wednesday maybe Friday and again even on a Sunday morning you have to go to the clinic because that protocol is rather regulus when these blood samples must be collected and it can be all days so it's seven days a week. And therefore, some people they would go out and party, but you're not allowed to do that. You have to relive a very you can say normalised life and you sign that you will not maybe either eat more or less than you normally do but you have to trust them. Of course, you can see in the results if they don't. You also tell them that they may not have the opportunity to have sex for a period of time, that is why you can compensate them because of course it is limiting the you can say life of your subjects but they're also paid for it and you can always say maybe you are not in a relation so you're saying I can easily sign but the next day you meet the whatever person you always wanted to meet and then the situation is difficult.
It's just to tell you a bit about the scene but you are right, that many people on the street if you ask him about a trial they would say "Isn't it dangerous?", there's a lot of misconception and the pool could be 10,000 is very small for first you can say [redacted] so with a clinic [redacted] I think it's not like you can say well known that they exist or known by many. I would hope you can say that maybe around students in that area it is more known but that we can also discuss it, I'm not even sure but you puts a students at least within the pharmaceutical medical dentist they may or may not be aware but those people would somehow during their education at least you can say have a chance to see that this should exist and then they can Google and it will take them 5 seconds to find. But maybe you need to you can they have in your mind that this opportunity exists and you can do it if you either maybe you have a family whatever, the friend who's suffering from lack of treatment, that could be you could say one reason or the other could be that you have financial problems and I think when I look what we pay in our trials for let's say some days where they stay a full day on the clinic, we pay them 6000 euros or something like that so that's quite a lot of money. Maybe it is too much because if you give people too much maybe they will do it even though they're afraid or they think it's risky and we cannot have that. But the good thing is it's always ethics who allows you to reimburse and they look how many days, how many blood samples, how many drugs do you have to swallow or whatever here it's injections so how many injections and then they say based on all these procedures we have a standard list with standard price, they added up and then they say you can give them 6000 euros and I say well that's a lot of money but I know it is also very demanding and for many many weeks they have to remember that they are part of this trial whenever they feel notion, whenever they have a headache, they have to report it so it's also rather demanding and it is actually 24/7 in all those days where they are participants, where they have to do certain things and they cannot choose to do everything maybe we also say you cannot run a marathon, not run a half marathon, you cannot even do hard exercise because that would you can say change your blood values. So yes, this was my introduction and maybe I have already said a lot but let's go to your questions and we will take it step by step.

It was a quite interesting introduction, thank you. You already mentioned some things I wanted you to talk about but anyway.
You already present yourself, that was my first question. But I wanted to know also if you were involved in the recruitment of healthy volunteers?

I should then go back and say my role in the company is that I'm a clinical project leader and you could translate that into a trial manager. We are a very small company of four or five people so I wear some different heads but you can say one of my responsibilities that is that when we plan a trial, it has to be very predictable you can say the conduct of the trial. So, the first thing

when I visit [redacted] that is that I asked them that we need this exactly healthy volunteers in that age range with both sex that can be included, how many do you have and how difficult do you believe it is? And then they would smile and they would say well you are very easy customer you can have almost let's say 8000 of the ten stars they would fit your criteria so we cannot have you can say very young and we cannot have older than let's say it was 50 so there's some that they would take away and then we say 1000 and I know that I need let's say 50 so I smile and I can go home and say I can put my hand on this very hot plate and I can promise we will not be delayed by you can say lacking recruitment or lack of recruitment. Very often, in all the latest age trials, what I constantly have to ask that is "can we prolong timelines" and in a world where patent is, you can say, the most important thing you have that is your pattern usually will last maybe 15-20 years from when you find it and that you do very early on you can say before your first trial for sure and then time is running. So, the only thing they don't want you to that is to say timelines will be extended and my job is to guard the timelines. So, I'm saying you can see on my LinkedIn profile that I am kind of feasibility expert, I try to see how well with this trial run once we start at you can say in reality. At the phase one units I say I relaxed I think this is easier right because it's not so difficult go right. Not all people, even though they could, know about it, there's lots of people we cannot reach out to, there are also lots of people we should not reach out to because they are not structured enough to be good participants. So, we really have to be careful it's not for all, it is only for those who have a mindset where if I give a commitment, I am true to that commitment. So, you have to exclude many because it is, as I was trying to say, rather requiring to be part of a trial there's really high expectations for what you can do and you cannot do and that's why I think we have to exclude a lot of people because they're simply not structured enough to take part and they would actually ruin your trial if they were allowed.

Do you think that the new EU CTR had a positive or negative impact on the recruitment in phase 1?

One of the changes is that you have to be much more open when you do a phase one trial. Openness, you can say is usually a good thing, as I was saying in the Pharmaceutical industry we like to keep secrets and for us the more open we are, the more the competitors can see what we're doing. *To our now*, the competitors already know that this little company called [redacted], they're doing this research and they can read a lot of things, certainly all this openness that is used by our competitors. In the best of worlds, why are we open? That was that people could really check our things, they could make up their mind, they could also see what was submitted to the authorities but then you would have to be very resourceful and you would have to have very good time because I think you get an informed consent and to me that's already drawn if you need information so I don't think you need this extra source of information. So, is it good or bad? I believe that the timelines were heavily extended so now whether it's phase one or phase three, they have up to more than 100 days to decide if you are allowed or not. In Belgium, I think they have promised they will do it faster when in phase one that's very good because I love to do trials in Belgium. But you know to me, I'm not sure if there was any big benefit except that I think openness is a good thing, I don't want secrets but I don't know here, it's like I cannot see the benefit of this openness because I think we were open in the informed consent that's where I talk to the potential participants and that's where I really want openness about all side effects, all risks, all the unknowns. We have to be very transparent that being paid 6000 for sure this is something there's a risk, we must be honest about it, and I think it's very important that you are very transparent with the risk. But whether people could go to this public database and search and then translate into is the risk bigger than I tell them or this big, that I don't think. So, I think that would require very few subjects could do so.

When we compared to other European countries, do you think Belgium decreases his good capacity of conducting clinical trials because of this new regulation?

Initially I was very much afraid that it's not just Belgium, but all EU countries would be deselected because US would be very fast, I don't know about Australia and New Zealand, but I would imagine they would be faster. So, the problem for me as a European citizen and as a Dane, I would love that clinical research is conducted in countries where I understand the culture, where I can easily travel, where there's no big-time difference. So, for me, it's much easier to do a trial in Europe than in the US and we do a lot of trials in US, very often you can say the market in America that is where they take the highest price, where it's most important to get it on the market first. So in order to satisfy the American authorities, FDA, then we usually do a lot of our trials within US and we also sometimes even do the phase one but I was thinking this is the end of phase one in Europe but it's certainly not because then the clinic in Belgium restarted before the legislation went into force, so we were approved under the old one, but they told me "[redacted], don't worry", we have already been given a promise that they will do it faster and I asked them "please keep tracked" and last limits on going what was the average approval time but I think it's much shorter than 100 days meaning that it is not a big problem but of course it takes longer now than it did. So, if you ask me "do I really like it?", I think I see many problems with this and it hasn't really proven its values yet. I believe in two or three years my answer would be different but now I have to say up front it was a lot of stress, there wasn't many things to consider and there's also those trials which will not end before this legislation falls or tries to be registered under the new law. And then that is to me, it was a lot of work to do trials already, now it's even more. And I *will be winning anything* I'm not sure but you know I'm one of those who are very much affected by the law and I cannot really see the big benefits but maybe you can also point where there will be benefits but in phase one, I am not sure I see it.

About recruitment failures in phase 1, in the literature they talk about factors that are linked to these recruitment failures including the participants-related factors such as the time they can spend at the clinical research unit, the lack of trust they may have with the physician or the insufficient motivation to take part. But next to that they highlight also staff-related factors that can lead to a lower recruitment rate. What do you think about those factors, do you think these are real weaknesses encountered?

I would say that weakness is where maybe the trial is so demanding or demand so much from you that you are not willing, even though you are eager to go into a phase one, you believe this phase one trial is maybe too much. So, I was doing a phase one trial in Germany some years ago and in that trial, we were looking for men who was volunteering to be chemically castrated. So, it was just for a short while maybe 2-3 months, we didn't know exactly how long actually that's always by we're investigating, but they would have an injection and that the drug would then dramatically lower their testosterone meaning that their *liberty* would go down and they would be feeling like if you were a ****** or something that then you can be chemically castrated and you can say it doesn't sound nice but here what we wanted to test was actually not the castration, that was a marketed products which have a known mechanism of action where it leads to castration but then under the skin we wanted to apply a gel where they would get testosterone so we could measure how well the gel would work. But in order to test the gel, we needed them to stop producing their hormones so we would only see something coming through the skin. And you can say how many men do you think we're saying "uh can I get it?", that was a phase one trial where I faced recruitment issues and where we started only recruiting locally trying to limit the cost of transportation and in the end I think if you said you would travel from

Turkey to this place in Germany we would have accepted it, we were so desperate and it was like such a surprise because I thought well it's only two or three months you're castrated. I didn't want myself maybe but still I thought they will be paid quite well so why not but what it ended up that was that even the clinic had maybe just the burden of the *topic* as being more bearable than it may be. And it's very hard to put yourself in the shoes of the volunteers, but a man he wants some money but then he may be looking for women or what do I know but here in this case he would be castrated and that wouldn't really be any action and therefore I think many minutes they realised that "I don't want to do this" and then we actually went to the ethics that telling them this is really to our surprise more difficult to recruit and they agreed that we could increase the reimbursement and we could increase the travel reimbursement and that helped but it took a bit longer to complete the trial then we had expected.
So, I have examples, but it is extreme examples so it's not what I would say you see all the time, this is what you see very rarely.

