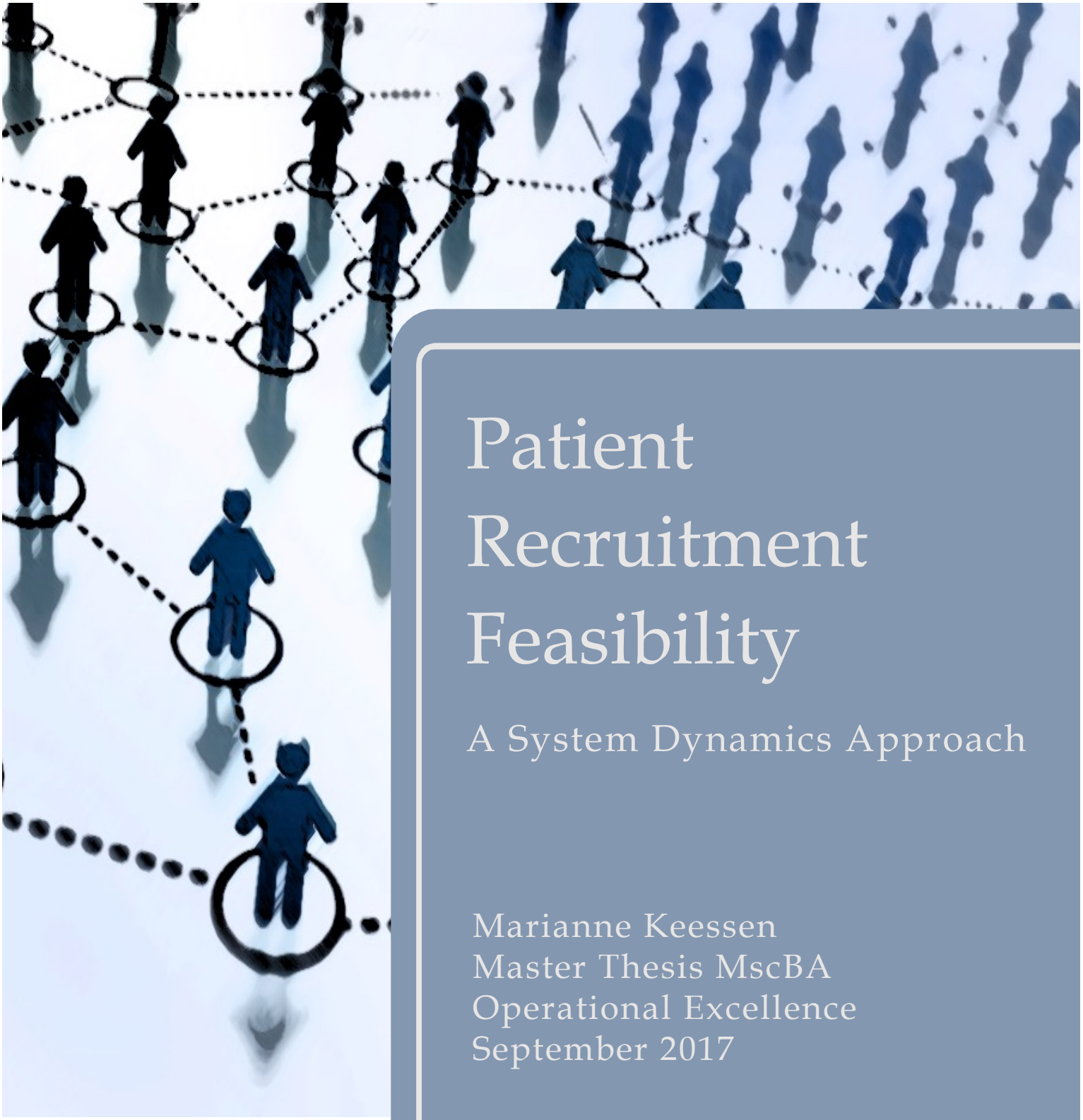

Patient Recruitment Feasibility

A System Dynamics Approach

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Preface

This exploring research all started with just one article: "Patient Recruitment Feasibility" by Matthew Kibby (2011), which I came across on the internet preparing site feasibility for our yet to commence phase III clinical trial. Our small company is a spin off from the Netherlands Cancer Institute, which is, although maintaining a strong academic and translational research environment, not set up for the large investments and resources needed for bringing an academically developed drug to market.

My continuing search on the internet surprisingly did not bring any further insights into finding the best practice to adapt for our young company's phase III preparations, emphasising the relevance of Kibby's (2011) key message to share experiences for "assessing and improving enrolment feasibility predictions and management strategies". Shortly before starting my master thesis, I had finished an essay on System Dynamics to finalize my major 'Operational Excellence' of the Master of Science in Business Administration and immediately conceived this as an opportunity to fill my knowledge gap, and possibly others', by combining the two in this thesis research.

My personal development from years as a nurse practitioner specialized in early clinical trials, towards coordinating clinical trials as a project manager on behalf of study sponsors, has provided me with experience from both a clinician, as well as a sponsor point of view. This combination enables a holistic view, which many specialists in clinical research do not have the opportunity to achieve. This, combined with my special interest for logistic challenges gave me the energy and motivation to proceed.

Fortunately, my co-workers, cooperating clinicians and contracted Clinical Research Associates do have extended experience in their field of expertise. To them I am more than grateful for their participation in the empirical part of this research. They have provided me with insights, that in a 'normal' work environment would have taken me years to discover. Therefore, I thank you so very much for your sharing and time invested during our interesting conversations.

To start operational excellence, and specifically System Dynamics research, without a thorough mathematical background is a challenging exercise. Which of course I like! However, this would never have been possible without the everlasting patience, confidence and advice given to me by my study coach, Roelof Kuik. You have made this a pleasurable learning experience for which I express my deepest thank you! As a methodological backbone, Lucas Meijs has been of great help in the course my learning process, both through the milestone sessions and by personal feedback as co-reader on my thesis. Thank you very much for this!

Also, a big thank you to my friends and colleagues for your emotional support, humour and patience during the final stages of this thesis.

Of course, all this could never have happened without my family supporting and understanding. Hopefully I will be able to make up for my lack of attention, missed dinners, etcetera, in the very near future. Loving you ever so much!

Abstract

Clinical trials are an important part of the drug research & development process. Specifically phase III clinical trials have an enormous impact, considering their importance in providing evidence on drug efficacy and safety, their size in number of actors and the related high cost of investments. However, it becomes clear from the extensive literature on the subject, that the current system is far from effective. Drug development costs are rising rapidly, with a low success rate in drugs coming to market. The inefficacy of the system is, in part, being related to slow patient recruitment and poor feasibility.

The patient recruitment feasibility process is defined and the current methods for prediction of patient recruitment are described. Further looking into the current status of patient recruitment, it is evident that an accurate prediction cannot be given using these methods, because factors influencing the patient recruitment process are complex, diverse and often subjective. To address this problem, challenges in patient recruitment are discussed, resulting in an exploration of the critical factors that influence the patient recruitment. This diversity of factors is grouped into four main categories: Study Design factors, System factors, Management factors and Human factors.

The System Dynamics theory and research method, because of its applicability in the field of both operations management and health care, is identified to be capable of gaining further insight into the complex process of patient recruitment by addressing the complexity and human alliances in the system and by simulation. Therefore, this method is adopted as an approach to understanding and predicting the (feasibility) process of phase III oncology clinical trials.

Continuing exploration, through in-depth literature research, of the identified critical factors, has provided the basis of a System Dynamics causal loop model, which is then validated in an empirical qualitative research by engaging in a discussion with field experts. This discussion exposes the enormous subjectivity and complexity of the patient recruitment process, confirming the literature found on this subject. Interdependencies between critical factors have been assessed and analysed, and then used to formulate propositions on the behaviour of the clinical trial system, as well as adapt and reverse the initial model into a System Dynamics stock and flow model equipped for simulation. The propositions are then taken as a base for scenario analysis, to test the model in simulation. The results indicate a linear behaviour, consistent with the changes made in the constant variables. However, with multiple negative incentives, combined with an increase in project management activity, the linearity decreases. Although the latter could be caused by inadequate equations, for which an expert mathematical approach is indicated, it may also be suggested that multiple negative incentives are difficult to manage, even with a substantial increase in project management activity.

It is concluded that the System Dynamics approach is suitable as a method for understanding and predicting patient recruitment (feasibility) in phase III clinical trials, by revealing the complexity and subjectivity of the patient recruitment feasibility process and taking these factors into account in simulation. Additionally, this research provided evidence for the important and dominant role of the human factors throughout the entire system, influencing

decisions and actions in all categories of critical factors. Not taking the important human factors into account, renders those techniques in predicting patient recruitment inadequate.

The extent of information found on patient recruitment, in combination with the results of simulations have highlighted the importance of the Study design factors and the role of Project management factors. Limiting factors in study design have been demonstrated to cause significant delays in planned study duration. Managing these appropriately will induce the need for resources, whereas personal contact and support has been shown to be most effective. The imperative role of the investigator is visualized in the model by its positioning and the number of interdependencies directed at the investigator. It is found that the investigator remains the main actor in recruiting patients in a clinical trial, by proposing participation. The effect of other (digital) information channels is expected to increase public awareness in the future. Several paradoxes in the eco-system of clinical research are revealed by the System Dynamics approach and are discussed, which may provide an onset for public discussion on drug development.

Future research into quantifying interdependencies between critical factors and including other mathematical resources in the model, as well as refining of equations is recommended.

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1. Introduction

Since early this year my employment at a pharmaceutical start-up company is aimed at managing the operational set-up and conduct of a large multicentre phase III randomized clinical trial. This start-up company is actually a spin-off from my previous employer, the Netherlands Cancer Institute, where a new oral formulation (a tablet) has been developed from a well-known anticancer drug registered as an intravenous (infusion) therapy for various types of cancer. Small early clinical trials performed locally in the past two decades have now provided sufficient evidence to move forward towards registration of the drug as a tablet and bring it to market. For the registration dossier a large international, randomized controlled clinical trial to sustain this evidence is needed, in which the original formulation as an infusion (intravenous delivery) will be compared to the new oral formulation as a tablet. Since the original formulation of the drug, administered in the hospital as an infusion, has already been available and used for more than thirty years, the primary benefit will not be found in the efficacy, rather in the patient convenience (oral administration at home instead of hospital admission) and a better safety profile (due to a lack of toxic excipients related to the intravenous formulation and a lower dose per delivery, administered in a higher frequency). Another advantage is the potential to deliver a cheaper treatment (as the treatment need not be delivered in the hospital) and the possibility to combine this oral chemotherapeutics with an increasing number of new oral anticancer drugs. Ultimately, the main objective of the trial will be to prove non-inferiority of the tablet compared to the standardized intravenous delivery of the drug. For patients with advanced prostate cancer, treatment with this drug is the primary standard chemotherapy option, and therefore this is a suitable population for this trial. The number that needs to be included in the clinical trial is 1050 patients with advanced prostate cancer, recruited from 80 hospitals in approximately 6 European countries. The estimated recruitment period will be three years.

Recruitment of such a large number of patients within this timespan, will be a challenging exercise for several reasons, as recognized by many researchers referred to in this thesis. Yet so far, although extensive literature is available, no consensus on best practices to address this issue seems to be achieved amongst experts. The issue of patient recruitment is challenging for large pharmaceutical companies, with large investment power and several potential drugs in development to spread the risk. For small start-up firms, focusing on one particular drug, the financial risk will be even more evident (Hay, Thomas, Craighead, Economides, & Rosenthal, 2014). As Moscicki & Tandon (2017) emphasize only approximately 10% of drugs that enter clinical studies will reach the point of registration, whereas the success rate for small-company programs is even lower than that of large companies. Limited resources and funding is a large challenge to overcome for these small companies, which in turn requires short timelines to be able to demonstrate progress to investors. Testing new formulations to enhance the action of an existing drug is one way for small companies to survive (Moscicki & Tandon, 2017), which also happens to be the existential reason for the start-up company leading towards the subject of this thesis.

To plan and execute a clinical trial today can take years and cost hundreds of millions of dollars (English, Lebovitz, & Giffin, 2010). Also, clinical trials consume a large and valuable portion of a patented drug's life span (Drennan, 2002). This makes timelines even more important, as

the limited patent time poses another considerable financial risk for drug developers of the investigational drugs, as found by Getz & Kaitin (2012), for a considerable amount of dollars in revenue are missed due to patent expirations.
Nonetheless, the ultimate goal of drug development is to speed new and improved medical treatments to patients throughout the world (English et al., 2010). Whether a clinical trial will meet its timelines is often determined during its recruitment phase (Beck, Esser, & Herschel, 2004).

Patient recruitment in clinical trials is of special interest as it has practical implications in both the initial planning (feasibility phase) and ongoing monitoring of trials, for it directly impacts the duration of a trial and hence its budgeting and resource allocation. Slow accrual is of particular concern as it may lead to a reduced and inadequate sample size for powerful results necessary for registration and marketing of a new drug (Zhang & Long, 2010). Yet, slow accrual is common in clinical trials, as more than 80 per cent of all clinical trials fall short of their original accrual goal (Bose, Sandhu, & Strommenger, 2017; Drennan, 2002; Zhang & Long, 2010). Therefore, the process of patient recruitment will be the subject for this thesis. Insight in this process may help in planning strategies for the feasibility and operational management of our phase 3 clinical trial which is planned to commence in the first half of next year.

Thesis outline

This thesis proceeds in the second chapter onto exploring the context, process and challenges of patient recruitment for clinical trials and phase III trials in particular. Current approaches to address this challenge and its similarities with the theory and research method of System Dynamics lead towards the research question to be investigated in this thesis. After formulating the specific research question, chapter three continues with an in-depth literature review to further explore critical factors influencing patient recruitment. This chapter results in a System Dynamics model of the Patient Recruitment (Feasibility) process based on the literature. Chapter 4 describes the conceptual framework and the methodology for empirical research and simulation testing of the model. The resulting data and analysis of this research are presented in chapter 5. Hereafter, in chapter 6, the research is summarized, general findings are discussed and the research question is reflected upon, including its limitations and contributions, to conclude with identifying areas for future research.

This research aims to contribute to theory by introducing system dynamics as a modeling method into patient recruitment research, and vice versa to introduce yet another operational field into the wide range of system dynamics applications. The main focus is towards patient recruitment in phase III oncology clinical trials, for this is the work environment from where this major issue has been identified and in which the empirical part of this study takes place.

2. Patient recruitment in (phase III) clinical trials

2.1. Clinical research and clinical trials

Clinical research and clinical trials are both used in the context of intervention studies in human patients. However, the definition for Clinical Research as used in this thesis is more broadly defined as: *"Any research design that studies humans (patients or subjects) or any material taken from humans"* (Glasser, 2008, p.4). Although clinical research in this broad definition will not be the focus for this study, it is relevant to reflect on the full context of the patient recruitment process of clinical trials, being a part of Research and Development programs performed by researchers all over the world in the pharmaceutical industry as well as institutional laboratories and hospitals.

"Clinical trials are the way the medical field tests whether a new therapeutic product performs as expected and actually makes a difference in treating disease", as explained by English, Lebovitz, & Giffin (2010) in their report on workshops organised by the Institute of Medicine (IOM) in the United States. The definition for Clinical Trials (or Interventional Study) as given by ClinicalTrials.gov[1] is: *"A clinical study in which participants are assigned to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study protocol. Participants may receive diagnostic, therapeutic, or other types of interventions."*

For the purpose of this thesis the focus for both Clinical Research and Clinical Trials will be on pharmaceutical drug interventions used in oncology clinical trials, and more specific, in phase III clinical trials.

In this subchapter, an introduction towards clinical trials will be given by starting with a global perspective on the drug development process, continuing with an outline of the clinical trial phases. Particularly phase III clinical trials will be discussed, as they represent the largest and most costly of clinical trials, intended to provide a sustainable basis for the registration dossier needed for regulatory authorities to register the drug for commercial use.

2.1.1. Drug development

In research centres all over the world new therapies are being tested in laboratories, in so-called preclinical studies, of which only a few will reach the actual stage of testing in human beings within clinical trials (English et al., 2010). This occurs only when this preclinical testing indicates the innovative therapy to be safe and beneficial for clinical use. To determine the safety and effect of the therapeutic compound, researchers will conduct a series of laboratory

[1] ClinicalTrials.gov is a Web-based resource that provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions. This Government Web site is maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH) in the United States.

and animal studies (PhRMA, 2015). Subsequently, executing clinical trials is necessary for establishing the medical efficacy and safety of these scientific findings in specific patient groups and is therefore crucial to translate the potentially beneficial basic research findings into clinical practice (Grunfeld, Zitzelsberger, Coristine, & Aspelund, 2002).

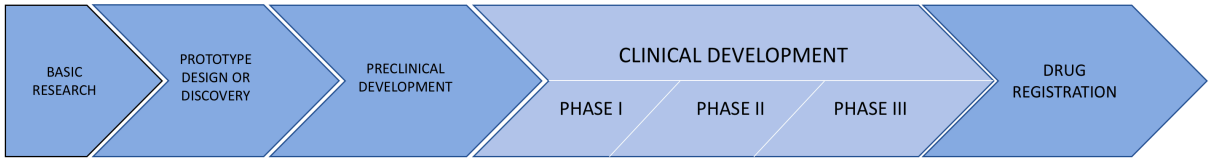


Figure 1: Phases in drug development (Modified from: Food and Drug Administration, 2004)

However, the success rate of clinical trials for new drugs in reaching the market is low. DiMasi, Feldman, Seckler, & Wilson (2010) found this to be as low as 12% from all therapies entering into the clinical stage, and only 7% specifically for drugs used in oncology. And this may even be declining. As found by Hay *et al.* (2014) this is only 10.4% of all drugs entering the clinical trial phase, and it is even found to be as low as 5.4% for drugs used in oncology. Hay *et al.* (2014) provide a benchmark for the broader drug development industry by including small public and private biotech companies and specialty pharmaceutical firms, whereas previous researchers have studied only large pharmaceutical companies. This results in the identification of contributing factors to the lower success rates found in this study, being the large number of small biotech companies represented in the data, as well as the more recent time frame and higher regulatory hurdles for new drugs. How these factors are accounted for, will be discussed further.

Innovation in the pharmaceutical industry is characterised by high costs (DiMasi, 2002), which has increased over several years with ongoing medical developments. The investments necessary will only then be returned when and if the fruits of the research and development efforts are realised. Therefore, the incentives for firms to engage in the discovery and development of new therapeutic compounds, depend largely on the expected costs for R&D and the returns that can be expected (DiMasi, 2002). For firms to recoup from the investments in drug development and make a profit, their intellectual property is protected through patenting of the drug, allowing for market exclusivity pricing after registration for a limited time period. After patent expiration, generic rival drugs may be produced by other firms at greatly reduced development costs, therewith engaging market competition and reducing the innovator drug company's revenues (Grabowski, DiMasi, & Long, 2015).

In a BIO Industry analysis from Thomas & Wessel (2005) it is found that oncology research accounts for 26% of all investments made in disease research from 2005-2014. This is explained by the complex nature of oncology. Oncology is not just one disease, but actually comprises of many different diseases in need for a broad range of investment interests to discover solutions for diverse and unmet medical needs. Thomas & Wessel (2005) state that these investments have continued to increase with over 90% of venture investments in the last decade, of which over 67% are made in emerging companies discovering innovative and promising advancements (e.g. immune-oncology, targeted treatments), as opposed to improvements of older regimes. The emerging company clinical pipeline in oncology is the largest of all disease areas, often introducing new products found in institutional settings. As explained by Dahlin,

Nelson, Haynes, & Sargeant (2016), pursuing novel products helps companies avoid the negative consequences of settling on suboptimal alternatives and keep pace with new technologies, competitors' innovative products and new customer demands. To maintain this innovative pipeline, it is vital for small therapeutic-focused biotechnology companies to be able to access capital and form strategic alliances. Thomas & Wessel (2005) found that the emerging company pipeline is heavily partnered (47%) and that most phase III clinical trial programs (addressed in the next paragraph) are being co-developed with partners.

Despite the risks in R&D, the pharmaceutical industry has made tremendous progress in R&D, enhancing patients' quality and quantity of life and reducing need for other health services. PhRMA examples show that the life expectancy of cancer patients has increased about 3 years, of which 83% is attributable to new treatments, and that 50-60% of increases in survival rate are due to medicines (PhRMA, 2010). This is predominantly due to investments made by the pharmaceutical industry in drug research. But it is questioned whether the current structure of drug development is sustainable.

Grabowski, Vernon, & DiMasi (2002) analysed the distribution of returns for 1990 to 1994 new drug introductions to be highly skewed, as only one third of new drugs had values that exceeded the average R&D costs. Combined with the concern raised by Getz & Kaitin (2012) that the number of products currently reaching the marketplace is too low to generate sufficient revenue to drive innovation into an era of rapidly rising R&D costs, indicates the need for the industry to find ways to limit R&D costs. In their Profile report of Biopharmaceutical Research Industry, PhRMA (2010) recognizes the increasing costs and complexity of R&D, which in turn decreases the odds of successful drug development. Key factors in increased costs and complexity are identified to be related to clinical trials, as trials have become larger and require more participants than before and they have expanded with more endpoints to test and observe the safety and effectiveness of the drug. This is indicated by the regulatory authorities to attain approval of executing a trial and for registration of a drug before bringing to market. Also, the potential of recent developments in genomics and molecular biology, although promising, is challenging and costly in applying to drug development (PhRMA, 2010).

Ultimately, abovementioned developments have resulted in a 14-fold multiplication of the average costs to develop one new approved drug in the past decades (DiMasi, Grabowski, & Hansen, 2016). These increasing costs in clinical research have significant implications for public health, as it affects drug companies' willingness to undertake clinical trials (Sertkaya, Birkenbach, Berlind, & Eyraud, 2014). Therefore, increasing cost and sophistication of clinical trials will, as indicated by Grand & O'Brien (2012), require cooperation to find strategies for risk management for trials, which leads to a reduction of costs, caused by study failure and slow accrual. They suggest a better understanding of the obstacles that are most likely to affect an individual trial and will help to improve current strategies.

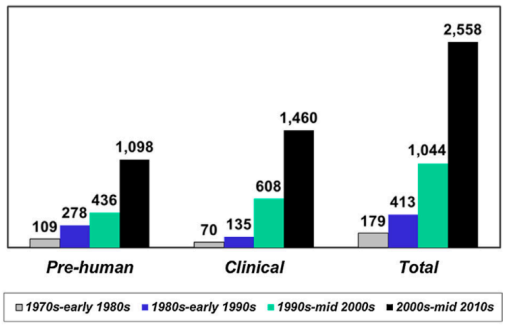


Figure 2: Trends in capitalized cost per approved new drug (DiMasi et.al., 2016)

Summarised the following facts and issues are key in drug development:

- Clinical trials are essential to establish the efficacy and safety of new drugs in humans
- Only 5.4% of oncology drugs tested in clinical trials will eventually come to market
- R&D depends largely on venture investments, for which incentives are based upon expected costs and returns, secured through patents for a limited time period
- Revenues in drug development are decreasing and predominantly related to high costs in clinical trials
- This urges the need to find ways to limit drug development costs and hence look into the obstacles of clinical trials to improve strategies

2.1.2. Clinical trials

Clinical trials are characterised by a highly dynamic and competitive environment (Buonansegna, Salomo, Maier, & Li-Ying, 2014), wherein several stakeholders are involved and connected through extensive networks and alliances. Clinical trial sponsors (often pharmaceutical companies), sites (most of the time hospitals), subcontractors (often contract research organisations (CROs)), and patients are the main actors. For the operational part of executing a clinical trial, the sponsor can directly collaborate with sites to run clinical trials or outsource parts or the entire operational process to subcontractors. When either partly or fully outsourced, the subcontractors will (also) collaborate with sites to run the clinical trials. Clinical trials can take up to 6–7 years (PhRMA, 2010). All the actors mentioned will interact and depend on each other during the course of the clinical trial.

Testing new drugs in humans comprises of three to four phases, each of which has its own distinctions, as described hereafter. Any patient participating in a clinical trial must be well informed, both orally and written, about the purpose of the trial, trial treatment specifics and procedures, foreseeable risks and inconveniences, reasonably expected benefits (also if there is no intended benefit), alternative treatments, subjects' responsibilities, compensations in case of injury, voluntary participation and the possibility to withdraw at any time (ICH-GCP, 2016)[2].

Phase I

Clinical drug testing typically starts with a small sample size in a phase I clinical trial, in which the primary aim is to test the safety and tolerability of an experimental drug (or treatment combination of drugs) in healthy volunteers or in patients, depending on the type of drug tested. Escalating doses are tested in small patient cohorts (3-6 patients) and when the previous dose level is found to be safe and tolerable, this continues until the highest safe dose for further

[2] ICH-GCP Guidelines on Good Clinical Practice (GCP) by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. It aims to provide a unified standard for the ICH regions to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. In Europe the GCP guidelines have been adapted into the European Directive on Good Clinical Practice in Clinical Trials 2001/20/EC.

clinical testing, the so-called Maximum Tolerated Dose (MTD), is defined. Since little is known about the experimental drug behaviour specifically in humans, pharmacokinetic and pharmacodynamic assessment is an important part of research in this early phase clinical testing. Oncology drug testing in healthy volunteers is not common as the risk of administrating the typically cytotoxic medications is unacceptable. Generally, oncology patients with various tumour types and for whom no (more) standardized treatment options are available, are invited to participate in phase I clinical trials.

Phase II

When preclinical data and/or preliminary results in phase I suggest benefit in specific diseases, a phase II study will commence including patients with the target disease. The primary aim of this phase II is to assess the efficacy of the new drug or drug combination. Further assessment of safety and tolerability of dosing is an important secondary aim, as clinical evidence is minimal after the small sized phase 1 trial(s).

Phase III

As results in phase II provide preliminary evidence that benefit can be expected from the experimental new drug (or treatment combination) and the exploitability of the new drug is deemed feasible by the sponsor, further testing in a phase III clinical trial is indicated for comparison with the (registered) standardized treatment. Characteristics of phase III clinical trials will be described in the next sub-paragraph.

Phase IV

A phase IV clinical trial, or so-called post-registration trial, may or may not be executed. In cases where the phase III clinical trial outcome proves beneficial for the target population and the drug may be approved by the regulatory authorities for marketing, it may be negotiated or mandated by the regulatory authority to conduct a phase IV clinical trial to reinforce safety and efficacy data. This is particularly the case for drugs that have had accelerated approval (Glasser, 2008).

An overview of the pre-registration clinical trial phases I to III is given by Buonansegna et al. (2014) in figure 2.

Phase	Phase I	Phase II	Phase III
Duration	6 months to 1 year	1–2 years	2–5 years
Patients	<100 Healthy subjects or patients with the target disease	100–500 Patients with the target disease	500–5000 Patients with the target disease in multiple centres
Scope	Determine the safety and tolerability over a wide range of doses Define a pharmacokinetic profile of the drug Obtain preliminary pharmacodynamics evidence	Assess the effectiveness of the drug (pharmacodynamics) Assess the dose(s) for phase III and the frequency of administration Determine the common short-term side effects and risks	Demonstrate the therapeutic efficacy, tolerability, and safety

Figure 3: Clinical trial phases I - III (Buonansegna et al., 2014)

2.1.3. Phase III clinical trials

Phase III clinical trials are distinguished from earlier phases, as the studied treatment drug(s) has passed the explorative character of the earlier phases and is now focussed specifically onto the efficacy of the treatment drug(s) in a large patient group with a defined indication. The main goal of a phase III clinical trial is to collect substantial evidence of superiority compared to the standardized treatment. It is essential to provide sufficient and powerful evidence of the drugs' competence and safety into the registration dossier, for regulatory authorities to review and approve before bringing a drug to market.
The typical characteristics of clinical trials are: randomisation, large study population, multiple centre, multinational and high costs. These characteristics will be addressed separately hereafter.

Randomized controlled clinical trials are recognized as a the golden standard to evaluate effectiveness and safety of drug interventions, to prevent selection bias (Treweek et al., 2013). This so-called 'randomisation' means that a treatment is assigned by chance. Tables with random numbers or computer-generated sequences are used to generate a random allocation sequence for assigning subjects to one or more equally divided treatment or control group in a clinical trial.

To attain statistically significant results, a large and widely spread population needs to be treated with the investigational drug or in the control group with the standardized option. Typically, more than one thousand patients are recruited from multiple centres (hospitals) in multiple countries to avoid a population bias. This is a growing trend, as approximately 60% of studies contain a global component, although posed with challenges due to cultural differences, multinational regulations, language barriers and customs (Drennan, 2002).

A phase III study set-up requires sufficient resources to be able to adequately support the execution of the clinical trial. A phase III clinical trial is by far the costliest part of all clinical research, in large due to the extended set-up of operational activities. This includes several actors as the multiple participating centres, and also outsourcing partners as, for example, Clinical Research Organisations (CRO's), specialized in regulatory affairs, project management, data management, monitoring, etc., and drug supply organizations.

Several consequences may result from poor recruitment, of which probably the most crucial is a potential of a phase III trial to be underpowered (Treweek et al., 2013). In such circumstances, differences that may be clinically relevant could be reported as statistically non-significant, which increases the chance of an effective intervention being either abandoned before its true value is established, or minimally, being delayed until conduct of further trials or meta-analyses.

Summarised, phase III studies are characterised by:

- being the last phase of (clinical) drug development research before registration
- recruiting a large population with a defined indication
- international to global set-up

- high cost, requiring sufficient (financial, human and facility) resources needed for operational activities
- multiple actors involved in the operational activities, including participating centres and outsourcing partners (e.g. CRO's, drug distribution)
- a large dependency on adequate patient recruitment

2.1.4. Regulatory processes

Clinical trials are highly regulated as it involves testing in humans. After some major medical disasters in the history of the past century and after gruesome human experimenting during World War II without participant consent, several regulations and laws have been adapted on the safeguard of experimental and medical interventions in humans (Abraham, Grace, Parambi, & Pahuja, 2009; Vijayananthan & Nawawi, 2008). The Nuremberg Code, stating the need for scientific based research, voluntary consent and protection of participants, as well as the Declaration of Helsinki, developed by the World Medical Association (WMA) as a set if ethical principles and regarded as a cornerstone for human research, are the basis for the ICH Good Clinical Practice (ICH-GCP, 2016) guidelines. Today the ICH-GCP guidelines are considered the 'bible' of clinical trials and have been adapted throughout the world (Vijayananthan & Nawawi, 2008) in national and international laws[2]. The ICH-GCP guidelines helped the regulatory authorities to frame their guidelines for conducting clinical trials to ensure less harmful effects and safety of the participants (Abraham et al., 2009).

Medical/ethical review of the clinical trial

Regulatory Authorities are bodies having the power to regulate. In the ICH-GCP guidelines the expression 'Regulatory Authorities' includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are also referred to as competent authorities (ICH-GCP, 2016). The Institutional Review Board / Independent Ethics Committee (IRB/IEC) should safeguard the rights, safety, and well-being of all trial subjects, with special attention to trials that include vulnerable subjects. The IRB/IEC consists of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. A clinical trial may only commence to recruiting subjects when a written confirmation of IRB/IEC approval/favourable opinion has been obtained. Procedures for submission to national and local IRB/IECs differentiate per country. The time from protocol release to regulatory approval may take up to almost 300 days for countries in Europe (Berthon-Jones et al., 2015).

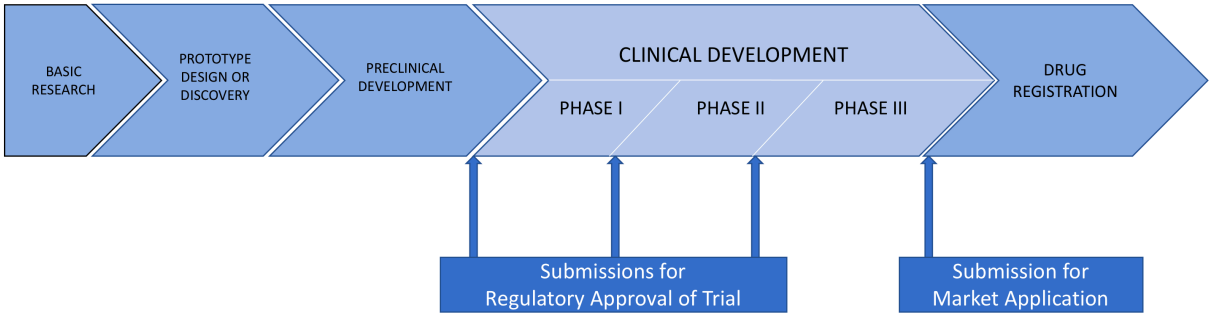


Figure 4: Regulatory Submissions (Modified from: Food and Drug Administration, 2004)

Drug registration authorities

When results of the phase III clinical trial are favourable and drug developers believe that they have enough evidence of safety and efficacy, the (pharmaceutical) company will submit a New Drug Application (NDA) for review and approval of market application to the governmental agencies, i.e. the Federal Drug Agency (FDA) in the United States and/or the European Medicines Agency (EMA) in Europe. This NDA requires a substantial registration dossier compiled of all results and relevant documentation of the clinical trials (Buonansegna et al., 2014; DiMasi, Hansen, & Grabowski, 2003). The time needed for review and approval may take up to 1,5 years (DiMasi et al., 2003).

Key elements of the regulatory processes are:

- the GCP guidelines are ethical principles underlying (inter-)national regulations
- IRB/IEC approval is required before including patients in a clinical trial
- FDA and/or EMA approval is required before marketing drugs
- regulatory processes may take a considerable amount of time

2.2. Patient recruitment feasibility

'Clinical trial feasibility' is defined by Rajadhyaksha (2010) as "*a process of evaluating the possibility of conducting a particular clinical program / trial in a particular geographical region with the overall objective of optimum project completion in terms of timelines, targets and cost*". It covers the broader scope of predicting whether a clinical trial will or will not perform as planned. It includes strategic, scientific, operational and patient recruitment considerations. Of these factors, early and efficient 'Patient recruitment feasibility' assessment addresses the clinical trial industry as a whole, for this common factor affects all actors involved (Kibby, 2011).

The definition of 'Patient recruitment feasibility', as given by Kibby (2011) is focussed on phase III clinical trials. Since phase III clinical trials are also the focus for this thesis, this definition is adopted:

"*Patient Recruitment feasibility is the process by which a clinical study sponsor can forecast and manage the probable randomization rate (number of patients per site per month) for a specific protocol and determine realistic parameters for site enrolment months (number of sites multiplied by number of open-to-enrolment months).*"

In Kibby's (2010) definition, the word '*forecast*'[3] is used in the context of predicting the 'randomisation rate' (which is synonymous to 'recruitment rate' in the context of phase III clinical trials). However, instead of 'forecast', in this thesis the word '*predict*'[4] will be used,

[3] Forecast, definition:
Merriam-Webster dictionary: "*To forecast is to calculate or predict (some future event or condition) usually as a result of study and analysis of available pertinent data*"

[4] Predict, definition:
Merriam-Webster dictionary: "*To predict is to declare or indicate in advance; especially: foretell on the basis of observation, experience, or scientific reason*"

based on the specific definitions given in the Merriam-Webster dictionary. In the definition of 'forecast', it is emphasized to be based on 'pertinent data', whereas the basis for 'predict' is based on observation, experience and scientific reason. Although, as clarified in the course of this thesis, some 'pertinent data' on 'patient recruitment' are available, most literature found is based on expert observation and experience.

2.2.1. Approaches in patient recruitment feasibility

As it is evident that adequate patient recruitment is key for a successful drug development process, many researchers and companies have tried to identify strategies to overcome this hurdle of unsuccessful patient recruitment. However, no best practice exists up to date. The current standard, as identified by Kibby (2011), consists of three steps, that are however broad and inconsistent, as they are variably interpreted by different sponsors. These three steps consist of:

1) medical specialists confirm the protocol design
2) the sponsor and/or CRO consider(s) logistical implications, and
3) the sponsor and/or CRO send(s) out surveys to possible participating sites to determine whether there is a potential number of patients for the recruitment to be successful.

However, according to Kibby (2011) the feasibility process may best be divided into two phases: protocol design and the operational planning for countries, sites (hospitals) and patients. The feasibility process, or 'frontloading process' as called and defined by Beck et al. (2004), is "*the sequence of actions and events between a Go-decision for a clinical trial and the inclusion of the first patient into this trial*". This starts with a preparatory phase plan that addresses the actions to be taken, which are related to: the feasibility check, selection process, staff experience, retroactive delays planning, communication plan, action plan, legal aspects, negotiating contracts and budgets.

Before the actual selection process of participating centres starts, the number of countries and sites needed to achieve the required recruitment rate, is calculated. Just a simple formula may be used (Kibby, 2011), formed by the following principle: [E = R * T * S]. In this formula E is Enrolment (the number of patients needed), R is the Recruitment rate (number of patients per month per site), T is the Time period for enrolment in months and S is the number of Sites actively recruiting patients.
Two approaches of specific interest for this thesis are: 1) the prediction of patient recruitment and 2) the selection of participating centres. These will be discussed hereafter.

Prediction of patient recruitment

Gajewski, Simon, & Carlson (2008) find that accrual rates are often subjective and ad hoc developed. The availability of objective tools for planning and monitoring of clinical trials is poor. Good planning tools are needed to construct realistic targets for sample size. And good monitoring tools are needed for timely interventions when accrual rates fall.

Current prediction methods for patient recruitment range from a simple calculation to more complex simulation methods. Barnard, Dent, & Cook (2010) have identified five major classes

of models, which are being discussed in their systematic review to predict recruitment to multicentre clinical trials. These are: the unconditional model, the conditional model, the Poisson model, Bayesian models and Monte Carlo simulation of Markov models. A short summary is given.
In the simplest approach, the unconditional model, no critical factors are taken into account. An example is the aforementioned model to calculate the number of countries and sites needed, which reversely may be used to calculate the recruitment rate. In this model, the accrual rate, meaning the number of accrued patients per month, is fixed.

The conditional model is a development of the unconditional model and allows the expected recruitment in any given month to vary. This may depend on other factors influencing the trial, as for example the time sequence in which participating centres start recruiting. Again, this aforementioned simple formula may be used to predict and manage probable recruitment by adding realistic parameters for enrolment, using results of the site selection and identifying factors that affect recruitment (Kibby, 2011). This model more closely matches the real-life experience of multi-centre trials relying on ad-hoc centre recruitment and by using relatively simple calculations this model can easily be constructed within a spreadsheet (Barnard et al., 2010).

A Poisson model assumes the rate that participants are recruited varies according to a Poisson distribution (Barnard et al., 2010). The process is characterized by rating the mean number of events divided by the number of patients in a unit of time (Anisimov, 2009) as the only one parameter. Therefore, this is acclaimed by Anisimov (2009) to be the most appropriate model in patient recruitment. Anisimov & Fedorov (2005) have applied this model retrospectively to GlaxoSmithKline (GSK) clinical trial datasets and suggest using the Poisson model combined with a gamma distribution, because rates will differ randomly over time. The model may be used for prediction planning before the trial commences and during the course of the trial. At the initial stage, when there are no actual recruitment data are available, assumptions are made on information provided by study managers and/or historical data (Anisimov, 2009). However, despite predictive modelling, the study will still be late with a 50% confidence, because of the random (stochastic) recruitment fluctuation during the course of the trial. Therefore, in the ongoing stage adaptive adjustment based on an actual data-driven approach is proposed (Anisimov & Fedorov, 2007), allowing for adjustments in, for example, the number of participating centres. In a later study Mijoule, Savy, & Savy (2012) compared Anisimov's work, with a Poisson model including a Pareto distribution. Even though the latter proved more accurate at some points, it was more difficult to use. Therefore, the Gamma-Poisson model was preferred.

A Bayesian model starts with a "prior" probability distribution for the value of interest, based on previous (subjective) knowledge, and adds new evidence as data accumulates (via a model) to produce a "posterior" probability distribution (Barnard et al., 2010). Gajewski et al. (2008) present a Bayesian based model, where a constant accrual rate is measured while adding actual data to the predictive data when this comes available. The 'weight' of data shifts towards posterior data as the study proceeds. One advantage of this method is seen in the fact that researchers combine predictive and actual data, so that these data are mixed and do not encourage ad hoc decisions based on short term actual data. Also, this method may be used to

analyse interim data without performing a full interim analysis of the clinical trial. Zhang & Long (2010) propose a stochastic variant of this model, with a better performance opposed to the constant measuring. Credible intervals (CIs) are adapted. Wide CIs are appropriate at early predictions, however less accurate. When more accrual data are available, projections appear more precise using tighter CIs, although decrease in significance at a late stage of the clinical trial. More recently Jiang, Simon, Mayo, & Gajewski (2015) propose an adaptive "prior" design, to avoid the use of misleading (e.g. miss-specification or over-estimating) priors. An important lesson learnt from this research is mentioned to be the complicating effect on evaluation of the models, due to variations in accrual. Strength is given to "priors", whereas strong "priors" (when the investigator has strong confidence in the accrual rate) are more predictive when accrual is on target, and weak priors work well in case of very slow accrual, because in that case early evidence of slow accrual is given more weight.

Finally, a Monte Carlo simulation Markov model considers "random" probability distribution as model inputs to produce hundreds or thousands of possible outcomes instead of a few discrete scenarios. The results provide probabilities of different outcomes occurring. A Markov chain uses Monte Carlo simulation (random number generation) to decide on the transition probability and whether, for example, a participant is recruited in a certain time period or not. (Barnard et al., 2010). Although a Markov model, as well as other linear systems models, is able to provide an analytic description upfront, it is not able to derive the dynamics of the system over time (Marshall, Burgos-Liz, Ijzerman, et al., 2015).

Recruitment time and rate is considered one of the key decision variables in the design stage of the study (Anisimov & Fedorov, 2007). Large varieties and variables within the dynamics of patient recruitment are also being recognised. Although several researchers are positive about their researched models (Anisimov, 2009; Gajewski et al., 2008; Jiang et al., 2015; Mijoule et al., 2012; Zhang & Long, 2010), none of the models found by Barnard et al. (2010) were able to match all their requirements, which were: simplicity, adaption to epidemiological changes, adaption to environmental changes, centre recruitment and ability to inform commissioning decisions. Consequently, as research programmes currently do not have a preferred model for clinical trial prediction, most applicants choose the simplest: the unconditional model. Furthermore, although recruitment of participating centres is recognised as a significant driver to overall patient recruitment, many modeling studies do not take the role of centre recruitment into account (Barnard et al., 2010).

Selection of participating centres

According to Harper & Zuckerman (2006) an ideal centre to participate in all studies does not exist. They advise on matching centre characteristics to specific requirements of the study, which includes: qualifications and experience of investigator and research staff, technical expertise and facilities required for the study, access to the appropriate patient population, staff resources and compliance with scientific, regulatory and ethical requirements.

Berthon-Jones et al. (2015) identified poor site selection in multicentre randomised clinical trials to result in delayed start-up, unmet target recruitment, poor data quality and/or research integrity, which relates to cost inefficiencies in resource and time allocation. This process of selecting and contracting investigating centres is often not well planned and hastily

done (Drennan, 2002), which may affect the success or failure of patient recruitment during the entire project.

Although sending out surveys to possible sites before selection is a common approach, the outcomes very often do not reflect the actual recruitment rates of participating centres. Reuter & Esche (2007) find that questionnaires should not be taken as a fact, as sites may be overly optimistic in what they can accomplish. Despite the fact that it is assumed that properly designed questionnaires address this issue, Reuter & Esche (2007) find that the statistical analysis they performed in a clinical trial with 65 participating sites, reveals that none of the commonly used questions in the questionnaire studied had a significant predictive value. Also, they found that 86% of the participating sites overestimated the number of patients they would enrol.

Summarised the key findings to current approaches in patient recruitment feasibility include:

- the trial feasibility process or preparatory phase is essential in planning patient recruitment
- several predictive models are being developed, yet no model matches all requirements and therefore an easy to use but imprecise model is most frequently used
- study requirements should match with centre characteristics
- sending out surveys to potential participating centres is common practice for selection, but is found to be highly inadequate

2.2.2. Current status of patient recruitment

The recruitment of qualified patients to participate in clinical trials is identified to be complex, competitive and costly. Moreover, it may, more often than not, significantly delay the submission of new drug applications (NDAs). At least 80% of trials fails to meet their enrolment deadlines, which contributes significantly to cumulative costs in drug development (Bose et al., 2017; Drennan, 2002). Additionally, Bose et al. (2017) find that approximately one-third (30%) of Phase III study termination can be contributed to enrolment difficulties. Another complicating factor is that study sponsors routinely underestimate the costs and time required for patient recruitment, resulting in 'crisis recruitment' which may further increase clinical trial costs (Drennan, 2002).

A well-known phenomenon, called the Lasagna-effect, is recognised by several researchers to be true, as the estimated number of patients with a certain condition, may drop down to 10% when the study starts, only to return when the study has ended (Bose et al., 2017; Mijoule et al., 2012; Torgerson, Arlinger, Käppi, & Sjöström, 2001). Additionally, it is not very helpful to ask an investigator for the number of patients expected to include within a given period of time, because an investigator interested in the trial is likely to over-estimate the recruitment potential (Beck et al., 2004; Reuter & Esche, 2007). Comis, Miller, Aldigé, Krebs, & Stoval (2003) find that the actual number of cancer patients who eventually enrol in clinical trials is less than 10%.