In the literature we found some strategies to overcome these recruitment failures, one of the strategies was really to have targeted approach to recruit the participants : knowing their character traits maybe to catch them in the population, build a good communication channel with them to overcome their fears, etc. So, do you think indeed we could recruit more participants by doing so?

Yes, I think if you are very desperate, if you suddenly realise that tomorrow we need 12 more. You realise instead of just 12, I need 24, then you could ask the 12 : "would you know anyone in your circles which resembles you quite a lot, which you could recommend this trial to?" and then if they say "well, I have a friend I could call him", and then you can say the barrier for one to one reference where one is already participating saying "it's nothing, I get 6000€, it's like I'm lying on a bit they take two blood sample today, this is life, I can I get food I get everything, I don't have to wash or clean, I'm in hospital settings, I have not allowed to go outside actually, they can use the Internet for as much as they please, they can do this I meant at the unit" and then if he says that to his good friend then it's much more likely that his good friend will put a path than if a doctor tells him you know pros and cons and a lot of details about the drug which he will not understand anyway.
So, I think that if you are squeezed on time then that strategy can work but I'm not advocating a lot to do it. To me, it also has this somehow cheating the, if you use one who is already in the trial, so I think it's very important that you get the acceptance from the ethics that you're doing this. If you have it, well I cannot see the problem, but I have to say you really have to make sure that you're not violating anything around that, they're not *cohesive* into a trial it's important that they have fair amount of information and they have ample of time to consider so maybe you cannot get them the day after. But you could say that the targeted I think is a good idea because it's very few who are very good. Sometimes we're saying firefighters, they're like very good health, they may have a lot of time, they are usually or all days those were the healthy volunteers very often, the fire station was close to the hospital, they could get a drug and you could collect some last samples. They were very suited being healthy volunteers and they're not afraid of giving blood they were like these strong men so no problem.

Another important factor identified in the literature about the recruitment failures was related to design phase. Did you already heard about tools that aim to improve the recruitment process, such as the QRI, the GREET project and the CTTI planning?

I have to admit that I google the all of them and you can say you're bombarded with information all the time, people are telling you about virtual trials, about doing things smarter and you

sometimes have almost too close your ears because you have to focus on what you're doing but on the other hand from an academic point of view recruitment is what I find very interesting and I actually joined the company [redacted] just to work on recruitment to be better at designing trials which have recruitment building in the design so you all up front all the time say "Is this cumbersome? Should we make more flexibility around this?", we would like women but if women always go with the kids to school maybe 8:00 to give a blood sample that's not the best timing if you want women that also have a normal life. So, I think I knew a lot of the initiative there were not new to me but Quintet not maybe not but it was certainly not new what they were coming up with their proposals. So, what I'm just saying it is much more relevant when you go into rare diseases or late stages research where there is already drugs on the market who are addressing the disease quite well. Then why on earth if you have asthma and you have no trouble with your asthma, I'm telling you now you can go into a trial and maybe your asthma may become worse, maybe it will become better and that's what we're going to find out : would you like I'll give you and I can pay your transport, I cannot even give you very much more because the problem is that once it's no longer phase one, the reimbursement is much lower so reimbursement is high in phase one which helps finding people who are willing to do it but once you go into late stage research, the reimbursement is almost none so you can only give them for time and then cost of transportation and that's where you have to have an appealing the reason why this is a good idea. And sometimes the only thing this will help, is maybe if your son or daughter has the same disease, maybe there will be a better treatment for them but for you taking part there's no direct benefit you have to be very honest here and you can tell them well we're not really being cured or anything, we're just using this to see if we can have the third drug on the market which will do as the two others already are doing. Then I would say that's where you have your almost a barrier, you cannot crawl over because you have to find out how on earth should I sell or promote this and then maybe from sometimes you go to the pharmacy, and they say we have shortage so if there's more products the risk of resources produced. So, it would be maybe that is the argument why you should participate in the search product being developed that is just to make sure that they will keep prices down and it will make sure that they ability of the drug is higher and then it's a strange argument but that would be one of the arguments I would try to somehow build into my material for how to recruit people because I think you should give people a good reason to do it, that's very important.

You probably already answered my last question a little bit but anyway, we know that patient's involvement in clinical trials is increasingly practiced and from this point of view I was wondering if involving healthy volunteers in some community could help to improve the recruitment? What is your point of view about that?

I can say that when working with the rare diseases, then where you get your recruitment that is the patient organisations. So, when patients are hard to find then the place to go and find them that is their own communities because usually if you are alone with a problem, you try to find others with the same problem. But for healthy volunteers the problem is maybe they need more money and then you should make a form for people needing more money where one option could be participating in clinical trials. I don't know, there's a million networks so maybe there isn't networks for healthy lunches I've not heard about it, I'm not seeing it. And when I look at the age and who is taking part of the trial, they're not that homogeneous and maybe that's very good because actually we want the whole society so it's not just students. There shouldn't be any imbalance and sometimes I'm sure there is a lot of students, they may or may not be the best to be in a trial. So, if we help too much, if I created this environment wouldn't I maybe bias it? So, it was a certain type of people who came into the trial, those who are on Facebook or those who are on LinkedIn already very young age. So honestly, I'm not sure we need it but

you can say how do we reach out to them and I think just having small conversions when people are buying stuff or whatever they're doing, then you could put in your commercial when the age group reflect what age group you're looking for, that's where you place it. Because then you get the broadest and unselected pool of people and then some would click on it, some would enter the phase one unit, some would book an appointment and some would go through the needle head being part of the child because I think it whenever they screen - maybe they screen two or maybe they screen three - before they have one which actually is healthy volunteer, because many people believe they're healthy enough to take part of the trial but not all are in fact.

And do you think it is not dangerous that some of these healthy volunteers become such professional and make it their job?

Yeah, it's something we're always very worried about because when we want them not to be healthy that's that we don't want two drugs to be in the blood and then we don't know which drug is doing what and therefore we look at their composition of their blood, if you draw a lot of blood then your red blood cell count would go down because you have missed it or it's taking away faster than their body can't produce it. So, you can sometimes tell and then you have databases where different clinics they register and when they did their money to the subject they know exactly the name and the identity of the subject and then other clinics can write that name and if the database tell them this is already taking part or part two or one months ago then usually there should be at least three months in between each trial. So, the professional subject, it is a concern always I think it is and then some may exist but it's more in your head than in reality a problem. I think they're quite good measures to how to control and avoid people doing this their living.

Interview 6 – 06/10/23 – Site side

What is your role in phase one clinical trials exactly? Are you really involved in the recruitment of healthy volunteers?

I am working at [redacted] at the university of Antwerp. I started here in 2010 first as sub-investigator and then later on Principle Investigator and now at the moment I'm the head of the ambulatory trial unit. So that's a little bit my role. So, we are centre that conduct only vaccine trials because you were talking about phase one trials and I know that then often we think of the medication studies but we are just like [redacted], I think it was a person who forwarded you to me and we have same kind of centre so we are only specialised on conduct of vaccine trials but of course there you also have phase one trials. In our team, the recruitment we do it a little bit together with the whole team and of course the principle investigator has to keep the oversight and see that we will manage to recruit the number of participants that are needed for a certain study but as you mentioned it is not always so evident that, that's true and sometimes we're sitting together with the whole team to see for this specific study what we can do extra for instance if the recruitment is going slowly or more difficult as expected.

You may probably know that there is e new Clinical Trials Regulation. Do you think that this new regulation had an impact - that can be both positive or negative - on the recruitment in phase 1 trials and why?

It's a difficult one because it just started this year, so we don't have that many trials already that started this year. What we see is that a study always starts with the signature of an informed consent but to do that the subject has to come of course on the first visit but if we recruit subjects we advertise, we put recruitment material on our website and we send an invitation e-mail or so to all the participants of our database and in these kinds of advertisements we always put also the in- and exclusion criteria, at least the most important ones that we know can have an effect on recruitment, but what we sometimes see is that if people are used to enter such a clinical trials that they don't always look very intently to the specific inclusion/exclusion criteria and then sometimes they come on the first visit and then already after one or two minutes you know it as an investigator he will not be able to come because some very easy factors that sometimes the subject always put it almost spontaneously during the interview and then it's a pity because of course the subject will not be able to enter the study, it's an appointment place that is gone and subject has been at this time for nothing. So, what we started to do is to amend our recruitment material in a way that people on our website see the inclusion/exclusion criteria but in a table and put this as a question on which they have to answer yes or no. So, for instance: are you a healthy person of an age between 18 and 50 years? Yes or no, something like that. If the person should have a BMI that is between certain range, may not be higher than 30 for instance then we say: Are you sure you have a BMI less than 30? Yes or no. Nothing more than that and if everything is fine then the person can click further and make the appointment. So in this recruitment material, our Ethics Committee is used to so they always agreed with us but now with the CTR, it's not our own Ethics Committee that refused recruitment material, it's definitely some another Ethics Committee that is not linked to our centre and they are very concerned that this in this way you also ask already some private questions for which the subject not yet has consented. So, we try to explain that we don't collect anything specifically that we just remind the subject "Are you sure" but still they refused it to the last time that we submitted so we cannot do that anymore. So, yeah that's perhaps a pity and then you can say perhaps it will have more impact on the recruitment.

What we also see is that since CTR started and because of Ethics Committees that are not used to our centres, that they ask a lot more questions and questions that we are not used to up till now. So, which makes that you do a submission, you get questions, you have to answer so it takes much longer before the study can start. So, this is difficult, the longer that you start, the shorter your recruitment periods is for the site to find all your subjects so in this way at this moment yes it can have an influence but I hope as with every system that is new, that's after a while we will become used to each other again and that it will go better. But like I said, this year was only some few studies, so I think it's just a new system, I think that's a big problem.

And especially compared to other European countries, do you think that Belgium decreases his good capacity of conducting clinical trial because of this regulation?

There are concerns, there are certainly concerns. Before Belgium always had the reputation to be fast, especially for phase one. Now at this time, we still have of course rather fast timelines but it's the number of comments, like I said, that can slow the process and indeed that can have influence on sponsors from external, if it could quickly in other countries but like I said it's just the beginning, I think we will have to re-evaluate this after some time.

About recruitment failures in phase 1, in the literature they talk about factors that are linked to these recruitment failures including the participants-related factors such as the time they can spend at the clinical research unit, the lack of trust they may have with the physician or the insufficient motivation to take part. But next to that they also highlight staff-related factors that can lead to a lower recruitment rate. What do you think about those factors, do you think these are real weaknesses encountered in the recruitment process?

I was just wondering, what was the last factor you mentioned?

The staff-related factors such as the lack of communication with the participant or maybe insufficient motivation to recruit participants.

I hope, and I can only speak from my own team of course, but I always hope that we have a nice environment here. Like I said there are people that participate often in study so after some years you get to know some people. I was GP a General practitioner before I came to work at the university, so for me it still has a little bit to feel the same, the subject is not a number, it is for in the CRF when we collect all the data but for us it's a subject that we get to know certainly as an investigator so I really hope that our participants feel that way. And like I said because I know that some people are coming back often, I think that's it feels good. But a phase one, I think is more difficult to recruit but you said the lack of trust I can understand if a subject is not used to participate in studies, then to do the first study, in phase one study, I can imagine that it feels weird because you only have for the subject then the results of the animal studies. But if you explain it very well, we have our informed consent which also explains already in an easy way to the subject what we are going to do, and if you also make the time at the first visit to explain everything and go together with the subject through the informed consent, I think that this can help. What I think in general is that people general in the community is the volunteering in clinical trials is not so known, that is something that I often think if I see in the clubs where I participate for sporting nobody knows if I mentioned sometimes what I'm doing they're really surprised so I think that is something that perhaps that would help if we can improve hat people are more young familiarised with.

Yes, I think the same, more vulgarization maybe to explain to the population that phase one trials do exist.

Yes, do exist. And I was surprised during COVID for instance this changed because everybody wanted a COVID vaccine as quick as possible to be able to go to skiing, in Austria whatever. So, at that time it was no problem at all to recruit people, everybody wants to although these phases one trials but at that time people really felt in need and then they didn't mind so much. But now in peacetime again you're looking people for a disease that they perhaps not know and because you can recruit people for flu studies for instance and this is also always a little bit easier than when you want to recruit for vaccine against chikungunya or dengue or something like that, most people don't know and don't feel the need here in the western country. So, I think we have to realise that there will not be any new vaccines, no new medication unless you have volunteers who want to do this. And I think we will have to explain also that it's very regulated, we have always the review of the regulatory authorities, of the ethics committees, I think people should be very well aware that we also - as an investigator - don't want to do a study where people will get very severe adverse events, so it's in the interest of our all so most of the time adverse events are not so severe but it's very it's done in a very controlled way. But the more that people know that this exists, and this is not so extraordinary I think this would help a lot.

Also, in the literature they talk about some strategies to overcome these recruitment failures, one of the strategies was really to have targeted approach to recruit the participants: understand them, knowing their character traits maybe to catch them in the population, build a good communication channel with them to overcome their fears, etc. So, do you think indeed we could recruit more participants by doing so?

Yes, I can say for my team if I'm looking at the duration of a first consultation in a study, the time that we spend as an investigator to go through the ICF it's easily 10-15 minutes so we really go through it and we just, not line by line, but we just see if the subject has still some worries or some concerns, I think this helps. But of course they first have to come to your first consultation and that is only by advertisements because beforehand you don't really have the means to call subjects out of the blue and say “hi my name is … what do you think do you want to participate?”, it's not like that so they should already be some interests of certain persons to do this and like I said if it is a topic that they feel acquainted to yeah, it is easier. For instance, flu is something that everybody knows but if it is something not so common then it's more difficult. I think it's different if you're doing a phase one studies in oncology for instance or in other specialised centre in hospital where people have a disease then they are, I suppose, more open to try anything that can help. But in our branch we're looking for healthy people and then it is to make people aware, you have the risk and the benefit balance, but this is imbalance and they really should know that there are always a little bit of risk when you vaccinate, there will be some pain in arm and perhaps you're having little bit symptoms of fatigue or something like that. But most of the time it's mild and it's proceeding in 2-3 days something like that and of course you are being followed up most of the time until six months after the last vaccination. But we are living in a western world where most of the people are working very hard and have already a very hectic life and they have to really make time for it.
So, there are lots of factors I think that counts.
But I think it's true what you said that once they come the better feeling that they have when they had been here, the more chance that they will come back for another study later on, that's true.

Yes, and perhaps the more chance they will stay for the whole study?

And for the whole study. I would say overall I think of course it's always possible people will move sometimes that's always possible but most of the people they proceed until the end of this study.

Another important factor that may influence the recruitment process and identified in the literature was related to design phase, the planification and organization of the study. Did you already heard about tools that aim to improve the recruitment process, such as the QRI, the GREET project and the CTTI planning?

No, not at all, I was saying not one of the three that you mention rings a bell for me.

And so, do you have maybe some internal tools that you use to have a better organization to plan your phase one recruitment trials?

The problem is that most of the trials come to us via the sponsor. So, the sponsor makes the design of the study and it depends very much sometimes if it is a new biotech company that has not so much experience with vaccine studies since we are involved very much in the beginning of the protocol and then we can do some suggestions but if these are large pharma companies they have their own way and then it's a complete package that is offered to us.

Patient's involvement in clinical trials is increasingly practiced and from this point of view I was wondering if involving healthy volunteers in some community could help to improve the recruitment by making some discussions with the new participants for instance ? What is your point of view about that?

I can understand that, I think healthy people that are already practising or that already participated in clinical trials and they experienced that everything went very well and very smoothly, that they are our best ambassadors to pass the message that it's really not so weird to do this. Sometimes we ask also on subject if recruitments are going very slowly and then we ask participants that are already in the study if they know perhaps some people or if they want to spread some advertisements in their clubs from sporting or whatever and often they're really willing to do this. So, I think that can help and of course like I said in the beginning you have to reach much more people on a community base and of course when someone of the centre itself going to speak in a in a TV show or something then this is of course they want to do for their own job, they're speaking at they just want to do their own job but if healthy participants that cannot really win or gain something by just telling their own experiences, I think this would give much more trust to people that never did this before.

Do you think it is not too "dangerous" that some of these healthy volunteers become such professional and make it their job?

That's something else because then it's also their job then it the same as someone of my centre who would come and ask to participate, that's different but on a smaller scale perhaps I think it's more worthwhile, if somebody says I did this, every everyone was nice, I didn't experience lots of adverse events and also the feeling that you contribute something for the community. I know that a lot of people say that people do it for the money there is some remuneration but it's not a large amount of money that you can earn in vaccine trials and in our trials people are vaccinated and going back home, so they are compensated for the time that they are here but it's not large amount of money. So, a lot of people are also interested in the outcome of the study and this can eventually contribute to the launching of a new vaccine. Like the ... vaccine that

now recently also been approved in Europe and we have done for many years studies with these … vaccine if you then can say to your participants well "yes this is the vaccine" then they are also proud, and I can understand they really did it and now we have a new vaccine. And that is something this feeling I think we should be able to explain to people.

Yeah, that they really would contribute to the research and make them more altruist.

Yeah and personally, I think certainly in our western country where we are rather rich and can do what we want and have not so much dangerous disease, I think if we then also can make a little bit of your time, spent a little bit of our time to contribute, to give something back to the community, I hope so. And I feel it also, sometimes in participants that asked: "when do you have the results and do you know already more?", yeah it shows that they are also really interested, it's not just coming.

Okay, interesting because in the literature they highlight that the main motivation why participants go in clinical trials remains the money and you're right, maybe there is more than that and people should probably be really interested in the study. The best person to catch in the phase 1 trials are those people.

But then to reach that you have to make time in the beginning to really explain why you are doing this study so that people really understand why we need a new vaccine for flu although we have already vaccines for flu for instance. But if you really explain them then they would say "ok yes I want to do this, I want to contribute" and then they know why it matters that they fill in their diary with adverse events even if they don't have any adverse events that is also worthwhile that we want to know. So, you know that's what you said perhaps the good relationship you have to make the time.

Interview 7 – 09/10/23 – Site side

Quel est votre rôle dans les essais cliniques de phase 1 et êtes-vous vraiment impliqué dans le recrutement en tant que tel des volontaires sains ?