Summarized the current status is clearly insufficient as:

- the majority of trials fail to meet their deadline, and
- patients appear to be much less available than predicted during the feasibility phase
- enrolment of cancer patients into clinical trials is less than 10%

2.2.3. Challenges in patient recruitment

Challenges in patient recruitment are widely acknowledged by authors with several backgrounds, ranging from clinical to pharmaceutical and from economical, managerial to social perspectives. These challenges are related to the various barriers and critical factors reported in the literature. Before identifying barriers and critical factors it is of importance to reflect on the timeframe in which a clinical trial needs to be executed and the necessity to speed up study procedures.

Timeframe

Recruitment performance is poor. Worldwide only 25% of participating centres is able to recruit the targeted number of patients, and only 10% will do so within the planned timelines. As a result in most clinical trials the recruitment period needs to be extended (English et al., 2010). Whether timelines will be met is ultimately determined during the recruitment phase of a clinical trial, although Beck et al. (2004) argue that it is during the preparatory phase, when operational decisions are being made, this is actually decided upon. Kibby (2011) identified key considerations that may affect study timelines during the feasibility phase. Identified are sponsor controlled considerations as business objectives, site contracting and activation and drug supply management. Considerations outside of sponsor control are the probable regulatory and ethics review, the availability of equipment/facilities, drug import licencing and data quality.

However, if for whatever reason slow accrual does occur, sponsors have to compromise on either the originally planned sample size, or on the length of the trial. In both cases this may affect the outcome of the trial negatively and undermine the power of the study. For example, a reduced sample size at the end of a study decreases the likelihood of obtaining results with sufficient precision and make meaningful scientific inferences (Gajewski et al., 2008; Jiang et al., 2015). Specifically if the accrual affects sample size calculations for time-to-event endpoints (Zhang & Long, 2010). Another effect as demonstrated by Butler et al. (2013) is that sites with lower recruitment, tended to recruit participants at higher risk, which correlated with worse study outcomes. Therefore, it was concluded that the site recruitment rate in itself may affect the generalizability of results and outcomes of the drug being tested in the trial. Finally, a negative effect may be the delay in roll-out of a potentially effective intervention (Treweek et al., 2013), which results in a delay in availability of new drugs and, therefore, slow the advancement of medical progress (Jiang et al., 2015).

Beside negative study effects, extending the length of the trial, also affects the sponsor through increasing cost and workload of the trial itself, therefore declining productivity of drug development process. In addition, shorter time to expiration of key patents, results in greater competition from generics and often short-lived market superiority for those few drugs that

do reach the marketplace (Moos & Mirsalis, 2009; Zhang & Long, 2010). Without the period of market exclusivity that patents provide, companies would not have the opportunity to recoup their R&D investments (Reichert & Milne, 2002). And ultimately, it would be a waste of precious and limited resources, including patient volunteers, when large clinical trials produce inconclusive results due to inadequate sample size as a result of slow accrual (Jiang et al., 2015; Treweek et al., 2013; Zhang & Long, 2010).

Barriers and predictors to patient recruitment

Major obstacles to conducting clinical trials in the United States were identified by Sertkaya et al. (2014) as high financial cost, the lengthy time frames, difficulties in recruitment and retention of participants, insufficiencies in the clinical research workforce, drug sponsor-imposed barriers; regulatory and administrative barriers, the disconnect between clinical research and medical care, and barriers related to the globalization of clinical research. High impact factors identified by Beck et al. (2004) include time to attain ethics committee approval, time to obtain trial permits, time to complete contracts, referral patterns, limited resources at the site, investigator moving and finding the right investigator fee.

Harper & Zuckerman (2006) find successful subject recruitment is inextricably linked to a feasible protocol design and qualified, well-suited, well-managed investigative sites. They identified factors to influence successful recruitment, related to protocol design, investigative site selection and subject recruitment. Factors addressing the investigative site (or participating centre) mainly concerned experience in clinical research, availability of resources, personnel skills and procedures. The role of Clinical Research Associates (CRAs) in managing and patient enrolment was mentioned specifically. External factors such as the regulatory climate and the competitive landscape were identified to also affect study outcomes but recognised as harder to predict or control.

The four factors: past performance, experience, investigative site focus, and historic speed to randomize the first study volunteer, were found by (Getz, 2011) to be promising in regards to predicting centre recruitment. In a later study sponsor and CRO focus on the selection and better management of investigative sites was found to be clearly a major lever to improve enrolment performance (Getz, 2012). Other identified key levers include: simplifying protocol design, expanding (broader outreach) and better educating, improving the accuracy and feasibility of study timelines.

In a study by Schroen et al. (2011) study chairs and statisticians were questioned about accrual influences. No consistent factors to explain accrual difficulties were found, suggesting that reasons for poor accrual are not well understood. This as opposed to factors attributing to accrual success, which they identified to be: perceived clinical relevance, lack of competing trials and a study protocol parallel to normal practice. Also Harper & Zuckerman (2006) linked a feasible protocol to successful patient recruitment, as well as qualified, well suited and well managed participating centres. Additionally, they found the regulatory climate and competitive landscape to affect successful accrual.

Grunfeld et al. (2002) questioned Clinical Research Associates (CRAs) involved in recruiting patients on their views about factors that acted as barriers or facilitators to accrual of patients

into clinical trials. These factors were classified into physician-related, patient-related, or system-related factors. Physicians were seen as important barriers to accrual of patients, because participation of a patient is primarily based on a physicians' decision to recruit. Physicians attitudes towards the trial and suitability of a patient effect recruitment. The patient-related barriers identified by the CRAs were either logistic factors adding stress to already burdened patients or attitudinal based on views towards trials, their physicians' expertise and their disease. System factors were found by the CRAs to have the greatest impact on the ability to recruit patients, due to increasing trial complexity and pharmaceutical/ regulatory requirements in combination with limiting timelines and a lack of centre resources. Although in a later study by Grand & O'Brien (2012) similar clinician, patient and system related factors were identified, they found that communication between physician and patient appeared to be a greater issue than previously reported. Therefore, they concluded clinical behaviour to be the most important obstacle to participation in randomized cancer clinical trials, herewith emphasizing the importance of this human related factor.

A quote from Beck et al. (2004): "*There may be an excellent statistician, a famous group of key opinion leaders who endorse the trial, regulatory agencies that approve of it – but it becomes a never-ending story finding patients for it. The magic triangle of speed, quality, and costs, needs to be changed in a square by adding human nature.*" Multiple factors, either barriers or predictive of success, have been identified as being critical to patient recruitment, yet none are found to be conclusive. This is probably related to the complex nature of conducting clinical trials.

Critical factors in patient recruitment

Before emphasising on the critical factors that are found as challenges in patient recruitment, the importance of timelines is discussed, as slow accrual:

- occurs in the fast majority of clinical trials
- affects study outcome and generalizability,
- delays the availability of drugs,
- burdens sponsor due to increasing costs and resources, and
- shortens the drugs patented life-time resulting in decreased profit time to make up for investments.

Barriers, as well as predictors to successful patient recruitment have been discussed. Summarizing these, the critical factors involved in patient recruitment are grouped into four main categories: Study Design Factors, Management Factors, System Factors and -last, but certainly not least- Human Factors. All factors form a critical part of the complex clinical trial process and affect the actors involved. The categorized critical factors are shown in figure 5.

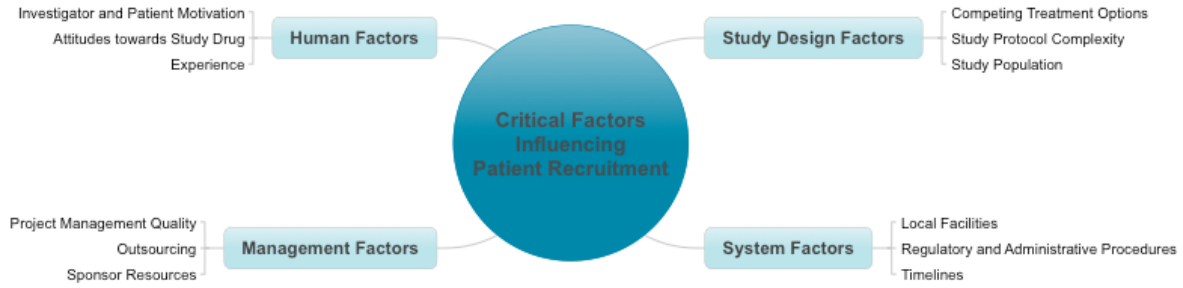


Figure 5: Critical factors in patient recruitment categorized

2.3. System Dynamics

The origin of System Dynamics is found in the Industrial Dynamics research performed by Forrester (1961) in the early sixties (Akkermans & Dellaert, 2005), which has led to a general methodology for modeling dynamic systems by Sterman (Will, Bertrand, & Fransoo, 2002). Sterman (2000, p.4) defines System Dynamics as a "*method to enhance learning in complex systems. Just as airlines use flight simulators to help pilots learn, System Dynamics is, partly, a method for developing flight simulators, often computer simulation models, to help us learn about dynamic complexity, understand the sources of policy resistance, and design more effective policies*". Furthermore, Sterman (2000, p.21-22) explains that natural and human systems have high levels of complexity, characteristics of which are: dynamic, tightly coupled, governed by feedback, nonlinear, history-dependent, self-organizing, adaptive, counterintuitive, policy resistant and characterized by trade-offs.

2.3.1. System Dynamics theory

Although Größler, Thun, & Milling (2008) recognise System Dynamics as a research method to depict, model and simulate dynamic systems, they also discuss the applicability of System Dynamics as a structural theory on the construction of dynamic social systems and propose formal models to be applied as content theory. In System Dynamics as a structural theory it is hypothesised that the structure of social systems is characterized by feedback loops, accumulation processes, and delays between cause and effect. In addition, as a structural theory, System Dynamics makes statements about the principal *interdependencies*[5] of elements in social systems. System dynamics as a content theory is represented by models of the system; variables represent real-world objects and the model contains linkages between the objects as they are hypothesized to exist in reality. Representing the real world in a model, by simulating a virtual world, allows for a double loop learning system (see figure 7), through feedback, and stimulates changes in the mental models (Sterman, 2000 p 87) which are retrieved from mental data in people's heads (Forrester, 1992).

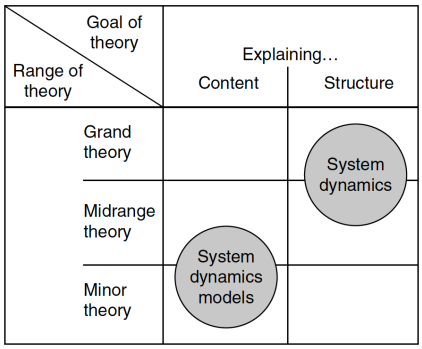


Figure 6: System Dynamics and System Dynamics Models as a Theory (Größler et al., 2008)

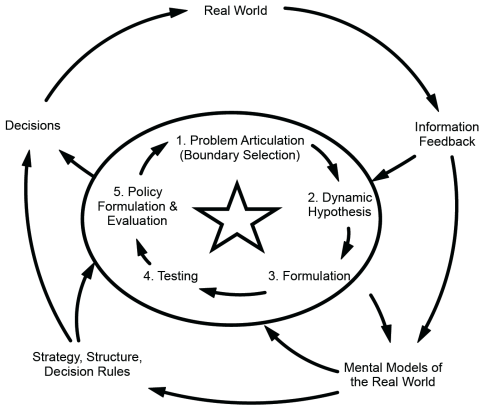


Figure 7: Double Loup learning (Sterman, 2000)

[5] Interdependence, definition: "*The dependence of two or more people or things on each other*" (https://en.oxforddictionaries.com/definition/interdependence)

2.3.2. Relevance of System Dynamics in operation management

The characteristics of natural and human systems identified by Sterman (2000, p.21-22) are well recognised by other researchers in the field of operation management. Earlier yet, in their article on System Dynamics in project management, Rodrigues & Bowers (1996) find that System Dynamics offers a strategic alternative, assuming a holistic view of the organisation with an emphasis on the behavioural aspects of projects and their relation with managerial strategies. They define a project as 'a man-made goal-oriented open system with a tendency to be unpredictable and instable'. Due to project complexity and environments, the subjective human factors have increased their disruptive effect. Where traditionally the project work is based on elements put together, the System Dynamic approach to project management, however, as Rodrigues & Bowers (1996) state, is based on a high-level, holistic view of the project management process and focusses on human factors, managerial policies and the feedback processes that take place within the project system. The three major problem areas in operations management Rodrigues & Bowers (1996) address are: project monitoring and control, rework generation and human resource management.
That rarely a study is seen on the effect of trends and patterns of events or data and how they relate to one another, is remarked by Cavana & Maani (2000). This represents a much deeper level of thinking on the interplay ('interdependence') of different factors that brings about the outcomes that are observed and on the 'mental models' of individuals and organizations that influence why things work as they do or should do. 'Mental models' are based on the beliefs, values, and assumptions that we hold, and underlie our reasons for doing things the way we do them (Cavana & Maani, 2000).

Georgiadis, Vlachos, & Iakovou (2005) posit that strategic supply chain management deals with a decision-making problem that effects the long-term development and operations of a firm. These management decisions, that also largely affects clinical research, are: determination of number, location and capacity of warehouses and manufacturing plants and the flow of material through the logistics network, inventory management policies, supply contracts, distribution strategies, supply chain integration, outsourcing and procurement strategies, product design, decision support systems and information technology. They express the need for holistic modeling efforts that capture the extended supply chain enterprise at a strategic level and found that has also been recognized by industry and academia. The Systems Dynamics theory is deemed suitable for this kind of research; therefore, they have adopted the System Dynamics methodology as a modeling and analysis tool for their research in a food supply chain.

In relation to usage in the field of operation management Akkermans & Dellaert (2005) refer to a previous article from Sharman (1984) for reasons when they explain the importance of supply chain management as a relevant part of operation management. According to Sharman (1984) mastery of logistics has become an essential ingredient of competitive success in an era of shrinking product life cycles, proliferating product lines, shifting distribution chains and changing technology. Akkermans & Dellaert (2005) themselves add a fifth reason: increased organizational complexity, because supply chains more recently have been cut into pieces and diversified in all sectors and regions, as a response to increased complexity and risks related

to managing large and complex supply chains. They state that it is necessary for a superior performance in supply chain management to have a better understanding of the complex dynamics that determines the performance of the supply chains and that the insights that the System Dynamics modeling can produce are needed.

Finally, Größler et al. (2008) identify five major areas of application of System Dynamics in operation management: 1) production flow and supply chain management issues, 2) improvement programs in operations, 3) project management issues, 4) new product development, innovations and diffusion, and 5) different production technologies.
In addition to operation management areas, Snabe & Größler (2006) describe in earlier research the usefulness of System Dynamics in supporting strategy implementations, to both refine and transfer the insights and understanding of the underlying strategy forming process.

In summary, the Systems Dynamics theory and research methodology is being identified as an appropriate approach in many areas of operation management. Its contribution is mainly emphasized in models where a complex environment and/or human factors need to be taken into account. Additionally, System Dynamics finds strategic purposes.

2.3.3. System Dynamics as a research method(s) in healthcare

Homer & Hirsch (2006) believe that in many cases the challenges of dynamic complexity in public health may be effectively addressed with the systems modeling methodology of System Dynamics. They have found that the System Dynamics approach has already made significant contributions to addressing epidemiological issues, as well as issues of health care capacity and delivery, and patient flow management. One example is a study conducted by (Jones et al., 2006), in which they tried to understand diabetes population dynamics. In this research, a System Dynamics simulation modeling was used to gain a better understanding of diabetes population dynamics and to explore implications for public health strategy. A model was developed to explain the growth of diabetes since 1980 and portray possible futures through 2050. Jones et al (2006) report on simulation experiments with a System Dynamics model developed to explore the past and future burden of diabetes—its morbidity, mortality, and costs. It is suggested that a combination of characteristics may cause intervention impacts look different in the short term than they do in the long term. In conclusion, it is found that System Dynamics simulation modeling and experimentation help diabetes policy planners and other stakeholders to better anticipate the multiple effects of interventions in both the short and the long term.

Health care delivery systems are found to be inherently complex, consisting of multiple tiers of interdependent subsystems and processes. These are adaptive to environmental changes and behave in a nonlinear fashion (Marshall, Burgos-Liz, Ijzerman, et al., 2015). As researchers and health care decision makers either underestimate or fail to consider the interactions among the people, processes, technology, and facility designs, interventions in health care delivery systems need to incorporate dynamics and complexities. Marshall, et al. (2015) state dynamic simulation modelling can be applied as a research method in the complex system of health care delivery through: 1) learning processes by building a model and simulation, 2)

identification of critical functional and relational aspects in complex systems, 3) understanding why a system behaves the way it does as a function of its organization (structure), and 4) shifting paradigms and mental models. Also, it can be used for evaluation of consequences of an intervention, by using "what if…?" scenarios, and be a tool for informing decision makers. Marshall et al. (2015) developed the SIMULATE checklist, consisting of eight elements for identifying the applicability of dynamic simulation modelling.

SIMULATE	Does your problem require:
System	Modeling multiple events, relationships, and stakeholders representing health care delivery processes?
Interactions	Including nonlinear or spatial relationships among stakeholders and their context that influence behaviors and make outcomes in the system difficult to anticipate?
Multilevel	Modeling a health care delivery problem from strategic, tactical, or operational perspectives?
Understanding	Modeling a complex problem to improve patient-centered care that cannot be solved analytically?
Loops	Modeling feedback loops that change the behavior of future interactions and the consequences for the delivery system?
Agents	Modeling multiple stakeholders with behavioral properties that interact and change the performance of the system?
Time	Time-dependent and dynamic transitions in a health care delivery system, either between or within health care system levels or in health status change?
Emergence	Considering the intended and unintended consequences of health system interventions to address policy resistance and achieve target outcomes?

Figure 8: SIMULATE checklist (Marshall et al., 2015)

In the subsequent article by Marshall, Burgos-Liz, IJzerman, et al. (2015), aspects of System Dynamics are described as a dynamic simulation modeling method applicable for strategic and operational problems in health care delivery systems, with a system-oriented perspective and emphasis on dynamic complexity, originating from a deterministic endogenous fixed structure. The exploratory and explanatory approach in System Dynamics offers resolution for homogeneous entities, continuous policy pressures and emergent behavior[6].

2.3.4. Patient recruitment and System Dynamics

Considering the patient recruitment feasibility process, the definition of System Dynamics as given by Sterman (2000, p.4) may be well appropriate in this context, because with the infinite number of potential conundrums, as mentioned by Kibby (2011), gaining a full understanding of which considerations will factor into a successful study, seems an insurmountable task. Buonansegna et al. (2014) also recognize this gap in insight and advise on further research into the interdependencies among the critical management issues identified in their study. These

[6] ***Emergent behavior*** is behavior of a system that does not depend on its individual parts, but on their relationships to one another. Thus, emergent behavior cannot be predicted by examination of a system's individual parts. It can only be predicted, managed, or controlled by understanding the parts *and their relationships*. Emergent behavior is also known as emergence, emergent property, or "the whole is greater than the sum of the parts."
(http://www.thwink.org/sustain/glossary/EmergentBehavior.htm)

interdependencies are not variables that are clearly manageable, but rely largely on complex human factors. In this regard, the theory of System Dynamics and research method may be appropriate to gain further insight. The complexity of critical factors challenging patient recruitment addresses all elements in the SIMULATE checklist formulated by Marshall et al. (2015). Also, the aspects of System Dynamics methods (Marshall et al., 2015) correspond with the complex nature of clinical research, further indicating System Dynamics could be an appropriate method to investigate patient recruitment.

In view of forecasting, Forrester (1992) acclaims this to be essentially a decision-making process, converting past and present information into results to indicate a course of action. The number of variables humans are capable of relating to behaviour is limited and intuitive judgement is quite unreliable. Decision processes may be reviewed rationally, based on forecasting with quantitative data, however this does not take into account the strong social and organisational forces of precedent, conformity, incentives, goals and pressures; and also, these data are reviewed from too great distances.

2.4. Research question

Exploring the context of clinical research, it is evident that patient recruitment is vital in the success of drug research and development (R&D) towards better treatment options for many (oncology) diseases. In R&D strategic planning and managerial decision making, considering the high costs involved, being able to predict the number of patients that can be recruited in a specific clinical trial within a certain timeframe is key. This is especially true in large multi-centre, international phase III clinical trials. However, reality is gaunt, with very low accrual rates and far from accurate predictions. Although the literature on patient recruitment is extensive, so far, no consensus on best practices to address the patient recruitment (feasibility) process has been achieved. This may be due to the many actors and at least as many perspectives from which this problem has been addressed. Yet, all these actors and perspectives play a critical role in the entire patient recruitment process, whereas current methods fall short in combining all of these. Therefore, finding a method for attaining a holistic insight of the critical factors and their effects may contribute to a better understanding[7] of the patient recruitment process, which is imperative to improve study feasibility and patient recruitment itself. This may ultimately result in a higher success rate of the entire drug development system.

Systems Dynamics has been identified as a theory and method to research complex processes, with characteristics as identified by Sterman (2000, p.4). It has the potential to enhance holistic insight into this complex process of patient recruitment, through forming causal loops created by the critical factors and revealing their interdependencies. At the best of my knowledge no

[7] Understanding, definition in the Merriam-Webster dictionary:
***1*:** a mental grasp **:** comprehension
2a*:** the power of comprehending; *especially:** the capacity to apprehend general relations of particulars
***2b*:** the power to make experience intelligible by applying concepts and categories
3: explanation, interpretation

studies have been published on this specific application so far, therefore the primary objective of this study will be to explore a System Dynamics approach as a research theory and method for the understanding and prediction of the patient recruitment process. Thus, the main research question for this thesis will be:

> **(How) Does a System Dynamics approach, based on identifying critical factors, contribute to better understanding and predicting the Patient Recruitment (Feasibility) process in phase III oncology clinical trials?**

After the broad introduction into drug development, (phase III) clinical trials and the Patient Recruitment (Feasibility) process in particular, the research question is further addressed in the continuing part of this thesis. Following an in-depth literature research on the critical factors, a System Dynamics Causal Loop (CL) model is built. Thereafter, empirical qualitative research is conducted to validate the model and to assess values for interdependencies between critical factors as input for a System Dynamics Stock and Flow (SF) model, suitable for simulation of clinical trial scenarios. Results of the qualitative research and the simulations are analysed consequently. Methodologies are being discussed before commencing onto the empirical research. Altogether the analyses are discussed in the final chapter, resulting in answering the research question.

3. System Dynamics Modeling of Patient Recruitment

Understanding the critical factors and interdependences, as well as drivers and effects involved in the patient recruitment process, requires further exploration of the existing literature. This in-depth literature search guides the building process of the System Dynamics model. The categorized critical factors identified in the introduction: Study Design factors, Management factors, System factors and Human factors, serve as the main building blocks, i.e. variables, in the model. Before building of the Patient Recruitment model commences in chapter 3.2., the basic principles of System Dynamics modeling are described in chapter 3.1.

3.1. Elements of System Dynamics modeling

Researchers in the field of patient recruitment have used several types of modeling, as discussed previously. This is primarily focussed on forecasting the recruitment rate and subsequently to refine necessary adjustments based on information during the course of the clinical trial, in order to aid the operational decision making. Quantitative historical and estimated data are being entered into these models to generate forecasting scenarios. System Dynamics however, takes on a different approach. It is conducted as an iterative process to build a model, by engaging system variables, including social forces (categorized as human factors) into the model. The dynamic behaviour of a system will be determined by changes in one variable and the way that causes changes in another (Forrester & Senge, 1980). Additionally, Sterman (2000) emphasizes on the importance of causal loops in representing system structures. It enables capturing hypotheses about causes, elicits and captures mental models of individuals and groups, and communicates feedbacks.

A causal loop model consists of the (inter)connection of dependent and independent variables by arrows denoting the causal influences. The causal links are assigned positive or negative polarities, indicating respectively an increasing or decreasing effect from the dependent towards the independent variable. I.e. in positive polarity, when the cause increases, the effect will also increase, whereas in negative polarity, when the cause increases, the effect will decrease. By connection of variables, balancing (-) and reinforcing (+) loops are identified. In the presence of at least one negative effect, this concerns a balancing loops, provided there is always an odd number of negative effects in the loops, as opposed to the number of even effects (Sterman, 2000).

Although a causal loop diagram may be easier to understand and may therefore be useful for communication of the model insights, Albin (1997) suggests to draw boxes around the stocks (accumulations) in the causal loop diagram, already during initial conceptualization, to have an idea of the stock and flow structure. Each causal loop must contain at least one stock, or the loop would be instantaneous and no changes in behaviour would occur over time. Additionally, Richardson (2011) strongly recommends to force the dynamic building to be endogenous, to enforce circular modeling, because the feedback loops in models are the consequences of assumptions in a closed boundary.

Northridge & Metcalf (2016) propose an iterative step-based approach to build the model, as shown in figure 9. Building the causal loop model represents the second step. The third step is conducted, after including the results of the empirical research, as a validation of the literature input and to assess interdependencies. The latter is used for specification of equations, after the model has been prepared for simulation. The model testing, step four and five are addressed in the scenario analysis.

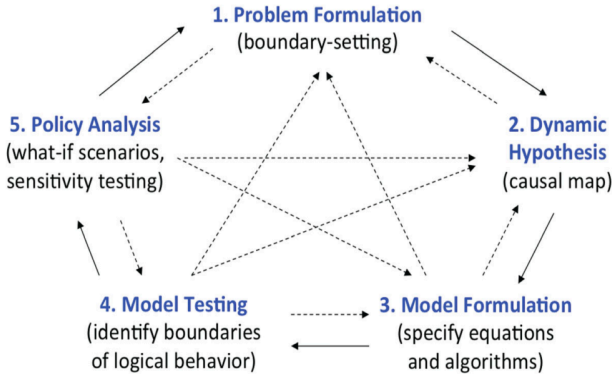


Figure 9: Step-based modeling process (Northridge & Metcalf, 2016)

For building the causal loop model of the patient recruitment process, Vensim® PLE software[8] is used, because this is available in a free of charge student (PLE) version and provides the assets needed for this research.

3.2. Building the Patient Recruitment model

In the process of patient recruitment, the study design factors and system factors represent the starting points, defining the way a project is managed, and ultimately leading to human factors deciding upon recruitment. In this sequence, the critical factor categories are discussed hereafter.

3.2.1. Study design factors

Conducting a clinical trial always starts with a study protocol in which study specifics, as for example rationale, target population and treatment procedures, are described. The Study Design factors: Study Population, Study Protocol Complexity and Competing Treatments each have an important contribution in determining the feasibility of the trial. This paragraph details the contribution of this category of factors.

Study population

Basically, the potential study population consists of the density of the population in the hospital region, as well as the incidence of the particular disease and condition that is being researched. When for example the incidence of the disease under investigation is low, and the population density within the hospital region is low, the chance of including patients will be constraint (Kibby, 2011). Both the incidence and density of the study population in the hospital

[8] Vensim® is industrial-strength simulation software for improving the performance of real systems. Vensim's rich feature set emphasizes model quality, connections to data, flexible distribution, and advanced algorithms. Configurations for everyone from students to professionals. Vensim® is used for developing, analyzing, and packaging dynamic feedback models.
Downloaded from: http://vensim.com/vensim-software/

regions, determine the number of participating hospitals that are needed to achieve an adequate recruitment.

Another limiting factor to the number potential patients may be the specification of a particular condition the potential patient is in. When too many criteria for eligibility of the patient into the trial are defined in the study protocol, this may serve as a funnel for the entire study population, resulting in a negative impact on results and ultimately on drug approval (Beck et al., 2004).

Study Protocol Complexity

Clearly in the past decade there has been an increase in complexity of the study design, as has been demonstrated by Tufts CSDD[9] research (Getz, 2014), see table 1. Increases contributing to complexity are seen in the number of study endpoints, procedures, eligibility criteria, sites and countries. These higher demands, both operational and scientific, affect patient recruitment negatively, as it evolves in the opposite direction (Getz, 2014; Getz & Kaitin, 2012; Getz, Wenger, Campo, Seguine, & Kaitin, 2008; Lamberti & Getz, 2015).

In the summary of a Tufts CSDD Impact Report (Tufts Center for the Study of Drug Development, 2012)) it is noted that 22,3% of all procedures are non-core, and only half of all procedures are supportive of the primary and important secondary endpoints of phase II and III clinical trials. Translated to budget this means that a substantial part is spent on extraneous data.

Design Characteristics (All Values are Means)	**2002**	**2012**
Total number of endpoints	7	13
Total number of procedures	106	167
Total number of eligibility criteria	31	50
Total number of countries	11	34
Total number of investigative sites	124	196
Total number of patients randomized	729	597

Table 1: Increased complexity of a typical phase III study protocol (Getz, 2014)

This phenomenon is attributed to the fact that more and more stakeholders have an influence on the protocol design, e.g. scientists, regulatory and competent authorities, operating managers, key opinion leaders, patient organisations, investigators, investors and policy makers (Getz, 2014). Procedures may be added precautionary for regulatory purposes, moreover when it is believed to be of marginal impact on the overall study. However, all added together has led to the dramatic increase in overall study complexity, associated with poor patient recruitment, longer cycle times, and an increase in protocol amendments, which in turn requires extra time for study conduct. Due to this complexity, unanticipated difficulties are highly likely to occur, therefore it is suggested by Campbell et al. (2007) that only flexible and robust trials will be successful.

[9] The Tufts Center for the Study of Drug Development (Tufts CSDD) is an independent, academic, non-profit research group at Tufts University in Boston, Massachusetts to develop strategic information to help drug developers, regulators, and policy makers improve the quality and efficiency of pharmaceutical development, review, and utilization. Tufts CSDD conducts a wide range of in-depth analyses on pharmaceutical issues and hosts symposia, workshops, and public forums, and publishes Tufts CSDD Impact Reports, R&D Management Reports, White Papers and Research Reports, providing analysis and insight into critical drug development issues.
Web: http://csdd.tufts.edu

Protocol complexity may influence investigators and patients on their perspective of requirements for study procedures and timelines, thereby affecting their attitude towards participation (Grand & O'Brien, 2012).

Competing trials

Globalisation of clinical trials have increased the chance of trials engaging the same patient population and they are actually competing for accrual, affecting both study and country performance (Rajadhyaksha, 2010). Several researchers found that trials competing to include the same patient population considerably decline the patient recruitment (Fayter, McDaid, & Eastwood, 2007; Gelinas, Lynch, Bierer, & Cohen, 2017; Harper & Zuckerman, 2006). Reversely, Schroen et al. (2011) found a lack of competing trials to be an important predictive factor for successful accrual in clinical trials. Gelinas et al. (2017) argue that it is of ethical importance that centres intentionally prioritise clinical trials, therewith minimizing the number of non-completing trials. They consider fairness of this approach towards several stakeholders, i.e. participants, investigators and funders, and suggest a prioritising model to be used.

3.2.2. System factors

Local facilities

The conduct of clinical research requires resources to be available in participating centres. These facilitating resources vary from supportive disciplines to diagnostic facilities. Grand & O'Brien (2012) find in their systematic review for clinician "Obstacles to participation in randomised clinical trials", that system factors, described as a lack of resources, are one of the most common factors to decline patient recruitment. Denicoff et al. (2013) noted that institutional commitment and strong leadership was consistently found to be key to successful accrual at the National Cancer Institute-American Society of Clinical Oncology Cancer Trial Accrual Symposium. Physicians with dedicated research teams and backed by a multidisciplinary approach were found to be especially important.

Academic Medical Centres (AMCs) have since long participated in investigator initiated and industry-sponsored clinical trials, which evolved to meet requirements in infrastructure and facilities needed for specific trials (Schuster & Mcgill, 2001). However, because of varied missions and bureaucracies within AMCs, slow responses to sponsor requests are being recognised as a threat. Considering the large investments needed in clinical research, there is an increased emphasis on speed, encouraging industry sponsors to turn to smaller hospitals and private institutions for faster patient recruitment. Schuster & Mcgill (2001) describe one AMC' effort to institutionalize an in-house Center for Clinical Studies, offering Sponsor, Institution and Investigator-oriented support to address challenges in competition, quality control, bureaucratic inefficiency and academic credibility.

In a Dutch study by Levi, Sluiter, Van Leeuwen, Rook, & Peeters (2013) collaboration in patient studies between AMCs and regional hospitals is found to benefit the academic output, measured in 'mean normalized citation score' (MNCS). Dutch AMCs, is reported, have a citation score (MNCS) far above global average. This is clearly lower for the regional hospitals,

however, in collaboration with AMCs the scores were very high. The optimal collaboration appears to be found in AMCs fulfilling an initiating and coordinating role, whereas the regional hospitals are capable of recruiting large quantities of patients (Levi et al., 2013).

Regulatory and administrative procedures

Information on the approval timelines and the specific regulatory requirements is recognised as an important part of a study feasibility assessment (Rajadhyaksha, 2010). Berthon-Jones et al. (2015) encountered in their multinational clinical study, the Altair Study, delays in approvals through either regulatory authority or local procedures. Sponsor delays occurred through late translation of study documents or prolonged review of local documents. Site delays occurred through (dis)ability to prepare an adequate submission package, obtaining signatures on documents and high workload. Significant differences between world regions in time from protocol release to Ethics and Regulatory submission and approval were found. These differences, however, did not predict the total patient recruitment per region.

Nefarma (2012), the Dutch Association for Innovative Medications discusses in the 2012 Monitor Report the potential of clinical research in the Netherlands. An important obstacle, however, are the long timelines for medical-ethical approval of clinical trials in the Netherlands, which is recognised and addressed. These long timelines, which are far beyond the European standard, render the interest of international pharma for Dutch research partnerships to decline. Therefore, this has led, in cooperation with the Dutch regulatory authorities, to implementation of an improved process and guideline for review and approval of multicentre clinical trials.

Timelines to drug approval

In addition to the timelines as described for regulatory and administrative procedures, the time to register a drug and obtain approval before being able to bring the drug to market, also poses challenges. These timelines are particularly important, since it is found likely that patents and exclusivity in regulatory provisions, remain the main core approach for providing industry incentives (Grabowski, DiMasi, & Long, 2015). Therefore, Tenuta, Klotz, & Parker (2014) suggest that the need for understanding risks for the pharmaceutical industry is high, due to lack of productivity, rising clinical development costs and an expected number of patent expirations in coming years. They have conducted an interesting research in prostate cancer, showing that the actual results of pass rates of drugs that successfully transitioned from phase I to phase II, phase II to phase III, or phase III to FDA approval, are significantly lower than industry wide expectations.

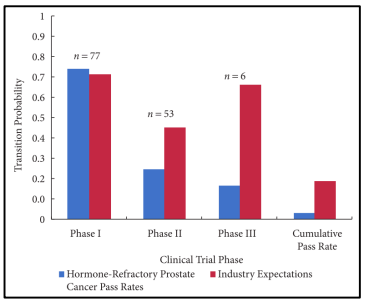


Figure 10: Actual versus expected pass rates of drugs (Tenuta, et al., 2014)

It is realised that the more time it takes to develop and test a drug in clinical research, the less time is left for the drug to be in the market, and earning returns of investment while still under patent exclusivity (Pellegrino & Smith, 2009). This indicates the need for calculations based on adequate predictions, as well as improved methods for enhanced patient recruitment.

3.2.3. Management factors

Sponsor resources

The success of a clinical trial may be largely dependent on the budgetary limitations of the sponsor. For example, small biotech companies have a lower success rate compared to larger companies, due to limited financial resources, experience and infrastructure (Moscicki & Tandon, 2017).

Another Tufts TSDD study (Getz, 2014) was conducted on the work effort required of site personnel for performing procedures as per study protocol and their related costs. These work efforts have increased in the past decade, related to the increasing complexity. Protocols associated with oncology were found to have one of the highest work efforts. However, although sponsors have extended reimbursements, it is not clear how much of the efforts are actually covered. As found by Roche et al. (2002) industry versus government sponsorship did not differ substantially in cost and time required to perform a clinical trial. The higher reimbursements offered by industry sponsors, were assumed to be rightly paid for work delivered. However, low reimbursement is nonetheless recognised as one of the physician barriers to patient recruitment (Kaplan et al., 2013).

Project management quality

Campbell et al. (2007) look at running a successful trial from a business management perspective, and recognise dimensions including marketing, sales and client management. They argue marketing to be especially important in clinical trials, as participants are volunteers that are asked to undergo treatment and assessments, yet may not gain any benefit themselves. Campbell et al. (2007) identify actors for whom a marketing strategy may be useful. These actors are: potential participants and their family, recruiting investigators and colleague doctors and, equally important, the research (nurse) coordinators that play a key role. Also, for trials to be successful, it may be crucial to involve key opinion leaders, as well as R&D departments and other groups that effect feasibility. As a result, they have included stakeholder support and project management into their Value Chain Model to execute clinical trials in order to provide value to medical knowledge.

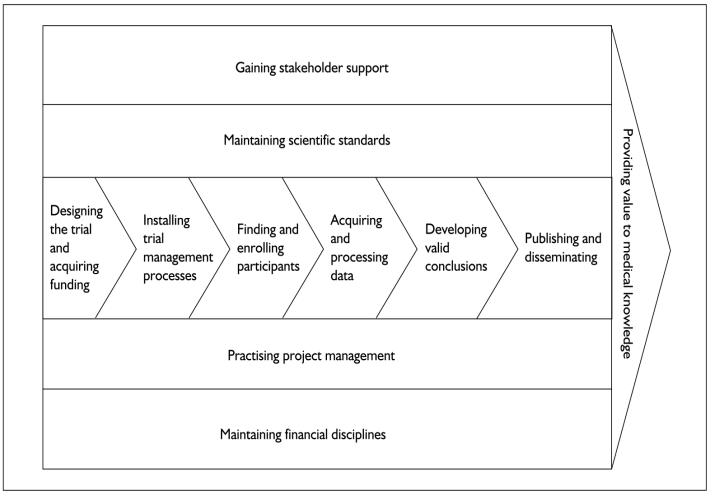


Figure 11: Value Chain Model of clinical research (Campbell et al., 2007)

Fung et al (2003) describe the implementation of a patient recruitment program in a biotechnology company. They have installed a patient recruitment project manager which they claim to be essential to the success of the program by overseeing and coordinating. Also CRO's have reported on better performance of investigative sites, was found by Getz (2011), through pro-active site support.

In recent years Quintiles, a substantial and well known CRO, has introduced the Clinical Trial Educator (CTE), a professional with the primary goal to accelerate patient recruitment (Quintiles, 2010; Rosen, Gallardo, & Sawyer, 2011; Rosen & Smith, 2017). The CTE operates by regular site visits, emails and phone calls to keep the study on the top of the minds of investigators and their team. Furthermore, they are capable to educate on patient identifying and recruitment techniques, assessing referral routes including informing other health care facilities as well as patients, and also by sharing best practices. This is confirmed by other companies, that also have reported on the success of introducing a CTE program (InVentiv, 2014; Kendall et al., 2012).

Outsourcing

Trial sponsors, either pharmaceutical companies or public sponsored trials, use outsourcing to efficiently and effectively manage the clinical part of the drug development process (Bryde & Joby, 2007). In fact, nowadays the majority of clinical trials are being outsourced to Clinical Research Organizations for executing the operational part (Contract Pharma, 2016). The type of outsourcing is distinguished between tactical, relating to short-term projects often based on lack of capacity, and strategic outsourcing, which is usually committed for three to five years. The latter seems to be preferred more and more, as many pharmaceutical companies are developing partnerships with CROs. Especially small and medium sized pharmaceutical companies are reliant on the CROs experience, infrastructure and efficiency (Contract Pharma, 2016; Renwick, 2008). In the 2016 Outsourcing Survey from Contract Pharma a 50/50% division between tactical and strategic outsourcing is reported. Lifecycle management and focus on core competencies are being mentioned as the main reasons for outsourcing. The biggest challenges mentioned in the survey by contract service providers in working with sponsors are the unrealistic timelines, insufficient information and infrequent communication. Vice versa, the sponsors mentioned communication and cultural differences as the biggest challenges (Contract Pharma, 2016).

From an investigator perspective, Roberts, Kantarjian, & Steensma (2016) have published on benefits, risks, burden and opportunities of CROs. They find that CROs have been active in the field of clinical research for 30 years, and by 2020 an estimated 70% of trials will be conducted by CROs. Although benefits are seen regarding faster development times and provision of experienced monitors, the concerns that CROs add another layer of complexity in the already established bureaucracy, are broadly discussed. Specifically mentioned are extensive procedures, low responsiveness, high turnover of (untrained) monitors, as well as ethical concerns. Suggestions are made towards adaptive reimbursement models based on desired output instead of task-based (input) pricing. Bryde & Joby (in 2007) already, presented a product-based approach for planning and management of deliverables. They introduce conceptual and systems thinking to the project management of clinical trials. Their interviews with project and contract managers found willingness in both pharma and CRO to try this approach and also some steps are being taken. However, resistance to the approach from finance departments need to be overcome.

3.2.4. Human factors

Experience

Experience is generally conceived to be related to a better prediction and an investigator and CRAs capability of recruiting the patients, as well as better project management capabilities. Outsourcing of clinical trial management activities to Clinical Research Organizations (CROs) is one example where expertise may benefit the patient recruitment.

Leadership competency profiles of project managers of successful projects with a high complexity, as shown by Müller & Turner (2010), have a high level of competencies related to Intellectual (IQ), Emotional (EQ) and Managerial (MQ) Competency groups. In this context competence is referred to as a combination of knowledge, personal characteristics and skills. These competencies may be acquired, and further developed through management experience and education.

However, although experience is frequently mentioned as a critical factor to positively influence patient recruitment, no specific evidence of this influence is found in the literature. In a survey amongst study chairs and statisticians of the US National Cancer Institute, Schroen et al. (2011) found in their study no association of trial leadership experience or academic seniority with a successful recruitment.

An obvious relationship was found between experience with previous trials and the likelihood of personal involvement towards future randomised trials, in a study with cancer patients on attitudes towards randomised clinical trials. Of the patients with previous experience 77% indicated they were willing to participate in a randomised trial again (Jenkins et al., 2010). In a study by Trauth, Musa, Siminoff, Katz Jewell, & Ricci (2000) this was found to be 55%.

Attitudes towards study drug

It is suggested that patients' personal beliefs or attitudes towards accepting randomisation are not amenable to change (Morrow, Hickok, & Burish, 1994). In the Jenkins et al. (2010) study, as an overall result it is found that 83% of the cancer patients would consider participation in clinical trials. Initially confirming Morrow et al. (1994), almost half of the patients were uneased by the prospect of randomisation. However, when additional information was given, two-thirds changed their minds and would consider participation. The additional information given is in accordance with the required information indicated for the informed consent process, as described in the Guidelines for Good Clinical Practice (GCP) and adapted in (inter)national laws and regulations. A typical finding in this study was the attitude of men, compared to women, to be more open to participation in randomised clinical trials. This was attributed to the fact that men by nature are likely to be less risk-averse than women (Jenkins et al., 2010). Willingness to participate in a clinical trial may differ per age, personal health status, whether a relative or friend is ill and previous experience with trials (Trauth et al., 2000). Furthermore, Trauth et al. (2000) find that, although the general public demands and expects pharmaceutical companies to develop new drugs, they are not aware of the important participative role that same public has in the development.

Personal attitudes of the physician could influence the discussion with patient. If for example a physician would be unwilling to be randomized in a similar situation, this could be cause for refraining the patient from participating (Morrow et al., 1994). This is confirmed by Taylor et al. (1994) who find that some physicians prefer specific trial arms based on personal experience, therefore being reluctant to place a patient on a clinical trial. Also, physicians may feel to compromise their relationship with a patient by undermining authority, decreasing autonomy and conflicting relationship between clinician and scientist. Physicians at a comprehensive cancer centre are more likely to have a positive attitude towards clinical trials (Albrecht, Blanchard, Ruckdeschel, Coovert, & Strongbow, 1999) and see trials as part of the mainstream treatment options routinely offered to patients (Cox & McGarry, 2003).

Provider attitudes and beliefs about clinical trials can be enhanced by education strategies (Denicoff et al., 2013). In a study by Michaels et al. (2015) primary care providers (PCPs) were interviewed on their attitudes towards cancer clinical trials, as they are acknowledged to have an important role in informing and referring patients while having an ongoing and established relationship with patients. It became clear these PCPs have misperceptions regarding the nature and role of cancer clinical trials, which affects their interest to engage in a discussion with their patients. It is suggested that education and communication with PCPs needs to be addressed by trainers and oncologists, as it is shown in some programs to have a positive influence on attitude and behaviour.