Alors donc en fait je suis anesthésiste de formation, je viens du Luxembourg et j'ai fait ma formation de médecine à [redacted] et où je suis resté *in fine* et après ma spécialisation j'ai fait un petit parcours de 8 ans au CHU de Nancy et l'université de Lorraine et voilà maintenant donc je suis de nouveau [redacted] mais qui, entre-temps comme vous le savez peut-être, on a fusionné les [redacted] enfin une partie en tout cas à savoir [redacted] comme hôpital académique, [redacted] comme institut de cancérologie et alors [redacted] ils font partie maintenant de ce qu'on appelle [redacted] donc l'idée c'est vraiment de les fusionner dans un seul centre pour bon avoir une masse critique un peu plus grande. Initialement le projet de l'université c'était d'y englober également les hôpitaux de la ville de Bruxelles indépendant du [redacted] à savoir [redacted] mais dont les conseils médicaux ont jusqu'à présent refusé de participer au projet voilà donc comme ça vous avez un peu le « paysage » hospitalier [redacted], point de vue [redacted]. Je fais donc l'anesthésie et plutôt l'anesthésie en chirurgie cardiaque thoracique vasculaire avec une certaine souplesse parce que bon la démographie médicale en anesthésie comme dans beaucoup de spécialités n'est pas vraiment optimal on va le dire hein donc on est quand même fort peu nombreux mais disons-le comme ça. Et donc dans les études et alors il y a il y a 2 types d'études : vous avez les études qui sont des études qui sont rapportées par les firmes pharmaceutiques ou disons par l'industrie au sens large et pour lesquelles il y a un sponsoring industriel et deuxièmement vous avez les études et là pour l'instant c'est la grande majorité de mes études c'est les études académiques pour lesquelles il n'y a pas d'industrie derrière et donc cela pose beaucoup plus de problèmes je dirais dans toute leur organisation, pas spécialement dans le recrutement en soi mais dans toute l'organisation et c'est juste un aspect financier en fait hein c'est si l'industrie est derrière et que bon vous avez un appui financier ça va assez facilement vous pouvez engager ou adjoindre le service d'une infirmière de recherche, d'une statico enfin il y a les services de recherche clinique qui met à disposition ce personnel mais ce n'est pas gratuit et donc s'il y a un si un sponsoring financier là ça va beaucoup mieux si c'est un sponsoring juste académique c'est plus difficile. Si on a des fonds du FNRS ou autres fonds de recherche bon ça on peut s'en sortir mais si c'est une étude qui est juste supportée par des fonds du service là ça devient plus compliqué.
Ah oui je m'occupe, avec mes collègues chacun s'occupe du recrutement des patients alors en théorie tout le service est au courant des études qui sont qui se font dans le service et donc tout le monde est supposé jeter un coup d'œil dessus à la consultation d'anesthésie et la veille de l'intervention mais dans la réalité c'est le pauvre PI qui parcourt les programmes opératoires pour voir ce qui est fait. Bon les gens étant débordés je ne peux pas leur en vouloir beaucoup mais ils ne regardent pas beaucoup ce que font les autres. Et donc moi je suis PI pour certaines études, je participe à d'autres étude, il y a certains de mes collègues qui ont une idée que je participe à leur étude alors c'est quelqu'un d'autre qui est PI ou moi je suis PI pour certaines études qui ne sont pas toutes de phase une, il y a aussi des phase 3 là-dedans mais bon voilà un peu de tout quoi.

Par rapport à la nouvelle régulation qui est entrée en vigueur concernant les essais cliniques en Europe, pensez-vous qu'elle ait eu un impact, aussi bien positif que négatif, sur le recrutement en phase 1 notamment ?

Si on parle de recrutement donc le fait de dire voilà j'ai les patients est-ce que j'arrive à les convaincre à ce qu'ils disent oui, est-ce que j'arrive à les mettre dans l'étude, ça n'a pas d'impact sur le recrutement per se. Mais sur l'organisation, la mise en place des études, là il y a un impact majeur. Donc depuis le premier février on est obligé de passer par le site, le Clinical Trial Information System européen. Alors il y a du pour et il y a du contre : le pour évidemment c'est un portail unique et donc c'est plus facile que chaque pays qui fait son petit portail de son côté voir même encore chaque région, donc c'est ça c'est le côté avantage c'est un seul portail, le désavantage c'est que c'est nouveau et donc on ne connaît pas très bien, que c'est assez lourd administrativement et là je rejoins ce que j'avais dit au départ si c'est une étude qui est un sponsoring enfin avec des moyens financiers derrière où on peut avoir plus de personnel administratif, ça pose peu de problèmes parce que c'est une question de document donc si je peux avoir une statico, une infirmière de recherche, un administrative qui s'occupe de ça parce que ça met des heures à soumettre quelque chose au CTIS et encore je pourrais dire des jours ou semaines et ça va beaucoup plus lent si j'ai une étude académique, comme j'en ai une que je vais faire une fois qu'on a raccroché, donc je vais me lancer dedans mais c'est un truc qui est purement académique sans aucun sponsoring et donc je vais me plonger moi-même dans l'histoire et donc ça va être comme d'habitude le soir, le samedi, le dimanche quand j'ai le temps entre 2 et ça va mettre du temps avec probablement un certain nombre d'allers-retours beaucoup plus importants que si c'est fait par des « professionnels ». Et le centre de recherche clinique de l'hôpital il n'a pas les moyens pour le faire pour tout le monde, ils sont je pense aussi 3 pelés 2 tondus donc ils le font quand c'est des études industrielles, sponsorisées parce qu'à ce moment-là ils ont une rétribution financière ce qui leur permet de payer leur personnel parce que le personnel généralement de recherche clinique il est peut être payé par l'hôpital mais l'hôpital demande aux investigateurs d'avoir suffisamment de rentrées financières que pour compenser leur salaire et donc les études doivent payer les gens et donc ils ont évidemment prioritairement mis sur des études qui ont un sponsoring financier. Donc le CTS, l'avantage c'est d'avoir un seul portail unique, une seule soumission et qu'on doit pas soumettre à droite à gauche en haut et en droit, à l'AFMPS, tous ces machins dont on en oublie chaque fois un, donc c'est un seul portail ça c'est bien mais le désavantage c'est que c'est une certaine lourdeur administrative avec un site qui n'est pas des plus user-friendly, il faut le dire et alors surtout pour tout ce qui est études non sponsorisée financières c'est vraiment un peu la croix et la bannière pour trouver le temps et le personnel pour le faire parce que si j'ai un étudiant qui veut faire son mémoire et je lui ai dit « Ben voilà on va faire ça, voilà le site CTIS », dans 3 ans on a toujours rien fait parce que si on ne connaît pas le système, si on n'est pas un peu formé c'est impossible de se démerder avec ce truc. Donc ça, c'est un problème mais *per se* sur juste le recrutement, si on parle que recrutement une fois que l'étude est montée et qu'on a les accords, le recrutement là ça n'a finalement pas d'impact que ce soit l'ancien système ou le nouveau système.

Donc à la limite, ce qui pourrait peut-être impacter le recrutement indirectement de ce que je comprends, c'est plutôt les retards que vous rencontrez pour commencer l'étude ?

Oui c'est ça, le délai est retardé pour passer par le CTIS, de mettre en route toutes les démarches administratives et réglementaires, d'avoir toutes les autorisations. Oui, le délai est plus important qu'avant. Mais encore une fois, pas tellement parce que c'est le nouveau portail – bon toute nouveauté va plus lentement c'est logique, il faut compter une bonne année pour s'y habituer – mais c'est surtout le fait que vu qu'on n'a pas les finances pour engager quelqu'un qui le fait à notre place, ça devient très lent comme procédure.

Et en comparant avec d'autres pays européens, pensez-vous que la Belgique, étant bien placée par rapport à la conduction des essais cliniques, aurait diminué sa capacité à conduire les essais suite à cette nouvelle régulation ?

Si je me fais « porte-parole » de l'industrie qui cherche des centres avec une certaine expertise pour mettre en place leurs études, dans les 10 15 dernières années ils se sont quand même fort détourné de l'Europe de l'ouest en faveur de l'Europe de l'est car c'est beaucoup moins cher, ils ont des procédures qui sont plus rapides, moins contraignantes, plus de personnel qui leur coûte moins cher et donc il y a quand même un shift des études vers les pays de l'Est voire maintenant aussi vers l'Asie et la Chine, bon là y a un petit problème de population parce que des études qui se font que sur une population chinoise elle n'a pas le même génotype, le même phénotype donc la généralisation est plus difficile. Mais l'Europe de l'Est fait une grande concurrence en tout cas en niveau industriel. Sinon globalement la Belgique a une bonne réputation pour la qualité de sa recherche ce qui est généralement les récriminations qu'on entend le plus c'est qu'il y a une certaine lenteur de mise en route, que ce n'est pas les meilleurs marchés mais cette lenteur de mise en route vient du fait que tous les centres sont sous-effectif et que pour avoir de l'effectif il faut des études enfin c'est un peu un cercle vicieux. Vous avez ici l'institut Bordet donc qui fait partie du HUB maintenant que l'institut de cancérologie, eux ils fonctionnent avec beaucoup d'études et notamment beaucoup de phases cliniques donc ça va un peu plus vite parce qu'ils ont un turnover plus important et que c'est très ciblé au niveau de des études. Mais voilà c'est plus ou moins ce qu'on « reproche », peut-être pas spécifiquement à la Belgique, mais un peu en Belgique, Allemagne, France, à tous les pays de l'Europe de l'Ouest, on trouve que ça ne va pas assez vite et que c'est trop cher.

Par rapport aux échecs rencontrés pour le recrutement et qui ont été identifiés dans la littérature, ils parlent notamment de facteurs qui sont liés aux participants et qui peuvent engendrer des faiblesses dans le recrutement tels que le manque de temps pour s'engager dans l'essai, le manque de confiance qu'ils peuvent avoir envers le PI, des motivations pas assez suffisantes pour pouvoir prendre part à l'essai. À côté de cela, il y aurait des facteurs liés au staff également donc le manque de communication qu'ils auraient avec les participants. Pensez-vous que ce sont de réelles faiblesses rencontrées en réalité envers le recrutement en phase 1 ?