Investigator motivation

Study chairs of 248 phase III cancer clinical trials attributed successful accrual to 1) perceived clinical relevance, 2) lack of competing trials and 3) a study protocol designed close to standard practice (Schroen et al., 2011). Earlier yet, Morrow et al. (1994) suggest physicians may be encouraged for cooperation in clinical trials if logistic barriers are lowered, efficient study procedures are adopted and if follow-up requirements comply with routine patient care. Also, additional funding for covering the cost of supportive personnel may increase investigator motivation. Fees that are paid per patient to participating departments in commercial trials may be used to fund departmental research programmes (Cox & McGarry, 2003).

Physicians, however, are often seen as a barrier towards clinical trial enrolment (Williams, 2006). In a summary of literature and market research reports, Williams (2006) mentions lack of awareness of ongoing trial, rigid protocol designs, stereotyping, ethical issues, not their role, lack of time to discuss trials with patients, communication difficulty, concerns about uncompensated staff time, beliefs of inferiority and concerns of burden, as the ways physicians serve as a barrier to patient recruitment. Grand & O'Brien (2012) additionally find that patients are systematically excluded outside of the eligibility criteria, of which a declined offering of participation to older patients is most frequently reported on. Furthermore, they state that, fundamentally, clinicians need to be convinced of the scientific value of a clinical trial.

The perception of increased time commitments negatively affects a physician's decision to recruit a patient in a clinical trial. This found is to be compounded by complex regulatory environment and the including of additional assessments and quality of life components in clinical trials (Grand & O'Brien, 2012).

Patient motivation

Williams (2006) finds patient motivations for participation in clinical trials to be based on: doctor's influence/recommendation, hope for therapeutic benefit, altruism/advance medicine, refusal to give up when no other treatment option is available, provides meaning, accessibility to specialists in cancer care and ability to receive the newest care available.

A very important factor to accrual is identified by Penckofer, Byrn, Mumby, & Ferrans (2011) to be the relationship of the patient to study personnel. If patients have high trust in their physician and see a personal benefit in participation in clinical trials, they are more likely to participate (Grand & O'Brien, 2012). Concerns about loss of control and treatment side effects are indicated as major factors to affect participation (Grand & O'Brien, 2012; Manne et al., 2015).

However, Rosen & Smith (2017) find the biggest barrier to reach recruitment goals is lack of awareness. They refer to patient surveys where it was found that patients were either unaware or unsure that participation in a clinical trial was an option. Also, many patients do not know how to obtain information. Comis, Miller, Colaizzi, & Kimmel (2009) find only 10% of patients were aware that participation in a randomized controlled clinical trial was an option at the time of diagnosis. The willingness of patients to enrol in a study is large though, which is reported to be 75% (Rosen & Smith, 2017). In the same range, Albrecht et al.(2013) found 77% of patients to accept whom participation in a clinical trial was offered.

Comis et al. (2009) find that, although the physician maintains a leadership role in informing patients, patients search for confirming information sources.

3.2.5. Key findings of critical factors

The key findings of critical factors enquire the building of the patient recruitment model and are summarized here, before commencement of building the System Dynamics model.

Protocol design factors

A study protocol is designed to address a specific research question in a specific patient group. The total recruitment of patients into the trial is based on the number of potential patients, i.e. incidence and density. The increasing complexity of study protocol, due to additional assessment and narrow indications, as well as the increasing competition in research, will reduce the number of available patients for one specific trial and influence investigators and patients in their perspectives.

System factors

Local facilities, varying from supportive disciplines to diagnostic facilities, are important to the conduct of clinical trials. The extent of local facilities is shown to benefit successful recruitment. Regulatory and administrative procedures are necessary to obtain approval from regulatory authorities before recruitment may commence. Times to approval vary widely, however this is not predictive of the total recruitment. Timelines to drug registration are very

an important in regards to study sponsoring, as it directly relates to the return of investment, which is found to be the main incentive for drug development.

Project Management factors

Resources from sponsors are required to reimburse for the clinical workload associated with the conduct of clinical trials. It is suggested that reimbursements from sponsors are sufficient, however lack of reimbursement is still mentioned as a limiting factor. From a business management perspective, project management and support is valued to execute clinical trials. Pro-active site support and education are recognised as effective methods and therefore initiatives with patient recruitment project manager and clinical trial educator are explored. Outsourcing of operational activities to specialized Clinical Research Organisations (CROs) is more common than not and is expected to increase. However, a downfall from this approach is recognised in the complexity of dealing with several organisational layers.

Human factors

Experience is frequently mentioned to benefit patient recruitment by management capabilities, although this does not lead to a higher recruitment directly. Experience however, is clearly indicated to influence the attitude towards clinical trials. This attitude is based on personal beliefs; however, educational interventions have shown to lead to a higher positive attitude towards clinical trials, in both patients and investigators. A physicians or patients attitude may influence the decision or proposition to participate. Investigator motivation is indicated to be positively influenced when the clinical relevance is high, no competing treatments exist, the study resembles standard practice and reimbursements are sufficient. However, investigators are seen as the largest barrier towards patient recruitment by not asking patients to participate, due to unawareness, time burden caused by study protocol and regulatory complexity, and personal attitudes. Patients' willingness to participate is large and mainly influenced by the relationship with their physician, although they search confirming sources. Their biggest barrier, however, is lack of awareness that participation in a clinical trial is an option.

3.3. A Systems Dynamics Model of Patient Recruitment

In building the System Dynamics model, the Study design factors (bottom-left) are taken as the base of the clinical trial process having a direct relationship with the potential patients by the Study protocol complexity related to specification of in- and excluding criteria. Study design factors are further connected to the system factors (bottom-right), which represent the current (regulatory) system in which the drug development occurs. Regulations effect in large the timelines, determining the expected revenues. The system factors lead to the actors with which a project is being managed (top side of the model). These are constructed of available resources, inducing managerial efforts to improve patient recruitment. The managerial efforts are focussed mainly towards the Human factors, being central to model and the clinical trial eco-system. These human factors ultimately determine the rate at which patients are recruited into the clinical trial.

To recognise the critical factors and their categories, the original figure 5 has been coloured (figure 13), to correspond with factors in the System Dynamics causal loop model (figure 12).

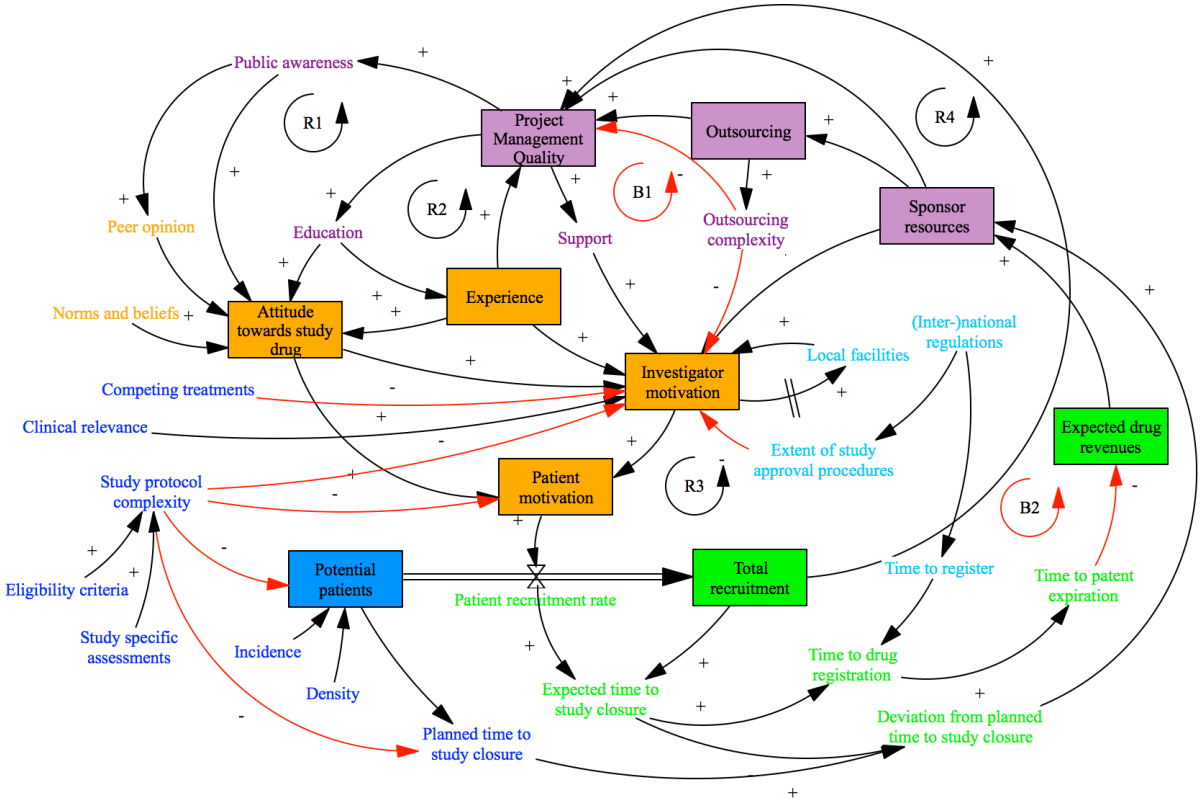


Figure 12: System Dynamics causal loop model

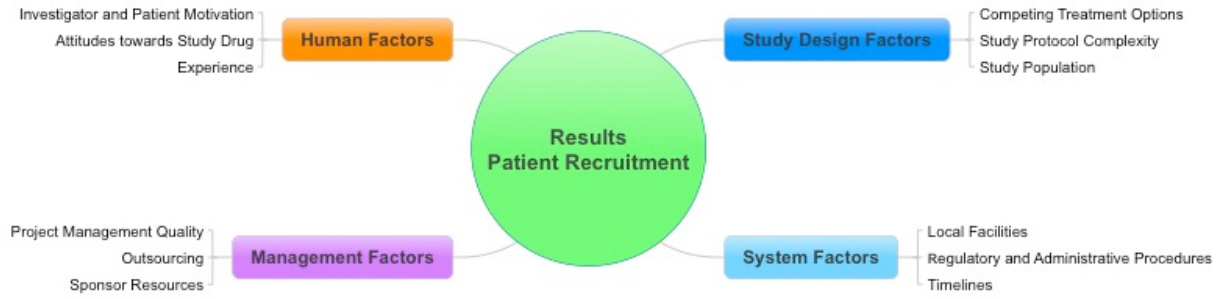


Figure 13: Colored categories of critical factors

3.3.1. Causal loops

In building the System Dynamics model, causal loops are identified to influence the system either by reinforcing (positive) or balancing (negative) interdependencies. The main loops recognised are indicated in the model by **R** (reinforcing) and by **B** (balancing). All loops flow counter-clockwise, inherent to the set-up of the model.

In the reinforcing loops, causing factors are 'reinforcing' or positive variables, which means that when the causing factor increases, this also causes the using factor to increase. The underlined factors in the balancing loops are 'balancing' or negative variables, which means that when this variable is increasing, the using variable will decrease, resulting in a balancing effect in the loop.

Reinforcing loops

R1) Project Management Quality
→ Public awareness → Peer opinion → Attitude towards study drug → Investigator motivation →Patient motivation → Patient recruitment rate → Total recruitment → Project Management Quality

R2) Project Management Quality
→ Education → Experience → Project Management Quality

R3) Investigator motivation
→ Patient motivation → Patient recruitment rate → Total recruitment → Expected time to study closure → Deviation from planned time to study closure → Sponsor resources → Investigator motivation

R4) Total recruitment
→ Project Management Quality → Support / Education / Public Awareness → Investigator motivation / Attitude towards study drug → Patient motivation → Patient recruitment rate → Total recruitment

Balancing loops

B1) Outsourcing
→ <u>Outsourcing complexity</u> → Investigator motivation → Patient motivation → Patient recruitment rate → Expected time to study closure → Deviation from planned time to study closure → Sponsor resources → Outsourcing

B2) Expected drug revenues
→ Sponsor resources → Investigator motivation → Patient motivation → Patient recruitment rate → Expected time to study closure → Time to drug registration → <u>Time to patent expiration</u> → Expected drug revenues

4. Research methodology

The System Dynamics model built from in-depth exploration of the literature serves as a basis for the empirical research into the recognition and estimated effect size of the critical factors, as experienced by experts in the field of clinical research. The System Dynamics model then needs adaption towards a Stock and Flow (SF) model, including changes as necessary that are indicated by the empirical outcome. The empirical data on estimated effect size will be transferred into equations and entered into the System Dynamics model. This final step completes the reversion of the initial causal loop model into a stock and flow model, which is then equipped as a model for simulation. This chapter describes the methodology used, before proceeding onto the analysis of empirical data and simulation.

4.1. Type of research

The primary orientation for this research is theory testing. No literature on the application of System Dynamics into clinical research, and specifically into patient recruitment in clinical trials, has been found, therefore it is concluded this has not been researched in this field so far. However, the application of System Dynamics has been studied in several other contexts, including healthcare, where it has shown to be a useful research methodology for gaining insight in complex health care processes (Marshall, Burgos-Liz, IJzerman, et al., 2015).

The critical factors identified in the extensive literature on patient recruitment are the basis for the Systems Dynamics model that has been built in the previous chapter. These critical factors may serve as both independent and dependent concepts when assessing interdependencies. Within the System Dynamics model, propositions are made on the interdependency, as a positive (reinforcing) and/or negative (balancing) effect, of each critical factor with other critical factors, thus identifying reinforcing and balancing causal loops. The recognisability of critical factors and the propositions on the interdependencies of critical factors that are displayed in the model (figure 5), will be further tested in the empirical part of this research.

Because little is found in the literature on the effect size of interdependencies on the recruitment rate, the secondary orientation of this research will be towards building theory. In complex systems, the outcome of interdependencies can be unpredictable. When various feedback loops, accumulation processes, and delays are combined, this frequently results in nonlinear behaviour of systems (Größler et al., 2008). Thus, by assessing literature and expert indications on impact size and measuring effects through simulation of scenario's, an onset for further theory building may be presented.

4.2. Conceptual framework

Causal loops, containing critical factors connected in reinforcing and balancing loops, are identified from building the System Dynamics causal loop model through in-depth exploration of the literature. However, the effect size of interdependencies which ultimately

influences patient recruitment has not been established so far. The empirical part of this research therefore includes both testing the theory of System Dynamics, as well as further building on theory by assessing interdependencies.

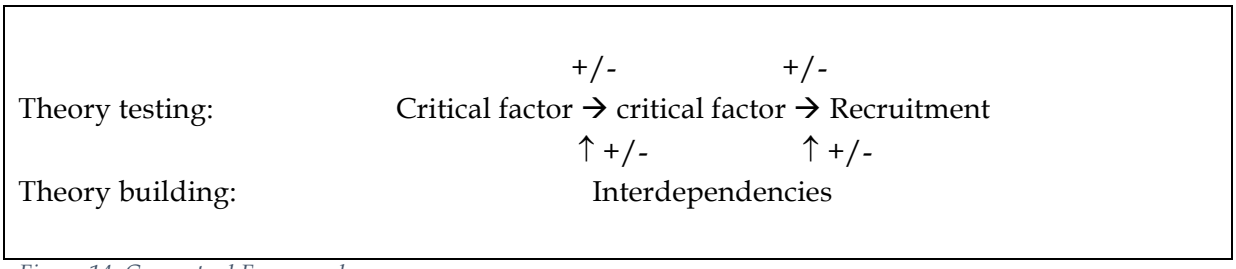


Figure 14: Conceptual Framework

This strategy is being underlined by Voss, Tsikriktsis, & Frohlich (2002), who provide a scheme matching research purpose with methodology. Purposes of building a theory are specified into identifying and describing key variables, linkages between variables and why these relationships exist. An in-depth field study matches a research structure to these purposes, which in this research is adapted as a qualitative interviewing method to address the theory building part indicated in the conceptual framework. For theory testing the purposes described by Voss, Tsikriktsis, & Frohlich (2002) include testing the developed theories and predicting future outcomes. It questions the compliance of the empirical data with the theory and whether predicted behaviour was achieved. One method that is indicated to be used is an experiment, which is being addressed in this research by simulation conducted as a scenario analysis.

4.3. Research methods

4.3.1. Qualitative interviewing in System Dynamics

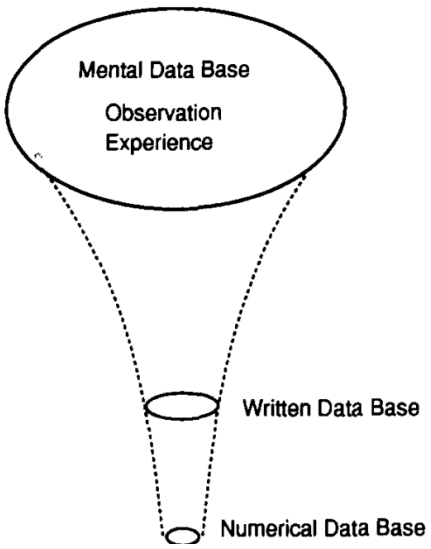


Figure 15: Information data bases (Forrester, 1992)

Forrester (1992) identifies the information sources available for modeling purposes. In the model, he emphasizes the decline of information available in the mental 'database' towards the numerical database. He explains that the 'remembered' information in the heads of humans is far more extensive than information available from other sources. Written information Forrester (1992) identifies as an "excellent source of information about system structure and the reason for decisions". He recognises however that the literature is not easy to use, as no publication has meaning by itself. The literature needs to be pieced together and then behaviour can be perceived by interpretation of policy and structure into a model. This interpretation can only be done by first-hand knowledge acquired by working

and living where the decisions are made. Persons highly knowledgeable of certain parts of the real system are capable to review and verify the structure of the model (Forrester, 1992).

Miles & Huberman (1994, page 10) identify the major features of qualitative data by their focus on naturally occurring events in natural settings, and their richness and holism with potential for revealing complexity. They recognise its main use in developing hypotheses, however underline a strong potential for hypotheses testing.

Methods for interviewing

Interviews are seen as an appropriate method to engage in a social conversation to validate the adequacy of a System Dynamics model, especially when the modeling relies on the qualitative patterns of behaviour (Luna-Reyes & Andersen, 2005). The role of the interviewer is guiding the dialog and clearing confusions about the system. After the interviews data will be analysed looking for patterns, stories and lessons that are cut across the material provided by the interviewees (Luna & Anderson, 2002). Luna-Reyes & Andersen (2005) provide an overview of possible approaches in qualitative interviewing methods suitable for enhancing System Dynamics modeling. They describe cases with a combination of methods for interviewing, including: technologies to use, type of questioning, presentation of model behaviour and structure, recording techniques, data processing and types of data analysis. Northridge & Metcalf (2016) argue these strategies to be suitable for deriving causal relationships.

Trustworthiness

The trustworthiness of qualitative interviews is extensively described by icons (Lincoln & Guba, 1985, page 301-327), and include credibility, transferability, dependability and confirmability. The first and latter may be addressed with triangulation, a technique combining different data collection modes or different designs in an investigation to enhance understanding. Transferability, a type of external validity can be achieved by thick description, describing in detail the phenomenon to evaluate the way conclusions are drawn and whether they are transferable to other settings or situations. Dependability checks may be performed by an external researcher to evaluate accuracy of data and analysis.

Validity of a System Dynamics model

According to Forrester & Senge (1980) the confidence or validity of a system dynamics model is its soundness and usefulness as a policy tool. Confidence can be increased by tests of the structure and behaviour of a model. In their article, Forrester & Senge (1980) provide methods to gain this confidence in the model on which the validity is based. The comparison for model structure and behaviour lies in descriptive knowledge of the real system structure or behaviour. In a Structure-verification test the model should represent a real system. This includes relevant literature describing organizational relationships, or review by persons highly knowledgeable of (parts) of the real system. Mostly this is first conducted based on the model builder's personal knowledge and then extended to include criticisms by others with direct experience from the real system. Another test, the Parameter-verification test, must validate the values to be reasonable and consistent with supporting observations and (conceptual) data. Three other tests are proposed: An Extreme Conditions test, which extends the operation outside the intended region to generate plausible behaviour conditions; the

Boundary-adequacy test, where the boundaries must match the purpose, meaning that it should include all the relevant factors important to the behaviour of interest; and a Dimensional-consistency test, which tests the model's rate equations through dimensional analysis.

4.3.2. Qualitative (semi-structured) interviews

The interviewees

Peers in clinical research have been interviewed to validate the critical factors and interdependencies found in the literature. If the results of the interviews indicate such, the model may be adapted accordingly. A (convenience) sample of ten experts from various backgrounds in the field of clinical research has been included. This variety in backgrounds was deliberately chosen to be able to address the full dynamic and complex nature of the system. The actors, as identified in the introduction, that are involved in clinical research include: clinical trial sponsors, (hospital) sites, sub-contractors (CROs) and patients (Buonansegna et al., 2014). All four actor groups, including regulatory, consulting and investing actors, are represented by the interviewees, whereas all have held positions in diverse types of organizations. This allowed the interviewees to achieve a broad vision and built extensive experience in the field of clinical trials. The interviewees have a minimum of 15 to more than 30 years of experience. Table 2 provides a summarized overview of the interviewees and their expertise. A detailed overview is added as appendix 2.

Table 2: Specification of interviewees

Professional title	**Organizations, current positions and experience**	**Actor experience**
Chief Executive Officer (CEO)	Currently CEO of a small pharmaceutical company and partnering an investment company for oncology biotech start-ups. Extensive experience in starting and managing Clinical Research Organizations (CROs) and pharmaceutical sponsors	Sponsor, CRO, investor
Chief Financial Officer (CFO)	Currently positioned in a small pharmaceutical company as CFO and partnering/managing a Clinical Research Organization (CRO)	CRO, sponsor
Project Director and Program Manager	Currently positioned in a small pharmaceutical company as Project Director and partnering/managing a Clinical Research Organization (CRO)	CRO, sponsor
Professor and Medical Oncologist	Professor in pharmacology, medical oncologist, head of the Clinical Research Unit (CRU) in a specialized oncology hospital; extensive experience as investigator in early phase clinical trials (phase I/II). Chairs the Scientific Advisory Board Oncology of the European Medicines Agency.	Investigator, regulator
Medical Oncologist	Medical oncologist in a specialized oncology hospital, experience as an investigator in phase I/II/III clinical trials. Coordinates a large multicentre Dutch trial	Investigator, regulator
Radiotherapist	Medical Doctor involved in combination drug-radiotherapy phase I/II/III clinical trials as an investigator	Investigator

Professional title	Organizations, current positions and experience	Actor experience
Clinical Research Associate (CRA)	CRA in a specialized oncology hospital, previous experience in several large commercial Clinical Research Organizations (CRO)	CRO, CRA
Clinical Research Associate (CRA)	CRA in a specialized oncology hospital, previous experience in several large commercial Clinical Research Organizations (CRO)	CRO, CRA
Clinical Research Associate (CRA)	CRA in a specialized oncology hospital, previous experience in several large commercial Clinical Research Organizations (CRO)	CRO, CRA
Site Strategy Consultant	(Global) Consultancy specialized in Enrolment & Retention of subjects into clinical trials. Previous experience as Lead CRA/Lead Start-Up CRA	Consultant, CRA
CSU Country Head	Currently working as Country Head CSU for a pharmaceutical company. Has held several project and strategic management positions in pharmaceutical companies and a Clinical Research Organization (CRO). Personal experience as an oncology patient and volunteer representative of patient associations	Sponsor, CRO, patient

Interviewing method

All expert-interviewees were welcomed with an oral introduction to the scope of this research and were presented with written information containing a short introduction, the figure of categorized critical factors (figure 5), a graphic summary of causes and uses (interdependencies) per key critical finding (extracted from the System Dynamics model built in Vensim® PLE software) and finally a picture of the developed System Dynamics causal loop model figure 12), including the coloured critical factors as reference (figure 13), which are based on the literature findings. This written information is added as appendix 1. In a semi-structured manner, by using the written information as base, the interviewees were invited to engage in a discussion to reflect on the identified critical factors and to estimate, based on their experience, the influence of these factors related to the other, i.e. the strength of interdependencies. During the interviews, the written information appeared to be too extended to use in an efficient manner, therefore the figure of categorized critical factors has mostly been used to lead the discussion, whereas the causes and uses-graphs have been used for reference when necessary. The interviews have taken place in the Dutch language, with an average length of one hour and continued until a certain level of saturation had been reached.

The first interview took place with the CRA's in a (focus) group session. This provided an enhanced discussion, whereas the CRA's were able to encourage each other's responses. All the other interviews were taken individually.

4.3.3. Qualitative interview analysis

All interviews are taped and afterwards transcribed and translated to English, into a summary of quotes. All quotes per interviewee are then labelled with the appropriate 'causing' variable

(critical factor) and where valid, the estimated influence on the connected 'using' variable is indicated. Next, relevant quotes are sorted per critical factor, to assume an overall view on opinions regarding the concerning factor. This overview of all quotes is appended in appendix 3. The influence from one critical factor to another, as described by the interviewees, is displayed in a matrix overview (table 3).

The System Dynamics model for patient recruitment has been built partly by personal knowledge extended with an in-depth exploration of the literature, identifying critical factors known to affect patient recruitment. The structural validity, in particular structure and parameter verification, of the System Dynamics model built in accordance with these factors, is addressed by conducting qualitative interviews with representatives of the real system. Vice versa the model, in combination with the interviews and in-depth literature review, provides triangulation of data by challenging perspectives and opinions, herewith addressing the credibility and confirmability to achieve trustworthiness of the qualitative data. Additionally, by detailed description of procedures and findings an effort towards transferability is being made.

4.3.4. Model transformation for simulation

One feature of System Dynamics is the ability to simulate complex processes. This is important when experimentation in real systems is infeasible and simulation becomes the main, and perhaps the only, way to discover how complex systems work (Sterman, 2000, p.38).

Transformation

Binder et al. (2004) consider causal loop diagrams to be an accessible tool for modeling of complex systems, because they do not need formal notation, double lines and system boundary symbols, causing 'cluttering' of the diagram. However, this lack of formal exactness, prohibits interpretation as a quantitative model. Therefore, it is imperative to adjust the initial causal loop model, to transform this into a stock and flow model suitable for simulation.

Stock and flow models generally consist of a combination of stocks, flows, auxiliaries and system boundaries. The latter represents an anonymous source or link (Binder et al., 2004), to ascertain a flow. There are two types of flows; the material flows, corresponding to flow factors and connect only to stocks, and the information flows, which do not point directly at stocks.

The Vensim® PLE -software used for building the causal loop model is continued to be used, as it is also capable of this conversion, by inserting equations to all variables, and enabling it to simulate.

Quantification

The process of enabling a stock and flow diagram to a simulation model is called quantification (Binder et al., 2004). In order to quantify, the model has to be provided with: start and end time for the simulation to run; factor values or equations of stocks, flows and auxiliary (including delays); and time-dependent functions. Peterson & Eberlein (1994) assert that equations are properly written by trial and error, whereas various methods are used to guess

at equations. Mentioned are adopting equations from other models, combine standard mathematical functions and assume optimal behaviour.

When the model is created, one can proceed with simulation. The first simulations are expected to be unsatisfactory, with error messages and unrealistic behaviour, however, after successively modifying equations and repeating simulations, satisfactory behaviour can be achieved.

Behaviour validity

Forrester & Senge (1980) also provide methods to test the behaviour and validity of a System Dynamics model. These tests include seven types: 1) Behaviour-reproduction test, where the model should parallel historical behaviour of the real system; 2) Behaviour-prediction test, which contains observing future behaviour by observing responds while introducing various policies 3) Behaviour-anomaly test, where the model must replicate the real system by arising assumptions and showing implausible behaviour; 4) Family member tests, meaning they would be applicable to similar families of social systems; 5) Surprise-behaviour test, exhibiting unrecognized behaviour; 6) Extreme-policy test, by altering a rate-equation in an extreme way; 7) Boundary-adequacy test, testing model boundaries by conceptualizing an additional structure; 8) Behaviour-sensitivity test, meaning that sensitivity shown by changing parameter values, must also be plausible and consistent with behaviour in the real system.
Also a third type of testing is discussed by Forrester & Senge (1980), which tests the implications of changes in policy. However, these tests are out of scope for this research as it compares the policy changes in the model with corresponding testing in reality.

4.3.5. Scenario analysis

In the patient recruitment model, most independent variables regarding Study Design Factors and System Factors have a constant value, and are therefore aligned to serve as base settings. As situations in real life may differ, the values of these constant variables may be changed to provide a variety of settings as a basis for scenario simulations. The dependent variables are mainly stocks, but may also be auxiliary. The stocks are a result of input and output during simulation. In turn, the stocks may also serve as independent variables to influence others. Ultimately the results of both stocks "Total recruitment' and 'Return of investment' are key in real life clinical trials.

The process of patient recruitment holds several plausible scenarios, depending on assumptions being made on constant variables and the effect size of interdependencies between all dependent and independent variables. Simulation based on real life experiences, require these (constant) variables and interdependencies to vary. Therefore, in each simulation, these variables are set to a certain value in the model, each of which may influence the entire process. Simulation with a number of subsets of the (constant) variables enables experimentation within a short timeframe, which in the case of clinical trials, in real life would not be possible. The subsets used for the scenario analysis are based upon propositions concluded from the literature and qualitative research.

A list of the used variables, including variable type, descriptions and the entered values and equations into the System Dynamics stock and flow model is attached as appendix 4.

The behaviour validity of the model is addressed through emerging several behaviour tests. First a behaviour-anomaly test is performed in finding the right settings and equations needed for simulating a baseline scenario. The assumptions used are based on the estimations made for our planned phase III trial. In this phase, although unintentionally, extreme-policy testing has been encountered in search of the right settings. Thereafter, behaviour-reproduction, behaviour-prediction and behaviour-sensitivity tests are performed based on propositions formulated as outcome of the literature research and qualitative interviews.

5. Data Analysis

Both the interviews and the scenarios of the System Dynamics model are analysed according to the methodology described in the previous chapter.

5.1. Results interviews

In this section, the results of the interviews are analysed and discussed in detail by using the transcribed quotes wherever applicable. A similar order as the literature research discussion on critical factor categories is maintained. a summary of the interpreted interdependencies of the variables (critical factors) in the model, is discussed and provided in a matrix overview. First however, a general analysis of the quotes is given.

5.1.1. General analysis

The total number of transcribed quotes is 546, originating from interviews with 11 experts in the field of oncology clinical trials. In the graphics underneath, the percentages of quotes on causing and using variables are shown. In addition, the graphic of using variables highlights the number quotes for uses specifically aimed at feasibility.

Causing variables

The analysis of quotes regarding causing variables shows that a significant part (19,7%) is addressing Project Management Quality (PMQ). PMQ has a causal relationship (interdependency) affecting Support (SUP, 6.8%), Education (EDU, 2.7%) and Public Awareness (PUA, 5.9%). Sponsor resources (SRE) is the next frequently discussed causing variable (11.4%), followed by Investigator Motivation (IMO, 8.3%).

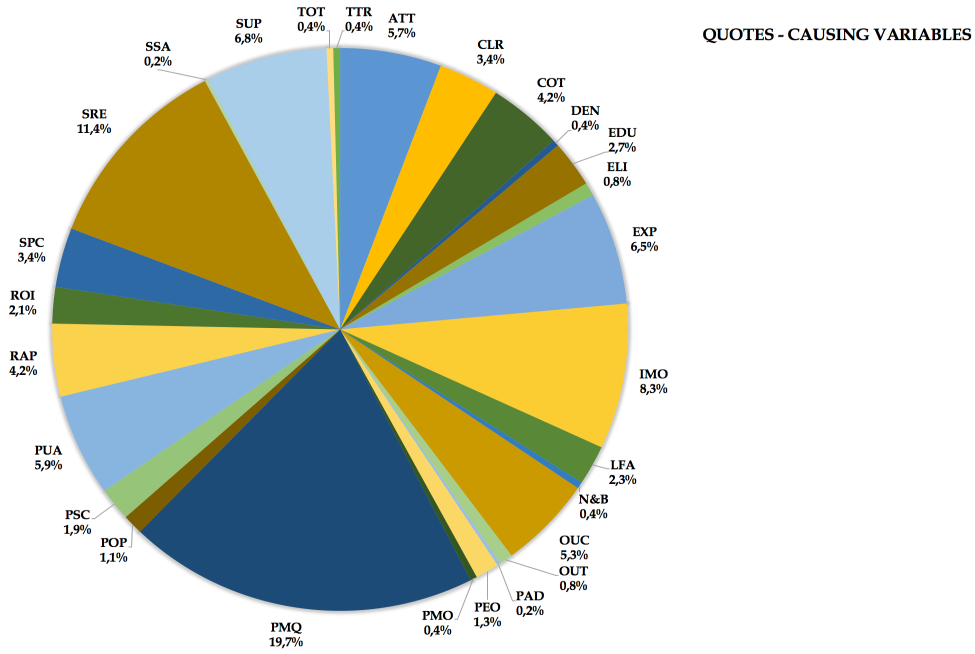


Figure 16: Analysis of quotes regarding causing variables

Using variables

Reviewing the quotes in regards to the using variables, a very significant majority of quotes (39,2%) is aimed at the investigator motivation (IMO). Patient motivation (PMO) accounts for a lesser, yet still significant part (10.3%) of discussed using variables. In this graph, the using variables aimed at feasibility, 15.2% in total, are specified in detail. The significant majority (66,3%) of these feasibility-aimed quotes, originates from the causing variable Project Management Quality (PMQ).

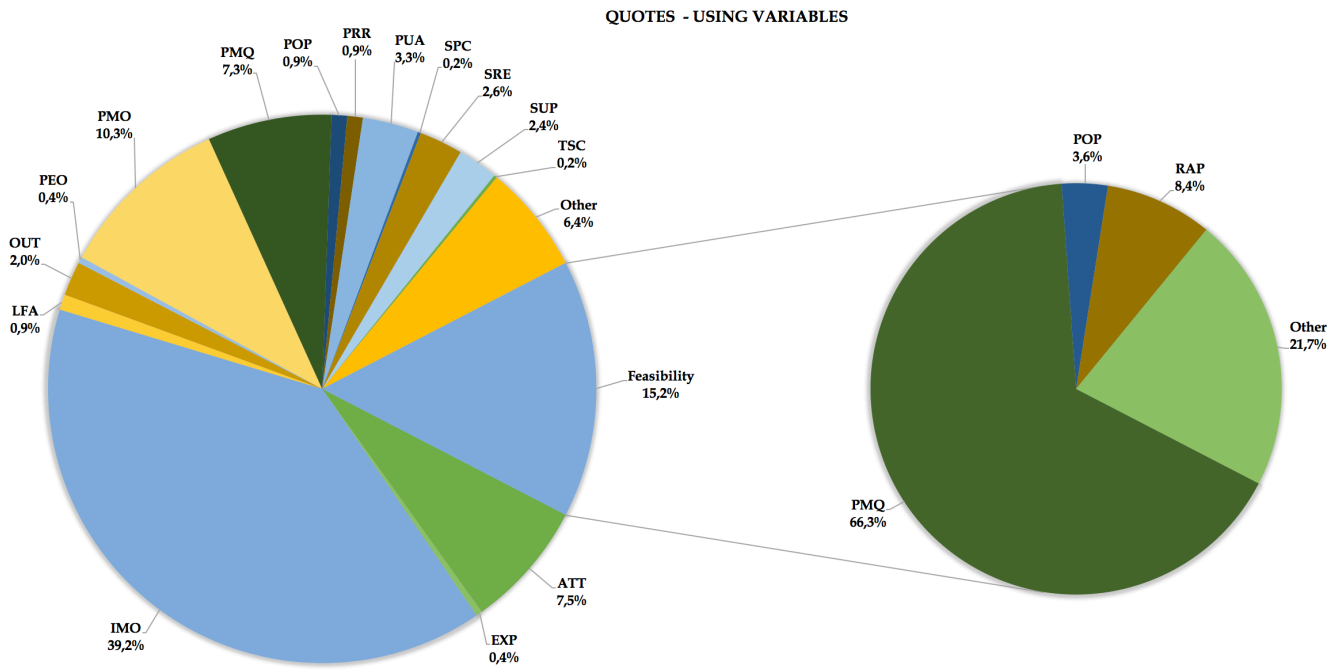


Figure 17: Analysis of quotes regarding using variables

In these graphs, the percentages of quotes on a certain factor are presented. A large number of quotes on a certain critical factor may be interpreted as a subject concerning a central role in the process. This is certainly true for the Project Management Quality (PMQ) and can most clearly be explained by the fact that all interviewees hold a managing position in one or more parts of the entire clinical trial process. The dominant discussion on Investigator motivation (IMO) as a using variable can be explained by the fact that most managerial efforts are aimed at the investigator, as it holds a centralized position in the clinical trial process, as visualized by the System Dynamics model and used as a guidance for the interviews. The number of quotes does however not indicate the type of influence this critical factor has on another critical factor, it merely indicates the experiences and concerns of the interviewees. Some critical factors with a strong influence on the process, may not need much discussion, as they are looked upon as facts.

5.1.2. Interview analysis of Study design factors

The study design is viewed upon as the base for starting a clinical trial. It is compiled of the Study population, the Study protocol (defining research question and methods) and the study exterior. Critical factors originating from the Study design have been discussed with the interviewees, from which the main findings are demonstrated with quotes.

Study population

The Potential population for a specific study consists of the Incidence and Density of the population, as indicated from the literature research. Depending on the incidence and density of the study population, it is decided how many centres will be involved in the clinical trial.

> "*Numbers of* (potential) *patients are naturally decisive for the success of the trial"*
> "*It is better to investigate where your patients are located"*
> "*Large academic hospitals often treat more patients"*

The number estimated during feasibility is mentioned to be often not correct.

> "*But what happens is the so-called 'Lasagna'-effect, suddenly there are less patients during the trial period"*
> "*When there is a new study protocol, at pre-feasibility, the physician will say, well, there are at least 10 patients that will want to participate, and then there are 8 that are actually eligible to participate. And then from the eligible patients 4 decide to participate, and in the end, there are 2 that finalize the study and are evaluable. And then you are lucky"*

Study Protocol Complexity

Study protocol complexity is being recognised by most interviewees as a strong limiting factor, in both Investigator motivation as well as in Patient motivation.

> "*The difference between protocol writer and practice is sometimes very large*",
> "*It is important to keep the study protocol as simple as possible, for example frequent scanning is limiting"*
> "*The site usually has little time, and then is not capable of performing these additional assessments"*
> "*All the fuss that is extra. Less patients are being asked because of that"*

Eligibility criteria are discussed at feasibility, however this is inadequate, when the study protocol is not finalized yet.

> "*Many times, feasibility is done before all eligibility criteria are known, because pharma needs to know as soon as possible how many countries and how many sites are needed"*
> "*The reason recruitment is behind on schedule is because there are inclusion criteria that have not previously been seen, or were not there yet"*

Study protocol complexity is also mentioned in relationship to Investigator motivation and Patient motivation, as well as to implications for the patients that are unacceptable.

> *"for example, when the trial design cannot be explained to the patient, when both the drug and the schedule are randomized"*

"Protocols become more complex all the time and what is asked of patients is more and more. Not being able to do things, attend the clinic more often, get medication that hasn't been tested thoroughly yet"

"Sometimes the patient wants to participate, but then has to participate for half a year and cannot go on a vacation or to work"

"Patients don't like these additional logistics, for some that is really a limitation, less freedom, they have to ask before they can go on a holiday"

Competing treatments and Clinical relevance

The impact of Clinical relevance and Competing treatment was evident to all interviewees:

"Clinical relevance and Competing treatments are both dominant factors, then all other factors are much less relevant"

In regards to Competing treatments (COT), also all interviewees felt strongly about this limiting factor towards Investigator motivation (IMO).

"Competing treatments and investigator/patient motivation works two ways: when another new drug/treatment is available no-one is motivated anymore"

Competing treatments consists of other trials, however also change in standardized treatments is considered important, especially when this is the comparator in the phase III trial.

"Other trials with a better scientific concept, better advantages, more aggressive strategy from sponsor"

"Change in standard of care is very important"

"Sometimes standard treatments are not used anymore, so it may be standard, but not regular"

"check whether the comparator is prescribed in the Netherlands, because if this is not the case, no patient will ever be included in the trial"

Competing treatments is indicated a reason not to participate in a study. This was commented on by investigators, CRAs and pharma.

"If there are two trials you will make an agreement with the first. In principle, I do not include in another phase III trial when there is already one running"

"It is my experience that investigators do take that into account, they always mention it".

"And if it would be the case, they make clear agreements on which trial first or on dividing patients"

"When there are many competing treatments, also pharma decides not to perform the trial"

When assessing the feasibility of a clinical trial, it is pointed out that it is important to inquire on all possible aspects in regards to competing treatment. For example:

"Nowadays you don't ask only for competing studies, but also how many studies are ongoing in the site, compared to the capacity"

"You can see all hospitals are full. Not just one study is open, but sometimes 3-4 for the same indication. So, then you will look for other countries. In the end, it's all about data".

"The problem may be solved, for example in less frequent SCLC, Karposi Syndrome"

On the positive impact of Clinical relevance (CLR) interviewees all agreed.

> *"Participating in the most interesting trial is #1. This leads to Investigator Motivation and may be the most important interdependency"*
> *"Of every 100 studies, there are maybe 80 of which the product is slightly better than standard. In those 20 trials with a product with a high clinical relevance everyone wants to participate.*
> *"In that way, clinical relevance is also very important for patients. Although they do get this information only via their treating physician. Without the physician, the patient wouldn't know about it"*

5.1.3. Interview analysis of System factors

System factors represent another basic setting in the conduct of clinical trials, however mainly concern external factors: Local facilities available in participating sites, Regulatory and administrative procedures, and timelines influencing Time to drug registration. Related critical factors have to be taken into account and may have a relevant influence on the recruitment of patients. This too is recognized by the interviewees, as discussed hereafter.

Local facilities

In feasibility, Local facilities (LFA) are seen as essential for a centre to be able to participate. This is identified in regards to equipment, logistics and local support.

> *"It's a condition, when the infrastructure is necessary for execution of the trial"*
> *"It is crucial there is a good organization onsite, fortunately you can see that change coming",*
> *"Local facilities are important, and also the local support from research coordinators"*
> *"The research nurses in oncology do not directly influence recruitment. They do however influence logistics, that may be viewed upon as local facilities"*
> *"And of course, an investigator needs to have the time and the facilities to be able to participate".*
> *"Limitation in East European hospitals is the facility of the participating centre. If it is sufficiently equipped, usually the best quality is found there"*

The ability to perform a clinical trial without local support is questioned.

> *"In this day and age have a physician perform the study all by him/herself? Then there would not be any time left to consult patients"*
> *"Local facilities are important. When an investigator has no time, and then also has to think about preparing informed consent etc., things will go wrong, Outpatient clinics get delayed etc. So, this is an essential factor"*
> *"Although it is my experience that in East-Europe the physician often does do all the work him/herself, because they earn much more that way. I have seen physicians become a CRA because they would earn so much more, you can hardly imagine…"*

The organisation of research activities differs per participating centre.

> *"There is a difference in organization between the hospitals. In some hospitals for physicians and nurses it is an activity besides the job, however in other hospitals it is really organized very well. That difference is clearly noticeable. And because they are well organized, decisions are made quickly"*

A positive reverse effect, although delayed, is noticed in inducement of the local facilities when the investigator has a high motivation. The effect however, is not very clear.

> *"When a doctor is successful and earns money, and somehow puts the hospital in a positive way to the outside world, yes, then the investigator may have a positive influence on local facilities"*
> *"Although I don't really control a budget as an investigator, a part of the investigator fee is allocated to my name. But that is a very complicated process. You have to be able to guarantee continuity if you hire someone"*

Regulatory and administrative procedures

The Regulatory and administrative (RAP) burden is recognised widely. This factor is considered to have a limiting influence on the total patient recruitment.

> *"There is so much you have to do as an investigator nowadays, and as a pharmaceutical company, regulations have become much stricter"*
> *"You have to fulfil regulations for good clinical practice, good manufacturing practice"*
> *"Regulatory submissions do not only influence the sites, but actually influence the country. When it takes too long, it could mean that a trial almost closes again, which may leave the site with only 3 months for example to recruit patients. Then all planned patients have already been included in another country, or there is insufficient time to recruit the intended number of patients"*
> *"A long regulatory period may be limiting if there is only a short recruitment period, then investigators stop. And sometimes the sponsors do too"*
> *"There are a number of things you cannot influence, like regulations. That is being decided from above"*
> *"...considering this, I don't see an easy way to change this, regulatory wise"*

Discussing contract agreements with the investigative sites are an important administrative procedure that may take a considerable amount of time.

> *"Contracts are a limiting factor also. It can be a very decisive step, this sometimes takes as much as two years. Then by the time negotiations are finished, there are other treatments and studies".*
> *"You may look up the time of regulatory procedures per country, however no-one is going to tell you how long it takes to finish contract negotiations"*

Another aspect of regulations is the time-consuming mandatory training, to be able to cooperate in a clinical trial. One example is the Good Clinical Practice training all study personnel must have had, additionally it is reinforced by several pharma to complete their own training courses per clinical trial.

> *"Sometimes there is no time for GCP training when this is required by a pharma, or when there is insufficient support for regulatory submissions"*

Regulations and not applying to them is exampled to have considerate consequences.

> *"The association for innovative medications reported an issue with a physician, whose site was being audited, although there was no capacity to support that"*
> *"When your research department is not in order, it will suppress you. And all you wanted to do, is do good for your patient. That is hardly manageable"*

Timelines

Timelines are reflected upon in regards to the regulatory and administrative procedures. These timelines may be expanded, however, as opposed to other remarks on the Regulatory and administrative procedures, they are not always limiting to efficient patient recruitment.

> *"Timelines for regulation are often long and yes, that too costs money. Based on existing information you have to find the right mix in countries"*
>
> *"For example, we had a trial with centres in Russia, that takes almost a year to achieve regulatory approval and open the site, but once open they recruited in three months almost half of all patients in the trial. That saved this study"*
>
> "*In a country like Poland for example, recruitment is good, but you have to realize that is takes very long before there is regulatory approval. You really have to consider that".*
>
> "*With new regulations* (including reduction of timelines for review) *in the Netherlands, it may be easier to attract sponsor studies to a small country like ours. Sponsors often look towards the 'Big 5' first"*

The US Food & Drug Administration (FDA) and the European Medicines Agency (EMA) are authorities concerned with guaranteeing the efficacy and safety of a new drug, before approval of marketing the drug. Although they are farther away from the specific clinical trial, they are recognised for scientific advice and improve on drug approval trajectories.

> *"The EMA is an authority that has more distance. The sponsor may ask for scientific advice, that can help. However, this is not done regularly. In the US for the FDA this is also optional, however it would be unwise not to do so. That is different in the Netherlands, where the national and local committees have more authority"*
>
> *"The 'time to register the drug' is shortening, the FDA and EMA have short trajectories", "They have improved in trajectories for target populations, which is good. That is why more research should be performed in elderly. Usually medications that are indicated for elderly, are not being tested in elderly"*

Considering the relevance of timelines in the clinical trial, they are similarly important,

> *"Recruitment in a clinical trial is one of the most relevant factors. In regards of the timelines maybe even the most relevant"*
>
> *"…because studies often take too long and the world around is changing, so the trial becomes less interesting, like "a virtual circle"*
>
> "*When the trial takes too long, there is a negative spiral effect. By the time the conclusion is there, no-one will be interested anymore. Automatically recruitment becomes even more slow"*
>
> "*A pharma company has little time and the site has little time, therefore both spend little time on feasibility. The result is that inaccurate information is generated and used. A lot could be gained there"*

5.1.4. Interview analysis of Project Management factors

Project management (quality) factors are the most discussed critical factors in the interviews and predominantly as causing variables. They represent an important means of managing and coordinating a clinical trial to assure patient recruitment is being completed in time.

Sponsor resources

The Sponsor resources (SRE) have predominantly been discussed in relation to the Investigator motivation (IMO). It is emphasized that study activities should be sufficiently reimbursed.

> *"The investigator fees and contracts are gaining importance, not so much from the investigator point of view, but mainly because of other disciplines that need to calculate their efforts"*
> *"It has a business structure, when the trial consumes more time than a standard treatment, it is only natural that this will be reimbursed"*
> *"Hospitals become more and more business-like institutions. When more time and money is spent on recruitment and the execution of the trial, then choices are easily made"*
> *"Recently an oncology study was denied for the Netherlands because of budget reasons. No matter how good we are"*

It is however stressed, that the reimbursement may not be exaggerated and inflict incentives other than compensation of costs, although this may not always be the case.

> *"You cannot pay exorbitant amounts, because then you get a distorted and unethical incentive, therefore you always pay a reasonable amount, comparable to other studies, because otherwise you will enforce unethical behaviour"*
> *"Money is an important incentive, especially in Eastern Europe, where one patient fee is as much as multiple months salaries"*
> *"As a sponsor/CRO you may choose between key opinion leaders and East-European countries. In East-European countries physicians earn less than CRAs. Earning a part of the patient fee, is therefore interesting"*

Apart from the financial reimbursements, there are important incentives, related to the academic interest and recognition of the investigator.

> *"A study could be financially beneficial, so the investigator may spend some money on own studies. Other studies could be financially less attractive, however have a high academic interest, with which the investigator could co-publish"*
> *"To co-publish is very important to investigators"*
> *"Publications are a relevant incentive, agreements on this are made in most contracts".*
> *"To author articles is important to academic hospitals, for other hospitals considerations are mainly budgetary"*

Financial incentives to pharmaceutical companies, are the base for Sponsor resources, as opposed to public funded clinical trials. Both may however, conflict with resources needed for the clinical trial.

> *"Drug revenue is important for pharma companies. It is the incentive. In case of Investigator Initiated Trials sponsored with public money, financial revenues are not important, only publications"*
> *"With public funding, you can do basic research, but it will not deliver sufficient funding for the full clinical research program that is needed to bring the product to market"*
> *"The problem is now that if something changes, the sponsor doesn't want to pay extra, they prefer to take the risk themselves, because they want to earn as much as possible"*

"So, in the end it is better to reserve more money for contact with the investigator, a CRA, a project manager or the sponsor itself, but yes you have to reserve money, to achieve that motivation"

"To make the sites feel comfortable is most important. If there is no money to do that, then it will become a cascade of triggering events"

Project management quality

The best effects in project management are gained from personal contact with the participating centre. This is important to gain in attention for the trial, good-will and information on restricting factors for adequate recruitment. The relational aspect is of major importance.

"The most important is personal contact, all the other factors you may influence, however yes, the biggest impact has personal contact. That personal contact must assure that you can influence the investigator in the best way possible, and also to find out why a site doesn't recruit. From simple things like persons who do not work well together, to problems with the study protocol design. Everything depends on the information you are able to acquire"

"In oncology, you must try to understand the disciplines. In specific cancer centres knowledge is fairly high level. What is needed? Support. And help to prioritize"

"You can help sites to prioritize, what we can live with and what is really important"

"Influencing as a CRA, is finding the balance how often you contact the site. Make good estimates, dependent on how many patients have been recruited and who you call. It is balancing on what you can and cannot do"

"The enthusiasm peak is usually right in the beginning. Indeed, it is important to keep everyone enthusiast"

"Without a good relationship you get nowhere, things will not work out, because it is all goodwill"

"In real life, you always work with people, for people, to treat people"

Clinical research associates (CRAs) are identified as the most important contact with the site. The project manager is important in overall coordination of the clinical trial.

"Most important is contact of the CRA with the site, not the project manager of the CRO. The CRA is in contact with the investigator and is in the position to motivate the site. The important task of the project manager is to keep an eye on the metrics and signal when necessary"

"Metrics are used for finding causes, in discussion with the site. Maybe a change in the protocol is necessary"

Project management not only concerns the operation of the clinical trial after it has started recruitment, especially the feasibility investigation is regarded as an important measure to assess the recruitment ability of a specific centre.

"My idea is that sites do not realize how important feasibility really is, especially in the start-up phase, because it has no use including in a study for which you are unable to recruit patients, then all it takes is time"

"I have experienced a few times that during the selection visit the in- and exclusion criteria are discussed and it is said that its clear, until you go through them during the initiation visit, and then it is said " oh no, I don't see these patients. And then I think: Where did this go wrong?"

Support

Support is identified to be the most direct and adequate tool to influence investigator motivation.

> *"Support, I think, is very important in general"*
> *"The CRA should be a person who helps the site. You could check a few things less, to check others better in order to improve recruitment"*
> *"Support may be given during monitoring visits, these are motivational visits. Take (educational) materials, combination of means"*
> *"It is important to have one contact person at a CRO. Not be slow in responding, but be supportive"*
> *"You will have to support very much and make sure you have good equipment. And professionals who know what it is about, that really engage"*
> *"My expectations of a CRO is that it has to be practical. For example, one time they did not want to provide a stock at the pharmacy. They assumed a 3-week delivery period, but that is not always right. That was a problem"*

Support is also based upon good relationships with the investigative centre.

> *"If you invest in visiting the site in the beginning, that is very important for the commitment of a site"*
> *"Our CRAs have very good relationships with the hospitals. They even receive wish cards from the hospitals they visit, in case of festivities or illness"*
> *"I always say: TLC, Tender Loving Care for the investigator. Make sure they have all the materials, make sure they are trained, and make sure that there are not too many vendors. And if you do provide materials, make sure they work well"*
> *"What we want is almost impossible of course. That is an experienced person, who responds at the right time, without bothering to much and asking too much attention. Of course that doesn't exist"*

Education

Education is discussed as a method to inform patients and investigators on the clinical trial and also deemed important to change perceptions.

> *"By education, I think, and giving insight in clinical studies, what it means and that it is not only pharma earning money over the backs of patients. By engaging in this mind-set, by being enthusiastic, I think you may reach much more patients"*
> *"With education, you may break habits"*

There are several methods to educate patients, investigators and study professionals, although there are regulations on what you are able to provide patients.

> *"We then provided supportive materials, and a video. Many kinds of materials are possible, also websites, etc. Most large CRO's have a separate department for that, specialized in patient recruitment. However, it really depends on budgets"*
> *"When they don't see you, they don't think of you, newsletters help to remember, its usually useful for research nurses. Keep them informed of inclusion criteria*
> *"Also from the government more education is needed, with films, videos on YouTube, etc."*
> *"The regulatory authorities are a limitation to inform people. Every regulatory committee in the Netherlands has its own views about informing patients via websites etc."*

"Professionals are maintained by succession planning, make sure your people are trained, including high level training in diseases, so that a CRA can understand at a fairly high level what the diseases are about"

Public awareness is reviewed at in various ways, whereas both advantages and down-sides are discussed.

"Raising public awareness by newspaper articles usually only confuses patients. What is written in the media is often not directed to a certain patient group"

"I remember, after publication of the death of a phase 1 patient in France, we did not accrue a single patient in France for months. And also, the regulatory agencies became panic"

"One example is a centre which had insufficient patients itself. An article in a national newspaper was efficient. This was reported to the regulatory authorities. Advertising is not permitted, but you have to find a way to get patients to come to the hospital"

"Public awareness in clinical trials is something else. Twice I have experienced an incident, which was all over the news. Then you would expect this to influence the trial negatively, however twice we experienced the opposite, we had an increase of participant. This was however mostly in studies with healthy volunteers"

"Public awareness will become very important, this will increase. People will start looking for trials"

"Public awareness can really help. If you are able to make patients aware of a solution for a condition they have. You may hope physicians will at least support and refer, etc."

Outsourcing

Outsourcing has established its position in clinical trials, is seen as a fact. Mostly discussed are the disadvantages related to the outsourcing to Clinical Research Organisations (CROs). Its business concept is indicated to need adaption to more effective methods to overcome the disadvantages.

"Big pharma usually hires some CRO"

"I think physicians rather would have someone from the pharma, then from a CRO. In pharma, you are closer to the development information and physicians liked that"

"As a CRO you are not allowed to visit a physician more frequently, because there is no more time and money to spend"

"If you would count the costs and add an additional 40%, then you may take all the risk as a CRO, that would benefit everyone. Now CRO's are not so bothered"

"When parameters change in the course of the study, you start adding up costs for the sponsor, therefore the risk of the CRO is not so big"

"New concepts as remote-control monitoring and risk-based monitoring brings the CRA even less in contact with the site. On the other hand, sponsors start investing more in web-based solutions, which in my opinion is also counter-productive"

The burden of CROs and some CRAs are discussed in a relational aspect, as well as in bureaucratic and administrative irritations.

"The CRO you choose matters a lot. Some are really terrible. For example, they don't give any support, no personal contact person, dumb and rude. Sometimes reactions are slow, they don't answer. Insufficient support in materials. Communication is over many layers"

"Some CROs are really annoying, then it doesn't matter how hard you try, it is never good enough. Communication may be in a hierarchic manner and not effective"
"More and more the CRAs are adapting an auditor's role, start correcting sites, however that is counter-productive. And then the auditors are becoming even more strict officers"
"then they (CRO/pharma) ask for things that are really unnecessary, you know. It is unrealistic if I have to sign off, when a PK sample was taken one minute after the scheduled time"
"Outsourcing complexity, yes, every time another CRA shows up it is bad for the study, it doesn't matter if it is for the same CRO or not"
"There is a large administrative burden, and it tends to overdo. Sometimes there are even more than 10 systems you have to log into and to maintain"
"So many log-ins for pharma, it makes you crazy. Lab system, regulatory, screening system. It prevents recruitment"

The overall influence of outsourcing complexity, however, is estimated with diversity.

"Important is: do I recognize myself in this work? Does it make me happy? Sometimes CROs are counterproductive in this way."
"Outsourcing complexity is not really of influence to the investigator motivation, mostly viewed at as a necessary inconvenience"
"When in the end all organization is taken good care off, then it won't withhold from recruiting patients, but altogether it takes longer"

5.1.5. Interview analysis of Human factors

Human factors are abundantly discussed during the interviews, indicating the importance, however also the insecurity of this critical factor category.

"Human factors are very important, attitude towards study drug"
"Many human aspects may have an impact on the recruitment rate, therefore we calculate with longer time and a slower rate. Unfortunately, often it has already been discussed with the board before agreements have been made with the people that have to do the work"

Experience

Experience is discussed as an important asset in operations management and also involving peers in the clinical trial, to raise awareness and status.

"If experience helps? Yes, someone who knows the ways, makes sure that everything moves fast and issues get solved"
"Experience is what defines a good or not so good investigator"
"Experience is important. Especially the experience you built with this type of studies and communication techniques. You ask quite a lot of your patients, the way you explain. Like what is extra about a study compared to standard treatment"
"Yes, it could be important to involve a key opinion leader, because then the doctors will be like, yes if that one and that one participates, then I would also like to participate"
"Experience from key opinion leaders are important, because else no other investigators will participate. That is why we usually have a national coordinator, to assure its acceptance in the field"

However, in terms of patient recruitment, it may not always be beneficial to include an experienced investigator.

> *"Experience of an investigator is not always an advantage. They assume they already know everything, because they perform many trials. Less experienced investigators may try harder to perform well"*
>
> *"The best recruiters are often the most unknown investigators, that want to be seen, they try harder than the more experienced investigators"*
>
> *"Experienced people are not necessarily the ones best recruiting, but politically it can be very good. Those are the key opinion leaders"*

Attitudes towards study drug

The attitude towards the study drug is influenced by the norms and values, and related cultural aspects. These are considered unchangeable.

> *"Norms and values are barely changeable; however, they may have influence on the attitude."*
>
> *"Then you get to the human factor, people's character. I think in the Netherlands people are quite critical. It is their right of course, but it means they do not immediately do what the doctors suggests"*
>
> *"In some cultures, patients are not well informed on their disease being cancer. They do get treated, because they are sick, but they don't know exactly what's wrong. Also, their families don't want to bother them"*

Peer opinions are considered important to influence the attitude towards the study drug, of both patients and investigators.

> *"Peer opinions are important as some kind of stimulus, you have to take it into account. It is also important to raise external funding"*
>
> *"Peer opinions are very important, also for the general perception. Take for example immunotherapy, all patients ask for that treatment since it has been in the news"*
>
> *"Peer opinions are definitely important to the investigator"*
>
> *"In any case attitude has a large impact on investigator motivation"*

Means to influence the attitude towards the study drug are discussed, which varies from transferring enthusiasm, patient associations, websites and even commercial initiatives to actively contact patient and inform them on the possibility of participation in a clinical trial.

> *"When you are enthusiastic yourself, you transfer that enthusiasm on someone else. Therefore, that also influences the patient. That is why you check the Informed Consent procedure during feasibility"*
>
> *"That is seen more and more, that patient associations try to get information and explain on treatments, also on trial. The more information you can provide, the better it is, that also prevents patients form hearing incorrect information"*
>
> *"The breast cancer association has a scientific committee. They see so many requests coming in, that they can hardly keep up with it. In the US, there are so-called patient advocates, but they are especially trained. This is being done more and more"*
>
> *"Little information is provided by, for example, the KWF (the Dutch public cancer fund), and more is from pharma. It is important to make people aware"*

"A website with all Dutch trial would be a good idea, but that is not present. An earlier initiative still doesn't work well. That would be really nice"

"What I do see is that there are companies now specialized in recruiting patients, they contact patients who could participate (companies like Acurian and I-clusion). They will search the Electronic Patient File of the hospital. If patients are positive about participation, they will be referred to the investigator"

"My current job is mainly to start a campaign to recruit patients. We contact patients, and when they agree we will refer them to an investigative site. We are a funnel in patient recruitment. In fact, that is not being used in oncology studies yet"

Investigator motivation

Discussed is the motivation for the investigator to participate in a clinical trial. The most important motivation is the clinical relevance, as well as an intrinsic motivation to engage in clinical research. There is however a limitation as to how much an investigator is able to perform.

"Mostly the enthusiasm of the investigator him/herself counts. I have experienced that in one arm it was noticed that patients did better, so investigators became enthusiastic themselves"

"We are very study minded, however the request has to reach the right person. That is kind of in between a system and a human factor"

"To me especially the subject has to be interesting. What is the aim? It has to fit into my research area

I would rather have several studies within the same subject, then you get more experienced in this particular area"

"As a young physician, I very much wanted to participate, but only when I grew older I realized there are only so much hours in a day, and that I can make 10 choices for things I should do √ And all of them are good for science and for the future and for patients"

"But there are so many that I have to reject. It is very personal what exactly you reject and what you actually do"

"The consideration is usually how much effort you have to put into it, and how much do you gain with it, and how much effort and gain it is to your team, your colleagues?"

The financial incentives for investigators motivation to improve patient recruitment into the clinical trial is limited. For ethical reasons this should be based to provide the best care for their patients.

"However, there is only a limited field in which you can operate. You cannot oblige something, you cannot set goals, well yes you can, but you cannot insist on these. That is not possible, it is a good thing that physicians are free to make a choice"

"The only direct financial incentive you may give in regards of recruitment is the investigator fee, that is however fairly standardized, so therefore, as I see it, is it not really an incentive"

"And that is ethically unacceptable, there is no way you may trigger a physician to include a patient in a clinical trial, while this patient may be better off in another study or standard treatment. Your financial input, because of this, is relatively limited"

"The way I look at it, the physician should participate because he/she believes in the product, and has the feeling it makes a difference for his/her patient. If the physician doesn't have that feeling, then maybe the product is not worth all the effort. In the end that same doctor must be willing to prescribe."

Apart from the motivation of the investigator, it is necessary to take other stakeholders into account, for example the trial nurses, referrers, and other care providers.

"The trial nurses are really very important, they have a pivotal role, often they know more than the investigator, especially in general practices"

"Referral however usually means that you lose your patient. Doctors don't like to do that, so that is a negative incentive"

"In my experience, physicians are prepared to let their patients go elsewhere and they will send the patients records. However, it depends on the physician"

"I have encountered once that patients had given their consent and went to the radiotherapy department for an appointment. Then they came back and withdrew their consent. What happened? Apparently, a radiotherapist did not agree with the protocol and advised against participating"

Patient motivation

The reasons why patients do or do not decide to participate in a clinical trial are discussed, in relationship to the manner information on participation is provided. The influence of the investigator is major in this sense, however a

"Of course, it's also the patient's decision, but they usually do as the doctor says"

"And then we are back at the 'what's-in-it-for-me' as a patient, you get something in return"

"Of course, also patients participate because they think they gain personally"

"In a phase III study patients have an option that they otherwise would not have had"

"It also has to do with how you are being asked. Because this was asked during the consultation and I had to answer immediately. Maybe if it would have been explained in a different way"

"If the information had been available via the patient association, then it would have made a difference"

"Or if the department would have had a research nurse taking the time after the consultation with the doctor to explain everything, with 2 days to think it over, then also it would have been different"

"So, you need someone who takes the time to explain, outside regular consultation time, because dealing with the message in one consultation is to complicated. And then time to consider it, in which you could maybe call someone for additional information"

"Always you have to make sure, that when the trial is finished, no matter how long it takes, that you inform the patients what their participation has contributed. That is very important. Nine out of ten times it is the physician informing the patient, and pharma will provide the information letter"

"Then I think of a website or a portal, where people can ask questions"

5.1.6. Conclusion of interview findings

Overall, the interviewees recognized the critical factors activated into the system, as well as the categorization used. Some critical factors were recognised immediately to have a major effect on the patient recruitment, others became clearer as the discussion evolved. Generally, at first sight, the interviewees were very impressed, and somewhat backed off, by the complexity of the model. However, after engaging into the discussion, for which the easier to

interpret figure 5 of categorized critical factors was mainly used, the interdependencies were validated by the many examples and views the interviewees were able to share. The focus of the discussion was related to the background of the interviewees, as expected. All brought their personal perspective and experiences into the discussion, which was then further elaborated on. During the last interviews, as the information progressively became saturated, attention was drawn more intentionally towards some areas that had not yet been discussed. In addition, several interviewees commented on their interest to review the model after it was finalized, if not for simulation purposes (this had not progressed at the time), at least as a tool to explain the complexity of the system to other stakeholders.

Study design factors

The study design factors are identified to be directly related to estimated and/or slow patient recruitment. Competing treatments and protocol complexity clearly have a negative effect on the motivation of both investigator and patient. Conversely clinical relevance is recognised as a critical factor to have a major positive effect, mainly on the investigator, which is confirmed by all interviewees.

System factors

The system factors are perceived as facts, especially the regulatory and administrative procedures that are enforced by laws and regulations and cannot be influenced. Facilities are deemed necessary for the conduct of the clinical trial, and must be taken into account when assessing centre feasibility. Timelines are recognized as very important, and often prolonged. Efforts are noticed from regulatory authorities to improve their trajectories.

Management factors

The management factors are discussed in respect to feasibility and as means to maintain attention on the clinical trial during the recruitment phase. Support is the major management factor, recognized to have a strong positive influence on the investigator motivation. Opinions differed on the negative effect of outsourcing complexity. By some this is perceived as merely annoying, whereas others consider this a limiting factor on investigator motivation, resulting in slow patient recruitment.

Human factors

The human factors are recognized as most important to the patient for ultimately deciding whether or not to participate. Experience is recognised as a factor required for management purposes, and reinforced when able to involve an important academic peer as motivational factor. Motivation and incentives are discussed, and the 'what's-in-it-for-me' factor appears to be a major driver for both the investigator and the patient.

A remarkable conclusion is the enormous influence of subjectivity, not related to one specific factor, but concerning and influencing the entire system. Many interdependencies are based on inter-relational aspects and creating good will, whereas others are based on estimates resulting from insufficient or inadequate information.

5.1.7. Summary of interdependencies

The interdependencies discussed by the interviewees and afterwards labelled, are presented in a matrix showing the interdependencies between variables (critical factors). In the matrix (table 3), the causing variables are represented in the Y-as, whereas the using variables are represented in the X-as.

Table 3: Matrix of interdependencies

Causing		Using	Patient recruitment rate	Deviation from planned study closure	Estimated Return of Investment	Total recruitment	Expected market time to patent expiration	Expected time to study closure	Clinical relevance	Competing treatments	Density	Eligibility criteria specificity	Incidence	Project is done	Potential patients	Planned study duration	Study protocol complexity	Study specific assessments	Total patients needed	Expected revenue	Local facilities	Patent duration	Extent of regulatory and admin proc	Planned time to drug registration	Time to register drug	Education	Outsourcing complexity	Outsourcing	Project Management Quality	Public awareness	Sponsor resources	Support	Attitude towards study drug	Experience	Investigator motivation	Norms and beliefs	Peer opinions	Patient motivation
Results	PRR	Patient recruitment rate																																			
	PSC	Deviation from planned study closure																										+		+							
	ROI	Estimated Return of Investment																												+							
	TOT	Total recruitment						+																													
	TPE	Expected market time to patent expiration																																			
	TSC	Expected time to study closure																																			
Study design factors	CLR	Clinical relevance																																++			++
	COT	Competing treatments																																--			-
	DEN	Density													+																						
	ELI	Eligibility criteria specificity													-																						
	INC	Incidence																																			
	POD	Project is done																																			
	POP	Potential patients	++																																		
	PSD	Planned study duration																																			
	SPC	Study protocol complexity																																			
	SSA	Study specific assessments															+																				
	TPN	Total patients needed																																			
System factors	ERU	Expected revenue																																			
	LFA	Local facilities																																+			
	PAD	Patent duration																																			
	RAP	Extent of regulatory and admin proc																												-				-			
	TDR	Planned time to drug registration																																			
	TTR	Time to register drug																																			
Project Management factors	EDU	Education																										+				+	+	+			
	OUC	Outsourcing complexity																										-						-			
	OUT	Outsourcing																										+									
	PMQ	Project Management Quality																												+		+		+			
	PUA	Public awareness																															+			+	
	SRE	Sponsor resources																										+	+					+			
	SUP	Support																																++			
Human factors	ATT	Attitude towards study drug																																+			+
	EXP	Experience																										+						+			
	IMO	Investigator motivation	+																		+							+									+
	N&B	Norms and beliefs																														+					
	PEO	Peer opinions																														+					
	PMO	Patient motivation	++																																		

Immediately noticeable is the concentration of influences in the bottom right half of the matrix concerning the Project management factors and Human factors. Within these factors Support (SUP) is highlighted as the single major influence, apart from Patient motivation (PMO), bottom left, which is the final deciding factor determining the Patient recruitment rate (PRR).

Another remarkable observation is the basic and major influence of three Study design factors: Potential patients (POP), Clinical relevance (CLR) and Competing treatments (COT).

5.1.8. Propositions on the behaviour of the system

Based on the abovementioned findings, extracted from the interviews, propositions are formulated to test the System Dynamics model once it has been adapted into a stock and flow model, and equipped for simulation.
These propositions are:

- Competing treatments and Clinical relevance are variables with a major influence on the Investigator motivation, resulting in a significant decrease resp. increase in study duration until total patient recruitment
- Combining negative incentives results in a significant decrease of study duration until total patient recruitment, which is difficult to compensate with managerial incentives

5.2. Stock and flow model of Patient Recruitment

To prepare the initial causal loop model for simulation, adjustments need to be made towards a stock and flow model. These are described in the first part of this sub-chapter. Thereafter, the propositions made, based on the results of the empirical research, are then used as scenarios for simulation.

5.2.1. Adjustments to the Patient Recruitment model

The following adjustments have been made, either related to their interdependency or to the stock and flow modeling technique. Also, some corrections have been made based on progressive insight in the system, after reflections with the interviewees.

- Auxiliary variables are included in the SF-model to complement the flows, i.e. Patent duration, Planned study duration, Total patients needed, Time, Study lateness, Project is done and Number of vendors
- Expected time to study closure is renamed to X time to study closure under current rate (TSC) to better reflect its purpose
- Only Eligibility criteria (ELI) determine the number potential patients, instead of the combined Study protocol complexity (SPC)
- Clinical relevance (CLR) and Competing treatments (COT) are also recognised as major factors by the interviewees, therefore the lines of these constant variable are think, indicating their accelerated effect on Investigator motivation (IMO)
- Experience (EXP) is not maintained as a stock. Although experience may grow, this effect is unclear and unlikely to influence the course of a clinical trial. Experience does however influence several factors and remains therefore included as an auxiliary variable
- Outsourcing (OUT) is not maintained as a stock. Outsourcing is generated from sponsor resources; however, the amount of resources does not determine the number of vendors. Also, outsourcing is common practice nowadays, and is therefore assumed as an auxiliary variable within the flow from Sponsor resources (SRE) towards Project Management Quality (PMQ).

- To define the Outsourcing complexity another variable is added, this Number of vendors. Increases in the number of vendors, increases the Outsourcing complexity (OUC), therewith affecting the PMQ and Investigator motivation (IMO)
- (Re-)actions in project management are based upon deviation from planned timelines, of which the most crucial is 'Deviation from planned study closure' (PSC). Therefore, the interdependency towards PMQ is changed from Total recruitment (TOT) to PSC
- The Extent of study approval procedures is replaced by Extent of regulatory and administrative procedures (RAP)
- 'International regulations' is deleted, as this equation was not similar to both Extend of regulatory and administrative procedures (RAP) and Time to register (TTR). Both are maintained as a constant variable
- Creating Public awareness (PUA) is perceived as being part of managing the clinical trial. Also, the effect of this variable is not clear, therefore it is replaced as stock, by an auxiliary variable
- Expected ROI (Return of Investment) vs the added Estimated ROI, whereas the first is a constant factor assumed at the start of the trial, and Estimated ROI is a stock, with its value based on current timelines
- A delay is added to the reporting of D Deviation from planned time to study closure (PSC) to Sponsor resources (SRE), resulting from the interviews

5.2.2. A System Dynamics stock and flow model

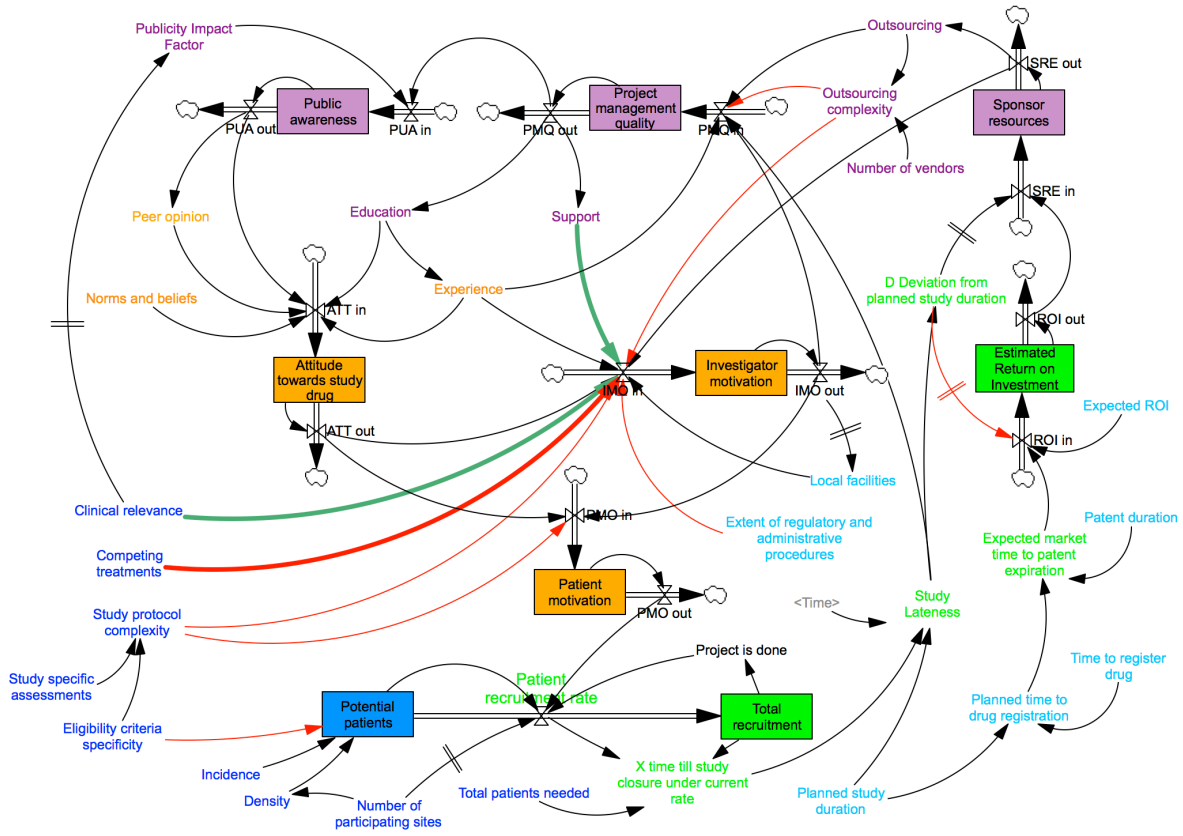


Figure 18: A System Dynamics stock and flow model

5.2.3. Model testing

The adjustments to the System Dynamics model enables a set up for simulation. Equations are added to all variables in the model, dependent on the type of variable.
After entering the equations, the model is tested in a 'trial and error' manner, until the baseline settings are reproductive in regards to the expected outcome. The baseline values of constant variables are set in accordance with random clinical trial assumptions, as indicated in table 4. The specifics of all equations are added as appendix 4.

Table 4: Baseline assumptions in the Stock and Flow model

Abbreviation	*Parameters/ variables*	*Unit*	*Base value*	*Min/max variety*
CLR	Clinical relevance	Dimensionless	1	1-2
COT	Competing treatments	Dimensionless	1	1-2
ELI	Eligibility criteria specificity	Dimensionless	1	1-2
INC	Incidence	Patients/months	45000/12	
NPS	Number of participating sites	Number	80	60-100
SSA	Study specific assessments	Dimensionless	1	1-2
TPN	Total patients needed	Patients	1000	
ERU	Expected revenue	€	10	
PAD	Patent duration	Months	120	80-180
PSD	Planned study duration	Months	36	
RAP	Extent of regulatory and administrative procedures	Dimensionless	1	0.5-1.5
TTR	Time to register drug	Months	10	8-16
VEN	Number of vendors	Number	1	1-3
N&B	Norms and beliefs	Dimensionless	1	0.5-1

In addition to these baseline settings of constant variables, several model reactions have been built into the equations of variables as described in table 5.

Table 5: Built-in variable reactions

Variable Type	*Abbreviation*	*Parameters/ variables*	*Unit*	*Reaction*
Rate	PRR	Patient recruitment rate	Patients/month	An exponential delay is included in the number of participating sites, to anticipate on an irregular start of accrual, due to extended study approval time
Auxilliary	PSC	D Deviation from planned study closure	Months	A delay of six months is taken for information on devation to reach the Sponsor resources (SRE)
Auxilliary	ROI in	Estimated return of investment (ROI in)	€/month	A maximum of 36 months D Deviation from planned study duration (PSC) is built in to prevent the system from reactions to negative incentives

Variable Type	*Abbreviation*	*Parameters/ variables*	*Unit*	*Reaction*
Stock	POP	Potential patients	Patients	In case of increased specificity of Eligibility criteria (ELI), the number of Potential patients (POP) decreases with 5%
Auxilliary	LFA	Local facilities	Dimensionless	For Investigator motivation (IMO) to stimulate an increase in Local facilities (LFA) a delay is included of 12 months
Auxilliary	OUC	Outsourcing complexity	Dimensionless	If the number of vendors exceeds 3, then the output Outsourcing complexity decreases by 50%
Auxilliary	PIF	Publicity Impact Factor	Dimensionless	A delay of three months is included for Clinical relevance (CRE) to have an effect on the Publicity impact factor (PIF)
Auxilliary	PMQ in	Project Management Quality (PMQ in)	Dimensionless	Project management quality (PMQ) reacts to Study lateness (STL) with a 20% increase of activity
Auxilliary	SUP	Support	Dimensionless	Support doubles the output of Project management quality as this factor is indicated to be of major influence
Auxilliary	SRE in	Sponsor resources (SRE in)	Dimensionless	Sponsor resources reacts to a delayed Deviation from planned study duration (PSC) of four months, with an increase of 50% output
Auxilliary	IMO in	Investigator motivation (IMO in)	Dimensionless	Investigator motivation (IMO) reacts with an increase of 50% to Clinical relevance (CLR) and a decrease of 50% to Competing treatments (COT). A decrease of 10% or 20% results from increased study Protocol complexity (SPC)
Auxilliary	PMO in	Patient motivation (PMO in)	Dimensionless	A decrease of 3% or 7% results from increased study Protocol complexity (SPC)

After the stability tests and adjustments to attain baseline settings corresponding with the assumptions (table 4), the propositions formulated as a result of the interviews, are tested in 8 consecutive runs, by changing the number of one or more constant variable(s), i.e. changing the scenario of the baseline environment of a clinical trial, into more complicated scenarios with positive and negative impulses.

5.3. Simulating the process of Patient Recruitment

Lead by the propositions, a number of mostly constant variables were changed. These changes are described as causing variables and their interdependencies.

1) The Study specific assessments (SSA) is increased, causing a 50% raise of study protocol complexity (SPC), which causes a decrease of 10% Investigator motivation. This is expected to cause a minor effect in study duration.
2) The Eligibility criteria specificity (ELI) is increased, causing a 50% raise of study protocol complexity (SPC), which causes a decrease of 10% Investigator motivation; and in a decrease of Potential patients of 5%. This is expected to cause somewhat increasing delay in study duration.
3) Both SSA and ELI are increased, causing doubling of study protocol complexity (SPC), which causes a decrease of 20% Investigator motivation; and a 5% decrease in Potential patients. It is expected to cause further delay in study duration, due to combining these factors
4) Competing treatments (COT) is increased, causing a 50% decrease of Investigator Motivation. In view of the major influence, this is expected to cause a significant delay in study duration.
5) Clinical relevance (CLR), is increased, causing a 50% increase of Investigator Motivation. The major effect of Clinical relevance is expected to significantly reduce the assumed study duration
6) Both CLR and SPC are increased, causing a 30% increase of Investigator Motivation, and a 5% decrease in Potential patients. Due to the balancing effect of combining an increase in both factors, it is expected to have no effect on the assumed study duration
7) Both COT and SPC are increased, causing a 70% decrease of Investigator Motivation, and a 5% decrease in Potential patients. When combining to relevant decreasing factors, it is expected to cause a significant delay in study duration
8) In addition to (7), the activity of Project management quality is increased by 100% when reacting to Study lateness (STL). This causes increases in activity of management factors, which causes an increase in the human factors. As a result of cumulating management efforts, it is expected to decrease the significant delay in study duration, caused by (7)

In table 6 the simulation runs and settings are depicted. The outcome in number of months until total patient recruitment is highlighted on the right.

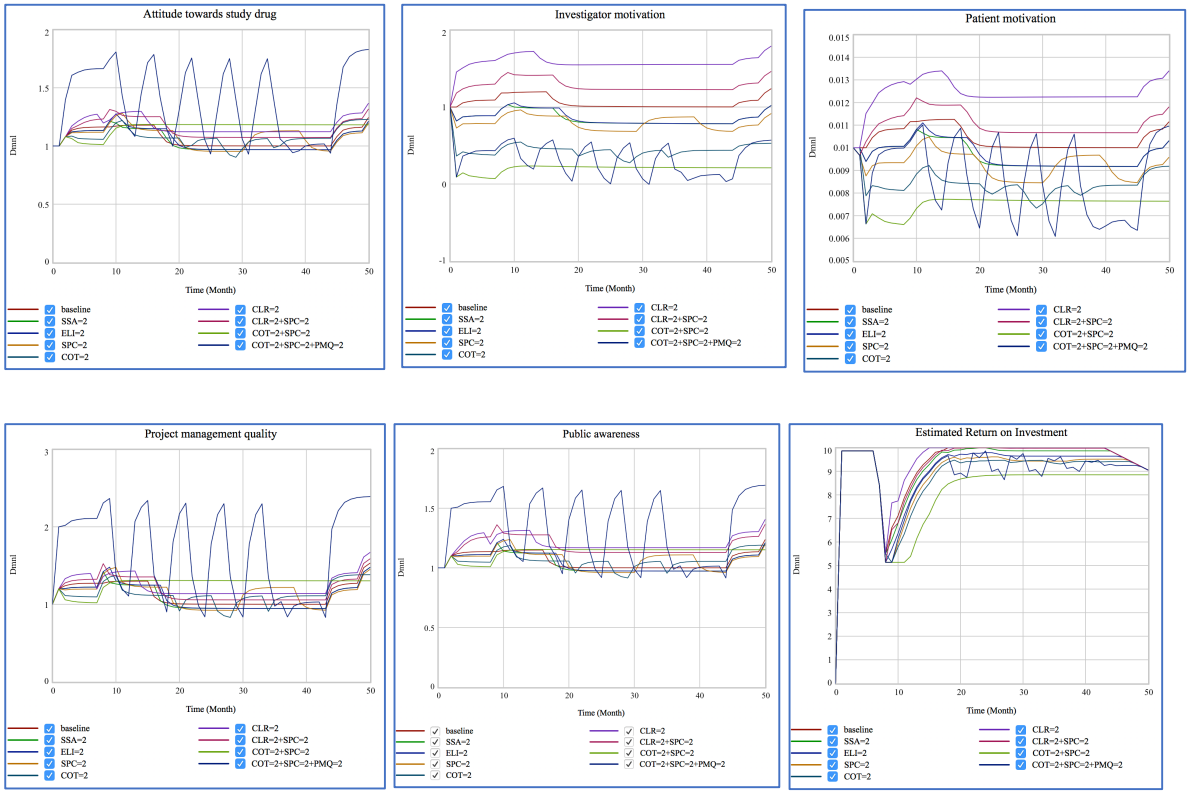
Table 6: Specifications of scenario simulations

Run	Specification	SSA	ELI	SPC	COT	CLR	SUP	PMQ	Study duration (months)
0	***Baseline***	*1*	*1*	*1*	*1*	*1*	*2*	*1.2*	*36*
1	**SSA=2**	2	1	1.5	1	1	1	1.2	37
2	**ELI=2**	1	2	1.5	1	1	1	1.2	39
3	**SPC=2**	2	2	2	1	1	1	1.2	40
4	**COT=2**	1	1	1	2	1	1	1.2	41
5	**CLR=2**	1	1	1	1	2	1	1.2	33
6	**CLR=2+SPC=2**	2	2	2	1	2	1	1.2	37
7	**COT=2+SPC=2**	2	2	2	2	1	1	1.2	45
8	**COT=2+SPC=2+PMQ=2**	2	2	2	2	1	1	2	41

5.3.1. Analysis of scenario simulation

Overall the results of run 1-7, indicate a linear behaviour, consistent with the changes made in the constant variables. As was expected both Competing treatments (COT) and Clinical relevance (CLR) demonstrated an effect that could be similar to reality, although it is noticeable that the reduction in study duration caused by CLR, is smaller than the delay caused by COT. Similar behaviour is confirmed in Study specific assessments (SSA), Eligibility criteria specificity (ELI) separate, and combined in Study protocol complexity, where an increasing pattern of delayed study duration is observed. Also expected, a positive and a negative incentive combined causes little delay in study duration, whereas the combination of two negative incentives demonstrate a further increased, and significant delay in study duration. However, when multiple negative incentives are combined with an increase in project management activity, as was enforced in run 8, the simulation demonstrates a strong non-linear behaviour. This could be caused by irregularities in the model, as a result from impulses caused by equations that are formulated too strong. An option to address non-linearity is by decreasing time steps. This was tested and demonstrated a partial response, as some non-linearity remained present. To further address this issue an expert mathematical approach may be indicated. Although, it may also be suggested that multiple negative incentives are difficult to manage, even with a substantial increase in project management activity.

The outcome of the simulation runs is presented in the graphs underneath.



In the graphs of stocks shown above, Attitude towards study drug (ATT), Investigator motivation (IMO), Patient motivation (PMO), Project management quality (PMQ), Public awareness (PUA) and Estimated return of investment (ROI), runs 1-7 clearly demonstrate a

linear behaviour, consistent with the outcome in study duration. Run 8 is demonstrated as the irregular line, with impulses of activity throughout the course of the clinical trial.

In the graphs underneath, Sponsor resources (SRE) and Total recruitment (TOT) a different behaviour is observed. Sponsor resources demonstrates an irregular course of action, most probably resulting from the delayed response to D Deviation from planned study closure (PSC), with an increase in output. The total recruitment is as it appears, not affected by the non-linearity concerning run 8, as all lines demonstrate a linear S-pattern.

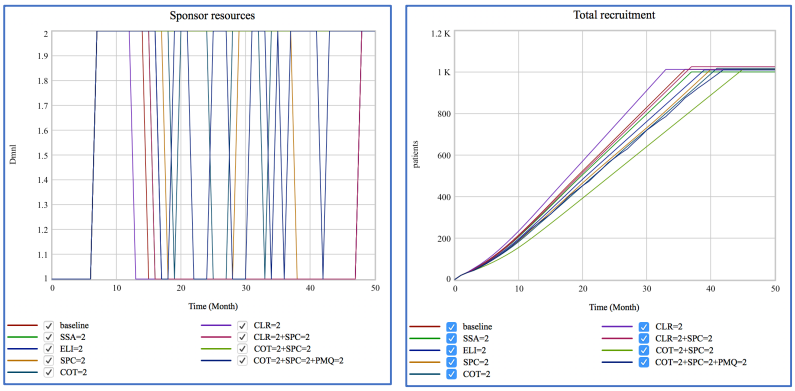


Figure 19: Simulation graphs

Results from the conducted simulation runs, indicate that the propositions formulated from the literature and empirical research appear to be valid.

- Competing treatments and Clinical relevance are variables with a major influence on the Investigator motivation, resulting in a significant decrease resp. increase in study duration until total patient recruitment.

  → This is tested in run 4 and 5 where Competing treatments and Clinical relevance are induced as single influencing factors. In addition, when combined with other negative or positive incentives in runs 6-8, the effect of strong influence is still noticeable.

- Combining negative incentives results in a significant decrease of study duration until total patient recruitment, which is difficult to compensate with managerial incentives

  → This proposition is tested in run 6-8, whereas run 6 and run 7 demonstrate the balancing resp. reinforcing effect of increasing negative effect of combining negative incentives

6. Discussion and conclusion

First, a summary of the research activities is given. In the discussion, important findings are discussed and reflected upon as paradoxes. The research question is then addressed based on the analyses of the empirical and simulation research, followed by the conclusion. Inevitably there are limitations to this study, due to its nature and size. These are discussed, as well as implications and contributions.