Tout à fait, je suis tout à fait d'accord avec vous.
Si on prend le côté investigateur, le fait que les investigateurs ne sont pas « assez nombreux », qu'ils n'ont pas nécessairement le personnel fait que on aborde les patients un peu en dernière minute, en étant pressé et donc du coup on a un peu moins de temps pour réellement leur expliquer. L'idéal, ce que j'aimerais bien qu'on fasse c'est qu'à la consultation on leur parle des études et qu'on leur dise il y a tel et tel essai, vous pourriez éventuellement convenir, en 2 mots ça implique ça et ça, voilà le sujet, voilà une brochure lisez ça à votre aise et quand vous revenez à l'hôpital on va venir vous voir et on rediscute de nouveau. Comme ça, ils ont le temps de lire, de digérer ça un tout petit peu. Et donc souvent cette première étape tombe à l'eau parce que les gens ont trop de travail « clinique » et donc ne regardent pas quels sont les essais en cours quand ils sont à la consultation et ne proposent pas aux gens, ne leur parlent pas. Du coup on tombe sur les gens, si on a de la chance, la veille de l'intervention ou on leur téléphone la veille mais le contact est déjà plus difficile quand on fait ça la veille par téléphone qu'avec un vrai contact direct. Mais avec la grande majorité des patients qui maintenant arrivent en « same-day admission », ils arrivent le matin-même de leur intervention à l'hôpital, le temps devient vraiment très court pour leur expliquer une étude autant de plus que normalement ils doivent quand même avoir un délai de réflexion et pas juste dire signez en bas à droite dans les 3 min. Donc ça au niveau de l'investigateur, ce phénomène-là fait qu'un certain nombre de gens disent

non parce que « vous me prenez de cours, j'aurais bien discuté avec mon médecin traitant, j'aurais bien discuté avec mon compagnon/ma compagne, j'aurais bien discuté avec ma famille, enfin quelqu'un et puis voilà mais bon là vous me prenez un peu de cours je dois me décider en une demi-heure ». Oui ça pose un problème.
Du côté participant à l'étude, je trouve que la majorité des gens finalement voient ça assez bien et d'un bon œil pourvu que on ne l'entend pas juste dessus comme j'ai dit 5 min avant leur intervention de chirurgie cardiaque du genre « à propos j'aimerais bien faire encore une petite étude sur vous », ça c'est moins bien vu. Mais s'ils ont le temps de réfléchir je trouve que la majorité sont assez ouverts mais il faut prendre le temps de leur expliquer, de leur laisser le temps de lire les documents, de revenir 2 jours plus tard pour qu'ils puissent en discuter une fois avec leur famille et puis expliquer les dernières choses s'ils ont éventuellement des questions du genre « mais est-ce que je dois revenir ? Est-ce que je dois revenir pour une prise de sang ? Est-ce que je ne peux pas la faire ailleurs ? Est-ce que ça va me coûter quelque chose si je dois faire une résonance cérébrale 3 mois après ? Ou - quand – comment - qu'est-ce que ça me coûte ? ». Enfin une fois qu'on a dissipé ces choses-là, globalement le taux d'acceptation est quand-même relativement élevé - je ne peux évidemment parler que pour moi - mais je dirais que globalement c'est quand même au-delà de 80% de gens qui disent oui pourvu qu'ils étaient un peu abordés dans des conditions convenables.
Là où j'ai un peu plus de difficultés avec un taux de refus beaucoup plus élevé, c'est en pédiatrie.

Ah oui il y a des essais qui se font sur des enfants sains aussi ?

Oui. Enfin là, j'ai une étude en cours mais ce n'est pas une phrase 1, c'est une phase 3, parce que des phases 1 anesthésie en pédiatrie, il n'y en a pas 25000. Donc ça je n'ai pas de phase 1 à vous citer mais j'ai une phase 3 en cours en tout cas et je dirais que le taux de refus est de 50 à 60%. C'est une phase 3 de comparaison de 2 médicaments pour la sédation pour les enfants pour des résonances magnétiques donc on compare un médicament A à un médicament B et on est juste encore en prémédication parce que l'anesthésie ou la sédation per examen est la même mais c'est très difficile de convaincre les parents. Enfin bon ce sont des petits dans mon étude ils ont quand même moins de 3 ans et donc là l'autorisation ou le consentement des enfants c'est généralement à partir de 6 ans mais c'est généralement à partir des 10 ans qu'on arrive à réellement avoir quelque chose. Donc disons que ce n'est pas tellement l'enfant c'est plutôt les parents-là qui sont réticents parce que bon c'est déjà stressant pour mon enfant pourquoi est-ce qu'on fait une résonance, c'est parce que généralement ils ont une tumeur donc bon ce n'est déjà pas très rigolo au départ, c'est anxiogène, c'est des pathologies lourdes et donc rajouter encore quelque chose là-dessus donc ça pose problème. Là j'ai un taux d'échec, de refus qui est beaucoup plus élevé que chez les adultes, même pour les phases 3 qui ne sont même pas des phases 1.

Et alors il existe aussi des stratégies pour contrer ces échecs de recrutement. L'une d'entre elle est en fait une approche ciblée qui permet de cibler les volontaires, de les comprendre, comprendre ce qui les motive, ce qui leur fait peur et construire un moyen de communication avec eux pour les faire entrer dans l'étude et surtout les garder durant toute l'étude. Avez-vous des exemples concrets de cette approche ciblée et êtes-vous d'accord avec les faits ?

Je suis tout à fait d'accord avec le concept surtout qu'on fasse des formations pour les gens qui qui recrutent mais ça c'est la théorie et ça marche. Je pense que si on explique aux gens comment aborder un patient, comment lui expliquer une étude, comment ne pas l'agresser mais lui laisser le choix tout en lui expliquant, cette toute une toute une approche qui est assez similaire finalement à l'approche qu'on doit avoir avec les donneurs d'organes quand vous approchez la

famille - alors bon en principe chacun de nous peut dire oui ou non et si on n'a pas dit non on est d'accord peu importe que la famille dit – mais dans la pratique il n'y a aucun hôpital qui passe outre l'avis de la famille, c'est juste une évidemment pas possible de dire à la famille « Ah bon écoutez voilà il était d'accord hein désolé on va prélever tout », non généralement on ne le fait pas. Et donc l'approche est un peu la même, il y a des formations notamment pour ça et il y a des formations aussi dans les études cliniques. Dans la pratique et sur le terrain je pense qu'il y a moins de 2% des investigateurs qui ont suivi une telle formation par manque de temps, par manque de moyens, par peut-être aussi manque d'intérêt, mais je pense qu'il y a une extrême minorité des gens qui ont suivi vraiment une synthèse ou au moins une approche structurée pour recruter les patients. Généralement on leur donne voilà le protocole tu vas expliquer aux patients, ça c'est la réalité du terrain mais ce n'est pas ça qui marche le mieux. Mais encore une fois pour que ça marche, il faut que l'hôpital ait suffisamment de personnel ou enfin suffisamment d'études pour avoir suffisamment de personnel pour que ça roule qu'il y ait des formations.

Un autre problème rencontré dans ce recrutement est plutôt lié à l'organisation et la phase dite de « design », c'est-à-dire comment va s'organiser le recrutement. Pour surmonter ça, 3 outils identifiés dans la littérature seraient apparemment utiles aux sponsors ou centres de recrutement pour les aider à planifier en quelques sortes les étapes du recrutement. Il y a le QRI, GREET project et le CTII Planning. Avez-vous déjà entendu parler de ces outils ?

Le dernier oui, les autres non.

Et avez-vous déjà utilisé un peu ces méthodes ou pas ?

Non, dans la pratique non. De nouveau, oui si c'est une industrie pharmaceutique qui est derrière généralement oui ça s'approche vers cette dernière méthode, que dans toutes les autres études non par manque de moyens, manque de temps, manque de ressources humaines.

Oui, ça semble logique par rapport à ce que vous avez déjà expliqué juste avant et je comprends bien. Et vous en tant que PI ici à [redacted], il se peut que vous soyez sponsorisé par l'industrie quand même ?

Ça arrive, en anesthésie c'est relativement « rare » parce que l'anesthésie pour l'industrie ça représente un marché nul, c'est une niche, vous avez 50000000 d'interventions sur l'année c'est rien ça et encore vous donnez un médicament pendant quoi quelques heures aux patients, on peut peut-être discuter de si on va lui donner pendant 2-3 jours mais enfin c'est tout quoi comparé à une statine que vous allez donner à 40% de la population *ad vitam*, les enjeux financiers pour l'industrie sont complètement différents et donc il n'y en a pas 25000. Il y a l'un ou l'autre, mais vous avez un nouveau médicament en anesthésie tous les 10 ans peut-être, c'est vraiment un cycle qui est relativement long. Le dernier médicament qui maintenant est mis sur le marché après avoir suivi les phases 1, 2,3, etc. c'est ... c'est un médicament, une sorte de benzodiazépine à courte réaction et bon les premières études commencé il y a 12 13 ans environ et maintenant il est sur le marché mais enfin c'est environ le dernier médicament qui était réellement mis sur le marché hein donc il n'y en a pas 25000 qui se mettent sur le marché. Mais donc voilà l'incitant financier pour l'industrie n'est pas énorme donc c'est un peu comme la pédiatrie, la pédiatrie c'est un marché de niche aussi hein, les chimiothérapies que vous faites en pédiatrie sont finalement forts calquées sur les chimiothérapies adultes et avant qu'ils investissent suffisamment que pour avoir des protocoles spécifique à la pédiatrie il faut

vraiment les convaincre parce que c'est un marché qui est c'est niche et donc, le monitor Investment n'est pas très élevé.

Ah oui ok, c'est un peu dommage alors même si c'est la réalité des faits.

Voilà éthiquement c'est dommage ou même répréhensible quelque part. C'est certainement dommage pour les différentes spécialités mais c'est toutes les maladies « rares » qui n'ont aucun financement et donc très peu de recherches sont faites sur eux ou la grande majorité des recherches se font finalement par des mandats FNRS en Belgique ou des équivalents au niveau américain-européen, le NIH. La grande majorité de ces recherches se font par des grandes gouvernementales au sens large.

On sait qu'il y a des communautés de patients qui se rassemblent et discutent de ce qui allait ou ce qui n'allait pas durant les essais, on implique également maintenant des patients dans les comités d'éthique, etc. Donc le patient est de plus en plus impliqué dans l'étude. Peut-être qu'en faisant de même avec les volontaires sains cela pourrait être une aide pour optimiser le recrutement et comprendre ces personnes qui ne sont pas malades mais simplement là pour aider et contribuer à la recherche. Pensez-vous qu'il serait possible de faire cela ?

C'est une idée effectivement. Effectivement au niveau des patients, oui on a des groupements de patients qui ont participé à des études et qui font activement à la limite même le la « publicité » ou qui partagent leurs opinions. Dans le comité d'éthique oui, je fais partie du comité d'éthique, et donc oui il y a des patients qui sont dedans et ça apporte quand même quelque chose. Ce n'est pas évident de divulguer dans la dans la population, c'est pas évident parce - quand c'est des patients on peut mettre en rapport les patients ou organiser une petite réunion entre patients - c'est beaucoup plus difficile d'organiser une réunion avec une population saine donc là c'est probablement beaucoup plus compliqué. C'est plus facile de réunir tous les patients enfin en disant voilà vous êtes atteints d'un cancer du sein, nous organisons une réunion ce soir qui peut vous expliquer la prise en charge, la recherche qui se fait avec des patients qui vont témoigner un petit peu, ça donne une population ciblée et vous pouvez les inviter parce que bon vous savez à qui vous adressez mais quand c'est tout le monde, c'est probablement beaucoup plus difficile.
Peut-être qu'il faudrait poser la question à l'unité de recherche clinique [redacted], qui est [redacted] ils ont accès à l'hôpital mais c'est une unité tout à fait à part et eux ils gèrent beaucoup de volontaires sains, peut-être ça serait une idée de voir avec eux comment est-ce qu'ils font, est-ce qu'ils organisent des réunions. Je vois parfois des affiches mais c'est chaque fois une affiche pour une étude, je n'ai jamais vu une affiche au sens large du terme c'est plutôt : vous avez entre 30 et 60 ans, est-ce que vous serez intéressé à participer à une étude sur la pathologie du cancer du côlon, par exemple. Mais c'est déjà au moins chaque fois ciblé quoi mais ce serait peut-être une idée de leur poser la question.

J'avais déjà essayé de les contacter mais sans succès réellement.

Je ne les connais pas enfin personnellement pas beaucoup même si c'est adjacent, c'est vraiment 2 choses différentes, ils se sont implantés ici parce qu'on leur a offert la possibilité pour s'ils ont besoin des examens sanguins ils sont faits dans le labo de l'hôpital, s'il faut des résonnances, des CT scans, enfin des choses comme ça, c'est plus facile d'être sur site ou alors s'ils ont un effet secondaire parce que ça arrive quand même, ils sont à l'hôpital et donc ils ont une aide

médicale urgente s'il faut. Donc on a un peu une collaboration dans ce sens-là mais sinon on n'est pas du tout impliqué dans leur protocole, on ne les connaît pas.

Vous avez mentionné que vous faisiez partie du comité d'éthique, je me demandais donc ce que vous pensiez du fait que certains volontaires qui font des essais cliniques leur job sachant que les essais cliniques en phase 1 sont bien rémunérées. Ne serait-ce donc pas trop dangereux d'avoir affaire à des volontaires sains professionnels éthiquement parlant et pour leur sécurité également ?

Normalement c'est déconseiller voire décourager d'avoir des « professionnels » et il existe un registre des gens qui ont participés et qui participent à des études de phase 1 par lequel on vérifie que les gens ne sont pas professionnels enfin qu'ils n'ont pas attendu x temps ou fait x études, qu'ils essaient de faire plusieurs études en même temps donc voilà il y a un contrôle autant que possible sur ce volet-là pour éviter d'avoir comme aux États-Unis par exemple des gens qui vivent de ça ou toute une gamme d'étudiants qui financent leurs études en participant à des essais à gauche et à droite. En Belgique, il y a une législation là-dessus et ils doivent être inscrits dans un registre et donc c'est limité la participation aux essais et le comité d'éthique vérifie à ce moment chaque fois qu'il y a une demande pour une étude que dans l'algorithme c'est prévu que le participant ne participe pas déjà ou n'a déjà pas participé à x études.

Interview 8 – 12/10/23 – Site side

What is your role in phase 1 clinical trials and are you really involved in the recruitment of healthy volunteers or not?

No, not in healthy volunteers. So, my background is surgical oncology and I have an interest in digestive tract cancer such as colon cancer, rectum cancer, small bowel cancer but also ovarian cancer and so the phase one studies that we are doing are funded by usually [redacted] maybe you've heard of it and they are in fact including patients with peritoneum metastasizes and so cancer on the peritoneum and the trials that you are doing are for instance trials where we nebulize as aerosol chemotherapy in the abdomen but these are always patients with disease, with cancer so I don't do any studies in healthy volunteers.

Alright, but maybe it will be also interesting to hear from your experience because maybe you also encounter same challenges or use same strategies that could be applied with healthy volunteers, I hope.
There is a new Clinical Trials Regulation which was put in place since January 2022. Do you think the new EU CTR had an impact (positive or negative) on the recruitment in phase 1 trials?

Well, I'm not sure in fact I don't know all the details of the new medical device regulation.
Is it medical device regulation that you're talking about or the clinical trial regulation?

The clinical trial one.

Because what we are seeing is - because I am in surgical oncology, so we use a lot of technology and devices - and so we see more impact of the medical device regulation. So, for the clinical trial regulation I think the execution of the trials is not very different, I think it's more the preparation and the paperwork and the consent process, etc that is this different but I think for the actual execution of the trial and the recruitment process I think there are - as far as I know - no many differences but again I'm not really familiar with all the details this is something that I leave to our ethical committee and or clinical trials unit to look at the regulations and the legislation.

And so, don't you think that Belgium decreases his good capacity of conducting clinical trials compared to other European countries because of this new regulation?

I don't think so, at least not in our hospital. The number of clinical studies is always increasing, so both the investigator driven and the sponsor trial, so the pharmaceutical trials are increasing every year. So, at least in our hospital, it's certainly not having an effect but I'm not aware of any national data. I'm sure that the Federal Drug Agency of Belgium will have these numbers and this information available so maybe you can ask with them if they have an idea on the yearly numbers.

About recruitment failures in phase 1 now. In the literature, they talk about factors that are linked to recruitment failures in phase 1 trials including participant-related factors such as the time they can spend at the CRU, lack of trust with the physician and their sometimes-insufficient motivations to take part in the trial – but maybe that's not the case in cancer trials. Staff-related factors also lead to lower recruitment due to a lack of communication with the participant and a lack of motivation to enroll them. Do you think these are real weaknesses in the recruitment process?

I think it's completely correct that you have patient related causes or variables and then treatment team related. I think communication is very important for the trials that I do we have PhD student who is specifically dedicated to the study and who really gets a lot of information, it's like one hour that she spends explaining to the patient and of course if you're a busy clinician you don't have the time to spent one hour explaining the aims of the study. So, that's why you really need a study team so either a PhD student or study nurse to explain what the study is about, to explain the potential risks. Of course, as you were mentioning, it's completely different for cancer trials compared to healthy volunteers' trials. In healthy volunteers trials, the motivation is obviously money because you get paid for being a volunteer and there the ethical issues are much more important because you put healthy people at risk and you give them money, so this could result in a kind of discrimination against people who have less financial means and who really need this money and then put themselves voluntarily at risk for maybe risky treatment. But for the studies that we are doing, the recruitment success is quite high because we are offering a treatment that is really often the last hope for patients and if they refuse it's either because of logistical issues and we get patients from all over the country and also from the Netherlands, from the UK, etc and patients need to travel. For instance, one week after the operation they need to come to the hospital for a blood draw, for a blood analysis and often this is really the problem the fact that the logistics are quite heavy and these patients who are already going through a lot often they still get chemotherapy and so normal systemic chemotherapy at the same time so the logistics can be important. Lack of trust this is not often an issue in the cancer trial during the trial that we do unless of course that the patient is informed that the risk of complications is severe and that the type of complications can be quite high and *so that's interior to our drawback*. About the studies that I am doing safety, well the risk is not quite high and so that's not really a bottleneck for the study that we are doing.

Cancer trials are really apart of the other one because motivation are not the same and treatments are heavy.

Indeed, yeah.

Strategies have been found in the literature such as adopting a "targeted approach" to overcome these participant-related recruitment failures and include understand the participants, their motivations, their fears and try to build a communication channel with them in order to catch them in the study. Could you maybe explain your experience with that kind of targeted approach if you use that?

No, I don't use that. The way that we try to get the patient is by announcing the trial on our website, so we have a website of the department and all the trials that we're doing are listed there. And then it's of course on clinicaltrials.com, so the trial is registered and specifically patients from outside of Belgium they are really aware of this register, and they just look for trials and then our contact data are there and so every few weeks I get an e-mail from patients from the US etc referring to clinicaltrials.gov asking about the possibility to participate in the trial. So, that's of course a major advantage to have to trial listed in a registry which is an obligation by the way, it's a compulsory thing to register our trial. But of course you should be careful with healthy volunteers like making announcements on social media and Facebook and Twitter trying to recruit volunteers, I don't think that's a good idea to be honest again because of the ethical restraint, you don't want to end up with a situation where people are entering trials because they need money and they are prepared to put themselves at risk, the same for medical students you have to be careful that they don't feel an obligation or they don't feel put under pressure by some professor to participate in one of his or her trials. So, you should be very

careful with volunteers, I think. But I think the pharmaceutical industry has a lot of possibilities to try to get healthy volunteers but I'm not aware how they do it or what strategies that they use. But we do it mainly through our website, the registries and also through the personal contacts that we have with the oncologists, the referring physicians, if we start a new trial, I send an e-mail to all of them. Like we have a contact list of maybe 200 oncologists' cancer surgeons that we work together with and I just send him an e-mail stating "we have this trial that will be opened if you have patients who are suitable you can refer them to us" and also I send them the results of the trial once it is published so that's also very helpful.