6.1. Summary of the research

Clinical trials are an important part of the drug research & development process. Specifically phase III clinical trials have an enormous impact, considering their importance in providing evidence on drug efficacy and safety, their size in number of actors and the related high cost of investments. However, it becomes clear from the extensive literature on the subject, that the current system is far from effective. Drug development costs are rising rapidly, with a low success rate in drugs coming to market. The inefficacy of the system is, at least in part, being related to slow patient recruitment and poor feasibility.

After the introduction, the patient recruitment feasibility process is defined and the current methods for prediction of patient recruitment are described. Further looking into the current status of patient recruitment, it is evident that an accurate prediction cannot be given using these methods, because factors influencing the patient recruitment process are complex, diverse and often subjective. To address this problem, challenges in patient recruitment are discussed, resulting in an exploration of the critical factors that influence the patient recruitment. This diversity of factors is grouped into four main categories: Study Design factors, System factors, Management factors and Human factors.

The System Dynamics theory and research method, because of its applicability in the field of both operations management and health care, is identified to be capable of gaining further insight into the complex process of patient recruitment by addressing the complexity and human alliances in the system. Therefore, this method is adopted as an approach to understanding and predicting the (feasibility) process of phase III oncology clinical trials.

Continuing exploration, through in-depth literature research, of the identified critical factors, has provided the basis of a System Dynamics causal loop model, which is then validated in an empirical qualitative research by engaging in a discussion with field experts. This discussion exposes the enormous subjectivity and complexity of the patient recruitment process, confirming the literature found on this subject. Interdependencies between critical factors have been assessed and analysed, and then used to formulate propositions on the behaviour of the clinical trial system, as well as adapt and reverse the initial model into a System Dynamics stock and flow model equipped for simulation. The propositions are then taken as a base for scenario analysis, to test the model in simulation. The results indicate a linear behaviour, consistent with the changes made in the constant variables. However, with multiple negative incentives, combined with an increase in project management activity, the linearity decreases as impulses flow through the system. Although the latter could be caused by inadequate

equations, for which an expert mathematical approach is indicated, it may also be suggested that multiple negative incentives are difficult to manage, even with a substantial increase in project management activity.

6.2. Discussion

Probably the most important outcome that has been demonstrated by this research is the infinitely dominant role of the human factors in the process of patient recruitment. Clinical research is subject to extensive regulations and administrations that undoubtedly reflects strongly on the workload and costs related to the clinical trial process. However, taking all these 'constant' variables into account, one would suggest the process to be manageable, taken the right measures and precautions. Even though managerial issues are extensively discussed in the literature, no overall view has led to an effective policy to adapt for patient recruitment, both in feasibility, as during the recruitment phase of the clinical trial. The subjectivity related to the human factors is most likely to cause this ineffective situation. However, it is found that in frequently used techniques to predict patient recruitment, this subjective human factor is insufficiently taken into account. This seems surprising, for this factor is in ongoing discussion since many years (Forrester, 1992). Nevertheless, reviewing the current situation in drug development, this urgently calls for an adaption in approach that does include the significant human part of the process. System dynamics, by principle, is a technique equipped for accounting these factors and suitable in health care settings (Homer & Hirsch, 2006; Marshall, et al., 2015; Sterman, 2006). The research that is conducted in the underlying thesis may provide an onset for this way of systems thinking in the specific area of clinical trials and could be beneficial to all actors involved by giving insight in the overall process of clinical trials and guidance to strategic and managerial decisions.

6.2.1. Paradoxes

Although not primarily intended for this research, the System Dynamics approach has revealed many paradoxes ongoing within clinical research, which may in part result from the significant effect caused by the subjective human factors. These paradoxes exist throughout all levels of the eco-system. To not discuss these would undermine the capability of the System Dynamics approach, as well as the relevance of reflection on the current system.

The perception towards pharma as 'money eaters' remains an issue in the general attitudes towards participation in clinical trials, from both investigator as patient perspectives. It is true, pharma has a commercial incentive, however, profits are similar to those of other major industries. The R&D costs to develop one drug are on average more than 2,5 billion dollars (DiMasi, Grabowski, & Hansen, 2016). And profits are decreasing rapidly, with a downfall of more than 50% in the past 10 years (Deloitte Centre for Health Solutions, 2016). One interviewee reflected "*That is what is strange in the discussion on expensive medications. I think about that a lot. Do you still see possibilities in the system?*". The majority of clinical trials are funded by pharma developing their drugs, although fundamental research supported by the public funds may also reach onto (early) clinical trials. At some point, however, commercial

investors and pharma are needed for further development of drugs, due to the high costs related to in particular phase III clinical trials. "*And yes, that is why you should be happy with the system the way it is. That basic research is funded by government money, but when large amounts of money are needed, the commerce can continue. Otherwise the eco-system will not work*". Considering the threats to continuation of the drug development process as maintained in the current system, it is relevant to shift attitudes and emphasize that many treatments would not have advanced, if successful clinical trials would not have been supported by commercial parties (Mills et al., 2006). And although a number of interviewees were employed by commercial parties, they all showed a strong intrinsic motivation for helping patients and improving treatment options, as opposed to a solely financial incentive.

In regards to the high costs related to clinical trials, the role of health insurers and policy makers was discussed. "*Insurances could maybe play a more active role in all of this. The more people are treated within clinical research, it would mean a decrease in costs for the insurance companies, because they do not pay for the care and the treatment then. However, if for example the insurance company would reimburse the care, then some of the study costs would not be on the pharma, and will not be included in the medication costs. Then there may be a shift of costs from pharma towards the insurer; only then there will be less profit, which we will spare, all of us, and I think, well yes fine for me*". Although this might seem as a plausible solution, another interviewee commented "*Once in a congress there was a panel including a patient, who said 'I really want that medication' (this concerned genetic therapy), but then there was someone from the government who said, 'well yes, but we are not going to give that yet, because we don't know the implications'. And the insurance company said, 'but I am not going to reimburse that, because its efficacy is not proven yet', and so they all moved it aside, and then the patient said, 'yes, but I really want to be able to get that medication and I am prepared to take all the risk myself'*". In the current system, a hospital is being reimbursed by the sponsor, for costs related to the conduct of a clinical trial, the so-called 'investigator fee', therewith consuming a large part of the trial budget. However, there is still insufficient local support and time to engage more patients into clinical trials. When health insurers would co-reimburse "y*ou also give more space and means to perform studies. If I look at those small pilot companies, when you look at a study, almost 40% is investigator fees, so if you could spare that, almost two studies can be done. And then there will be more research*". The discussion, however, "*is all about liability, who is liable when things would go wrong for this patient*". This is one issue by far not finished yet, whereas an insight provided by the System Dynamics model may be of aid in the discussion on current policies.

Bureaucracy, both on the side of pharma and on the side of the non-profit organizations causes another type of paradox found to concern the feasibility of a clinical trial. In pharmaceutical companies, to inform strategic level business planning, early, though accurate information on clinical trial feasibility is requested. "*Many times, feasibility is done before all eligibility criteria are known, because pharma needs to know as soon as possible how many countries and how many sites are needed*". This however, leads to unrealistic predictions, because information on estimates of patient recruitment often appear incorrect when the trial protocol is finalized with additional eligibility criteria and study specific assessments, therewith reducing the number of potential patients. Hospitals too, have their share in bureaucracy; when requests to participate in a clinical trial is accepted, substantial time and financial investments, as well as agreements on reimbursement are being made to include the hospital. However, a lack of time, insufficient

support and increasing workload are identified as obstacles for adequate recruitment, leaving one to question the accuracy of answering the feasibility questionnaire and the reason why the hospital intended to participate in the first place.

Additionally, for ethical reasons, hospitals are not in any way to be held responsible for achieving their estimated recruitment. Incentives, other than the best interest of the patient, are deemed unethical, also from a commercial perspective "*And that is ethically unacceptable, there is no way you may trigger a physician to include a patient in a clinical trial, while this patient may be better off in another study or standard treatment. Your financial input, because of this, is relatively limited*". However, incentives as co-authoring publications, are generally accepted. And it is accepted that the investigator and study team will only be motivated, when surrounded with TLC (Tender Love and Care), support and good relationships. "*It always surprises me that so much of this depends on soft factors, whether the research coordinator gets along with the CRA is already a 50% gain. It is about people being prepared to put your study on top*". "*I always say: TLC, Tender Love and Care for the investigator. Make sure they have all the materials, make sure they are trained, and make sure that there are not too many vendors. And if you do provide materials, make sure they work well*". If not, patients will not even be asked to participate. How can that be ethical?

And even paradoxes in human nature play a role, for everybody wants to do 'good' and needs this intrinsic motivation to participate, although everyone in the system at one point or another considers a 'What's-in-it-for-me?'. This is equal to all actors involved in health care, as exampled in the before mentioned reliability issue. From a clinical perspective, it is said: "*As a young physician, I very much wanted to participate, but only when I grew older I realized there are only so much hours in a day, and that I can make 10 choices for things I should do. And all of them are good for science and for the future and for patients. But there are so many that I have to reject. It is very personal what exactly you reject and what you actually do. The consideration is usually how much effort you have to put into it, and how much do you gain with it, and how much effort and gain it is to your team, your colleagues?*". And, "*In that way, clinical relevance is also very important for patients. Although they do get this information only via their treating physician. Without the physician, the patient wouldn't know about it. And then we are back at the 'what's-in-it-for-me' as a patient, you get something in return*".

Researchers have found the majority of patients want to participate in a clinical trial if asked, however, mostly they are not being asked. As Comis, et al. (2003) conclude in their research on "Public attitudes towards participation in clinical trials": "*These results indicate that the primary problem with accrual is not the attitudes of patients, but rather that the loss of potential participants is the result of the unavailability of an appropriate clinical trial and the disqualification of large numbers of patients. The pool of willing patients is further reduced by the reluctance of some physicians to engage in accrual*". It is directed by law to inform patients, before they consent to participation in a clinical trial. Information that needs to be given, is indicated in the Guidelines for Good Clinical Practice (ICH-GCP, 2016). However, it also depends on the way this is being asked: enthusiastic or not, with additional information or not, sufficient decision time or not. "*It also has to do with how you are being asked. Because this was asked during the consultation and I had to answer immediately. Maybe if it would have been explained in a different way*", and, "*When you are enthusiastic yourself, you transfer that enthusiasm to someone else.*

Therefore, that also influences the patient. That is why you check the Informed Consent procedure during feasibility".

The unawareness of patients however, may not solely the responsibility of physicians. Many questions can be asked on this issue. For example: Is there a public responsibility to generally inform patients? How can patients be made aware that progress in medicine is dependent on their participation in clinical trials? Is the public aware of the failure costs caused by poor patient recruitment? What are roles of patient associations? Is there a responsibility for insurance companies? Governments? "*Yes, it goes both ways,* (besides pharma) *also the government has to put more effort into it. Well actually 3 ways: patients also have a say*". "*More and more a change is noticeable in patients, they are more study-minded. Also, patients are becoming more assertive and do some research themselves*". A media-based campaign "Get randomized" in Scotland (MacKenzie et al., 2010) was successful in raising public awareness and understanding of clinical trials. It is suggested that *"Perhaps a concerted national effort is needed to improve public engagement and continue to raise awareness of the importance of clinical research"*. Strategies in active patient recruitment are introduced by a new type of organisations, which may be successful, although this is adding another layer in the already overly bureaucratic system. "*We work together with sites, but are being paid by pharma. We get reimbursed when patients are included. And sometimes we even reimburse the sites for cooperating with us. However, we are still quite unknown. And yes, we are again another vendor...".*

Clearly all the issues and concerning factors discussed, are interdependent of one another, and subject to the prevailing eco-system policies. All actors involved feel the incentive to improve healthcare, whereas each has its own responsibility in some part of the system. Reviewing the system as a whole, may encourage engagement in a joint effort to improve. To end-quote Sterman (2006): "*It requires crossing boundaries between departments and functions in an organization, between disciplines in the academy, between the private and public sector. It requires breaching barriers of culture and class, race and religion. It requires listening with respect and empathy to others – then using these systems thinking capabilities to act in consonance with our long-term goals and deepest aspirations*".

6.2.2. Addressing the research question

Returning to the research question: "**(How) Does a System Dynamics approach, based on identifying critical factors, contribute to better understanding and predicting the Patient Recruitment (Feasibility) process in phase III oncology clinical trials?**", this is addressed in regards to both the understanding and the predicting contributions of the System Dynamics.

Understanding

Using a System Dynamics approach for understanding the Patient Recruitment (Feasibility) process, this research has shown to enable insight and an overall view of the system by gathering an overwhelming amount of information found in the literature and analysed from the interviews, which revealed its many paradoxes. Understanding the manner in which a system operates, can be used for both strategic and operational purposes (Marshall, et al., 2015; Sterman, 2006). Simulating several clinical trial scenarios has shown the capacity of the system

to produce insight in reinforcing and balancing critical factors, and to inform on the effectiveness of (re)actions on the total patient recruitment.

In addition, insight and understanding the system could be very beneficial to a global discussion with all actors and stakeholders related to clinical research. Because, for the current system to continue unchanged is deemed impossible, considering the rapidly increasing costs opposed to decreasing profits. And these profits are, as in every big industry, an important incentive, whereas in the current system pharma companies are still the main enablers of clinical research (Grabowski, et al., 2015). This threat is recognised by researchers, companies, as well as the experts in this study: "*…something has to change in drug development, it isn't much longer feasible this way…"*, and "*… the system threatens to fail, and indeed, patient recruitment is an essential part"* (Deloitte Centre for Health Solutions, 2016; Joseph A. DiMasi et al., 2016).

Predicting

Using a System Dynamics approach for predicting the Patient Recruitment (Feasibility) process, this research has shown that the significant influence of the subjective human factors can be taken into account, whereas no currently used systems are capable in this way. Forrester (1992) finds forecasting to be essentially a decision-making process, in which the results that are based on past and present information, indicate a course of action. However, as stated by Sterman (2006), "*The most insightful model accomplishes nothing if the interface is obscure and the protocol for its use ineffective*", and the converse may be worse when "*a poor model embedded in a potent interface may teach harmful lessons more effectively than ever before*". This research has grounded views and insights, from both literature and interviewing several actors involved in clinical trials, into the System Dynamics model, therewith validating the content of the model.

In regards to embedding the model in a potent interface, this recalls to the requirements as indicated by Barnard, et al. (2010) for a model to be efficient. These requirements are: simplicity, adaption to epidemiological changes, adaption to environmental changes, centre recruitment and ability to inform commissioning decisions. With modest statistical and mathematical background this model is built; also, it requires simple moderations to take into account several 'constant' factors, referring to epidemiological and environmental changes, as well as study protocol specific aspects. Subsequently simulating the model, results in two major steering drivers: 'Total patient recruitment' and 'Expected return of investment'. When additionally built into a user-friendly interface, it may fulfil all requirements indicated. Opposed to the most frequently used unconditional model during the feasibility phase of the clinical trial, which solely provides an indication of the expected recruitment rate or the number of centres needed to participate, this method may gain a more thorough insight, in the consequences of onset conditions.

6.2.3. Contributions and limitations

The contributions of this research to practice and literature are discussed. As in all research, limitations are present. These are discussed in regards to the empirical research technique, as well as to the System Dynamics methodology used in this thesis.

Contributions to practice and literature

Bringing forth a relationship of mental models, attained from literature, empirical research and simulation, provides the opportunity of learning from the modelling process (Northridge & Metcalf, 2016). The model of patient recruitment has demonstrated with the methods used, to provide the opportunity and to gain insight in the complexity of the process and to assess interdependencies between factors, as indicated to be needed by Buonansegna, et al. (2012). Involvement of several actors has provided broad in-depth data to be obtained in the model.

The lack of including the important human nature influencing the patient recruitment process may cause other prediction methods to be unsuccessful, whereas this method of including these factors into the System Dynamics model has shown to be successful. This enquires strategic decision making, by providing a basis for system redesign to improve its behaviour (Forrester & Senge, 1980), which is urged by recent developments (Deloitte Centre for Health Solutions, 2016; DiMasi, et al., 2016)

Another attribute of the System Dynamics model may be the ease with which it can be operated, given the output it is capable of producing, as opposed to other methods that have been used in patient recruitment prediction so far, which either lack in factors to take into account or are too difficult to operate (Barnard, et al., 2010).

Limitations to the empirical research

The interviews that are conducted included several actors in the field of clinical research. The variety of actors was intended to provide a broad scope of visions on the entire system. This may have missed the in-depth view a specific group of actors could have been able to provide. In addition, most interviewees were selected based on convenience; they are resided in the Netherlands Cancer Institute and/or in regular contact with the interviewer, which may have influenced their responses and attitude towards clinical trials in general, as Kaplan et al. (2013) has found physicians in National Cancer Institutions (NCIs) to be more likely to discuss and refer patients for clinical trials, compared to any other practice environment. Reviewing the size of the eco-system reflected upon in the model and the number of actors involved, the sample size may be limited to fully attain all aspects influencing the behaviour.

Another limitation to the empirical research is the single 'interviewer bias', that may have had an effect on the type of questions asked, which is influenced by the interviewers own conceptions of reality. Also, the interpretations of the interviews are conducted by the interviewer. Credibility is advised to be addressed by 'Member checks', i.e. testing data, analytic categories, interpretations and conclusions with members of stakeholder groups (Lincoln & Guba, 1985). This has in part been done by checking literature data with the interviewees, however requesting feedback on the interview interpretations by the interviewees themselves, was prohibited by a lack of time.

Limitations to the System Dynamics research

This research into patient recruitment in phase III clinical trial has resulted in describing and including a substantial part of the entire clinical research eco-system. The first principle for successful use of System Dynamics, Sterman (2000, page 79) indicates, is not to develop a system, but rather develop a model to resolve a particular problem. The problem encountered

leading to this research was the lack of consensus on the practice of assessing patient recruitment feasibility. Reviewing the literature this developed into a detailed exploration of a multifaceted problem, which lacks understanding and predicting capabilities. However, this has led to the pitfall of modeling a complex system. The approach may have been clearer when only parts of the system were addressed.

Several researchers find that System Dynamics lacks the mathematical soundness of other research techniques (Akkermans & Dellaert, 2005; Größler, et al., 2008), whereas System Dynamics is grounded in empirical observations, similar to this research. On the other hand, as found by Rodrigues & Bowers (1996), also in the traditional approaches assumptions are made on the individual elements of the project system, which are perceived to be of minor relevance, and therefore empirical assumptions can easily be made. It is in the System Dynamics approach these individual elements may be encountered. However, incorporating results from other research approaches could have been beneficial to the results.

A final limitation is encountered in part of the validation of the model, whereas the extreme-policy condition test, has not been fully met, due to the non-linear behaviour seen in the final run. Also, the soundness of the method could have been expanded with more extensive and more types of behavioural tests.

6.3. Conclusion

The System Dynamics approach has demonstrated to be capable of providing understanding and predicting patient recruitment (feasibility) in phase III clinical trials and to reveal the complexity and subjectivity of the patient recruitment feasibility process. Four major categories of critical factors involved in patient recruitment have been identified: Study design factors, System factors, Management factors and Human factors. This research provided evidence for the important and dominant role of the human factors throughout the entire system, influencing decisions and actions in all categories. Not taking the important human factors into account, renders those techniques in predicting patient recruitment inadequate.

The extent of information found on patient recruitment, in combination with the results of simulations have highlighted the importance of the Study design factors and the role of Project management factors. Limiting factors in study design have been demonstrated to cause significant delays in planned study duration. Managing these appropriately will induce the need for resources, whereas personal contact and support has been shown to be most effective. The imperative role of the investigator is visualized in the model by its positioning and the number of interdependencies directed at the investigator. It is found that the investigator remains the main actor in recruiting patients in a clinical trial, by proposing participation. The effect of other (digital) information channels is expected to increase public awareness in the future. Several paradoxes in the eco-system of clinical research are revealed by the System Dynamics approach and are discussed, which may provide an onset for public discussion on drug development.

6.4. Recommendations

Taking a System Dynamics approach in researching patient recruitment, no studies have been published on before. Therefore, the main objective of this research was to explore this method for understanding and predicting patient recruitment. Findings have highlighted many areas in which further research is indicated. The resulting System Dynamics model has been grounded with input from the literature, combined with empirical data assessed in qualitative interviews. Although, this qualitative method enables an in-depth view, it is however limited to a small sample size. For validation of the results found on the interdependencies of critical factors, it is recommended to enlarge the sample size in a quantitative research, e.g. survey research. An attribution to the System Dynamics model could be made by enrichment with historical and numerical data, therewith enforcing some mathematical soundness into the system, as suggested by several researchers (Homer & Hirsch, 2006; Jones et al., 2006; Sterman, 2000). Further improvements are necessary to the System Dynamics model by refining equations and pursuing linear behaviour under all circumstances.

Bibliography

Abraham, S., Grace, D., Parambi, T., & Pahuja, S. (2009). Milestones In Development Of Good Clinical Practice. *The Internet Journal of Health*, *9*(1), 1–5. https://doi.org/10.5580/2193

Akkermans, H., & Dellaert, N. (2005). The rediscovery of industrial dynamics: The contribution of system dynamics to supply chain management in a dynamic and fragmented world. *System Dynamics Review*, *21*(3), 173–186. https://doi.org/10.1002/sdr.317

Albin, S. (1997). Building a System Dynamics Model Part 1: Conceptualization. *MIT System Dynamics in Education Project*, 34.

Albrecht, B. T. L., Blanchard, C., Ruckdeschel, J. C., Coovert, M., & Strongbow, R. (1999). Strategic Physician Communication and Oncology Clinical Trials. *Journal of Clinical Oncology*, *17*(10), 3324–3332.

Albrecht, T. L., Eggly, S. S., Gleason, M. E. J., Harper, F. W. K., Tanina, S., Peterson, A. M., … Ruckdeschel, J. C. (2013). Influence of Clinical Communication on Patients' Decision Making on Participation in Clinical Trials. *Journal of Clinical Oncology*, *26*(16), 1–15. https://doi.org/10.1200/JCO.2007.14.8114.Influence

Anisimov, V., & Fedorov, V. (2005). Modeling of enrolment and estimation of parameters in multicentre trials. *Gsk Bds Tr*, *1*(January 2014), 2005.

Anisimov, V. V. (2009). Recruitment modeling and predicting in clinical trials. *American Pharmaceutical Outsourcing*, *10*(2).

Anisimov, V. V., & Fedorov, V. V. (2007). Modelling, prediction and adaptive adjustment of recruitment in multicentre trials. *Statistics in Medicine*, *26*(27), 4958–4975. https://doi.org/10.1002/sim.2956

Barnard, K. D., Dent, L., & Cook, A. (2010). A systematic review of models to predict recruitment to multicentre clinical trials. *BMC Medical Research Methodology*, *10*(1), 63. https://doi.org/10.1186/1471-2288-10-63

Beck, J., Esser, P. J., & Herschel, M. B. (2004). Why Clinical Trials Fail Before They Get Even Started : the " Frontloading " Process. *The Quality Assurance Journal*, *8*, 21–32. https://doi.org/10.1002/qaj.261

Berthon-Jones, N., Courtney-Vega, K., Donaldson, A., Haskelberg, H., Emery, S., & Puls, R. (2015). Assessing site performance in the Altair study, a multinational clinical trial. *Trials*, *16*(1), 138. https://doi.org/10.1186/s13063-015-0653-x

Binder, T., Belyazid, S., Haraldsson, H. V, Svensson, M. G., Kennedy, M., Winch, G. W., … Yanni, J. M. (2004). Developing System Dynamics Models from Causal Loop Diagrams. *Proceedings of the 22nd International Conference of the System Dynamics Society*.

Bose, S. K., Sandhu, A., & Strommenger, S. (2017). Clinical Trials : A Data Driven Feasibility Approach. *Pharmaceutical Outsourcing - The Journal of Pharmaceutical & Biopharmaceutical Contract Services*, *18*(1), 1–5. Retrieved from http://www.pharmoutsourcing.com/Featured-Articles/333830-Clinical-Trials-A-Data-Driven-Feasibility-Approach/

Bryde, D. J., & Joby, R. (2007). Product-based planning: The importance of project and project management deliverables in the management of clinical trials. *R and D Management*, *37*(4), 363–377. https://doi.org/10.1111/j.1467-9310.2007.00482.x

Buonansegna, E., Salomo, S., Maier, A., Li-Ying, J., & Schultz, C. (2012). Towards a framework of success factors for clinical trials.

Buonansegna, E., Salomo, S., Maier, A. M., & Li-Ying, J. (2014). Pharmaceutical new product development: why do clinical trials fail? *R&D Management*, *44*(2), 189–202. https://doi.org/10.1111/radm.12053

Butler, J., Subacius, H., Vaduganathan, M., Fonarow, G. C., Ambrosy, A. P., Konstam, M. A., … Gheorghiade, M. (2013). Relationship between clinical trial site enrollment with participant characteristics, protocol completion, and outcomes: Insights from the

Everest (efficacy of vasopressin antagonism in heart failure: Outcome study with Tolvaptan) trial. *Journal of the American College of Cardiology*, *61*(5), 571–579. https://doi.org/10.1016/j.jacc.2012.10.025
Campbell, M. K., Snowdon, C., Francis, D., Elbourne, D., McDonald, A. M., Knight, R., … STEPS group. (2007). Recruitment to randomised trials: strategies for trial enrollment and participation study. The STEPS study. *Health Technology Assessment (Winchester, England)*, *11*(48). https://doi.org/10.3310/hta11480
Cavana, R. Y., & Maani, K. E. (2000). A Methodological Framework for Systems Thinking and Modelling (ST&M) Interventions. *1st International Conference on Systems Thinking in Management*, 136–141. https://doi.org/10.13140/2.1.3051.3609
Comis, R. L., Miller, J. D., Aldigé, C. R., Krebs, L., & Stoval, E. (2003). Public attitudes toward participation in cancer clinical trials. *Journal of Clinical Oncology*, *21*(5), 830–835. https://doi.org/10.1200/JCO.2003.02.105
Comis, R. L., Miller, J. D., Colaizzi, D. D., & Kimmel, L. G. (2009). Physician-related factors involved in patient decisions to enroll onto cancer clinical trials. *Journal of Oncology Practice / American Society of Clinical Oncology*, *5*(2), 50–6. https://doi.org/10.1200/JOP.0922001
Contract Pharma. (2016). *2016 Annual Outsourcing Survey*.
Cox, K., & McGarry, J. (2003). Why patients don't take part in cancer clinical trials: an overview of the literature. [Review] [46 refs]. *European Journal of Cancer Care*, *12*(2), 114–122.
Dahlin, E., Nelson, G. M., Haynes, M., & Sargeant, F. (2016). Success rates for product development strategies in new drug development. *Journal of Clinical Pharmacy and Therapeutics*, *41*(2), 198–202. https://doi.org/10.1111/jcpt.12362
Deloitte Centre for Health Solutions. (2016). *Balancing the R&D equation - Measuring the return pharmaceutical innovation 2016*. https://doi.org/10.1016/j.jacceco.2015.03.004
Denicoff, A. M., McCaskill-Stevens, W., Grubbs, S. S., Bruinooge, S. S., Comis, R. L., Devine, P., … Meropol, N. J. (2013). The National Cancer Institute-American Society of Clinical Oncology Cancer Trial Accrual Symposium: summary and recommendations. *Journal of Oncology Practice / American Society of Clinical Oncology*, *9*(6), 267–276. https://doi.org/10.1200/JOP.2013.001119
DiMasi, J. A. (2002). The value of improving the productivity of the drug development process: faster times and better decisions. *PharmacoEconomics*, *20 Suppl 3*, 1–10. https://doi.org/10.2165/00019053-200220003-00001
DiMasi, J. A., Feldman, L., Seckler, A., & Wilson, A. (2010). Trends in Risks Associated With New Drug Development: Success Rates for Investigational Drugs. *Clinical Pharmacology & Therapeutics*, *87*(3), 272–277. https://doi.org/10.1038/clpt.2009.295
DiMasi, J. A., Grabowski, H. G., & Hansen, R. W. (2016). Innovation in the pharmaceutical industry: New estimates of R&D costs. *Journal of Health Economics*, *47*, 20–33. https://doi.org/10.1016/j.jhealeco.2016.01.012
DiMasi, J. A., Hansen, R. W., & Grabowski, H. G. (2003). The price of innovation: New estimates of drug development costs. *Journal of Health Economics*, *22*(2), 151–185. https://doi.org/10.1016/S0167-6296(02)00126-1
Drennan, K. B. (2002). Patient recruitment: The costly and growing bottleneck in drug development. *Drug Discovery Today*. https://doi.org/10.1016/S1359-6446(01)02137-7
English, R. A., Lebovitz, Y., & Giffin, R. B. (2010). *Transforming Clinical Research in the United States*. Washington, D.C.: National Academies Press. https://doi.org/10.17226/12900
Fayter, D., McDaid, C., & Eastwood, A. (2007). *A systematic review highlights threats to validity in studies of barriers to cancer trial participation*. *Journal of Clinical Epidemiology* (Vol. 60). https://doi.org/10.1016/j.jclinepi.2006.12.013
Food and Drug Administration. (2004). *Challenge and Opportunities on the Critical Path to New Medical Products*. https://doi.org/http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/Cri

ticalPathInitiative/CriticalPathOpportunitiesReports/ucm113411.pdf
Forrester, J. W. (1992). Policies, decisions and information sources for modeling. *European Journal of Operational Research*, *59*(1), 42–63. https://doi.org/10.1016/0377-2217(92)90006-U
Forrester, J. W., & Senge, P. M. (1980). Tests for Building Confidence in System Dynamics Models. In *Building confidence in system dynamics models* (pp. 209–228).
Gajewski, B. J., Simon, S. D., & Carlson, S. E. (2008). Predicting accrual in clinical trials with Bayesian posterior predictive distributions. *Statistics in Medicine*, *27*(13), 2328–2340. https://doi.org/10.1002/sim.3128
Gelinas, L., Lynch, H. F., Bierer, B. E., & Cohen, I. G. (2017). When clinical trials compete: prioritising study recruitment. *Journal of Medical Ethics*, medethics-2016-103680. https://doi.org/10.1136/medethics-2016-103680
Georgiadis, P., Vlachos, D., & Iakovou, E. (2005). A system dynamics modeling framework for the strategic supply chain management of food chains. *Journal of Food Engineering*, *70*(3), 351–364. https://doi.org/10.1016/j.jfoodeng.2004.06.030
Getz, K. (2012). Enrollment Performance: Weighing the" Facts." *Applied Clinical Trials*, *21*(5), 17–19. Retrieved from http://www.appliedclinicaltrialsonline.com/print/207659?page=full&id=&sk=&date=&=&pageID=3
Getz, K. A. (2011). Predicting Successful Site Performance. *Applied Clinical Trials*, *12*, 10–12. Retrieved from http://www.appliedclinicaltrialsonline.com/print/208587?page=full&pageID=1
Getz, K. A. (2014). Improving protocol design feasibility to drive drug development economics and performance. *International Journal of Environmental Research and Public Health*, *11*(5), 5069–5080. https://doi.org/10.3390/ijerph110505069
Getz, K. A., & Kaitin, K. I. (2012). Open innovation: the new face of pharmaceutical research and development. *Expert Review of Clinical Pharmacology*, *5*(5), 481–483. https://doi.org/10.1586/ecp.12.44
Getz, K. A., Wenger, J., Campo, R. A., Seguine, E. S., & Kaitin, K. I. (2008). Assessing the impact of protocol design changes on clinical trial performance. *American Journal of Therapeutics*, *15*(5), 450–7. https://doi.org/10.1097/MJT.0b013e31816b9027
Glasser, S. P. (2008). *Essentials of Clinical Research*. (S. P. Glasser, Ed.). Springer Science and Business Media B.V.
Grabowski, H. G., DiMasi, J. A., & Long, G. (2015). The roles of patents and research and development incentives in biopharmaceutical innovation. *Health Affairs*, *34*(2), 302–310. https://doi.org/10.1377/hlthaff.2014.1047
Grabowski, H., Vernon, J., & DiMasi, J. A. (2002). Returns on Research and Development for 1990s New Drug Introductions. *PharmacoEconomics*, *20*(Supplement 3), 11–29. https://doi.org/10.2165/00019053-200220003-00002
Grand, M. M., & O'Brien, P. C. (2012). Obstacles to participation in randomised cancer clinical trials: A systematic review of the literature. *Journal of Medical Imaging and Radiation Oncology*. https://doi.org/10.1111/j.1754-9485.2011.02337.x
Größler, A., Thun, J.-H., & Milling, P. M. (2008). System dynamics as a structural theory in operations management. *Production and Operations Management*, *17*(3), 373–384. https://doi.org/10.3401/poms.1080.0023
Grunfeld, E., Zitzelsberger, L., Coristine, M., & Aspelund, F. (2002). Barriers and facilitators to enrollment in cancer clinical trials: Qualitative study of the perspectives of clinical research associates. *Cancer*, *95*(7), 1577–1583. https://doi.org/10.1002/cncr.10862
Harper, B. D., & Zuckerman, D. (2006). Critical Success Factors for Planning for Site Selection and Patient Recruitment Planning. *BioExecutive International*, *2*(6), 16–28.
Hay, M., Thomas, D. W., Craighead, J. L., Economides, C., & Rosenthal, J. (2014). Clinical development success rates for investigational drugs. *Nat Biotech*, *32*(1), 40–51. https://doi.org/10.1038/nbt.2786\rhttp://www.nature.com/nbt/journal/v32/n1/abs

/nbt.2786.html#supplementary-information
Homer, J. B., & Hirsch, G. B. (2006). System dynamics modeling for public health: Background and opportunities. *American Journal of Public Health*. https://doi.org/10.2105/AJPH.2005.062059
ICH-GCP. (2016). *GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2) by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*. *European Medicines Agency*.
InVentiv. (2014). *Clinical Trial Educators: Game Changers in Patient Enrollment*.
Jenkins, V., Farewell, D., Batt, L., Maughan, T., Branston, L., Langridge, C., … Fallowfield, L. (2010). The attitudes of 1066 patients with cancer towards participation in randomised clinical trials. *British Journal of Cancer*, *103*(12), 1801–7. https://doi.org/10.1038/sj.bjc.6606004
Jiang, Y., Simon, S., Mayo, M. S., & Gajewski, B. J. (2015). Modeling and validating Bayesian accrual models on clinical data and simulations using adaptive priors. *Statistics in Medicine*, *34*(4), 613–629. https://doi.org/10.1002/sim.6359
Jones, A. P., Homer, J. B., Murphy, D. L., Essien, J. D. K., Milstein, B., Seville, D. A., & Barnes, K. (2006). Understanding diabetes population dynamics through simulation modeling and experimentation. *American Journal of Public Health*. https://doi.org/10.2105/AJPH.2005.063529
Kaplan, C. P., Nápoles, A. M., Dohan, D., Hwang, E. S., Melisko, M., Nickleach, D., … Haas, J. (2013). Clinical trial discussion, referral, and recruitment: Physician, patient, and system factors. *Cancer Causes and Control*, *24*(5), 979–988. https://doi.org/10.1007/s10552-013-0173-5
Kendall, B., Städeli, R., Schegg, B., Olbrich, M., Chen, E., Harmelin-Kadouri, R., … Hildemann, S. K. (2012). Clinical Trial Educator program – a novel approach to accelerate enrollment in a phase III International Acute Coronary Syndrome Trial. *Clinical Trials*, *9*(3), 358–366. https://doi.org/10.1177/1740774512440760
Kibby, M. (2011). Patient Recruitment Feasibility. *Applied Clinical Trials*. Retrieved from http://ezproxy.lib.ucf.edu/login?url=http://search.proquest.com/docview/880068037?accountid=10003%5Cnhttp://sfx.fcla.edu/ucf?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&genre=article&sid=ProQ:ProQ:abitrade&atitle=Patient+Recruitment+Feasi
Lamberti, M. J., & Getz, K. (2015). *Profiles of New Approaches to Improving the Efficiency and Performance of Pharmaceutical Drug Development*. Boston.
Levi, M., Sluiter, H. E., Van Leeuwen, T., Rook, M., & Peeters, G. (2013). Medisch-wetenschappelijk onderzoek in Nederland. *Nederlands Tijdschrift Voor Geneeskunde*, *157*(A6081), 1–7.
Lincoln, Y. S., & Guba, E. G. (1985). Naturalistic Inquiry. *Naturalistic Inquiry*, 416. https://doi.org/10.1177/1473325006070288
Luna-Reyes, L. F., & Andersen, D. L. (2005). Interviewing as a Strategy for the Assessment of System Dynamics Models. *Proceedings of the 23rd International Conference of the System Dynamics Society*, *52*(222), 104. https://doi.org/10.2139/ssrn.2122111
Luna, L. F., & Anderson, D. L. (2002). Using Qualitative Methods in the Conceptualization and Assessment of System Dynamics Models. *20th International System Dynamics*, 1–21. Retrieved from http://www.systemdynamics.org/conferences/2002/proceed/papers/Luna1.pdf
MacKenzie, I. S., Wei, L., Rutherford, D., Findlay, E. A., Saywood, W., Campbell, M. K., & MacDonald, T. M. (2010). Promoting public awareness of randomised clinical trials using the media: The "Get Randomised" campaign. *British Journal of Clinical Pharmacology*, *69*(2), 128–135. https://doi.org/10.1111/j.1365-2125.2009.03561.x
Manne, S., Kashy, D., Albrecht, T., Wong, Y. N., Lederman Flamm, A., Benson, A. B., … Meropol, N. J. (2015). Attitudinal barriers to participation in oncology clinical trials: Factor analysis and correlates of barriers. *European Journal of Cancer Care*, *24*(1), 28–38.

https://doi.org/10.1111/ecc.12180
Marshall, D. A., Burgos-Liz, L., IJzerman, M. J., Crown, W., Padula, W. V., Wong, P. K., … Osgood, N. D. (2015). Selecting a Dynamic Simulation Modeling Method for Health Care Delivery Research—Part 2: Report of the ISPOR Dynamic Simulation Modeling Emerging Good Practices Task Force. *Value in Health*, *18*(2), 147–160. https://doi.org/10.1016/j.jval.2015.01.006
Marshall, D. A., Burgos-Liz, L., Ijzerman, M. J., Osgood, N. D., Padula, W. V., Higashi, M. K., … Crown, W. (2015). Applying dynamic simulation modeling methods in health care delivery research - The SIMULATE checklist: Report of the ISPOR simulation modeling emerging good practices task force. *Value in Health*, *18*(1), 5–16. https://doi.org/10.1016/j.jval.2014.12.001
Michaels, M., D'Agostino, T. A., Blakeney, N., Weiss, E. S., Binz-Scharf, M. C., Golant, M., & Bylund, C. L. (2015). Impact of Primary Care Provider Knowledge, Attitudes, and Beliefs about Cancer Clinical Trials: Implications for Referral, Education and Advocacy. *Journal of Cancer Education*, *30*(1), 152–157. https://doi.org/10.1007/s13187-014-0662-6
Mijoule, G., Savy, S., & Savy, N. (2012). Models for patients' recruitment in clinical trials and sensitivity analysis. *Statistics in Medicine*, *31*(16), 1655–1674. https://doi.org/10.1002/sim.4495
Miles, M. B., & Huberman, M. A. (1994). *Qualitative Data Analysis* (Second edi). SAGE Publications.
Mills, E. J., Seely, D., Rachlis, B., Griffith, L., Wu, P., Wilson, K., … Wright, J. R. (2006). Barriers to participation in clinical trials of cancer: a meta-analysis and systematic review of patient-reported factors. *The Lancet Oncology*, *7*(2), 141–148. https://doi.org/10.1016/S1470-2045(06)70576-9
Moos, W. H., & Mirsalis, J. C. (2009). Nonprofit organizations and pharmaceutical research and development. *Drug Development Research*. https://doi.org/10.1002/ddr.20326
Morrow, G. R., Hickok, J. T., & Burish, T. G. (1994). Behavioral aspects of clinical trials. An integrated framework from behavior theory. *Cancer*, *74*(9 Suppl), 2676–2682.
Moscicki, R. A., & Tandon, P. K. (2017). Drug-Development Challenges for Small Biopharmaceutical Companies. *New England Journal of Medicine*, *376*(5), 469–474. https://doi.org/10.1056/NEJMra1510070
Müller, R., & Turner, R. (2010). Leadership competency profiles of successful project managers. *International Journal of Project Management*, *28*(5), 437–448. https://doi.org/10.1016/j.ijproman.2009.09.003
Nefarma. (2012). *NCTD Monitor 2012: Klinisch geneesmiddelenonderzoek in Nederland*.
Northridge, M. E., & Metcalf, S. S. (2016). Enhancing implementation science by applying best principles of systems science. *Health Research Policy and Systems*, *14*(1), 74. https://doi.org/10.1186/s12961-016-0146-8
Pellegrino, J., & Smith, R. (2009). *Predictive Modeling in Clinical Trial Enrollment*.
Penckofer, S., Byrn, M., Mumby, P., & Ferrans, C. E. (2011). Improving subject recruitment, retention, and participation in research through Peplau's theory of interpersonal relations. *Nursing Science Quarterly*, *24*(2), 146–51. https://doi.org/10.1177/0894318411399454
Peterson, D. W., & Eberlein, R. L. (1994). Reality check: A bridge between systems thinking and system dynamics. *System Dynamics Review*, *10*(2–3), 159–174. https://doi.org/10.1002/sdr.4260100205
PhRMA. (2010). Profile Biopharmaceutical Research Industry 2010. *Pharmaceutical Research and Manufacturers of America*.
PhRMA. (2015). Profile Biopharmaceutical Research Industry 2015. *Pharmaceutical Research and Manufacturers of America*, 76. Retrieved from http://www.phrma.org/sites/default/files/pdf/2015_phrma_profile.pdf
Quintiles. (2010). Clinical Trial Educators: The key to faster enrollment and fewer barriers in clinical trials. *Fact Sheet*, 1–2.

Rajadhyaksha, V. (2010). Conducting feasibilities in clinical trials: an investment to ensure a good study. *Perspectives in Clinical Research*, *1*(3), 106–9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21814631%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3146075

Reichert, J. M., & Milne, C.-P. (2002). Public and Private Sector Contributions to the Discovery and Development of ???Impact??? Drugs. *American Journal of Therapeutics*, *9*(6), 543–555. https://doi.org/10.1097/00045391-200211000-00016

Renwick, V. (2008). Supporting critical Phase I-IV clinical studies by outsourcing supporting elements. *Pharmaceutical Technical Europe*, (March).

Reuter, B. S., & Esche, G. (2007). " Can You Handle the Truth ?" How Effective are Site Questionnaires in Predicting Site Performance ? *Journal of Clinical Research Best Practices*, *3*(4), 3–6.

Richardson, G. P. (2011). Reflections on the foundations of system dynamics. *System Dynamics Review*, *27*(3), 219–243. https://doi.org/10.1002/sdr

Roberts, D. A., Kantarjian, H. M., & Steensma, D. P. (2016). Contract research organizations in oncology clinical research: Challenges and opportunities. *Cancer*. https://doi.org/10.1002/cncr.29994

Roche, K., Paul, N., Smuck, B., Whitehead, M., Zee, B., Pater, J., … Walker, H. (2002). Factors affecting workload of cancer clinical trials: results of a multicenter study of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*, *20*(2), 545–556. https://doi.org/10.1200/jco.2002.20.2.545

Rodrigues, A., & Bowers, J. (1996). System dynamics in project management: a comparative analysis with traditional methods. *System Dynamics Review*, *12*(2), 121–139. Retrieved from http://www.academia.edu/download/40063693/System_Bynamics_in_Project_Management_A_20151116-3898-67dktq.pdf

Rosen, S. H., Gallardo, S., & Sawyer, S. (2011). Deploying Clinical Trial Educators to Increase Clinical Trial Recruitment. *Monitor*, (February), 36–38.

Rosen, S. H., & Smith, N. (2017, April). The growing role of clinical trial educators. *Pharmaceutical Commerce*, 1–9. Retrieved from http://pharmaceuticalcommerce.com/clinical-operations/growing-role-clinical-trial-educators/#

Schroen, A. T., Petroni, G. R., Wang, H., Thielen, M. J., Sargent, D., Benedetti, J. K., … Djulbegovic, B. (2011). Challenges to accrual predictions to phase III cancer clinical trials: a survey of study chairs and lead statisticians of 248 NCI-sponsored trials. *Clinical Trials (London, England)*, *8*(5), 591–600. https://doi.org/10.1177/1740774511419683

Schuster, D. P., & Mcgill, J. (2001). Attract Clinical Trials to an AMC. *Applied Clinical Trials*, *10*(11), 44–52.

Sertkaya, A., Birkenbach, A., Berlind, A., & Eyraud, J. (2014). *Examination of Clinical Trial Costs and Barriers for Drug Development*. Lexington.