And just want to come back to one thing that you said about clinicaltrials.gov, which is also the registry where I found a lot of people to contact for my interviews. I was wondering how people were aware about this site, as you said that patients checked on this registry to contact you through this?

Well, usually of course it's not the average patient who is doing that. Usually, they are very well-educated people who are informed by their oncologists in the US. People are more and more knowledgeable and informed about their healthcare and about treatment options. So, either they Google it and click and find clinicaltrials.gov or they are informed by a physician, by their GP or by their oncologist look if you want to find the trial you can have a look there. But again, it's not the average patient, the average patient is not aware of this trial it's just listening to the advice of the GP or of the treating physician, but you have a specific stratum of highly educated people who are really taking initiatives themselves to find treatment options.

Another important factor in the recruitment failure identified in the literature was more related to the design phase, the organization of the different step of recruitment. Did you already heard about or used tools to improve phase 1 recruitment such as the QRI, Greet Project, CTTI planning?

No, I have never heard of these tools, and I have not used them. But I think what you are saying is correct, you should indeed try to involve patients in trial designs and this is now something that is done on a systematic basis for instance the charity that I work with a lot really require that you involve patients in the design of a trial, that you get the feedback of patients and also the score of the project if you submit it is for 30% given by a patient committee or patient Commission. So, patient involvement in trials is getting more and more important so I think it's indeed something that you should take into account but these specific tools I'm not really familiar with.

But this is really interesting what you just mentioned now because my last question is related to that. As you said, patient's involvement in clinical trials is increasingly practiced. From this point, we were wondering if involving healthy volunteers also could be also a key to improve the recruitment strategies because they know how people like them might be interested in participating. Do you think it could be possible in reality to make some healthy volunteers commission as you have patients commission?

That makes sense, I think. I think it's certainly possible and I think it's a good idea and of course you have to make sure that they are really independent, but I think if you do that within a hospital or within a healthcare setting this may be a good idea. Are there already examples of that ? Do you know that?

No that's why I'm asking, I didn't find any information about that in the literature so that's why I was wondering if maybe it could be feasible in the reality of the field and if may be some people had already tried an if it had some success or not and if it was maybe ethically possible, I don't know.

I think it's ethically not a problem if you are independent. Of course, if they are paid by the pharma industry it's another story but if you are independent then I think it's ethically acceptable and probably a good idea.

I hope maybe it could be feasible to put that in place because I'm pretty sure that communication by participant and have the experience of other people who already participated in a trial can maybe help recruitment and just share their experience can maybe make people aware about the trial and make them to participate also, I don't know but that's my point then.

Yes, it's an interesting question and indeed that's maybe one of the topics you can investigate for your thesis.

Yes, I will try. Because patient involvement is really a good thing I don't know since where it is in place?

I think it started about 10 years ago slowly but now it's really systematically included also in the outcomes: patient reported outcomes, patient relevant outcomes, etc.

That's very interesting. Then maybe you could also answer the last point because the healthy volunteers at the difference with patients are paid for participating and so they do not have the same motivation and the money is the main one, as you said previously. Then do you think that we not have to pay attention to healthy volunteers that become professional and make it maybe their job?

Yeah, indeed there is a risk and people should be protected against that. But I think that's an important ethical consideration, the fact that you will attract people from a certain social economic stratum who will put themselves at risk for the money and I can imagine that there are people who are needing money and who are constantly looking for opportunities to participate in phase one trials and if that is picked up then probably these people should not be allowed to participate any longer because of course that's not what you want, always same people who are just doing it for the money, I think it's a bad idea. You should maybe have some kind of database that is shared between the pharmaceutical companies.

I suppose in the cancer trials, you don't face those problems?

No of course not.

Interview 9 – 13/10/23 – Sponsor side

Quel est votre rôle dans les essais cliniques de phase 1 et êtes-vous vraiment impliqué dans le recrutement en tant que tel des volontaires sains ?

À [redacted], là où je travaille actuellement, je m'occupe plus du suivi des études cliniques donc le suivi du travail de la CRO au jour le jour, faire en sorte que le médicament arrive à terme, que la soumission soit faite donc là je ne suis pas impliquée vraiment dans le recrutement des patients de phase 1, là c'est plus la CRO ou le site clinique qui se charge de ça. Cependant à [redacted], là c'était autre chose parce que là j'étais vraiment au site investigateur donc là il fallait mettre en place les annonces pour recruter les patients. Eux avaient déjà une base de données avec plusieurs listes de patients donc là il fallait déjà faire un premier screening donc avec une personne qui était là-bas pour savoir qui pouvait correspondre déjà aux critères des volontaires qu'on recherchait et de les contacter déjà, faire déjà un premier tri. Donc, avant d'aller en extérieur déjà de se baser sur le pool de volontaire sains qu'on avait dans cette base de données. Donc voilà j'ai eu les 2 pôles : côté sponsor et côté investigateur.

Par rapport à la nouvelle régulation qui est entrée en vigueur concernant les essais cliniques en Europe, pensez-vous qu'elle ait eu un impact, aussi bien positif que négatif, sur le recrutement en phase 1 notamment ?

Non parce que ça n'affecte pas le patient. Par contre, au niveau sponsor c'est une nouvelle façon de travailler. Pour les phases unes en général comme ce sont des petites études ça concerne en général qu'un seul pays voire même qu'un seul centre clinique donc ça n'aura pas beaucoup d'impact mais pour les autres phases où là on peut être multi centre et faire une étude clinique internationale là oui. J'ai eu une formation dernièrement, je pense que ça ne va pas faciliter les choses mais plus au niveau sponsor car après une fois que l'étude sera lancée, qu'on aura toutes les autorisations, que les soumissions seront faites, je pense que là il n'y aura pas de souci parce que ça restera quand même localisé au pays où on voudra faire l'étude.

D'accord et donc ce serait plutôt au niveau du sponsor que ça change mais quelque part cela n'aurait-il pas un impact indirect sur le recrutement si des retards surviennent etc ?

Oui, ce sera peut-être plus long, ça dépendra parce que ce sera plus de ressources à mettre en tout cas en place pour pouvoir gérer ces différents centres. Parce qu'en fait ça avait été mis en place normalement pour bien harmoniser la soumission dans les différents pays mais il y a quand même une partie il faudra quand même dans chaque pays refaire une soumission tout ce qui est document relié au patient comme le consentement éclairé qui doivent être dans la langue du pays etc. donc à ce niveau-là oui ça va augmenter les délais. Mais une fois qu'on aura toutes les autorisations et que on aura le « Go » pour démarrer l'étude là ça ne changera plus rien après au niveau du site clinique et du pays qui sera engagé dans l'étude. C'est vraiment au démarrage mais après une fois qu'on a les autorisations on va dire que ça roule mais ça ne changera rien par rapport à ce qui est fait actuellement.

Et en comparant avec d'autres pays européens, pensez-vous que la Belgique, étant bien placée par rapport à la conduction des essais cliniques, aurait diminué sa capacité à conduire les essais suite à cette nouvelle régulation ?

Non je ne pense pas parce que j'avais discuté avec les personnes lors de ma formation et non ça n'avait pas vraiment d'impact, c'était vraiment au niveau sponsor encore, que la réflexion devait

vraiment se faire bien en amont et comme on est aussi très limité en termes de timing en termes de soumission ou de réponse aux questions que les autorités c'est vraiment ça le point bloquant, en tout cas le point qui risque de plus poser problème. Mais une fois que l'étude sera lancée, cette régulation n'affecte pas les patients en eux-mêmes. Justement, le patient aura accès à beaucoup plus de d'informations parce qu'il y a beaucoup plus d'informations qui vont devoir être divulguées par rapport à l'étude clinique, par rapport à ce qui est fait, ce qui a été fait avant sous la directive. Donc au niveau du patient ce sera beaucoup mieux, c'est plutôt au niveau des autorités compétentes et au niveau des sponsors où ça va nous demander un petit peu plus de travail.

Oui c'est très intéressant ce que vous dites ici car j'ai lu qu'il y avait plus de transparence grâce au CTIS. Le public ayant accès à cette base de données, les gens peuvent plus facilement se renseigner.

Oui d'un côté ça peut plus les rassurer et faciliter le recrutement parce qu'ils auront beaucoup plus d'informations sur le médicament qu'ils vont recevoir et à tester. À ce niveau-là je pense donc que c'est un point d'amélioration.

Par rapport aux échecs rencontrés pour le recrutement et qui ont été identifiés dans la littérature, ils parlent notamment de facteurs qui sont liés aux participants tels que le manque de temps pour s'engager dans l'essai, le manque de confiance qu'ils peuvent avoir envers le PI, des motivations pas assez suffisantes pour pouvoir prendre part à l'essai. À côté de cela, il y aurait des facteurs liés au staff également donc le manque de communication qu'ils auraient avec les participants. Pensez-vous que ce sont de réelles faiblesses rencontrées en réalité envers le recrutement en phase 1 ?

C'est vrai qu'en général on se dit, c'est une phase 1, ce sont des volontaires sains et on ne se base que sur l'incitant financier. Mais je pense qu'il y a des personnes qui recherchent beaucoup plus.
En fait prendre ce médicament et faire comme une campagne de pub, je sais que c'est peut être un gros truc mais vraiment raconter l'histoire qu'il y a derrière, dire pourquoi est-ce qu'on développe ce médicament, vraiment raconter du début jusqu'à la fin et montrer l'importance que ça peut déjà avoir même si ce sont des volontaires sains qui puissent déjà tester ce médicament et vraiment raconter l'histoire de comment fonctionne l'essai, quelles sont les différentes étapes pour mettre un médicament sur le marché donc voilà qu'on commence déjà sur les volontaires sains pour voir si le produit est safe ou pas et de que même si eux ne sont pas malades et qu'ils sont sains mais qu'ils peuvent participer justement à faire en sorte qu'on puisse mettre sur le marché un médicament qui pourra servir pour des gens qui sont vraiment malades après.