Snabe, B., & Größler, A. (2006). System dynamics modelling for strategy implementation-case study and issues. *Systems Research and Behavioral Science*, *23*(4), 467–481. https://doi.org/10.1002/sres.773

Sterman, J. D. (2000). *Business Dynamics-Systems Thinking and Modeling for a Complex World*. Irwin McGraw-Hill. Retrieved from http://www.lavoisier.fr/notice/frJWOAR6SA23WLOO.html

Sterman, J. D. (2006). Learning from evidence in a complex world. *American Journal of Public Health*. https://doi.org/10.2105/AJPH.2005.066043

Taylor, K. M., Feldstein, M. L., Skeel, R. T., Pandya, K. J., Ng, P., & Carbone, P. P. (1994). Fundamental Dilemmas of the Randomized Clinical-Trial Process - Results of a Survey of the 1,737 Eastern-Cooperative-Oncology-Group Investigators. *Journal of Clinical Oncology*, *12*(9), 1796–1805.

Tenuta, A., Klotz, L., & Parker, J. L. (2014). Clinical trial risk in castration-resistant prostate

cancer: Immunotherapies show promise. *BJU International*, *113*(5 B), 82–89. https://doi.org/10.1111/bju.12309

Thomas, D., & Wessel, C. (2005). Emerging Therapeutic Company Investment and Deal Trends. *US Venture Capital and Public Offerings Global Licensing and Acquisitions*, (June), 2005–2014.

Torgerson, J. S., Arlinger, K., Käppi, M., & Sjöström, L. (2001). Principles for enhanced recruitment of subjects in a large clinical trial: The XENDOS study experience. *Controlled Clinical Trials*, *22*(5), 515–525. https://doi.org/10.1016/S0197-2456(01)00165-9

Trauth, J. M., Musa, D., Siminoff, L., Katz Jewell, I., & Ricci, E. (2000). Public Attitudes Regarding Willingness to Participate in Medical Research Studies. *Journal of Health & Social Policy*, *12*(2), 23–43. https://doi.org/10.1300/J045v12n02

Treweek, S., Lockhart, P., Pitkethly, M., Cook, J. A., Kjeldstrøm, M., Johansen, M., … Mitchell, E. D. (2013). Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis. *BMJ Open*, *3*(2), e002360. https://doi.org/10.1136/bmjopen-2012-002360

Tufts Center for the Study of Drug Development. (2012). One in five procedures generates extraneous clinical trials data. *Tufts CSDD Impact Reports*, *14*(6), 2012.

Vijayananthan, A., & Nawawi, O. (2008). The importance of Good Clinical Practice guidelines and its role in clinical trials. *Biomedical Imaging and Intervention Journal*, *4*(1), 1–4. https://doi.org/10.2349/biij.4.1.e5

Voss, C., Tsikriktsis, N., & Frohlich, M. (2002). Case research in operations management. *International Journal of Operations & Production Management*, *22*(2), 195–219. https://doi.org/10.1108/01443570210414329

Will, J., Bertrand, M., & Fransoo, J. C. (2002). Operations management research methodologies using quantitative modeling. *International Journal of Operations & Production Management*, *22*(2), 241–264. https://doi.org/10.1108/01443570210414338

Williams, S. (2006). Clinical Trials Recruitment and Enrollment : Attitudes , Barriers , and Motivating Factors Attitudes toward Clinical Trials Lack of Information / Awareness about Clinical Trials Enrollment Obstacles / What Prevents People from Participating once Recruited. *University of Rudgers*, (August), 1–13. Retrieved from http://cro.rbhs.rutgers.edu/documents/clinical_trials_recruitment_and_enrollment.pdf

Zhang, X., & Long, Q. (2010). Stochastic modeling and prediction for accrual in clinical trials. *Statistics in Medicine*, *29*(6), 649–658. https://doi.org/10.1002/sim.3847

Appendices

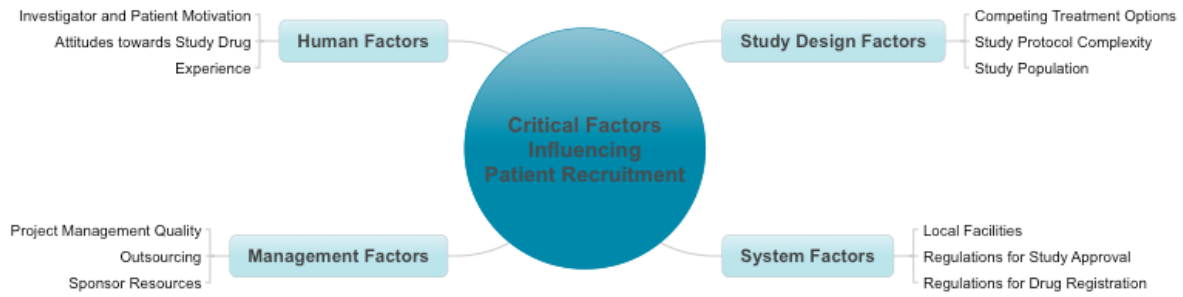
Appendix 1: Interview introduction

Introduction

This thesis research is being conducted as the final part of my Master of Science in Business Administration (MscBA) and concerns the process of Patient Recruitment Feasibility in clinical research.

Our phase III study that is expected to commence in 2018 led to the exploration of an adequate Patient Recruitment Feasibility Process and methods to predict the recruitment rate. However, none of the methods found have proven to be fully adequate.

Subsequently, an exploration of the extended literature has led to the identification of critical factors influencing patient recruitment. These factors are divided into four main categories: Study Design Factors, System Factors, Management Factors and Human Factors.



Considering the critical factors, a System Dynamics model has been built. System Dynamics is based on the assumption that real-time environments are complex, in which several factors, not in the least human factors, influence others. This may lead to an unpredictable outcome due to unforeseen effects of causes and uses within the complexity.

The interviews are intended to engage in an open discussion with experts in the field to verify the model and discuss interdependencies between factors. For example, negative or positive effects, high or low impact, the occurrence of delays and duration of effects may be discussed.

On the next pages, critical factors will be sketched, with causes/input on the left side and uses/output on the right side to serve as a basis for discussion.

Interview

Date: Place:

Time: Duration:

Recorded: Y / N

Demographics interviewee

Name:

Job title:

Job description:

Number of years involved in clinical research:

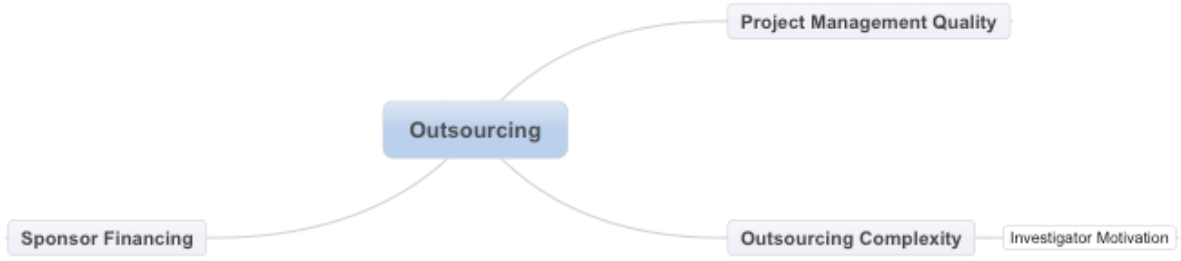
Type of experience in clinical research:
(e.g. investigator, coordinator, CRA, financial, HR, investor, etc.)

Project Management

Causes **Uses**

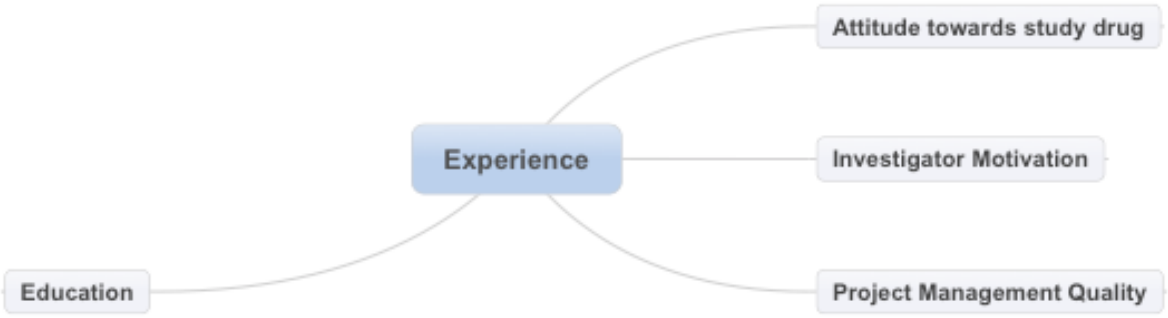
Outsourcing

Causes **Uses**



Experience

Causes **Uses**

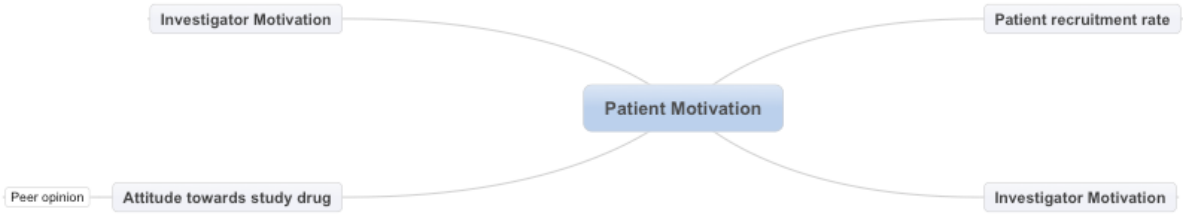


Attitude towards study drug

Causes **Uses**

Patient Motivation

Causes **Uses**

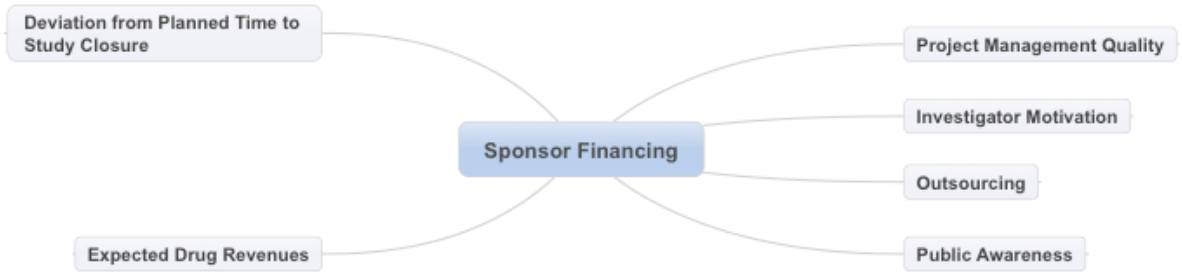


Investigator Motivation

Causes **Uses**

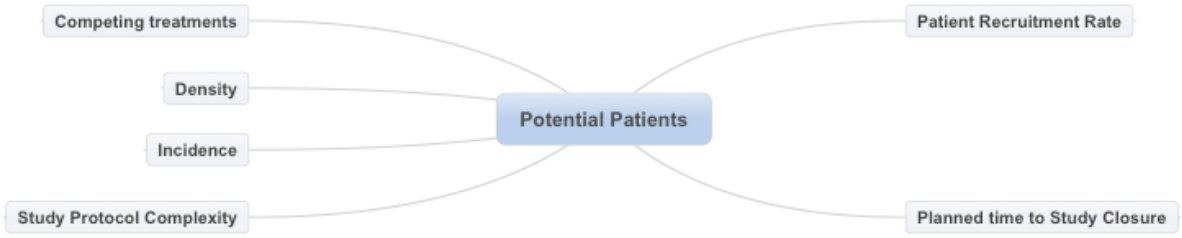
Sponsor Financing

Causes **Uses**

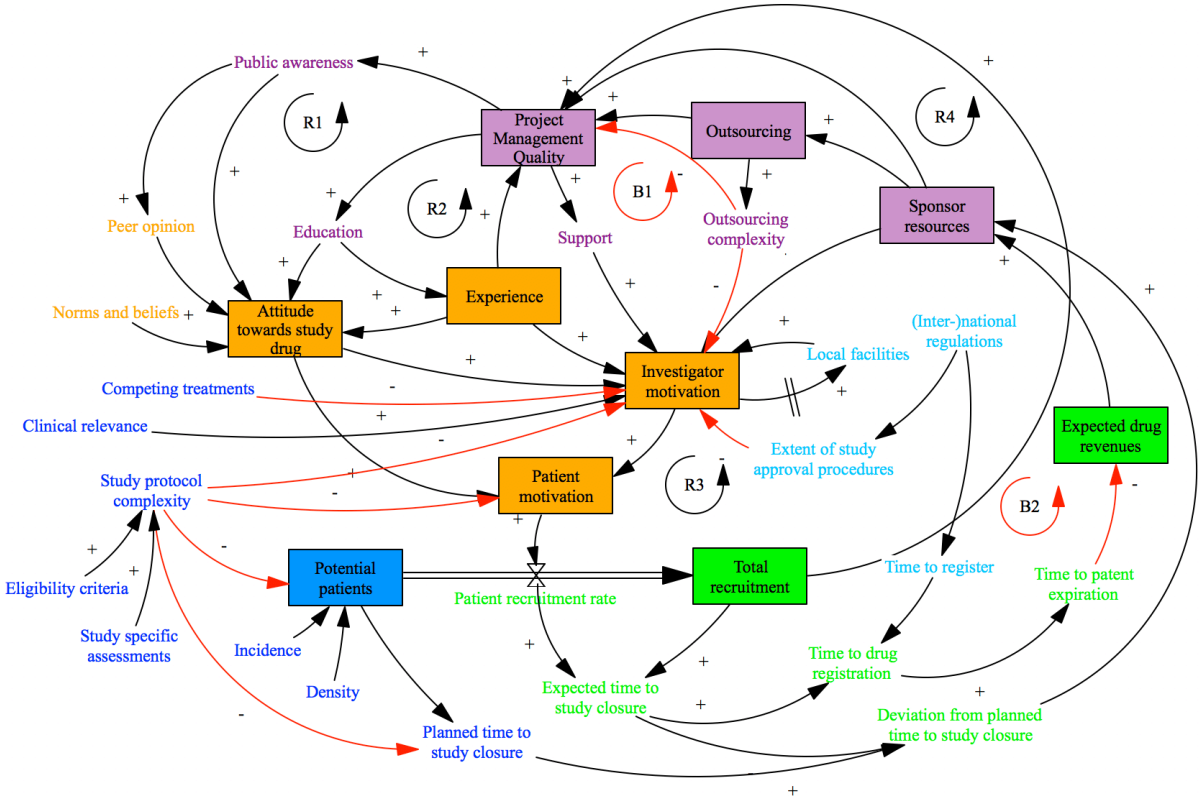


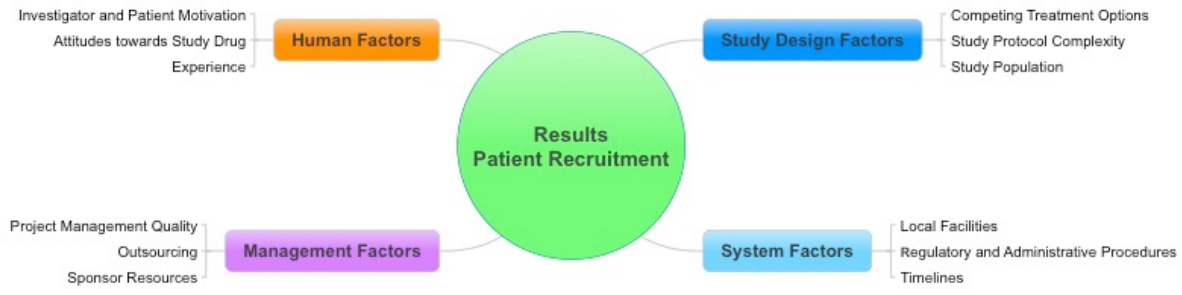
Potential patients

Causes **Uses**



System Dynamics Model of Patient Recruitment in Clinical Research





Appendix 2: List of interviewees

Name	Professional title	Organizations, current positions and experience	Actor experience	Years of experience	Date interview	Interview duration	Interview taped
E. van der Putten	Chief Executive Officer (CEO)	Currently CEO of a small pharmaceutical company and partnering an investment company for oncology biotech start-ups. Extensive experience in starting and managing Clinical Research Organizations (CROs) and pharmaceutical sponsors	Sponsor, CRO, investor	25+	14-07-17	00:23 + ~00:30	Part
C. Huiskamp	Chief Financial Officer (CFO)	Currently positioned in a small pharmaceutical company as CFO and partnering/managing a Clinical Research Organization (CRO)	CRO, sponsor	10	08-09-17	01:07	Yes
K. Vercruysse	Project Director and Program Manager	Currently positioned in a small pharmaceutical company as Project Director and partnering/managing a Clinical Research Organization (CRO)	CRO, sponsor	16	24-07-17	01:00	Yes
J. Schellens	Professor and Medical Oncologist	Professor in pharmacology, medical oncologist, head of the Clinical Research Unit (CRU) in a specialized oncology hospital; extensive experience as investigator in early phase clinical trials (phase I/II). Chairs the Scientific Advisory Board Oncology of the European Medicines Agency.	Investigator, regulator	25+	28-07-17	00:42	Yes
N. Steeghs	Medical Oncologist	Medical oncologist in a specialized oncology hospital, experience as an investigator in phase I/II/III clinical trials. Coordinates a large multicenter Dutch trial	Investigator, regulator	13	28-08-17	00:24	Yes
B. van Triest	Radiotherapist	Medical Doctor involved in combination drug-radiotherapy phase I/II/III clinical trials as an investigator	Investigator	9	24-07-17	01:01	Yes

Name	Professional title	Organizations, current positions and experience	Actor experience	Years of experience	Date interview	Interview duration	Interview taped
Y. Groot	Clinical Research Associate (CRA)	CRA in a specialized oncology hospital, previous experience in several large commercial Clinical Research Organizations (CRO)	CRO, CRA	23	20-07-17	01:02	Yes
E. Meijer	Clinical Research Associate (CRA)	CRA in a specialized oncology hospital, previous experience in several large commercial Clinical Research Organizations (CRO)	CRO, CRA	17	20-07-17	01:02	Yes
R. Zucker	Clinical Research Associate (CRA)	CRA in a specialized oncology hospital, previous experience in several large commercial Clinical Research Organizations (CRO)	CRO, CRA	11	20-07-17	01:02	Yes
A. Janssen	Site Strategy Consultant	(Global) Consultancy specialized in Enrollment & Retention of subjects into clinical trials. Previous experience as Lead CRA/Lead StartUp CRA	Consultant, CRA	20	07-09-17	01:01	Yes
A. van der Donk	CSU Country Head	Currently working as Country Head CSU for a pharmaceutical company. Has held several project and strategic management positions in pharmaceutical companies and a Clinical Research Organization (CRO). Personal experience as an oncology patient and volunteer representative of patient association	Sponsor, CRO, patient	22	12-09-17	00:59	Yes

Appendix 3: Transcribed quotes of all interviews

All interviews are transcribed into quotes. These quotes are all combined in this appendix. In order to reflect clearly on its value, the quotes are bundled by causing variables and sorted in alphabetical order.