C'est ça, c'est vraiment leur montrer qu'ils sont importants pour la recherche.

Oui puis aussi c'est important de répondre à leurs questions, leur dire qu'ils ne sont pas que des « cobayes » mais qu'ils prennent une part active là-dedans.
Il faut aussi faire en sorte que pour les phases 1 ça ne prenne pas trop de temps car on fait de la pharmacocinétique donc les patients doivent en générale rester là toute une journée, toute une nuit et sont piqués toutes les heures donc c'est sûr que ce n'est pas le séjour le plus agréable mais je pense que si on explique le pourquoi du comment derrière et que leur rôle est important, cela pourrait jouer aussi.

C’est justement le point sur lequel je comptais embrayer. Pour surmonter les échecs rencontrés dans le processus de recrutement, il est important de prendre le temps de bien expliquer, de bien communiquer, de rassurer les participants. On peut parler d’approche ciblée, chaque participant est différent mais par ailleurs, un article soulignait le fait que la plupart des participants présentent aussi certains traits de caractères particuliers tels que l’altruisme, l’extravasion etc. donc la question se pose de se dire que c’est important de cibler ces personnes-là pour augmenter le taux de recrutement. Je ne sais pas si vous avez une expérience par rapport à ça ?

Non du tout parce que comment est-ce qu'on pourrait cibler ce genre de choses ? Après, ce qui serait bien, parce qu'en général tout ce qui est volontaire sain on cible beaucoup les jeunes, les étudiants qui ont un petit peu plus de temps, qui sont plus jeunes qui sont en bonne santé, et donc tout ce qui est réseaux sociaux ça par exemple on avait testé tout ce qui est Facebook tik-tok ou autre. Moi je suis juste LinkedIn, je ne suis pas très réseaux sociaux mais ça touche les jeunes donc ça pourrait marcher parce que parfois certains ne sont même pas au courant qu'il y a des études cliniques qui se font et qu'on recherche des volontaires sains donc voilà faire de la pub en fait et expliquer.

Oui, c’est sûr. Mais ça je suppose que d'un point de vue du sponsor qui est vraiment la personne qui finance ou la compagnie qui finance le tout, dont le financement du recrutement, ça coûte de l'argent je suppose ?

Ah oui ça oui. Après ça peut être un simple message sur LinkedIn. Par exemple nous on a un compte sur LinkedIn, on avait ouvert justement un compte Facebook pour justement faciliter le recrutement, c'était une de phase 2. Il y a une équipe qui s'occupe de ça donc je veux dire ça passait dans le budget général de la société. Mais après s’il faut mettre des flyers dans - pas forcément pour les phases 1 mais pour les prochaines phases, quand on cherche vraiment des patients malades - les cabinets des médecins généraux ou des cabinets spécialisés pour cibler vraiment la population qu'on veut.
Donc voilà c’est plutôt du marketing et presque rien à voir avec le pharma on sous-estime beaucoup voilà.

Oui, en effet il y a vraiment du marketing derrière mais il faut rester dans quelque chose d'assez éthique aussi.

Oui c'est vrai j'ai et vraiment bien expliquer et faire prendre conscience aux gens de la population générale que ça existe et que c'est possible et qu'ils peuvent jouer un rôle là-dedans.

Un autre problème rencontré dans ce recrutement est plutôt lié à l’organisation et la phase dite de « design », c’est-à-dire comment va s’organiser le recrutement. Pour surmonter ça, 3 outils identifiés dans la littérature seraient apparemment utiles aux sponsors ou centres de recrutement pour les aider à planifier en quelques sortes les étapes du recrutement et aider à sa bonne organisation. Il y a le QRI, GREET project et le CTII Planning. Avez-vous déjà entendu parler de ces outils ?

Non mais je veux bien que tu m’envoies les noms par mail. Moi je suis restée à Excell pour faire ça.

D’accord, et c’est quoi les stratégies alors que vous mettez en place pour faire ça ? Excell permet d’organiser un peu le processus ?

Ça permet vraiment de suivre et d'organiser et de se dire que sur x temps ou sur le mois il nous faudrait au moins 5 patients et qu'on puisse traiter tout ça. Mais en général les phases 1 c'est très peu de patients donc on essaie de s'arranger pour que tous les patients soient - en tout cas pour l'étude qu'on avait conduit pour notre produit - en même temps dans le site clinique. Le site clinique savait gérer 24 patients en même temps donc comme ça l'étude elle était vraiment très courte et c'était vraiment simple. Donc on a pris plus de temps à trouver tous les patients mais une fois qu'on les avait, l'étude elle s'est faite en quelques jours c'était bouclé. Donc, il faut aussi qu'on sélectionne le bon site clinique qui a vraiment une bonne base de données sur laquelle on peut se baser pour pouvoir lancer cette étude.

Quand vous dites une bonne base de données, c'est avec beaucoup de volontaires sains dedans je suppose ?

Voilà et qui re correspondent à nos critères. Parce que là par exemple on faisait une étude sur des adultes donc ça, ça va mais si un jour on veut faire une étude chez des enfants, il faut s'assurer que cette base de données contient suffisamment d'enfants ou si ce sont des personnes âgées, voilà qu'ils aient suffisamment de personnes âgées. En général pour une phase 1, les critères d'inclusion sont très peu restrictifs donc c'est plus simple mais après par rapport à l'âge ou au critère d'obésité et compagnie, on peut déjà faire un premier tri.

Et cette base de données-là, les sponsors y ont accès ?

Non, on n'a pas accès aux données, c'est vraiment le site clinique.

Donc comment est-ce que vous pouvez savoir en tant que sponsor si la base de données est assez importante ?

Pendant la sélection de la CRO avec qui on veut travailler, c'est une des questions de base. On a déjà les critères principaux de recrutement et on pose la question en fait « combien de participants auriez-vous avec ces critères-là ? ». Après on n'est pas sûr que le volontaire acceptera ou pas de participer à l'étude mais ça nous donne déjà une idée.

Et vous auriez une fourchette pour laquelle ce serait une bonne base de données pour une phase 1 ?

Je dirais 200-300 pour être sûr qu'on ait au moins une trentaine de volontaires. Les phases 1 en général comptent maximum 30-40 volontaires sains.

On sait qu'il y a des communautés de patients qui se rassemblent et discutent de ce qui allait ou ce qui n'allait pas durant les essais, on implique également maintenant des patients dans les comités d'éthique, etc. Donc le patient est de plus en plus impliqué dans l'étude. Ceci est illustré dans la littérature mais ils ne parlent pas du cas des volontaires sains. Peut-être qu'en faisant de même avec les volontaires sains cela pourrait être une aide pour optimiser le recrutement et qu'ils puissent témoigner et partager leur expérience. Pensez-vous qu'il serait possible de faire cela ?

Je pense que s'ils ne sont pas mis dans ces comités d'éthique c'est parce que ce n'est pas la cible finale. L'objectif c'est vraiment de se préoccuper des besoins du patient malade alors même si le patient sain est là et qu'il va nous aider pour les premières phases, on veut vraiment être

focalisé sur les besoins et ce dont le patient aurait envie que le médicament lui apporte et ça le patient sain ne saura pas répondre à ces questions.

D'accord. Et alors plutôt dans une optique de vulgarisation parce que comme mentionné tout à l'heure, parfois les gens ne sont juste pas au courant ?

Ça oui, mais alors pas dans les comités d'éthique. Mais ça on peut, je ne sais même pas si ça existe sur les sites cliniques. Mais en général les sites cliniques de phase 1, ce sont des petits centres et - en tout cas quand j'étais chez [redacted]- le contact avec les volontaires se fait vraiment facilement donc là c'est vrai qu'on peut avoir leur retour aussi par rapport à « cette étude est vraiment trop lourde, il y a beaucoup trop de choses à faire » donc ça c'est un point important à faire mais c'est pas directement lié au comité d'éthique c'est vraiment après au site clinique à lui à s'adapter puis le site clinique remonte aussi après vers le sponsor pour dire « ouf un avec un design pareil on va galérer à trouver à trouver des patients qui voudront faire ça, c'est beaucoup trop lourd, il y a beaucoup trop de paramètres à mesurer, c'est beaucoup trop long » Donc le sponsors peut réfléchir et se dire que ce n'est peut-être pas nécessaire pour ce qu'on veut mesurer et on peut le mettre de côté ce sera mesuré après.

Parfois aussi et peut-être aussi plus d'un point de vue éthique mais c'est important aussi d'avoir l'avis du sponsor - pour qui on pourrait croire ne pense qu'à l'argent – mais certains volontaires sains pourraient faire de ça leur métier et donc je me demandais si vous aviez déjà remarqué ça parce que ça peut être dangereux non ?

Mais en fait, enfin en tout cas nous - mais je pense que la plupart des sponsors aussi et ça doit être aussi dans la loi - on est limité à un nombre d'études cliniques, du moins pour les volontaires sains, pour les patients malades je ne sais pas. Mais pour volontaires sains, on est limité à un nombre d'études par an et en général on indique toujours dans les protocoles un délai pour lequel un patient n'a pas participé à une autre étude précédente, c'est entre 3 et 5 mois donc ça limite en général le nombre de participations.

Oui donc ils ne pourraient pas en faire leur métier et vivre de ça ?

En belgique non, dans d'autres pays je ne saurais pas te dire mais en Belgique en tout cas c'est réglementé.