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
all	+	**IMO**	*In practice, I also see all arrows are aimed at investigator motivation, but what my company is focusing on more and more, is that the patient also has a 'what's-in-it-for-me'*	Ik zie in de praktijk ook dat alle pijlers gericht zijn op de investigator motivation, maar wat mijn bedrijf ook steeds meer gaat zien is dat de patient ook een 'whats-in-it-for-me' heeft	**AD**
ATT	-	**IMO**	*No referral due to loss of income, distance*	Geen verwijzing ivm gederfde inkomsten, afstand	**JS**
ATT	-	**IMO**	*At the level of potential referrers there may be clear factors that contribute to a referral stream or the opposite*	op niveau van potentiele verwijzers duidelijke factoren waardoor een verwijzingsstroom op gang kan komen of kan opdrogen	**JS**
ATT	+	**IMO**	*We are very study minded, however the request has to reach the right person. That is kind of in between a system and a human factor*	Heel erg studie minded. Moet bij de goede persoon terechtkomen. Dat is wel tussen een systeem factor en een human factor in	**BT**
ATT	+	**IMO**	*Human factors are very important, attitude towards study drug*	Human factors heel erg belangrijk, zoals attitude towards study drug	**BT**
ATT	+	**IMO**	*The culture in our NKI is so different, every doctor immediately considers a study the patient might fit into. That is in the air, a very strong mind-set*	De cultuur in het NKI is ook zo'n verschil, iedere arts denk direct, oh in welke studie past deze patient? Dat ademt hier gewoon, een sterke mind-set	**EM**
ATT	+	**IMO**	*Inside the hospital emotional factors may matter*	Binnen het ziekenhuis kunnen emotionele factoren een rol spelen	**JS**
ATT	+	**IMO**	*Important is: do I recognize myself in this work? Does it make me happy? Sometimes CROs are counterproductive in this way.*	Herken ik mij in dit werk? Word ik blij van het werk? Is soms contra-productief.	**JS**
ATT	+	**IMO**	*To contribute to advances in medical science should be a leading force for organizations like EORTC and investigators. But yes, there are contradictions*	Bijdragen aan advanced medical science moet drijfveer zijn voor EORTC, investigators. Is een contradictie.	**JS**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
ATT	+	**IMO**	*In phase III clinical trials you would expect physicians to know there may be an advantage for their patient*	Bij fase 3 verwacht je dat de dokter inziet dat er een voordeel voor de patient is	**NS**
ATT	+	**IMO**	*It is very often that the physician just doesn't think about it*	Heel vaak zo dat de dokter er niet aan denkt	**NS**
ATT	+	**IMO**	*Fellows are very motivated, but sometimes they do not know which studies are available*	Fellows willen wel graag, maar weten soms ook niet welke studies er allemaal zijn.	**NS**
ATT	+	**IMO**	*As a young physician, I very much wanted to participate, but only when I grew older I realized there are only so much hours in a day, and that I can make 10 choices for things I should do*	Later pas gerealiseerd, er zitten maar zoveel uren in een dag dat ik kan werken, en daarin kan ik 10 keuzes maken voor allemaal dingen die ik moet doen	**NS**
ATT	+	**IMO**	*And all of them are good for science and for the future and for patients*	En die ook goed zijn voor de wetenschap en voor de toekomst en voor patienten,	**NS**
ATT	+	**IMO**	*But there are so many that I have to reject. It is very personal what exactly you reject and what you actually do*	Maar moet er ook zoveel laten liggen. Het is heel persoonlijk wat je laat liggen en wat je doet	**NS**
ATT	+	**IMO**	*The consideration is usually how much effort you have to put into it, and how much do you gain with it, and how much effort and gain it is to your team, your colleagues?*	Overweging hoeveel belasting zit er voor jezelf aan, hoeveel winst zit er voor jezelf aan, en hoeveel belasting en winst zit er voor je team, collega's?	**NS**
ATT	+	**IMO**	*there is much conflict of interest within the system*	Veel belangenverstrengeling in het systeem	**NS**
ATT	++	**IMO**	*In any case attitude has a large impact on investigator motivation, and what is not in the model is publications*	In ieder geval de attitude heeft een grote impact op de investigator motivation, en wat er niet bijstaat in het model zijn de publicaties	**KV**
ATT	-	**PMO**	*In some cultures, patients are not well informed on their disease being cancer. They do get treated, because they are sick, but they don't know exactly what is wrong. Also, their families don't want to bother them*	In sommige culturen worden patienten ook niet goed ingelicht dat ze kanker hebben. Daar krijgen ze wel een behandeling omdat ze ziek zijn, maar weten niet precies wat. De familie wil de patient ook niet belasten	**RZ**
ATT	+	**PMO**	*Therefore, also the patient needs to be convinced to participate*	Dus ook de patient moet overtuigd zijn dat ie mee wil doen	**AD**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
ATT	+	**PMO**	*What I do see is that there are companies now specialized in recruiting patients, they contact patients who could participate (companies like Acurian and I-clusion). They will search the Electronic Patient File of the hospital. If patients are positive about participation, they will be referred to the investigator*	Wat ik wel zie is dat er nu bedrijven zijn die patienten benaderen, dat ze mee zouden kunnen doen (zoals I-clusion, Acurian). Zij gaan op zoek in het EPD van het ziekenhuis. Als de patient positief is over participatien, dan worden ze doorgestuurd naar de investigator	**AD**
ATT	+	**PMO**	*And then we are back at the 'what's-in-it-for-me' as a patient, you get something in return*	En dan kom je weer terug op de 'what's-in-it-for-me' als patient, je krijgt er iets voor terug	**AD**
ATT	+	**PMO**	*Always you have to make sure, that when the trial is finished, no matter how long it takes, that you inform the patients what their participation has contributed. That is very important. Nine out of ten times it is the physician informing the patient, and pharma will provide the information letter*	En altijd zorgen dat je als het onderzoek is afgelopen, hoe lang het soms ook duurt, dat je terug hoort wat jouw bijdrage heeft opgeleverd. Dat is heel belangrijk. Negen van de tien keer is dat de arts die de patient informeert, dan voorziet de farma in een brief	**AD**
ATT	+	**PMO**	*It also depends on the patient group, if they are prepared to travel a lot, etc.*	Scheelt ook per patientengroep hoe bereid ze zijn om de reizen ed	**AJ**
ATT	+	**PMO**	*My current job is mainly to start a campaign to recruit patients. We contact patients, and when they agree we will refer them to an investigative site. We are a funnel in patient recruitment. In fact, that is not being used in oncology studies yet*	Vanuit het huidige werk voornamelijk opzetten van een campagne om patienten te werven. Benaderen patienten, indien akkoord dan gaan de patienten naar de site. Fungeert als een funnel. Dat is feitelijk niet bij oncologische studies	**AJ**
ATT	+	**PMO**	*More and more a change is noticeable in patients, they are more study-minded. Also, patients are becoming more assertive and do some research themselves*	Je ziet steeds meer een omslag bij patienten, die zijn meer studie minded. Patienten worden ook steeds mondiger en gaan zelf op onderzoek uit	**AJ**
ATT	+	**PMO**	*Suppose your physician does not participate in a certain trial, and a physician in a hospital not so far away does, then patients are willing to go there*	Stel dat jouw arts niet meedoet met een bepaald onderzoek en een arts in een ziekenhuis iets verderop misschien wel, dan willen patienten daar wel naartoe	**AJ**
ATT	+	**PMO**	*There are technological and biological developments. In radiotherapy counts, once the machine is there, you will go ahead and use it*	Er zijn technologische en biologische ontwikkelingen, Voor radiotherapie geldt, als er een nieuw apparaat is, dan ga je daar wel mee door	**BT**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
ATT	+	**PMO**	*That may be different in other countries. " When the doctor says so, it will be…". And also age is a factor*	Dat kan in andere landen nog heel anders zijn. "Als de dokter het zegt, dan zal het wel.." En ook de leeftijd doet mee	**EM**
ATT	+	**PMO**	*Considering oncology studies, then patient motivation is fairly high*	Kijkend naar oncologie studies dan is de patienten motivatie wel hoog	**KV**
ATT	+	**PMO**	*Then you get to the human factor, people's character. I think in the Netherlands people are quite critical. It is their right of course, but it means they do not immediately do what the doctors suggests*	Dan kom je ook bij de human factor, het karakter van de mensen. Ik denk dat in Nederland mensen wel heel kritisch zijn, en dat is hun goed recht, maar die doen niet direct wat de dokter zegt	**YG**
CLR	+	**IMO**	*the way I look at it, the physician should participate because he/she believes in the product, and has the feeling it makes a difference for his/her patient. If the physician doesn't have that feeling, then maybe the product is not worth all the effort. In the end that same doctor must be willing to prescribe.*	In mijn ogen moet die arts dat doen om dat die in dat product gelooft, en dat ie het gevoel heeft dat de patient daarvan beter wordt. Kijk als ie dat gevoel niet heeft, dan is het product misschien uberhaupt niet de moeite waard om verder te testen. Uiteindelijk moet die arts dat ook gaan voorschrijven	**CH**
CLR	+	**IMO**	*In case of one physician it may be a question, however in 5 of 10 physicians, well then maybe it is best to terminate the study*	Bij 1 arts kan dat nog een vraag zijn, maar als dat bij 5 van de 10 artsen is, nou dan moet je misschien wel je studie stoppen	**CH**
CLR	+	**IMO**	*Other trials with a better scientific concept, better advantages, more aggressive strategy from sponsor*	Andere trials met een beter wetenschappelijk inhoudelijke concept, betere voordelen, agressievere strategie van sponsor	**JS**
CLR	+	**IMO**	*In a phase III study patients have an option that they otherwise would not have had*	Bij een fase 3 is er voor patienten een optie die ze anders niet hadden gehad	**NS**
CLR	+	**IMO**	*Of course, also patients participate because they think they gain personally*	Ook patienten doen uiteraard mee omdat ze denken dat ze daar een persoonlijk belang bij hebben	**NS**
CLR	++	**IMO**	*In that way, clinical relevance is also very important for patients. Although they do get this information only via their treating physician. Without the physician, the patient wouldn't know about it*	In zoverre is clinical relevance ook heel belangrijk voor patienten. Maar ja, die krijgen die informatie feitelijk alleen via de behandelend arts. Zonder de dokter weet die er niets vanaf	**AD**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
CLR	++	**IMO**	*Clinical relevance and competing treatments are both dominant factors, then all other factor are much less relevant*	Als het klinisch heel relevant is, of als er competing treatments zijn, die zijn heel dominant, dan doet de rest er eigenlijk niet meer zo toe.	**AD**
CLR	++	**IMO**	*To me especially the subject has to be interesting. What is the aim? It has to fit into my research area*	Voor mij moet het onderwerp vooral interessant zijn, wat is het doel. Passend binnen 1 onderwerp	**BT**
CLR	++	**IMO**	*I would rather have several studies within the same subject, then you get more experienced in this particular area*	Liever een aantal studies binnen hetzelfde onderwerp, dan krijg je daar meer ervaring in zeg maar	**BT**
CLR	++	**IMO**	*You learn from all studies and you can use that for others*	Van al die studies leer je weer en die ervaring kan je gebruiken bij andere studies	**BT**
CLR	++	**IMO**	*When it becomes a new standard, and you can really contribute for your patients*	Nieuwe standaard, echt iets toevoegen voor de patienten.	**BT**
CLR	++	**IMO**	*Of every 100 studies, there are maybe 80 of which the product is slightly better than standard. In those 20 trials with a product with a high clinical relevance everyone wants to participate*	Van de 100 studies zijn er misschien 80 waarvan het product net iets beter is dan de standaard. Aan die 20 studies met een product die een hoge klinische relevantie heeft, wil natuurlijk iedereen wel meedoen	**CH**
CLR	++	**IMO**	*Participating in the most interesting trial is #1. This leads to IMO and may be the most important interdependency*	Meedoen met meest interessante trial is #1 Leidt tot investigator motivatie, is misschien wel de belangrijkste interactie	**EP**
CLR	++	**IMO/ PMO**	*On the contrary, positive data positively affect recruitment (IMO/PMO)*	aan de andere kant, wanneer er positieve data komen dan gaat het de goede kant op	**EP**
CLR	++	**IMO/ PMO**	*However, it is usually the other way around, because studies often take too long and the world around is changing, so the trial becomes less interesting, like "a virtual circle"*	Maar meestal andersom, omdat studies vaak te lang duren en de wereld daaromheen verandert, dus de trial wordt steeds minder interessant "een vicieuze cirkel"	**EP**
CLR	++	**IMO/ PMO**	*When the trial takes too long, there is a negative spiral effect. By the time the conclusion is there, no-one will be interested anymore. Automatically recruitment becomes even more slow*	Negatieve spiraal, trial duurt te lang, als antwoord ooit komt zit niemand daar meer op te wachten. Automatisch nog minder patienten in	**EP**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
CLR	++	**PMO**	*People really want to participate when there is a trial with a proven and registered product, however for another indication. Then participating is a chance to be treated*	Mensen doen graag mee als er een onderzoek is met een bewezen geregistreerd middel, maar met een andere indicatie. Dan is meedoen een kans om het middel te krijgen	**AD**
CLR			*You need to investigate the medication, but sometimes also the idea behind it*	Je wilt het medicijn onderzoeken, maar soms ook het idee daarachter	**AD**
COT	-	**IMO**	*Competing treatments may be a problem, but sometimes also the timelines are not clear, for example when the trial delays when there is no regulatory approval, by that time another trial may have opened*	Competitieve studies kan een probleem opleveren, maar soms zijn de tijdlijnen ook niet duidelijk, wanneer de trial bijvoorbeeld opschuift als er nog geen regulatoire goedkeuring is en tegen die tijd kan er ook een andere trial open gaan	**AJ**
COT	-	**IMO**	*It is my experience that investigators do take that into account, they always mention it*	Het is mijn ervaring wel dat investigators daar rekening mee houden, ze geven dat goed aan	**AJ**
COT	-	**IMO**	*And if it would be the case, they make clear agreements on which trial first or on dividing patients*	En mocht het wel zo zijn, dan maken ze duidelijk afspreken om te verdelen	**AJ**
COT	-	**IMO**	*Competing studies that reimburse a higher patient fee may happen sometimes, but not usually. Most investigator have a high integrity. Lately you don't see that anymore. And it is difficult to find out anyway, because these data are not out in the open*	Competing studies die een hogere patient fee geven komt een enkele keer voor, maar meestal niet. De meeste artsen zijn daar heel integer in. Maar de laatste tijd zie je dat eigenlijk niet meer. Er is ook moeilijk achter te komen, want die gegevens zijn niet open	**AJ**
COT	-	**IMO**	*Especially in single institution trials it is important to make agreements on competing studies. Which study comes first?*	Speciaal voor single institution studies erg belangrijk om goede afspraken te maken over competing studies. Welke studie gaat voor?	**BT**
COT	-	**IMO**	*An example in a multicentre study, where I think the national study coordinator could have streamed better, because the protocol did not equal standard practice*	Multicenter RT studie, nationale coordinator had dat beter kunnen stroomlijnen, omdat het protocol niet overeenkwam met de praktijk	**BT**
COT	-	**IMO**	*Outside the hospital there are other hospitals that may have other studies running*	Buiten het ziekenhuis andere ziekenhuizen die een studie hebben geopend	**JS**
COT	-	**IMO**	*An interim analysis that takes too long, then the momentum/interest disappears*	interim analyse die lang duurt, momentum verdwijnt/interesse	**JS**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
COT	-	**IMO**	*Sometimes standard treatments are not used anymore, so it may be standard, but not regular*	Soms worden standaardbehandelingen al niet (meer) ingezet, dus wel standaard maar niet gebruikelijk	**JS**
COT	-	**IMO**	*Nowadays you don't ask only for competing studies, but also how many studies are ongoing in the site, compared to the capacity*	Tegenwoordig vraag je niet alleen meer naar competing studies, maar ook naar hoeveel studies er in een ziekenhuis lopen ten opzichte van de capaciteit	**KV**
COT	--	**IMO**	*For example, they check whether the comparator is prescribed in the Netherlands, because if this is not the case, no patient will ever be included in the trial*	Bijvoorbeeld checken zij of de comparator in Nederland ook wordt voorgeschreven, want als dit niet zo is, dan komt er geen patient in je trial	**AD**
COT	--	**IMO**	*Clinical relevance and competing treatments are both dominant factors, then all other factor are much less relevant*	Als het klinisch heel relevant is, of als er competing treatments zijn, die zijn heel dominant, dan doet de rest er eigenlijk niet meer zo toe.	**AD**
COT	--	**IMO**	*When there are many competing treatments, also pharma decides not to perform the trial*	Als er veel competing treatments zijn, dan zegt de farma ook, dan doen we die trial niet hier	**AD**
COT	--	**IMO**	*Change in standard of care is very important*	Verandering van standard of care is heel belangrijk	**EP**
COT	--	**IMO**	*The problem may be solved, for example in less frequent SCLC, Karposi Syndrome*	Probleem opgelost, bijv minder vaak voorkomend SCLC, Karposi syndroom	**JS**
COT	--	**IMO**	*Key factors are: competing trials, whether doctors think about the trials and/or if there is a referral patern*	Key factoren: competitieve trials, of dokters eraan denken en of er een verwijzingspatroon is	**JS**
COT	--	**IMO**	*When a clinical trial is not recruiting there are always the same questions you may ask: for example, is there competition with other trials. This is very dynamic. You have to make an inventory of competing trials, numbers of patients. Do doctors think about the trial?*	Wanneer er een niet rekruterende klinische trial is, dan zijn het altijd dezelfde vragen die je jezelf stelt: bijvoorbeeld, competitie met andere trials, heel dynamisch, inventarisatie competitieve sdtudies, zijn de patienten er? Denken dokters er aan?	**JS**
COT	--	**IMO**	*If there are two trials you will make an agreement with the first. In principle, I do not include in another phase III trial when there is already one running*	Als er 2 trials zijn dan maak je afspraken met de eerste. Ip sluit ik geen 2e fase 3 studie af als ik er al een heb lopen	**NS**
COT	--	**IMO**	*One example is a French study in GIST, that I agreed not to participate in another study, but then those French appeared not to be reliable and then I quit*	Bijvoorbeeld GIST bij een Franse studie afgesproken dat ik een andere studie niet zou doen, maar toen bleken die Fransen helemaal niet betrouwbaar en toen ben ik ermee gestopt	**NS**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
COT	--	**IMO/ PMO**	*Competing treatments and investigator/patient motivation works two ways: when another new drug/treatment is available no-one is motivated anymore,*	Investigator en patient; werkt 2 kanten op: bij ander nieuw middel is niemand meer gemotiveerd,	**EP**
COT	feasibility		*You can see all hospitals are full. Not just one study is open, but sometimes 3-4 for the same indication. So, then you will look for other countries. In the end, it's all about data*	Je ziet gewoon in alle ziekenhuizen, ja dat zit gewoon vol. Daar loopt niet 1 studie, daar lopen soms wel 3-4 voor dezelfde indicatie. Dus dan ga je uitwijken naar meer inheemse landen. Het gaat uiteindelijk om de data	**CH**
COT	feasibility		*that is why you observe a shift towards other countries*	Daarom denk ik dat je een verschuiving gaat zien naar andere landen	**CH**
DEN	+	**POP**	*Large academic hospitals often treat more patients*	Grote academische ziekenhuizen hebben vaak wel meer patienten	**AJ**
DEN	+	**POP**	*It is better to investigate where your patients are located*	Je kunt beter kijken waar zitten je patienten	**CH**
EDU	+	**ATT**	*By education, I think, and giving insight in clinical studies, what it means and that it is not only pharma earning money over the backs of patients. By engaging in this mind-set, by being enthusiastic, I think you may reach much more patients*	ik denk juist met voorlichting, door inzicht te geven in klinische studies, wat dat inhoudt, en dat het niet alleen farma is die over de rug van patienten geld wil verdienen. Door die mindset aan te nemen, door er enthousiasme in te stoppen, denk ik dat je veel meer patienten kunt bereiken	**AJ**
EDU	+	**ATT**	*With education, you may break habits*	Met voorlichting doorbreek je taboes	**AJ**
EDU	+	**ATT**	*Education of patient associations for example, by engaging in a conversation at congresses etcetera*	Educatie van patiëntenverenigingen, op congressen bijvoorbeeld.	**AJ**
EDU	+	**ATT**	*Also from the government more education is needed, with films, videos on YouTube, etcetera*	Ook vanuit de overheid kan veel meer voorlichting komen, met filmpjes, YouTube, etc.	**AJ**
EDU	+	**ATT**	*For pharma, there are strict regulations regarding education materials for patients*	Voor de farma is er ook strikte regelgeving omtrent informatie aan patienten	**AJ**
EDU	+	**EXP**	*Professionals are maintained by succession planning, make sure your people are trained, including high level training in diseases, so that a CRA can understand at a fairly high level what the diseases are about*	Vakmensen kun je waarborgen door succesion planning, zorgen dat mensen getraind zijn, hoge trainingen ook qua ziektebeeld, zodat ook een `CRA op redelijk goed niveau kan begrijpen wat de ziektebeelden inhouden	**AD**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
EDU	+	**EXP**	*Employees are not allowed to work any less then 80% in this company, and I fully agree with that. Because if you want to attend courses and keep up with SOP's, and you work less than that, you are only available for the actual work one day a week, the other two days you will be training*	Mensen mogen hier niet minder werken dan 80% en daar sta ik ook helemaal achter, want als jij de trainingen moet volgen en je SOPs bij moet houden, en je werkt minder, dan kan je maar 1 dag per week ingezet worden, want die andere 2 dagen ben je aan het trainen	**AD**
EDU	+	**IMO**	*Previously as a CRO I have send someone to help out. For example, for education, nowadays most pharma companies are united in Transcelerate, this approves courses, so that when you have followed one approved course, it will not be necessary to do another for another company*	Als CRO heb ik wel eens iemand gestuurd om te helpen. Bijvoorbeeld geven van trainingen, veel pharma verenigd in trancelerate, die heeft cursussen goedgekeurd, zodat als je bij de een een cursus hebt gedaan, dan bij de ander niet meer nodig is	**AD**
EDU	+	**IMO**	*We train sites per study. You could hire someone to help out locally, but this person has to be escorted, if they can look into patient files*	Vanuit ons krijgen sites trainingen per studie. Je kunt wel iemand sturen om lokaal te helpen, maar dan moet die wel met iemand meelopen, want je kunt dan alle patientengegevens inzien	**AD**
EDU	+	**IMO**	*And if the investigator is informed well, he/she also knows to inform the patient. Anyway, in every study protocol it should be made clear what the benefit will be for the patient*	En als de investigator het goed weet, dan weet die het ook op zijn patient over te brengen. Maar, elk protocol moet duidelijk hebben wat het oplevert voor de patient	**AD**
EDU	+	**IMO**	*There was one incidence in a first-in-men study that no investigator dared to include the first patient. All wanted to see the effect in other patients, before they would suggest the study to a patient of their own. In that case good education may be beneficial*	Wel eens meegemaakt bij een first-on-man studie dat geeninvestigator wilde beginnen met includeren. Die wilde eerst het effect bij een patient van een ander afwachten. In dat geval dan kan goede voorlichting helpen	**CH**
EDU	+	**IMO**	*Nowadays investigator meetings are much less frequent, 10 years ago it was, and we had some good discussions then*	Tegenwoordig steeds minder investigator meeting, 10 jaar geleden nog wel, en dan waren er toch goede discussies	**CH**
EDU	+	**IMO**	*The concept of a clinical trial educator: personally, I don't even want to think about it, but it may help less experienced centers*	Concept clinical trial educator: moet er persoonlijk niet aan denken, maar kan meer onervaren centra wellicht helpen	**JS**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
EDU	+	**PMQ**	*There should be a qualification for CRA's. It works good for all parties, when there is qualification at all levels*	Voor CRAs zou er een kwalificatie moeten komen. Het werkt voor alle partijen goed als op alle niveaus de juiste kwalificatie is	**CH**
ELI	-	**POP**	*Study protocols still maintain a maximum age most of the time*	Er is nog steeds wel een maximum leeftijd bij veel protocollen	**AD**
ELI	-	**POP**	*The reason recruitment is behind on schedule is because there are inclusion criteria that have not previously been seen, or were not there yet. Or they wished to try*	De reden waarom de recruitment toch achter blijft is vaak omdat er inclusie criteria zijn die eerder niet gezien zijn, of er nog niet waren. Of ze dachten we proberen het wel	**AJ**
ELI	-	**POP**	*What we see in our CRO, is that we accept studies when recruitment is not achieved. First you start looking at the patient population. If that is sufficient, it is mostly about motivation of people. When there are studies for which patients are hard to find, you have to amend the protocol*	Wat wij zien binnen Sourcia, is dat wij studies wel eens overnemen waar de recruitment niet gehaald wordt. Dan kijk je eerst naar beschikbare patienten. Als die er zijn dan gaat het vaak om motivatie van de mensen. Als er studies zijn met moeilijk vindbare patienten, dan moet je het protocol amenderen	**KV**
ELI	feasibility		*Many times, feasibility is done before all eligibility criteria are known, because pharma needs to know as soon as possible how many countries and how many sites are needed*	Feasibility wordt al gedaan voordat alle selectie criteria bekend zijn, omdat de farma zo snel mogelijk in kaart wil hebben hoeveel centra in hoeveel landen nodig zijn	**AJ**
EXP	-	**IMO**	*Experience of an investigator is not always an advantage. They assume they already know every thing, because they perform many trials. Less experienced investigators may try harder to perform well*	Ervaring van de investigator is niet altijd een pre. Dan 'weten ze het wel', want ze doen al veel onderzoek. Minder ervaren ziekenhuizen kunnen veel harder hun best doen om het goed te doen.	**AJ**
EXP	-	**IMO**	*Hospitals have different procedures themselves, although it is improving, but there are still big differences and it improves slowly*	Ziekenhuizen hebben ook verschillende procedures, dat wordt al iets beter, maar er zijn nog steeds grote verschillen en gaat het moeizaam	**AJ**
EXP	-	**IMO**	*Investigator inexperience may be an advantage*	Onervarenheid van een investigator is juist een pré	**EP**
EXP	-	**IMO**	*An experienced investigator is not necessarily beneficial to the patient either, since they often don't get to see the investigator, who is busy and often unavailable. Hands-on help is usually from less experienced doctors*	Voor patienten ook niet perse een pré, ervaren dokter krijgt de patient vaak niet te zien, die is druk en vaak niet aanwezig. Hands on hulp vaak van minder ervaren dokters	**EP**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
EXP	-	**IMO**	*The best recruiters are often the most unknown investigators, that want to be seen, they try harder then the more experienced investigators*	Beste recruiters zijn vaak de meest onbekende dokters, die nog gezien willen worden, die lopen harder dan de ervaren club	**EP**
EXP	+	**IMO**	*Experience from key opinion leaders are important, because else no other investigators will participate. That is why we usually have a national coordinator, to assure its acceptance in the field*	Experience van key opinion leaders wel belangrijk omdat anders andere investigators ook niet meedoen. Daarom hebben we vaak ook een national coordinator, zodat men weet dat het ook gedragen wordt vanuit het veld	**AD**
EXP	+	**IMO**	*Experience counts of course, although it is not always deciding*	Experience telt mee natuurlijk, maar niet altijd doorslaggevend	**AD**
EXP	+	**IMO**	*Experience from an investigator may be advantage, but it may work against you as well. There is no one way*	Ervaring van een arts kan een voordeel zijn, maar kan ook tegen je werken. Dat kan je niet over een kam scheren.	**AJ**
EXP	+	**IMO**	*Experienced people are not necessarily the onces best recruiting, but politically it can be very good. Those are the key opinion leaders*	Ervaren mensen zijn niet perse degene die goed gaan recruteren, maar dat kan politiek soms erg goed zijn. Dat zijn je peer opinion leaders	**AJ**
EXP	+	**IMO**	*Experience is important. Especially the experience you built with this type of studies and communication techniques. You ask quite a lot of your patients, the way you explain. Like what is extra about a study compared to standard treatment*	Ervaring is belangrijk. Vooral de ervaring die je opbouwt met dit soort studies en gesprekstechniek. Je vraagt toch iets van de patient, de manier waarop en de uitleg. Wat is nou extra aan zo'n studie ten opzichte van de standaardbehandeling	**BT**
EXP	+	**IMO**	*Experience also grows with the product and study specific assessments*	Ervaring groeit ook met middel en specifieke studiehandelingen	**BT**
EXP	+	**IMO**	*Yes it could be important to involve a key opinion leader, because then the doctors will be like, yes if that one and that one participates, then I would also like to participate*	Ja het kan wel belangrijk zijn om een key opinion leader te betrekken, dan hebben artsen zoiets van, ja als die en die meedoet, dan wil ik ook wel meedoen	**EM**
EXP	+	**IMO**	*However young inexperienced investigators may be more enthusiastic and they still want to show the world what they can do*	Maar het enthousiasme is misschien wel weer groter bij jonge onervaren artsen en die willen nog laten zien wat ze kunnen	**EM**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
EXP	+	**IMO**	*Experienced investigators have gained experience by participating in many trials. They have co-published but often not based on the number of patients recruited. Nowadays publications are more frequently based on sequence of enrolment*	Ervaren onderzoekers zijn ervaren geworden door veel mee te doen aan trial. Meegepubliceerd, maar vaak niet obv aantal ingesloten patienten. Tegenwoordig meer op volgorde van enrollment	**EP**
EXP	+	**IMO**	*Pharma usually looks out for some key-opinion leaders in West-Europe, but the largest recruitment is from lesser known East-European investigators*	Pharma zoekt vaak een aantal key opinion leaders is West-Europa, maar de grootste inclusie is vanuit minder bekende Oost Europa	**EP**
EXP	+	**IMO**	*Experience is what defines a good or not so good investigator*	Dat onderscheid een goede of een minder goede onderzoeker, wel/meer ervaring	**JS**
EXP	+	**IMO**	*I don't overestimate recruitment myself, because I don't want to be in a position that patient numbers are not correct*	Ik doe dat zelf niet, want wil niet in zo'n situatie komen dat ik niet aan de aantallen kom	**JS**
EXP	+	**IMO**	*If experience helps? Yes, someone who knows the ways, makes sure that everything moves fast and issues get solved*	Iemand die meer ervaring heeft? Ja, of iemand die de lijnen goed kent en zorgt dat alles snel en soepel wordt opgelost	**NS**
EXP	+	**IMO**	*In this hospital, there is a large offering of trials, in a smaller peripheral hospital this number will be much smaller*	In dit ziekenhuis enorm aanbod aan studies, een studie zal in de perifere ziekenhuizen wat specialer zijn	**NS**
EXP	+	**PMQ**	*However, your employees must know what they are talking about, and have good communication skills, and good organizational skills*	Maar je mensen moeten weten waar ze het over hebben, en goede communication skills hebben en ook organisatie skills	**AD**
EXP	+	**PMQ**	*Experience is absolutely a factor in this. When you have more experience, you know better to judge what is needed for a particular site. Either follow, or be more resolving*	Ervaring heeft daar absoluut mee te maken. Als je meer ervaring hebt, kun je beter inschatten wat een site nodig heeft. Meer meegaand zijn, of meer oplossend	**AJ**
EXP	+	**PMQ**	*A project manager is a manager that has to have a global look at progress, a CRA has to be more (scientifically) social. The CRA has to be able to get the message through to the site, without annoying someone*	Projectmanager is echt een manager die moet op globaal niveau kijken, een CRA moet meer (wetenschappelijk) sociaal zijn. Die moet de boodschap ook kunnen overbrengen, zonder dat je iemand tegen het hoofd stoot	**AJ**
EXP	+	**PMQ**	*You have to have experience to decently run the trial*	Je moet ervaring hebben om die studie fatsoenlijk te kunnen afronden	**CH**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
EXP	+	**PMQ**	*You have to know which steps to take and when you have to include other parties*	Je moet weten wanneer je welke stappen moet nemen en wanneer je welke partijen in moet schakelen	**CH**
EXP	+	**PMQ**	*Basically, it all depends on a few key figures. There is one end responsible at the sponsor end, and one responsible at the CRO, en they have to work well together*	Eigenlijk hangt het hele gebeuren af van maar een paar sleutelfiguren. Uiteindelijk is er een verantwoordelijke bij de sponsor en een verantwoordelijke bij de CRO en die moeten samen goed door een deur kunnen	**CH**
EXP	+	**PMQ**	*A CRA may be essential at site level, but in a large international study, with many sites, one dysfunctioning CRA, well yes you should replace, but the complete trial doesn't depend on it*	Een CRA is misschien wel essentieel op site niveau, maar als er bij een grote internationale studie 1 CRA is die niet goed functioneert, tja dan moet je die vervangen, maar daar hangt niet de hele trial vanaf	**CH**
EXP	+	**PMQ**	*Investigator experience may help a lot when estimating the numbers of patients and the study specific assessments*	Investigator experience kan heel erg helpen bij het inschatten van aantallen patienten en het uitvoeren van handelingen	**EM**
EXP	+	**PMQ**	*Good project management is keeping an eye on your metrics, it's very important as a steering instrument*	Goed projectmanagement is de matrix in de gaten houden, belangrijk sturings element	**EP**
EXP	+	**PMQ**	*Even the most experienced person may be hit by an audit*	Zelf de meest ervaren persoon kan bij een audit afgeschoten worden.	**KV**
EXP	+	**PMQ**	*It doesn't help if someone who has recently started doesn't have the experience and freedom to take decisions*	En iemand die net begint heeft niet de vrijheid om beslissingen te nemen? Nee, en dat vind ik wel lastig	**NS**
EXP	++	**PMQ**	*A good PM is able to see trends in recruitment and detect causes, this is based on experience and keeping your metrics up-to-date*	Goede projectmanager ziet trends in recruitment en kan oorzaken detecteren, ervaring en goed je matrix bijhouden	**EP**
EXP	feasibility		*That's why a good feasibility is so important. For example, can I involve key opinion leaders, are there other connections we may use?*	Daarom een goede feasibility doen. Kan ik de key opinion leaders betrekken, zijn er nog andere aansluitingen mogelijk?	**RZ**
EXP			*Motivation is more important than experience*	Motivatie is belangrijker dan ervaring	**KV**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
EXP			*Rather to have someone with motivation that you can still mould, then someone with a lot of experience*	Neem liever iemand aan die kneedbaar is met veel motivatie, dan iemand die veel ervaring heeft en zegt te weten wat ze doen	**KV**
IMO	+	**LFA**	*As a doctor, you may influence this somewhat*	Als dokter kan je hier wel wat invloed op uitoefenen	**BT**
IMO	+	**LFA**	*Although I don't really control a budget as an investigator, a part of the investigator fee is allocated to my name. But that is a very complicated process. You have to be able to guarantee continuity if you hire someone*	Eigenlijk geen budgetverantwoordelijkheid als investigator, wordt wel een deel van de fee gealloceerd op mijn naam. Maar dat proces is wel ingewikkeld. Je moet wel continuiteit kunnen garanderen als je iemand in dienst neemt	**BT**
IMO	+	**LFA**	*You have to react to that, in the hospital organization*	Op inspelen: organisatorisch in het ziekenhuis	**NS**
IMO	+	**LFA**	*When a doctor is successful and earns money, and somehow put the hospital in a positive way to the outside world, yes, then the investigator may have a positive influence on local facilities*	Als de arts succes heeft en geld binnen haalt, en daardoor het ziekenhuis op een of andere manier positief naar buiten komt, ja dan kan de investigator een positieve invloed op de lokale faciliteiten	**RZ**
IMO	+	**LFA**	*Working together on a study with several disciplines, or hospitals may also generate a positive effect in cooperation in general*	Samenwerking met verschillende disciplines, of verschillende ziekenhuizen voor een studie kan ook een positief effect hebben op de samenwerking tussen afdelingen binnen het ziekenhuis	**RZ**
IMO	-	**PMO**	*I, myself, have once been asked to participate in a phase III clinical trial, and then I refused. That particular moment was so emotional, and I could not oversee what was going to happen. Therefore, I chose for what was known, with the standard treatment they could tell me: You have a 70% change and from the new treatment they couldn't say anything. And then I work in clinical research for many years…*	Zelf heb ik ooit ook de vraag gekregen of ik met een fase III onderzoek mee wilde doen, en dat heb ik toen toch niet gedaan. Dat moment was te emotioneel en ik kon het allemaal niet overzien. Dusik ging voor zekerheid, met de standaardbehandeling konden ze me zeggen, u heeft 70% kans en van de nieuwe behandeling niet. En dan werk ik al jaren in onderzoek	**AD**
IMO	-	**PMO**	*Well known investigators often recruit slow and then also patients in poor physical condition*	Bekende onderzoekers recruteren vaak slecht en dan ook nog slechte patienten	**EP**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
IMO	-	**PMO**	*Referral however usually means that you lose your patient. Doctors don't like to do that, so that is a negative incentive*	Doorverwijzen betekent echter altijd dat je de patient kwijt bent. Dat doen artsen dus niet graag. Dat is een negatieve incentive.	**EP**
IMO	-	**PMO**	*You see sites that do not include a single patient, although they did want to participate in the first place*	Je ziet heel veel centra die geen patient includeren, of nauwelijks. Wilde wel meedoen	**NS**
IMO	-	**PMO**	*It is hard to motivate colleagues, they have other interests. That is why many patients are missed*	Moeilijk om collega's gemotiveerd te krijgen, die hebben andere belangen. Daardoor worden weer veel patienten vergeten	**NS**
IMO	-	**PMO**	*I have encountered once that patients had given their consent and went to the radiotherapy department for an appointment. Then they came back and withdrew their consent. What happened? Apparently, a radiotherapist did not agree with the protocol and advised against participating*	Ik heb ook een keer meegemaakt dat patienten toestemming hadden gegeven en vervolgens naar de radiotherapie afdeling gingen voor een afspraak. Dan weer terugkwamen en hun toestemming introkken. Wat was het geval? Een radiotherapeut was het niet eens met dit protocol en heeft negatief geadviseerd.	**RZ**
IMO	-	**PMO**	*Or another example, the surgeons would not refer their patients for neo-adjuvant therapy, because they wanted to operate on them first to get reimbursed*	Of, een ander voorbeeld, de chirurgen sturen patienten niet door voor neo-adjuvante therapie, omdat ze deze patienten eerst willen opereren om geld te kunnen krijgen ofzo	**RZ**
IMO	+	**PMO**	*It also has to do with how you are being asked. Because this was asked during the consultation and I had to answer immediately. Maybe if it would have been explained in a different way*	Het heeft ook te maken met hoe je gevraagd wordt. Want dit wordt gevraagd in het consult en moest ik ala minute antwoord geven. Misschien als het me toen anders was verteld	**AD**
IMO	+	**PMO**	*If the information had been available via the patient association, then it would have made a difference. Or if the department would have had a research nurse taking the time after the consultation with the doctor to explain everything, with 2 days to think it over, then also it would have different*	Als die informatie via de patientenvereniging beschikbaar was geweest, dan was het heel anders geweest. Of als deze afdeling een researchnurse had gehad die na het consult alles rustig had kunnen uitleggen en twee dagen bedenktijd, dan was het ook al anders geweest	**AD**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
IMO	+	**PMO**	*So, you need someone who takes the time to explain, outside regular consultation time, because dealing with the message in one consultation is to complicated. And then time to consider it, in which you could maybe call someone for additional information*	Dus je hebt iemand nodig die daar de tijd voor neemt om het uit te leggen, buiten de tijd van het reguliere consult, want dezelfde boodschap in een is veel te ingewikkeld. En dan nog even bedenktijd, waarin je iemand misschien nog even terug kunt bellen.	**AD**
IMO	+	**PMO**	*And a study protocol is way too complicated, therefore you need to explain in simple words. What happens in the trial, what will happen to you, what is expected?*	En zo'n protocol is veel te complex, dus leg dat iemand in eenvoudige taal uit. Wat gebeurt daar, wat gebeurt er met jou, wat kun je verwachten, wat wordt er van jou verwacht	**AD**
IMO	+	**PMO**	*The trial nurses are really very important, they have a pivotal role, often they know more than the investigator, especially in general practices*	Die trial nurses zijn echt heel belangrijk, die hebben echt een pivotal role, die weten vaak meer dan de investigator. In een huisartsen praktijk helemaal	**AD**
IMO	+	**PMO**	*In oncology patients have a tight relationship with their treating physician*	In de oncologie heeft de patient een nauwe band met de arts	**AJ**
IMO	+	**PMO**	*In my experience, physicians are prepared to let their patients go elsewhere and they will send the patients records. However, it depends on the physician*	Mijn ervaring is dat artsen ook wel bereid zijn om hun patienten daar naartoe te laten gaan en gegevens door te sturen, maar dat verschilt misschien per arts	**AJ**
IMO	+	**PMO**	*When you are enthusiastic yourself, you transfer that enthusiasm on someone else. Therefore, that also influences the patient. That is why you check the Informed Consent procedure during feasibility*	Als je zelf enthousiast bent, dan breng je dat enthousiasme ook op iemand anders over. Dus dat beïnvloedt zeker ook de patient. Bij de feasibility vraag je daarom ook naar de ICF procedure	**AJ**
IMO	+	**PMO**	*Our PA's are study-minded. It is important that patients are discussed in MDOs and get to the right people*	PA's zijn studieminded. Belangrijk dat patienten in MDOs worden besproken en bij de goede mensen terecht komen	**BT**
IMO	+	**PMO**	*Do I select people based on personal preferences? No, in principle I ask anybody if they fullfil the eligibility criteria. Everybody should get a chance to participate*	Voorselectie van patienten? Nee ip vraag ik iedereen als ze aan de selectiecriteria voldoen. Iedereen moet de kans krijgen	**BT**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
IMO	+	**PMO**	*I treat my study patients very good. We see them a lot and it requires a lot from them also. We have to make sure things are arranged as good as possible for them*	Ik pamper mijn studiepatienten wel heel erg. We zien ze vaker en het vergt wel veel van ze. We moeten dat zo goed mogelijk proberen te regelen	**BT**
IMO	+	**PMO**	*Age is a very bad criterion, I think. So is distance. You never know which choices patients make*	Leeftijd vind ik een slecht criterium. Afstand ook. Je weet nooit welke keuze iemand maakt	**BT**
IMO	+	**PMO**	*You cannot leave any responsibility regarding recruitment with the investigator either, because that would not be ethical. The investigator must have the freedom to choose whether the patient is eligible or not*	Bij de investigator kun je ook geen verantwoordelijkheid neerleggen qua inclusie, want dat zou niet ethisch zijn. Die moet de vrijheid hebben om te zeggen dat die patient er wel of niet inpast	**CH**
IMO	+	**PMO**	*However, there is only a limited field in which you can operate. You cannot oblige something, you cannot set goals, well yes you can, but you cannot insist on these. That is not possible, it is a good thing that physicians are free to make a choice*	Alleen er zit een beperkt veld moment waar je invloed op kan uitoefenen. Je kunt niks verplicht stellen, je kunt geen doelen stellen, ja dat kan wel, maar je kunt de ziekenhuizen er niet aan houden. Dat kan ook niet. Het is ook wel goed dat de arts uiteindelijk die keuze moet maken	**CH**
IMO	+	**PMO**	*The physician should remain responsible for its own decisions, you should never change that in my view, so yes, you will always be dependent on that*	Die arts moet verantwoordelijk blijven voor zijn eigen beslissingen, daar zou je nooit aan mogen tornen in mijn ogen, dus ja, je bent altijd afhankelijk daarvan	**CH**
IMO	+	**PMO**	*In a difficult study, I have noticed, that it also depends on the way a physician informs the patient, with supporting materials, etc. That makes a difference.*	Bij een ingewikkelde studie, heb ik gemerkt dat de manier waarop de arts een patient inlicht, met ondersteunende materialen ed, dat dat heel erg scheelt	**EM**
IMO	+	**PMO**	*Doctors firstly want to help patients, depending on how much time doctors have*	Eerste plaats willen artsen patienten helpen, hangt af van hoeveel tijd artsen hebben	**KV**
IMO	+	**PMO**	*For example, it is being said, you have to come in more often, but we will scan and investigate you more often*	Er wordt bijvoorbeeld ook gezegd, je moet vaker komen, maar daarvoor wordt je ook vaken gescand en vaker onderzocht	**RZ**
IMO	+	**PMO**	*Mostly the enthusiasm of the investigator him/herself counts. I have experienced that in one arm it was noticed*	Vooral het enthousiasme van de onderzoeker zelf speelt mee. Ik heb wel meegemaakt dat in een arm	**YG**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
			that patients did better, so investigators became enthusiastic themselves	gemerkt werd dat de patienten het beter doen, dus dat enthousiasmeert ook de arts	
IMO	+	**PMO**	*In oncology studies doctors are more involved then for example in cardiology hypertension studies, there the investigator is at a distance and are the research coordinators/nurses much more important. They are the ones selecting and approaching the patients*	Bij oncologie studies zijn artsen veel meer betrokken dan bij bijvoorbeeld cardiologie hypertensie studies, daar is vaak de investigator veel verder uit beeld en spelen de research coordinatoren/researchverpleegkundigen een veel belangrijker rol. Die selecteren en benaderen de patienten vaak zelf	**YG**
IMO	++	**PMO**	*If you look at the full picture (model), yes, this investigator motivation is very logic, that is where I believe is the biggest driver*	Als je naar het plaatje (model) kijkt, ja dit is een hele logische, die investigator motivation, daar zit in mijn ogen de grootste drijver in	**CH**
IMO	++	**PMO**	*Indeed, in oncology the investigator is the most important factor influencing recruitment*	Bij oncologie is de arts inderdaad wel het belangrijkste factor met de meeste invloed op recruitment	**EM**
IMO	++	**PMO**	*The doctor's advice is probably the most important motivation for the patient*	Investigator "wat de dokter zegt" eigenlijk wel de belangrijkste motivatie voor de patient	**EP**
IMO	++	**PMO**	*IMO is the most important factor in patient recruitment*	Investigator motivation is de belangrijkste factor in patient recruitment	**EP**
IMO	++	**PMO**	*Of course, also the patients decision, but they usually do as the doctor says*	Uiteraard ook de patient, maar die doet meestal wat de dokter zegt	**EP**
IMO	+	**PMQ**	*and then later they find out, oh I don't have that many patients. It is important that they do that sooner, really looking into their database*	en dan komen ze er later achter, oh zoveel patienten heb ik helemaal niet. Belangrijk dat ze dat eerder doen, daadwerkelijk in de database kijken	**EM**
IMO	+	**PMQ**	*And one doctor may want to participate, but that doesn't mean that the hospital or your colleagues are willing to cooperate*	En 1 dokter kan het willen, maar dat betekent niet dat het hele ziekenhuis/collega's mee willen werken	**NS**
IMO	+	**PMQ**	*The investigator will have to make colleagues from other departments as enthusiastic*	De PI zal zijn collega's van andere afdelingen ook moet enthousiasmeren	**YG**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
IMO	+	**PRR**	*PMQ could have some influence on the recruitment, however that is more related to site motivation*	PMQ kan wel wat invloed hebben op de recruitment, maar dat is meer gekoppeld aan site motivatie	**EP**
IMO	feasibility		*Often investigators only have 2 days time to fill out the 3-4 pages document, and therefore this cannot be done very carefully. This happens for example in a BID-defence*	Vaak hebben artsen maar 2 dagen de tijd om in te vullen, een 3-4- pagina's tellend document, en dus dat wordt even tussen neus en lippen door gedaan. Bijvoorbeeld bij een BID-defence.	**AJ**
IMO	feasibility		*The feasibility questionnaire is usually completed by the research coordinator/nurse, not by the investigator*	De feasibility wordt in veel gevallen ingevuld door de research coordinator/ verpleegkundige, niet door de investigator zelf	**AJ**
IMO	feasibility		*Investigators often make promises they cannot keep; promises, estimates*	Artsen maken beloftes die niet nagekomen worden, beloftes of toezeggingen of inschattingen	**YG**
LFA	+	**IMO**	*And of course, an investigator needs to have the time and the facilities to be able to participate*	En natuurlijk moet een investigator de tijd en de faciliteiten hebben dat ie het kan doen	**AD**
LFA	+	**IMO**	*There is a difference in organization between the hospitals. In some hospitals for physicians and nurses it is an activity besides the job, however in other hospital it is really organized very well. That difference is clearly noticeable. And because they are well organized, decisions are made quickly*	Er is zeker verschil in organisatie in de verschillende ziekenhuizen. In sommige ziekenhuizen doen de artsen en verpleegkundigen het er maar een beetje bij, maar in andere is het gewoon heel goed geregeld. Dat verschil merk je heel duidelijk. En omdat het goed op elkaar is afgestemd, dan kunnen beslissingen snel genomen worden	**AJ**
LFA	+	**IMO**	*It is crucial there is a good organization onsite, fortunately that change is coming*	Het is cruciaal dat er een goede organisatie is op de site. Die omslag zie je wel steeds meer komen	**AJ**
LFA	+	**IMO**	*Local facilities are absolutely an important motivation, difficult stuff is not fun*	Lokale faciliteiten absoluut een belangrijke motivatie, gepruttel dingen zijn niet leuk	**BT**
LFA	+	**IMO**	*Local facilities are important, and also the local support from research coordinators*	Lokale faciliteiten zijn belangrijk, en ook de lokale ondersteuning van research coordinatoren	**BT**
LFA	+	**IMO**	*As said before, the research nurses in oncology do not directly influence recruitment. They do however influence logistics, but that may be viewed upon as local facilities*	Zoals gezegd, hebben de research nurses inde oncologie niet direct invloed op de recruitment. Wel op de logistiek, maar dan kan het meer gezien worden als local facilities	**EM**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
LFA	+	**IMO**	*Limitation in East European hospitals is the facility of the participating centre. If it is sufficiently equipped, usually the best quality is found there*	Beperking in Oost-Europa is dat het centrum goed geoutillerd moet zijn. Anders daar de beste kwaliteit.	**EP**
LFA	+	**IMO**	*In Eastern Europe support from a study nurse may be less valued. The investigator prefers to coordinate and report him/herself to earn the full patient fee*	Ook in Oost-Europa niet altijd nodig/gewenst, investigator doet graag alles zelf voor de opbrengst van patientfee	**EP**
LFA	+	**IMO**	*Local facilities are important. When an investigator has no time, and then also has to think about preparing informed consent etc., things will go wrong, Outpatient clinics are delayed etc. So, this is an essential factor.*	Lokale faciliteiten wel belangrijk. Als een onderzoeker geen tijd heeft en dan nog ICF moet voorbereiden bijvoorbeeld, dan wordt het helemaal niks, anders loopt de poli uit etc. Dus dat is een essentiele factor	**JS**
LFA	+	**IMO**	*But then they have so much standard therapies that there is hardly any time left for research*	Die hebben een overvloed aan standaard patientenzorg, dus die hebben ook niet veel tijd	**NS**
LFA	+	**IMO**	*In this day and age have physician perform the study all by him/herself? Then there would not be any time left to consult patients*	In deze tijd nog een studie uitvoeren door alleen de arts? Dan ziet die bijna geen patienten meer	**YG**
LFA	feasibility		*Local facilities are a condition, when infrastructure is necessary for execution of the trial*	Lokale faciliteiten is wel een voorwaarde, infrastructuur van belang als dat nodig is voor de trial	**EP**
N&B	0	**ATT**	*Norms and values are really not influential, that takes too much time*	Normen en waarden zijn eigenlijk niet te beinvloeden, duurt veel te lang	**EP**
N&B	+	**ATT**	*Norms and values are barely changeable; however, they may have influence on the attitude. However, I don't have experience with that*	De normen en waarden zijn nauwelijks te veranderen, maar dit kan misschien wel invloed hebben op de motivatie, maar daar heb ik geen ervaring mee	**EP**
OUC	0	**IMO**	*Outsourcing complexity is not really of influence to the investigator motivation, mostly viewed at as a necessary inconvenience*	Outsourcing niet echt van invloed op de motivatie van investigator, wordt meer gezien als noodzakelijk kwaad bij complexe gevallen	**EP**
OUC	0	**IMO**	*Complexity in outsourcing is seen as a nuisance, does not have more influence then that*	Complexe outsourcing situaties wordt gezien als een nuisance, heeft niet meer invloed dan dat	**EP**
OUC	0	**IMO**	*When in the end all organisation is taken good care off, then it won't withhold from recruiting patients, but altogether it takes longer*	Als het uiteindelijk allemaal goed geregeld is, dan weerhoudt het niet om patienten te recruteren, maar het duurt wel weer allemaal langer	**JS**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
OUC	-	**IMO**	*Sometimes there are 10 open studies and all have a different eCRF and another set of rules*	Soms hebben ze 10 studies lopen en allemaal hebben ze ander CRF en andere regeltjes	**AD**
OUC	-	**IMO**	*There is a large administrative burden, and it tends to overdo. Sometimes there are even more than 10 systems you have to log into and to maintain*	Er is veel administratieve last van een trial, en dat slaat nu een beetje door. Je hebt per studie soms meer dan 10 systemen waar je in moet loggen en die je bij moet houden	**AJ**
OUC	-	**IMO**	*One notices that the research coordinators disagree, and they are not so happy to see you coming*	Je merkt dat vooral de researchcoördinatoren daartegenin gaan, die zien je ook niet zo graag komen	**AJ**
OUC	-	**IMO**	*I think physicians rather would have someone from the pharma, then from a CRO. In pharma, you are closer to the development information and physicians liked that*	Ik denk dat artsen liever iemand van de farmaceut zien komen dan iemand van de CRO. Je zit ook dichter bij het vuur, en dat vonden artsen ook prettig	**AJ**
OUC	-	**IMO**	*As a CRO you are not allowed to visit a physician more frequently, because there is no more time and money to spend*	Bij een CRO is het ook zo dat je in feite niet vaker de arts mag bezoeken, omdat daar geen tijd en budget voor is	**AJ**
OUC	-	**IMO**	*Complexity through different vendors can be a burden for the patient, it takes time and money, they cannot use seeing the patient, so yes, the influence is on final recruitment*	Complexiteit door verschillende vendors kan echt belastend zijn voor de patient, dat kost tijd en die tijd kunnen ze niet besteden aan het zien van een patient, dus ja, dat heeft ook invloed op de uiteindelijke recruitment	**AJ**
OUC	-	**IMO**	*So many log-ins for pharma, it makes you crazy. Lab system, regulatory, screening system. It prevents recruitment*	Op hoeveel dingen moeten inloggen van pharma, daar wordt je gewoon gek van. Labsysteem, regelementen, screeningssyteem. Dat houdt wel tegen.	**BT**
OUC	-	**IMO**	*Some CROs are a real 'pain', then it doesn't matter how hard you try, it is never good enough. Communication may be in a hierarchic manner and not effective*	Sommige CROs zijn lastig, het maakt niet uit hoe hard je je best doet, maar het is nooit goed genoeg, communicatie verloopt hiërarchisch	**JS**
OUC	-	**IMO**	*The CRO you choose matters a lot. Some are really terrible. For example, they don't give any support, no personal contact person, dumb and rude. Sometimes reactions are slow, they don't answer. Insufficient*	Welke CRO je kiest is belangrijk, sommigen zijn echt verschrikkelijk. Bijv geen steun vanuit het team. Persoonlijk aanspreekpunt, dom en bot. Traag, geven geen antwoord. Onvoldoende	**JS**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
			support in materials. Communication is over many layers	ondersteuning, bijv pomp, onbegrip, gaat over veel schijven	
OUC	-	**IMO**	*Complexity has a negative influence on investigator motivation*	Complexity heeft een negatieve invloed op de investigator motivatie.	**KV**
OUC	-	**IMO**	*80% of the trial is performed by the research nurses/coordinators, not by the investigator itself, but nonetheless hears al the complaints*	80% wordt uitgevoerd door studiecoördinatoren, niet door de investigator, maar die hoort wel de klaagzangen	**KV**
OUC	-	**IMO**	*More and more the CRAs are adapting an auditor's role, start correcting sites, however that is counter-productive. And then the auditors are becoming even more strict officers*	Meer en meer nemen CRAs de rol van auditor, gaan centra op de vingers tikken, maar dat werkt contraproductief. En dan gaan auditors nog sterkere agenten zijn	**KV**
OUC	-	**IMO**	*New concepts as remote-control monitoring and risk-based monitoring brings the CRA even less in contact with the site. On the other hand, sponsors start investing more in web-based solutions, which in my opinion is also counter-productive*	Door nieuwe concepten als remote control monitoring en risk-based monitoring komt de CRA eigenlijk steeds minder in contact met de site. Daarentegen gaan de sponsors meer investering in web-based oplossingen, en dat mijns inziens contraproductief	**KV**
OUC	-	**IMO**	*Not too many monitor visites, administrative procedures, it has to be useful*	Niet te veel monitorvisites, administratieve handelingen moeten nuttig zijn	**NS**
OUC	-	**IMO**	*A large administrative burden really prohibits to ask patients, for example when the nurse practitioner is on a holiday. I really cannot find the time to do all this additional administration*	Grote administratieve last houdt echt tegen om patienten te vragen, bijv. VS op vakantie. Echt geen tijd voor	**NS**
OUC	-	**IMO**	*But then they (CRO/pharma) ask for things that are really unnecessary, you know. It is unrealistic if I have to sign off, when a PK sample was taken one minute after the scheduled time*	Maar ze vragen ook dingen die echt onzinnig zijn, weet je. Het is toch echt onzinning als ik een handtekening moet zetten als de PK-afname 1 minuut over tijd is afgenomen	**NS**
OUC	-	**IMO**	*When I have to have telephone contact with a monitor, although it was agreed this would be with a sub-investigator, however her boss says that it also has to be with me. But I don't have to say anything, and I don't have to, she only contacts me because she has to and then she can say that she has*	Als ik telefonisch contact moet hebben met een monitor, terwijl afgesproken is dat die met de subinvestigator, maar van haar baas daarna nog echt met mij moet praten. Maar ik heb niets te zeggen, en dat hoeft ook niet, ze moet alleen dat	**NS**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
				doen van haar baas. En dan kan ze zeggen dat ze dat heeft gedaan	
OUC	-	**IMO**	*And also, larger issues that become such a burden, like you have a toxicity documented a day earlier or later in the patient file. It is really not relevant if someone had belly pain one day earlier or two years earlier for that matter*	Veel grotere dingen nog die zo'n ontzettende rompslomp zijn, je hebt de tox een dag eerder of later opgeschreven in de decursus Of iemand een dag eerder of een dag later, 2 jaar geleden, buikpijn kreeg… dat is niet relevant	**NS**
OUC	-	**IMO**	*No-one thinks about the costs implied with these this (queries)*	Er wordt niet over nagedacht dat daar (queries) juist de kosten inzitten	**NS**
OUC	-	**IMO**	*Outsourcing complexity, yes, every time another CRA shows up it is bad for the study, it doesn't matter if it is for the same CRO or not*	Bij outsourcing complexity, ja inderdaad als er iedere keer een andere CRA komt dan is dat slecht voor de studie, maakt niet uit of dat voor dezelfde CRO is	**RZ**
OUC	-	**IMO**	*It seems as if investigators would rather see a monitor from the pharma sponsor then from a CRO, but then CRAs are the face of the pharma. However, that world has almost come to an end. Every time another CRA, no, that is not good for your study*	Lijkt alsof artsen liever een monitor van de farma zien in plaats van een CRO, CRAs zijn het visitekaartje van de farma. Maar ja, die wereld is bijna voorbij. Iedere keer een andere CRA, nee, dat doet geen goed voor je studie	**YG**
OUC	-	**IMO**	*Procedures, yes some really overdo in procedures, it is not clear to me if that genuinely influences recruitment*	Procedures, ja sommige slaan echt door in de procedures, niet duidelijk of dat nu echt de recruitment beïnvloed	**YG**
OUC	-	**PMQ**	*To intercept the disadvantages of complexity it's important to maintain a direct relationship with the medical director*	Om de nadelen van de complexiteit te ondervangen is het wel belangrijk om de directe relatie met de medical director te houden	**CH**
OUC	-	**PMQ**	*There is more strictness in the CRO organizations compared to pharma's own project management*	Grootste probleem is de striktheid in organisatie CRO tov pharma eigen PM	**KV**
OUC	-	**PMQ**	*Many rules have been made, based on some incidents. But now we are crossing the line.*	Veel regels opgesteld, op basis van enkele voorvallen. Maar we gaan stilletjes wel over de grens	**KV**
OUC	+	**PMQ**	*Outsourcing complexity provides some independence. Of course, the sponsor has a very direct interest, the CRO is somewhat more independent*	Outsourcing complexiteit genereert wat meer onafhankelijkheid. De sponsor heeft natuurlijk een	**CH**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
				heel direct belang, de CRO heeft een iets meer onafhankelijke positie	
OUT	+	**PMQ**	*And the way projects are managed*	En de manier waarop je projecten managed	**CH**
OUT	+	**PMQ**	*The capacity you get as a CRO has a large impact on how you may solve queries at a site*	De capaciteit die je als CRO krijgt heeft een impact op het kunnen oplossen van queries bij de site	**KV**
OUT	++	**PMQ**	*Outsourcing is almost common practice. There are hardly any pharma companies anymore that do the operational work themselves*	Outsourcing is eigenlijk wel standaardpraktijk. Er zijn bijna geen pharma bedrijven meer die het CRO werk zelf uitvoeren	**EP**
OUT	feasibility		*Another CRO may possibly be asking the feasibility with the same site*	Een andere CRO kan bij dezelfde centra een feasibility doen	**AJ**
PAD	feasibility		*Personally, I would not choose Asia, but this has to do with patent protection. You might fear product copying, but that is mainly a concern for small biotechs*	Azie zou ik niet direct voor kiezen, maar meer in verband met patent bescherming. Daar kan je wel angsten hebben dat je product gekopieerd wordt, maar dat is vooral voor kleine biotechs een uitdaging	**CH**
PEO	0	**ATT**	*Of course, you don't want to miss the boat, want to participate. And of course, you want to be a part of it, but if that recruits more patients is still a question*	Je wil niet buiten de boot vallen, wil overal aan meedoen, een hype. Je wil vooral erbij horen. Maar of dat meer patienten rekruteert is maar de vraag	**NS**
PEO	+	**ATT**	*Peer opinions are important as some kind of stimulus, you have to take it into account. It is also important to raise external funding*	Peer opinions wel belangrijk als vorm van stimulans, je moet er wel rekening mee houden. Belangrijk voor externe funding	**BT**
PEO	+	**ATT**	*Peer influence is another important factor I think*	Peer influence is ook wel een grote factor denk ik	**EM**
PEO	+	**ATT**	*Sometimes influenced by media, via family and friends*	Soms wel nieuwsbericht, via familie en bekenden	**EP**
PEO	++	**ATT**	*Peer opinions are very important, also for the general perception. Take for example immunotherapy, all patients ask for that treatment since it has been in the news*	Peer opinion: is heel belangrijk, ook voor de algemene perceptie. Neem bijv. immunotherapie, in de publiciteit komt dat hier de immunotherapie plaatsvindt, dus alle patienten vragen daarnaar. Die komen daarvoor. Hoewel volkomen misplaatst	**JS**
PEO	++	**IMO**	*Peer opinions are definitely important to the investigator*	Peer opinions zijn zeker belangrijk voor investigator (zie investigator motivation)	**EP**
PEO	+	**PMO**	*(Peer opinions) Sometimes also for patients*	(Peer opinions) Soms ook voor patienten	**EP**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
PMO	0	**IMO**	*Patients will come and say I have read this and that. But I doubt if that increases the recruitment*	Heel dubbel. Patienten komen met ik heb dit gelezen, ik heb dat gelezen. Betwijfel of er daardoor meer patienten in de studie komen	**NS**
PMO	++	**PRR**	*Patient motivation is especially in our hospital an important factor, it is a specific patient group*	Patiënten motivatie is voor het AVL heel belangrijk, specifieke patientengroep die snel ja zeggen	**BT**
PMQ	+	**IMO**	*It always surprises me that so much of this depends on soft factors, whether the research coordinator gets along with the CRA is already a 50% gain. It is about people being prepared to put your study on top*	Het verbaast me wel dat zoveel daarvan afhangt van softe factoren, of de researchcoördinator toevallig goed overweg kan met de CRA scheelt al 50%. Kijk het gaat erom dat die mensen genegen moeten zijn om jouw studie bovenop de stapel te leggen	**CH**
PMQ	+	**IMO**	*In case of a problem it is advisable to have the monitor contact the site or come along. I have noticed that works better. It is good to have an escalation plan upfront. CROs have that as a standard.*	Bij een probleem, laat de medical monitor contact opnemen of meegaan. Merkt dat dat meer helpt. Escalatieplan, goed om van tevoren te hebben. CROs hebben dat standaard.	**EM**
PMQ	+	**IMO**	*The Pi signs the escalation plan, as does the PI. So, in case there is a problem you can go back to the initial agreement*	De PI tekent dit, en de PI ook. Wanneer er een probleem is, dan kan je terug naar de afspraken	**EM**
PMQ	+	**IMO**	*It also depends on the person*	Ja, het is ook per persoon afhankelijk	**EM**
PMQ	+	**IMO**	*And on project management, it is important you are on top of things*	En projectmanagement, het is heel belangrijk dat je daar bovenop zit.	**EM**
PMQ	+	**IMO**	*The enthusiasm peak is usually right in the beginning. Indeed, it is important to keep everyone enthusiast*	De enthousiasme piek heb je vooral aan het begin. Inderdaad belangrijk om iedereen 'warm' te houden	**EM**
PMQ	+	**IMO**	*Metrics are used for finding causes, in discussion with the site. Maybe a change in the protocol is necessary*	Dan kan je de oorzaak uitzoeken, met de site in gesprek. Misschien is wel een verandering in het protocol nodig	**EP**
PMQ	+	**IMO**	*Most important is contact of the CRA with the site, not the PM of the CRO. The CRA is in contact with the investigator and is in the position to motivate the site.*	Belangrijkste is het contact met de CRA, niet de PM. De CRA heeft contact met de investigator en die kan de site motiveren. PM is belangrijk om de metrics in de gaten te houden en te signaleren	**EP**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
			The important task of the PM is to keep an eye on the metrics and signal when necessary		
PMQ	+	**IMO**	*It is also important that you built a trusting relationship*	Het is ook belangrijk dat je zo'n vertrouwensbasis opbouwt	**RZ**
PMQ	+	**IMO**	*I have seen one example from a colleague that did not do a good job. In this case there was a key opinion leader, however the study nurse was from the "bad kind". Many patients were included; however, the documentation was a catastrophe. The problem was also that the CRA involved was not strong enough, could not get through to the site. So yes, the CRA can make a difference*	Ik heb een voorbeeld gezien van een collega die het niet goed deed. In dit geval was er een key opinion leader, maar study nurse was 'van de slechtere kant'. Veel geïncludeerd, maar de documentatie was een catastrofe, probleem was ook dat de CRA die daarop zat, die had geen 'standing', die kon niet doorzetten	**RZ**
PMQ	+	**IMO**	*And say 'no', this is not working, I keep sending queries and don't receive any responses, so we don't get any further*	en zeggen 'nee, dit loopt niet, ik blijf queries sturen en ik krijg geen antwoord en we komen hier niet verder	**RZ**
PMQ	+	**IMO**	*Something like that is really bad and has to be escalated*	En zoiets is echt kwalijk, dat moet geëscaleerd worden.	**RZ**
PMQ	+	**IMO**	*It is very important that the monitor that visits the sites is well trained for the study*	Van belang dat de monitor die langskomt goed opgeleid is voor de studie	**RZ**
PMQ	+	**IMO**	*Influencing as a CRA, it is finding the balance how often you contact the site. Make good estimates, dependent on how many patients have been recruited and who you call. It is balancing on what you can and cannot do*	Beinvloeden als CRA is het net de balans hoe vaak je contact opneemt. Goed inschatten, afhankelijk van hoeveel patienten meedoen en ook wie je belt. Het is balanceren op wat kan en niet kan	**YG**
PMQ	+	**IMO**	*Also, here the 80-20 rule applies: which means that 20% of the sites, accrues 80% of the patients*	Hier gaat ook de 20-80 regel op: dat wil zeggen 20% van de sites recruteert 80% van de patienten	**YG**
PMQ	+	**PUA**	*I have witnessed studies without recruitment, of course you explore all means*	Ik heb studies meegemaakt waar je een jaar geen patient inkrijgt, dan grijp je natuurlijk alle middelen aan	**CH**
PMQ	+	**PUA**	*Contact with patient associations may help*	Contact met patienten verenigingen kan ook zeker helpen.	**CH**
PMQ	+	**PUA**	*There are regulations on education/patient materials, but of course you may publish in a national newspaper, so you can do something with that*	Reguleringen zeggen iets over educatie/patienten materialen, maar je mag natuurlijk wel iets publiceren in de krant, dus daar kan je wel iets mee doen	**CH**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
PMQ	+	**PUA**	*By newsletters and investigator meetings it is again on the top of their minds, for sometimes it sinks a bit. They have so many other things to do, and raising the awareness somewhat, can never do any harm*	Door nieuwsbrieven en investigator meetings zijn ze toch weer alert, soms zakt het ook een beetje weg. Ze hebben toch ook veel andere dingen te doen, en een beetje awareness kan dan geen kwaad	**EM**
PMQ	+	**PUA**	*In the US websites are being used a lot. Partly via patient associations*	In Amerika wordt wel veel gebruik gemaakt van websites ed. Ook veel via patiëntenverenigingen/patient associations	**EM**
PMQ	+	**PUA**	*Yes, we have contacted patient associations ourselves, however you need permission from the regulatory authorities to do so*	Ja, we hebben ook zelf patiëntenverenigingen benaderd, maar daar heb je wel eerst toestemming voor nodig van de METC	**EM**
PMQ	+	**PUA**	*That is why it is important to share positive experiences*	Daarom is het belangrijk om positieve ervaringen te delen	**EM**
PMQ	+	**PUA**	*However, the role of the project manager is limited in public awareness*	Maar rol PM beperkt bij public awareness	**EP**
PMQ	+	**PUA**	*In raising public awareness, it depends on the national regulation. It defers per country. Recruitment publicity is not permitted in several countries, publications are permitted*	De vraag is wat in alle landen mag. Niet in alle landen mag direct publiciteit. Wel publicaties	**EP**
PMQ	+	**PUA**	*Yes, that helps! Share tips and tricks. Or organize calls. Share experiences and then a lot may come forward.*	Ja, dat helpt echt! Tips en tricks. Of calls organiseren. Ervaringen delen en dan kan er veel naar voren komen	**RZ**
PMQ	+	**PUA**	*And then only mention the centre number, not the centre name, or else there will be an argument*	Dat moet je wel zo doen dat het niet voor iedereen te zien is welk centrum het betreft. Alleen centrumnummer noemen, niet de naam, want dat zorgt echt voor ruzie!	**RZ**
PMQ	+	**PUA**	*However, this really puts some competition between centres, and you will be amazed at what happens*	Maar dit zet de centra echt een beetje in concurrentie en het zal je verbazen wat er dan gebeurt	**RZ**
PMQ	+	**PUA**	*In one study, it made sure that within a certain timeframe many patients were recruited, ánd that all documentation was complete, so we could present the first outcomes at ASCO in a very short time*	Bij een studie heeft het er toch voor gezorgd dat er binnen een bepaalde tijd veel patienten waren gerekruteerd én dat de documentatie er was, zodat we op de ASCO al de eerste uitkomsten konden presenteren	**RZ**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
PMQ	+	**PUA**	*That is seen more and more, that patient associations try to get information and explain on treatments, also on trial. The more information you can provide, the better it is, that also prevents patients form hearing incorrect information*	Dat heb je wel dat steeds meer patiëntenverenigingen proberen informatie te krijgen en uitleg te geven, ook over studies. Hoe meer info je kunt verstrekken hoe beter, dat voorkomt ook dat patienten het fout te horen krijgen	**RZ**
PMQ	+	**PUA**	*Also, interim calls or meetings. Then you visualize how many patients are included, how many responses are seen, etcetera. It motivates.*	Ook interim calls of meetings. Dan laat je zien zoveel hebben wij nodig, zoveel zijn geïncludeerd, zoveel responsen zijn gezien, etc. En dit loopt goed daar qua inclusie en daar qua motivatie en daar loopt het niet zo goed.	**YG**
PMQ	++	**PUA**	*Important is the study PR, there are companies specialized in this, to gain awareness*	Belangrijk is PR van de studie, daarvoor zijn er bedrijven, die daarin zijn gespecialiseerd, om aandacht te vragen,	**EP**
PMQ	+	**SUP**	*You always have to make sure there is a national coordinator, that organises meetings throughout the country, makes sure there are good newsletters with valuable news*	Je zorgt altijd dat er een nationale coördinator is, organiseert meetings in het land, zorgt dat er goede nieuwsbrieven zijn waarin echt iets gemeld wordt	**AD**
PMQ	+	**SUP**	*Indeed, to the investigators we always send newsletters, the intensity depends on the type of study. If patients have to come in only twice per year, then we will only send a newsletter once or twice a year, otherwise more frequent. And especially during the recruitment phase, when there is international competitive recruitment*	Naar de investigator sturen we inderdaad altijd nieuwsbrieven, de intensiteit hangt af van de studie. Als mensen maar 2x per jaar hoeven komen dan doen we dat maar 1 of 2 keer per jaar, maar anders vaker. En zeker in de recruitment fase, als het competitief is over de hele wereld	**AD**
PMQ	+	**SUP**	*So, in the end it is better to reserve more money for contact with the investigator, a CRA, a project manager or the sponsor itself, but yes you have to reserve money, to achieve that motivation*	Dus uiteindelijk kun je beter meer geld reserveren voor het contact met die studie investigator, een CRA, een projectmanager of de sponsor zelf, maar ja daar moet je geld insteken, om daar die motivatie uit te betalen	**CH**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
PMQ	+	**SUP**	*I agree this is a very complex system, we have experienced a trial in which no patient was recruited for a full year, and then we looked closely, it was a very small issue concerning the study nurse, so you have to take time and attention to solve that*	Ik ben het helemaal met je eens dat dit een heel complex systeem is, wij hebben zelf ook meegemaakt dat er een jaar lang geen patient gerecruteerd werd en als je dan gaat kijken, dan kom je bijeen heel klein dingetje wat bij die studie nurse ligt en daar moet je tijd en aandacht aan besteden om dat op te lossen	**CH**
PMQ	+	**SUP**	*It is a kind of customer relation management that you have to do*	Het is een soort relatiemanagement dat je moet doen	**CH**
PMQ	+	**SUP**	*We then provided supportive materials, and a video. Many kinds of materials are possible, also websites, etc. Most large CRO's have a separate department for that, specialized in patient recruitment. However, it really depends on budgets*	Wij hebben toen ondersteunende materialen gemaakt, en een video. Er is veel materiaal mogelijk, ook websites etc. De meeste CROs hebben daar een aparte afdeling voor, die toegespitst zijn op patient recruitment. Maar ja, het hangt echt af van budgetten	**EM**
PMQ	+	**SUP**	*When they don't see you, they don't think of you, newsletter help to remember, its usually useful for research nurses. Keep them informed of inclusion criteria*	Uit het oog, uit het hart, newsletter herinnering, meestal research nurses. Op de hoogte van criteria	**EP**
PMQ	+	**SUP**	*The project manager doesn't have so much influence, not so much impact. This job is mostly for organizing, facilitating,*	Projectmanager niet zoveel invloed, niet veel impact. Met name organiseren/faciliteren, gemoedstoestand	**KV**
PMQ	+	**SUP**	*The CRA should be a person who helps the site. You could check a few things less, to check others better in order to improve recruitment*	De CRA zou een persoon moeten zijn die het centrum helpt. Je kunt een aantal zaken mider controleren om andere zaken beter te controleren, die in het belang zijn van een goede recruitment	**KV**
PMQ	+	**SUP**	*The most important part is personal contact, to motivate the site and to get information on why the trial is not recruiting*	Allerbelangrijkste is het persoonlijke contact, om te motiveren en om informatie te krijgen waarom het niet loopt	**KV**
PMQ	+	**SUP**	*Important is that, one of the prevailing laws that I have learned right at the start, is that you have to make sure the synopsis is clear and complete*	Belangrijk is dat, een van de hoofdwetten die ik aan het begin geleerd heb, is dat je ervoor moet zorgen dat de synopsis duidelijk en volledig is	**RZ**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
PMQ	+	**SUP**	*One by one going through the inclusion criteria after the protocol was send, and then the doctor said: " oh wait, I don't see these patients at all". Fortunately, you find out in time.*	Een voor een inclusiecriteria doornemen nadat het protocol was toegestuurd en dat de arts zei, oh, maar wacht, die patienten zie ik helemaal niet, want dat geven wij niet, gelukkig kom je er dan nog op tijd achter	**YG**
PMQ	++	**SUP**	*Support may be given during monitoring visits, these are motivational visits. Take (educational) materials, combination of means*	Support in de vorm van frequente monitoring visits, is motivational visits. Materialen meenemen, combinatie van meerdere middelen inzetten	**EP**
PMQ	feasibility		*We have employed medical advisors, separate from the medical department or sales/marketing, so especially for clinical support*	Wij hebben medical advisors in dienst die niet op de medische afdeling zitten of in de sales of marketing, dus echt voor de klinische ondersteuning	**AD**
PMQ	feasibility		*They perform a pre-feasibility and based on this, headquarters will decide where the trial will be opened*	Zij doen een pre-feasibility en op basis daarvan besluit het hoofdkantoor waar de studie wordt uitgevoerd	**AD**
PMQ	feasibility		*And then they consider the life standard per country, because our investigators are quite expensive compared to other countries in South or East Europe*	En dan kijken ze naar de levensstandaard in een land, want onze investigators zijn dan weer heel duur in vergelijking met landen in Zuid- of Oost-Europa	**AD**
PMQ	feasibility		*Treatment-naive diabetes for example, you should not investigate in the Netherlands*	Treatment-naïef diabetes bijvoorbeeld, moet je toch echt niet meer in Nederland zijn	**AD**
PMQ	feasibility		*But we are always included in rear diseases trials. Even though it is only two patients that will be included, the whole circus will be initiated*	Maar wij doen als Nederland altijd mee als het om rare diseases gaat. En soms gaat dat maar om 2 patienten, maar daar zet je het hele circus voor op.	**AD**
PMQ	feasibility		*Our company has decided to do this anyway, as a kind of moral obligation*	Ons bedrijf heeft besloten om dit wel te doen, als een soort morele verplichting	**AD**
PMQ	feasibility		*Recently an oncology study was denied for the Netherlands because of budget reasons. No matter how good we are*	We hebben pas geen oncologie studie in Nederland gekregen, vanwege budget reasons. Hoe goed wij in Nederland ook zijn	**AD**
PMQ	feasibility		*but it can be complicated with other investigators, it is not easy to make agreements with other specialists*	Met andere investigators altijd ingewikkeld, lastig om afspraken over te maken tussen specialismen	**BT**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
PMQ	feasibility		*And you never know, something may always come up that you haven't thought of before!*	Soms kan er iets bijkomen wat je aan het begin niet bedenkt	**BT**
PMQ	feasibility		*You always have to take recruitment serious, perform a good feasibility and then good management thereafter*	Wat je altijd wel moet doen is dat hele recruitment verhaal serieus nemen, goede feasibility en dan goed management daarna	**CH**
PMQ	feasibility		*I have experienced a few times that during the selection visit the in and exclusion criteria are discussed and it it said that its clear, until you go through them during the initiation visit, and then it is said " oh no, I don't see these patients*"	Paar keer meegemaakt dat bij de selectievisite, van de protocol in en exclusie criteria wordt gezegd, ja, ja duidelijk en dan wordt het bij de initiatie visite doorgenomen en dan oh ja nee, maar die patienten heb ik niet	**EM**
PMQ	feasibility		*And then I think: Where did this go wrong?*	En dan denk ik, waar is dit misgegaan?	**EM**
PMQ	feasibility		*At that moment (selection visit) I already had to do some kind of prescreening, either from their minds, or with a database, like, how many patients do we really have, but mostly they don't do that at that moment*	Ik moest op dat moment al een soort van prescreening doen, of in hun hoofd, of met een database, zo van hoeveel patienten hebben we werkelijk, em meestal doen ze dat op dat moment niet	**EM**
PMQ	feasibility		*And concerning the respons, I notice that if you have a good research nurse or coordinator, it works better than the PI*	Wat betreft de respons, dat ik merk dat als je bijv een goede research nurse of een coördinator hebt, dat dat beter werkt dan de PI	**EM**
PMQ	feasibility		*You can either go through the eligibility criteria or you really start a discussion*	Je kunt even snel de inclusiecriteria doorlopen of je gaat echt het gesprek aan	**EM**
PMQ	feasibility		*In a country like Poland for example, recruitment is good, but you have to realize that is takes very long before there is regulatory approval. You really have to consider that*	Bij een land als Polen bijvoorbeeld, dan gaat de recrutering heel lekker, maar je moet je wel realiseren dat het heel lang duurt voordat er regulatoire toestemming is. Dat is echt een afweging die je moet maken	**EM**
PMQ	feasibility		*Which is why more centres must be included*	Daarom meer centra aansluiten.	**EP**
PMQ	feasibility		*In triage choices are being made --> you should unravel the stream*	In de triage kunnen al keuzes gemaakt zijn --> Stroom ontrafelen	**JS**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
PMQ	feasibility		*Feasibility may be too optimistic, afraid of not being interesting enough and therefore deliberately suggesting more patients; oncologists may be positive about their own ability; lack of insight*	Feasibility soms veel te optimistisch, bang zijn niet interessant gevonden te worden, dus bewust meer patienten opgeven, oncologen optimistische over hun eigen kracht, gebrek aan inzicht;	**JS**
PMQ	feasibility		*You may inquire for numbers, but reality is always different*	Cijfermateriaal kan je vragen, maar de werkelijkheid is altijd anders.	**KV**
PMQ	feasibility		*The synopsis is not always similar to the final protocol, many times the synopsis is written to early, before the protocol is finalized*	Synopsis komt niet altijd overeen met finale protocol, wordt in veel gevallen te vroeg gedaan wanneer finale protocol er nog niet is	**KV**
PMQ	feasibility		*The biotech industry is an industry that requests short term results, while the development actually takes very long*	De biotech industrie is een industrie die op korte termijn resultaten wil behalen terwijl het ontwikkel traject eigenlijk heel lang duurt	**KV**
PMQ	feasibility		*We work with surrogate patients, but that may work in Belgium, but it does not in the Netherlands or in Germany. Every country is different.*	Wij werken soms met MOK-patienten, maar dat werkt misschien in België, maar weer niet in Nederland of Duitsland. Ieder land is zo weer anders	**KV**
PMQ	feasibility		*Europe is fairly divided, so you can do something right in one country or hospital, and not somewhere else*	Europa is redelijk verdeeld, dus je kunt in het ene land/ziekenhuis iets goeds doen, maar ergens anders niet	**KV**
PMQ	feasibility		*You may look up the time of regulatory procedures per country, however no-one is going to tell you how long it takes to finish contract negotiations*	Je kunt opzoeken hoe lang de goedkeuringsprocedure is in een land, maar niemand gaat je zeggen hoe lang het gaat duren om een contract op te stellen.	**KV**
PMQ	feasibility		*Many human aspects may have an impact on the recruitment rate, therefore we calculate with longer time and a slower rate. Unfortunately, often it has already been discussed with the board before agreements have been made with the people that have to do the work*	Veel menselijke aspecten die een impact kunnen hebben op de snelheid. Daarom nemen wij meer tijd om op te starten en houden een lagere rate aan. Helaas zijn er vaak al afspraken met de board gemaakt voordat afspraken zijn gemaakt met de mensen die het moeten gaan doen	**KV**
PMQ	feasibility		*When you ask the operational people, then there would much less a reported delay, this would decrease with at least 50-60%*	Als je het vraagt aan de operationele mensen, dan is er veel minder vaak sprake van een delay, gaat zeker met 50-60% naar beneden	**KV**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
PMQ	feasibility		*When there are no patients at a site, you may ask yourself if this was the right site to open*	Wanneer er geen patienten zijn kun je je afvragen of dit wel het juiste centrum was om te openen	**KV**
PMQ	feasibility		*The reason sites ask for a start-up fee, is that some pharma first have a site started and then decide not to open. Sites require to have their start-up costs covered*	De reden dat centra een start up fee vragen is dat sommige farma een centrum eerst helemaal opstarten en dan besluiten om het centrum toch niet te openen. Hiermee willen centra de kosten gedekt krijgen	**KV**
PMQ	feasibility		*In real life, you always work with people, for people, to treat people*	In de realiteit werk je altijd met mensen, voor mensen, om mensen te behandelen	**KV**
PMQ	feasibility		*That is why you try to do your feasibility as good as possible. There may be many reason why a site may recruit or not*	Daarom probeer je bij fase III zo goed mogelijk je feasibility te doen. Daar kunnen heel veel redenen zijn waarom een site wel of niet gaat rekruteren	**KV**
PMQ	feasibility		*The basic lead in our discussion is that it is hard to find one specific item*	De rode draad in de discussie is dat het moeilijk is om er een specifiek punt uit te halen	**KV**
PMQ	feasibility		*You have to deal with several levels, countries, sites. It is difficult to calculate the impact everywhere*	Verschillende niveaus: landen, site. Moeilijk om de overall impact te berekenen	**KV**
PMQ	feasibility		*The most important question to answer as fast as possible, is if a product is effective or not*	Belangrijkste is hoe snel kan ik weten dat een product niet werkt	**KV**
PMQ	feasibility		*That is because time is too short on site, so the PI doesn't get to reading the protocol thorough upfront*	Komt door tijd te kort onsite, zodat de PI er eigenlijk niet aan toekomt om het protocol goed te lezen vooraf	**RZ**
PMQ	feasibility		*It is called synopsis, but you do have to include all eligibility criteria fully, because usually only the synopsis is read and when something has to be looked at in detail, the study nurse will do that*	Het heet synopsis, maar je moet wel alle inclusiecriteria volledig benoemen, omdat ze meestal echt alleen die synopsis lezen en als er echt iets in detail uitgezocht moet worden, dan doet de study nurse dat	**RZ**
PMQ	feasibility		*We have done this for a study in HER2 breast cancer patients, we did that in the Netherlands, in Belgium and in Germany. And what we can say about the answers that were returned on this rare patient group is rather alike. All indicated 5 patients*	We hebben dit voor een studie gedaan HER2-neg borstkanker patienten, dat hebben wij in Nederland gedaan, in België en in Duitsland. En wat wij kunnen zeggen over de antwoorden die we terug hebben gekregen over deze rare	**RZ**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
				patientengroep was redelijk overeenstemmend. Allen 5 patienten aangegeven	
PMQ	feasibility		*Indeed, you always have to involve the team, because the PI will say yes to anything*	Inderdaad, je moet altijd proberen het team te betrekken, want de PI zegt voor alles ja en amen	**RZ**
PMQ	feasibility		*We have asked a coordinator, who said, "no that doesn't work, because I am alone and a colleague is on maternity leave", or "our boss already has ten open trials", so then please don't*	We hebben een coördinator gevraagd en die zei, dat lukt niet, ik zit hier alleen en collega is met zwangerschapsverlof of ons baas heeft al tien trials lopen, dan alsjeblieft niet doen	**RZ**
PMQ	feasibility		*They want to do the study, but cannot handle more administration and that is also important. Ask study nurses for their capacity*	Ze willen de studie wel doen, maar ze kunnen niet nog meer administratie daarbij doen en dat is ook van belang. Study nurse vragen naar de capaciteit	**RZ**
PMQ	feasibility		*As CRA you can make a difference in site selection*	Als CRA kun je wel een verschil maken in de site selectie	**RZ**
PMQ	feasibility		*But it serves no one if the site is included in a study, but is actually not capable to. Everyone has been busy and then sentences like: "If I had known beforehand, I would not have participated"*	Maar er is ook niemand mee gediend als een site een studie aanneemt, maar eigenlijk niet instaat is. `zinnetjes van: had ik dat van tevoren geweten, dan had ik noot meegedaan'	**RZ**
PMQ	feasibility		*It can also make a difference if you engage in a good conversation in the beginning, that that will be the basis for a good relationship later on*	Het kan ook het verschil maken als je een goed gesprek aangaat, dat dat voor later een goede basis voor een vertrouwensrelatie vormt	**RZ**
PMQ	feasibility		*Internal communication, already in an early phase; in the feasibility report, already you may describe early worries*	Communicatie intern, in de vroege fase al, in het feasibility rapport kun je al zorgen opschrijven	**RZ**
PMQ	feasibility		*Therefore, it is important to find out about their work environment. Your investigator may be very enthusiastic, but if others in the hospital are not, then it won't work*	Daarom uitzoeken hoe is de stemming in huis? Jouw PI kan zo bevlogen zijn om dit te doen, maar als anderen dat niet zijn dan lukt het niet	**RZ**
PMQ	feasibility		*A rule you learn is that when a doctor says to include 10 patients during the feasibility visit, is that you have to divide this number by two, some say even divide by four*	Regel die je leert is dat als een arts bij de feasibility visite 10 patienten zegt, dat je dit door 2 deelt, of sommigen zeggen wel door 4	**YG**
PMQ	feasibility		*Very often though, it is too late, and when you realize how much time and money has been put into it by both parties, that is more than frustrating*	Heel vaak is het al te laat, en als je dan bedenkt hoeveel tijd en geld er dan door beide partijen al ingestoken is, dat is meer dan frustrerend	**YG**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
PMQ	feasibility		*And it is the same with a feasibility questionnaire, then there are doctors that look upon it like "all those questionnaires with questions about freezers and so on", but it is actually important that you ask these questions*	En ook al met een feasibility questionnaire, dan zijn er artsen die daar wel tegenaan kijken van zo al die questionnaires over die vriezers en zo, maar wel belangrijk dat je juist wel die vragen stelt	**YG**
PMQ	feasibility		*What also came up, was that about one of the standard treatments that was in the protocol it was said: we don't give that, or it has to be reimbursed*	Wat er ook uitkwam, was dat van een van de standaardbehandelingen die werd gegeven in het protocol, werd gezegd: dat geven wij niet of wij moeten dat vergoed krijgen	**YG**
PMQ	feasibility		*Indeed, that is not standard for us (in the Netherlands). But then, are you able to see enough of these patients?*	Inderdaad dat is bij ons (in Nederland) geen standaard. Kan je van dit collectief patienten dan wel voldoende zien?	**YG**
PMQ	feasibility		*I would do that already at feasibility. It would make them think. Then they will find out. AT that moment it is minor information, but they have to think about it*	Dat zou ik zelfs al bij de feasibility doen, dan zet je ze aan het denken. Dan komen ze vanzelf wel langs, op dot moment is het kleine info, maar ze wel daarover nadenken	**YG**
PMQ	feasibility		*The PI wants a publication and then the research nurses say: Hey wait!*	De PI wil een publicatie hebben en dan zeggen de research nurses "ja, maar wacht even"	**YG**
PMQ	feasibility		*Not that you can decide on the sites, but in the report, you may recommend whether you think the site is suitable, with arguments. In the end, upper management will decide with the pharma if the site will participate*	Het is niet aan jou de keuze wel of niet deze site, maar in het rapport geef je aan: vind je deze site geschikt en onderbouwen. Uiteindelijk gaat het upper management met de farma beslissen of de site meedoet	**YG**
PMQ	feasibility		*And then there is another factor: pharma. Because if they see a certain doctor as an opinion leader, even if you have no previous experience with this site, then this site will participate anyway*	En dan komt er nog een andere factor kijken en dat is farma, want als die een bepaalde arts als key opinion leader zien, maar je hebt geen goede ervaring met deze site uit voorgaande studies, dan gaat deze site gewoon meedoen	**YG**
PMQ	feasibility		*And also ask the question: "which criteria could prohibit inclusion according to you?" And: "Which assessments are an obstacle for you?" That enables you to filter.*	En ook nog de vraag stelt: welke criteria kunnen de inclusie volgens u belemmeren? En welke assessments zijn voor u een belemmering? Dan filter je dat er wel uit.	**YG**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
PMQ			*Once I have experienced that a large phase III study had to be drawn back for safety reasons. The benefit did not outweigh the side effects. But that was very dramatic of course*	Ik heb ook een meegemaakt dat er een grote fase 3 studie was en die hebben ze toch terug moeten trekken om safety redenen. En de benefit woog niet op tegen de bijwerkingen. Maar dat is drama natuurlijk	**AD**
PMQ			*My previous experience as a CRO is that if there are insufficient funds to finish a study, as a CRO you take the responsibility to finish the study, because you have already subjected patients in the trial. That is also a moral obligation*	Mijn eerdere ervaring als CRO is dat als er onvoldoende gelden zijn om een studie af te maken, dat je dan als CRO de verantwoordelijkheid hebt om de studie af te maken, omdat je eerdere patienten al hebt blootgesteld aan het onderzoek. Dat is een ethische overweging	**AD**
PMQ			*Everyone is on top of project management*	Projectmanagement daar zit iedereen bovenop	**AD**
PMQ			*Trials in general are mainly operational driven as opposed to financially driven*	Trials in algemeenheid zijn meer operationeel gedreven dan financieel	**CH**
PMQ			*You cannot pressure centres to maintain the recruitment estimates. Maybe somewhat in phase I studies, but certainly not in phase III*	Je kunt weinig tot geen druk op het centrum zetten om zich aan de recruitment te houden. Misschien nog wel iets met fase I, niet meer met fase III	**KV**
POP	+	**PRR**	*But what happens is the so-called Lasagna effect, suddenly there are less patients during the trial period*	Maar wat er gebeurd is het zogenaamde Lasagna effect, er zijn ineens minder patienten zolang de trial open is	**EP**
POP	+	**PRR**	*One of the factors would be the study population*	Een van de factoren is dan toch die study population	**YG**
POP	++	**PRR**	*Numbers of patients (potential patients) is naturally decisive for the success of the trial*	Aantallen patienten uiteraard beslissend voor de trial	**EP**
POP	feasibility		*When there is a new study protocol, at pre-feasibility, the physician will say, well, there are at least 10 patients that will want to participate, and then there are 8 that are actually eligible to participate. And then from the eligible patients 4 decide to participate, and in the end there are 2 that finalize the study and are evaluable. And then you are lucky*	Er komt een protocol en dan gaan we een pre-feasibility doen, en dan zegt de arts, nou, er zijn zeker 10 patienten die mee willen doen, en uiteindelijk worden dat er 8 die mee kunnen doen. En dan komt de patient, waarvan er 4 mee willen doen, en uiteindelijk zijn er 2 patienten die het ook	**AD**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
				nog volhouden en evalueerbaar zijn. En dan mag je in je handjes knijpen	
POP	feasibility		*Competition between pharma is difficult, but if there is a sufficient patient population, that doesn't matter*	Competitie tussen verschillende farmaceuten is daarin wel lastig, maar als er voldoende patienten zijn, dan maakt dat weer niet uit	**CH**
POP	feasibility		*in Russia for example were many untreated diabetes patients, so there the trial was easily completed. We don't have those patients here*	In Rusland waren bijvoorbeeld veel onbehandelde diabetes patienten, dus daar werd de trial snel gevuld. Die patienten hebben wij hier niet	**CH**
PSC	+	**PMQ**	*Therefore, you have to remain alert, monitor on a monthly basis and act as soon as possible*	Kien op zijn en van maand tot maand monitoren en zo snel mogelijk schakelen.	**CH**
PSC	+	**PMQ**	*Never have I experienced a trial finishing faster than planned*	Ik heb ook nog nooit meegemaakt dat een studie sneller gaat	**CH**
PSC	+	**PMQ**	*Once I experienced that we opened an additional center and we ended recruitment in time. It cost some more money, but without loss of patent time, which was much more profitable*	Een keer meegemaakt dat we extra centra hebben geopend en uiteindelijk nog op dezelfde eindtijd zijn uitgekomen. Dat heeft dus iets meer geld gekost, maar uiteindelijk niet afgedaan van de patent tijd, die vele malen meer opgeleverd	**CH**
PSC	++	**PMQ**	*PMQ is keeping an eye on the study dashboard, to undertake timely action when recruitment is low*	Qua projectmanagement in de gaten houden met dashbord, op tijd iets doen aan matige recruitment	**EP**
PSC	+	**SRE**	*When a sponsor should have some sense, they would make decisions based only on timelines*	Als de sponsor een beetje verstand zou hebben, dan zou die uiteindelijk alleen maar op tijdlijnen een beslissing moeten nemen	**CH**
PSC	+	**SRE**	*Slow recruitment hurts double*	Slow recruitment doet namelijk dubbel pijn	**CH**
PSC	+	**SRE**	*In product development, you typically look at cash flows for the future. Study costs are now 100%, that is now. For future income, which is not sure, there are discount steps based on risk factors. Therefore, if the project is delayed it will cost and extra one million in discount, and in the future it will cost because of a shorter patent time*	Voor een productontwikkeling nu kijk je feitelijk naar de cash flows voor de toekomst. De kosten voor de studie zijn 100%, dat is nu. De toekomstige inkomsten die er komen, die zijn natuurlijk niet zeker, dus heb je discount stappen op basis van risicofactoren. Dus als het langer duurt kost het nu een miljoen aan extra discount en in de toekomst aan een kortere patent tijd	**CH**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
PSC	+	**SRE**	*As soon as you notice a delay, you have to act upon it, by opening more sites for example. Because if you wait another few months and then you need another couple of months to open other sites, you are already too far*	Zodra je vertraging ziet, moet je gelijk daar actie op ondernemen, meer sites openen bijvoorbeeld, want als je nog een paar maanden gaat wachten en dan nog een aantal maanden nodig hebt om andere sites te openen, dan ben je alweer te ver	**CH**
PSC	+	**SRE**	*The argument that there may not be enough money is actually not valid, because it will cost more in the end anyway*	Het argument dat er niet meer geld is, is niet valide eigenlijk, want het kost net zoveel in de lengte als in de breedte. Als een trial langer gaat duren, dan kost het uiteindelijk ook meer	**CH**
PSC	+	**SRE**	*Especially in biotech there is a time delay in discussing problems with the net level, people don't like to report bad news to the board or investors. And everyone has a positive attitude and will think things will get better*	Zeker bij biotech zit er een tijdgat bij bespreken met de volgende laag, rapporteren niet graag naar board, investors. En iedereen is ook wel positief ingesteld, dus dan denk je, ah dat komt nog wel	**CH**
PUA	-	**ATT**	*I remember, after publication of the death of a phase 1 patient in France, we did not accrue a single patient in France for months. And also, the regulatory agencies became panic*	Na publicatie van een overleden patient in een fase 1 studie zoals toen in Frankrijk, nou toen hebben we maanden geen Franse patient meer in de studie gekregen. En ook de METCs die werden panisch	**EM**
PUA	-	**ATT**	*Raising public awareness by newspaper articles usually only confuses patients. What is written in the media is often not directed to a certain patient group*	Krantenartikelen invloed? Patienten raken er vaak alleen maar van in de war. Heel ongericht wat in de media komt	**NS**
PUA	+	**ATT**	*Ah, the website for clinical trials in the Netherlands, well yes, someone has to be responsible for that. I know the breast cancer association keeps it up to date for their patients*	Oh ja die website voor clinical trials in Nederland, maar ja, daar moet iemand verantwoordelijk voor zijn. De borstkanker vereniging houdt dat bij voor eigen patienten	**AD**
PUA	+	**ATT**	*Clinicaltrials,gov is much to complicated for patients*	Clinicaltrials.gov is veel te ingewikkeld voor patienten	**AD**
PUA	+	**ATT**	*The diabetic association has its own Facebook page and so does the breast cancer association, on which they inform members of current clinical trials*	De diabetes vereniging heeft een besloten facebook pagina en de borstkanker vereniging ook, waarop ze leden op de hoogte gaan houden van trials	**AD**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
PUA	+	**ATT**	*The breast cancer association has a scientific committee. They see so many requests coming in, that they can hardly keep up with it. In the US there are so-called patient advocates, but they are especially trained. This is being done more and more*	Bij de borstkankervereniging is een wetenschapscommissie. Die zien nu zoveel aanvragen binnenkomen dat het bijna niet bij te houden is. In Amerika heb je daar de zogenaamde patient advocates voor, maar die worden daar speciaal voor opgeleid. Daar gaat steeds vaker op ingezet worden	**AD**
PUA	+	**ATT**	*Public awareness in clinical trials is something else. Twice I have experienced an incident, which was all over the news. Then you would expect this to influence the trial negatively, however twice we experienced the opposite, we had an increase of participant. This was however mostly in studies with healthy volunteers*	Public awareness voor het doen van klinische trials is ook nog wel een dingetje. Ik heb nu 2x een incident meegemaakt, wat echt overal in de publiciteit is gekomen. Dan verwacht je dat dat een tegenslag gaat geven en je krijgt juist een toeloop, we hebben een toeloop gekregen 2x, terwijl het slecht in de publiciteit is gekomen. Dit was merendeel bij gezonde vrijwilligers	**AD**
PUA	+	**ATT**	*And nine out of ten times pharma is not projected in the right way, on what it does. People think they are big spenders, driving expensive cars and flying all over the world. Well that time is long gone. At least I never see it anymore. Why you should participate and also explaining this, is quite something*	Farma komt 9 van de 10 keer ook niet goed in beeld, van wat zij doet. Mensen denken dat het grote graaiers zijn en in dure auto's rijden en vliegen de hele wereld over. Nou dat is allang niet meer zo, ik maak het in ieder geval echt niet mee. Waarom je zou meedoen en dat nog uitleggen, dat is nog best heel groot.	**AD**
PUA	+	**ATT**	*There should be cooperation to do something about this, but thats costs money, and who will initiate this*	Eigenlijk moet je daar gezamenlijk iets aan doen, maar dat kost geld, en wie neemt dat op zich	**AD**
PUA	+	**ATT**	*Once in a ZonMW congress there was a panel including a patient, who said I really want that medication (it was about genetic therapy), but then there was someone from the government who said, well yes, but we are not going to give that yet, because we don't know what that implies. And the insurance company said, but I am not going to reimburse that, because its efficacy is not proven yet, and so they all shoved it off, and then the patient*	een keer in een ZonMW congres daar was een panel met een patient die zei ik wil dat middel graag hebben (dat ging over gentherapie), maar er zat iemand van de overheid en die zei, ja, maar we gaan dat nog helemaal niet geven, want we weten nog helemaal niet wat dat betekent, de ziektekosten verzekeraar zei, maar dat ga ik helemaal niet vergoeden, want het is nog helemaal	**AD**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
			said, yes, but I really want to be able to get that medication and I am prepared to take all the risk myself	niet bewezen en zo schoven ze alles door en die patient zei, ja, maar ik wil dat heel graag krijgen en ik ben bereid om het risico helemaal te dragen	
PUA	+	**ATT**	*And then it is all about liability, who is liable when things would go wrong for this patient*	En het gaat dan alleen nog maar over aansprakelijkheid, wie is er aansprakelijk als het wel fout zou gaan bij deze patient	**AD**
PUA	+	**ATT**	*That is the reason the insurance company doesn't want to have anything to do with clinical research, because if they do, who is responsible when something goes wrong?*	Dat is ook de reden dat de verzekering niets te maken wil hebben met klinisch onderzoek, want als ze dat wel doen wie is dan aansprakelijk als er iets mis gaat?	**AD**
PUA	+	**ATT**	*One can see more is developed for patients to find studies*	Je ziet dat er ook steeds meer ontwikkeld wordt voor patienten om studies te kunnen vinden	**AJ**
PUA	+	**ATT**	*The trial register is there; however, it is not being used much yet. There are initiatives to make this information available via an app, and also companies like Acurian take initiative in this development*	Het trialregister is er wel, maar wordt nog niet echt gebruikt. Er zijn initiatieven om dit via een trial-app nu makkelijker beschikbaar te maken en ook via bedrijven als Acurian die initiatieven nemen	**AJ**
PUA	+	**ATT**	*Little information is provided by, for example, the KWF (the Dutch public cancer fund), and more is from pharma. It is important to make people aware*	Er komt weinig voorlichting vanuit bijvoorbeeld de KWF, meer vanuit de farma. Belangrijk om patienten bewust te maken	**AJ**
PUA	+	**ATT**	*A website with all Dutch trial would be a good idea, but that is not present. An earlier initiative still doesn't work well. That would be really nice*	Website voor Nederlandse trials zou heel goed zijn, maar die is er niet echt. Eerder initiatief is nog steeds niet goed van de grond gekomen. Dat zou heel goed zijn.	**BT**
PUA	+	**ATT**	*DUOS is a patient association that was started to address this*	DUOS is patiëntenvereniging die wel hiervoor is opgericht	**BT**
PUA	+	**ATT**	*Public awareness will become very important, this will increase. People will start looking for trials*	Awareness bij het publiek gaat heel belangrijk worden, dat gaat toenemen. Meer mensen gaan zoeken naar studies	**BT**
PUA	+	**ATT**	*then I think of a website or a portal, where people can ask questions*	Ik denk aan een website, een portal, waar mensen met vragen terecht kunnen	**BT**
PUA	+	**ATT**	*Even on the NKI website we could show much more new developments. It could be by theme, roulating*	Zelfs op de website van het AVL zou je nog veel meer nieuwe dingen kunnen laten zien, dat kan thematisch, roulerend	**BT**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
PUA	+	**ATT**	*Public awareness can really help. If you are able to make patients aware of a solution for a condition they have. You may hope physicians will at least support and refer etc.*	Public awareness kan wel echt helpen. Als je patienten bewust kan maken van iets waar zij mee worstelen. Dan mag je hopen dat de artsen in ieder geval kunnen helpen met verwijzing en dergelijke	**CH**
PUA	+	**ATT**	*Especially in orphan indications patient associations are very interested, they are very motivated*	Zeker in wees indicaties zijn patienten organisaties daar erg in geïnteresseerd, die zijn enorm gedreven	**CH**
PUA	+	**ATT**	*That is a beautiful interaction to witness, then you are really doing well*	Die interactie is ook heel mooi, dan ben je samen ook iets goeds aan het doen	**CH**
PUA	+	**ATT**	*One example is a centre which had insufficient patients itself. An article in a national newspaper was efficient. This was reported to the regulatory authorities. Advertising is not permitted, but you have to find a way to get patients to come to the hospital*	Ja, ervaring mee. Voorbeeld gentherapie bij prostaatCA. Heel gespecialiseerd, alleen in VU. Centrum zelf onvoldoende patienten, artikel in Telegraaf heeft wel gewenst effect gehad. Wel gemeld bij CCMO. Reclame mag niet, maar patienten moeten wel 'gelokt' worden naar het centrum	**EP**
PUA	+	**ATT**	*Important to have referring doctors, therefore stimulate health care professionals. It helps when the patient askes for it.*	Belangrijk om verwijzende artsen te hebben, daarom health care professionals stimuleren (*public awareness*). Het helpt als patient daarom vraagt	**EP**
PUA	+	**ATT**	*Haven't heard anything anymore from that national trial website. It may be useful to contact patient associations*	trial website in NL niet meer van gehoord. Contact opnemen met patiëntenverenigingen om de zichtbaarheid van de trials te verbeteren	**JS**
PUA	+	**ATT**	*Newsletter I seldom read, I really don't have any time for that*	Nieuwsbrieven lees ik zelden, daar heb ik echt geen tijd voor	**NS**
PUA	+	**ATT**	*Newsletters, well indeed, there are people who read those*	En nieuwsbrieven, tja, er zijn mensen die ze lezen inderdaad	**NS**
PUA	+/-	**ATT**	*Publicity may work for you or against you*	Het kan voor je werken en het kan tegen je werken	**YG**
PUA	+	**PEO**	*Aiming at patient peers is difficult. People like to focus on the negative. For example that one trial in England, then that is booming business. There is hardly any positive news*	Richten op peers van patienten is moeilijk. Mensen focussen toch graag op het negatieve. Bijvoorbeeld die ene trial in Engeland, dan is dat booming business. Er komt weinig positief nieuws	**AJ**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
PUA	+	**PEO**	*I think that if you want to reach many PI's, that newsletters will help. They can compare with each other*	Ik denk dat als je veel Pis wil bereiken dat nieuwsbrieven naar de sites echt wel bijdragen. Ze kunnen met elkaar vergelijken.	**YG**
RAP	-	**IMO**	*There is so much you have to do as an investigator nowadays, and as a pharmaceutical company, regulations have become much stricter*	Er is zoveel wat je tegenwoordig moet doen als investigator en als farmaceut, die regulering wordt steeds strikter	**AD**
RAP	-	**IMO**	*You have to fulfil regulations for good clinical practice, good manufacturing practice*	Je moet voldoen aan Good Clinical Practice, je moet voldoen aan Good Manufacturing Practice	**AD**
RAP	-	**IMO**	*The association for innovative medications reported an issue with a physician, whose site was being audited, although there was no capacity to support that*	De vereniging innovatieve geneesmiddelen meldde een probleem met een arts die geaudit werd, maar waar geen capaciteit voor was	**AD**
RAP	-	**IMO**	*When your research department is not in order, it will press on you. And all you wanted to do, is do good for your patient. That is hardly manageable*	Als je dan je researchafdeling niet goed op orde hebt, dan ga je helemaal onderuit. En dan wil je eigenlijk goed doen voor je patient, he. Dat is bijna niet op te brengen	**AD**
RAP	-	**IMO**	*That is why general practitioner studies are so hard, because costs for them are too high*	Daarom zijn huisartsen studies zo moeilijk, want dat is voor huisartsen te veel kosten	**AD**
RAP	-	**IMO**	*regulatory submissions do not only influence the sites, but actually influence the country. When it takes to long, it could mean that a trial almost closes again, which may leave the site with only 3 months for example to recruit patients. Then all planned patients have already been included in another country, or there is insufficient time to recruit the intended number of patients*	De regulatoire indieningen hebben niet alleen invloed op de site, maar eigenlijk in heel Nederland heeft dat invloed. Wanneer dat te lang duurt, dan kan het zijn dat een trial al bijna weer sluit, en dan heeft de site bijvoorbeeld nog maar 3 maanden om patienten te rekruteren. Dan zijn of alle patienten al geïncludeerd in andere landen of er is nog te weinig tijd om aan het aantal patienten te komen	**AJ**
RAP	-	**IMO**	*A long regulatory period may be limiting if there is only a short recruitment period, then investigators stop. And sometimes the sponsors do too*	Een lange goedkeuringsprocedure kan limiteren als er maar een korte tijd is om te rekruteren, dan haken investigators soms wel af. En de sponsors zelf ook wel	**EM**
RAP	-	**IMO**	*Contracts are a limiting factor also. It can be a very decisive step, this sometimes takes up to two years. Then*	Contracten is ook een limiterende factor. Dat is ook een hele bepalende stap, dat duurt soms wel 2 jaar.	**JS**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
			by the time negotiations are finished, there are other treatments and studies	Tegen de tijd dat dat rond is zijn er weer andere behandelingen/studies etc.	
RAP	-	**IMO**	*System factor are also limiting*	Systeem factoren	**NS**
RAP	-	**IMO**	*Sometimes there is no time for GCP training when this is required by a pharma, or when there is insufficient support for regulatory submissions*	Wanneer geen tijd voor bijv GCP-trainingen, of geen indiening ondersteuning	**NS**
RAP	-	**PUA**	*A limitation are the regulatory authorities, they assume it as advertising. Texts have to be reviewed before it is published on the website. I feel that we do not service our patients sufficiently*	Ligt vaak aan METC, is erg terughoudend, die ziet het als reclame. Teksten moeten dan eerst beoordeeld worden voor het op de website komt. Zelf vind ik dat wij onze doelgroep niet voldoende servicen	**JS**
RAP	-	**PUA**	*The regulatory authorities are a limitation to inform people. Every regulatory committee in the Netherlands has its own views about informing patients via websites etc.*	Regulatory is een beperking om mensen te informeren. Iedere METC heeft zijn eigen ideeën over het informeren van patienten via websites en dergelijke.	**JS**
RAP	+	**SRE**	*The EMA is an authority that has more distance. The sponsor may ask for scientific advice, that can help. However, this is not done regularly. In the US for the FDA this is also optional, however this would be unwise to do. That is different in the Netherlands, where the national and local committees have more authority*	EMA staat meer op afstand, sponsor vragen om scientific advice, dat kan helpen. Wordt niet standaard gedaan. Bij FDA hoeft dat ip ook niet, maar is onverstandig om dat niet te doen. In Nederland ligt dat wel anders, in de US is er een hogere verplichting	**JS**
RAP	feasibility		*Timelines for regulation are often long and yes, that too costs money. Based on existing information you have to find the right mix in countries*	De tijdlijnen voor regulering, zijn vaak lang en ja, dat kost natuurlijk ook geld. Op basis van de informatie die je hebt moet je eigenlijk een goede mix van landen hebben	**CH**
RAP	feasibility		*Fir example, we had a trial with centres in Russia, that takes almost a year to achieve regulatory approval and open the site, but once open they recruited in three months almost half of all patients in the trial. That saved this study*	We hebben bijvoorbeeld een studie gehad met centra in Rusland, dat duurt bijna een jaar voordat het open is, maar daarna hebben ze in 3 maanden bijna de helft van de patienten gerekruteerd. Dat heeft uiteindelijk de studie gered	**CH**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
RAP	feasibility		*Yes, it goes both ways, also the government has to put more effort into it. Well actually 3 ways: also, patients have a say*	Ja, dat is van beide kanten, ook de overheid moet er moeite voor doen! Eigenlijk van drie kanten meedenken, ook patienten	**RZ**
RAP	feasibility		*With new regulations in the Netherlands, it may be easier to attract sponsor studies to a small country like ours. Sponsors often look towards the 'Big 5' first*	Met de nieuwe regelgeving in Nederland, wordt het misschien ook makkelijker om sponsor studies aan te trekken naar een klein land als Nederland. Sponsors gaan vaak eerst naar de 'big 5'	**YG**
RAP	feasibility		*And also, our patients benefit from that, patient associations would really like that*	En daar zijn patienten ook bij gebaat, patiëntenverenigingen willen dat graag	**YG**
RAP	feasibility		*Opening centres is costly, yes, but it is mostly about countries. It is better to have many sites opened in one country*	Het is kostbaar om centra te openen, ja, maar het gaat vooral om landen. Je kunt beter veel sites in 1 land hebben	**YG**
RAP	feasibility		*For a specific condition, the Netherlands is a fairly small country*	Bij een specifieke indicatie is Nederland wel heel klein	**YG**
RAP			*There are a number of things you cannot influence, like regulations. That is being decided from above.*	Er zijn een aantal dingen waar je geen invloed op kunt uitoefenen, zoals de regulations. Dat wordt van bovenaf opgelegd	**AD**
RAP			*However, considering this, I don't see an easy way to change this, regulatory wise*	Maar als ik ernaar kijk, dan zie ik niet makkelijk een manier om daar qua regelgeving een verandering in te brengen	**CH**
ROI	+	**SRE**	*In a small market that financial margin is much lower, when it concerns a small patient population*	Bij een kleine markt is die marge natuurlijk wel veel lager, als het een kleine doelgroep betreft	**CH**
ROI	+	**SRE**	*When the present value of your future cash flows is very small, then you know there is not much buffer in costs, because the market will not increase*	Als de present value van je toekomstige cashflows heel klein is, dan weet je dat je niet heel veel buffer hebt in de kosten die je gaat maken, want die markt wordt niet groter	**CH**
ROI	+	**SRE**	*Even after successful phase III, still products fail. That just costs a lot of money*	Zelfs na een succesvolle fase 3 vallen er nog drugs af. Dat kost gewoon veel geld	**CH**
ROI	+	**SRE**	*It is very simple indeed, if you can make 4 billion from every 5 billion that the development of one product costs, then you will spare 1 billion to develop new products*	Het is wel heel simpel inderdaad, als je op voor iedere 5 miljard die een productontwikkeling kost, daar 4 miljard van kunt maken, dan houd je 1	**CH**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
				miljard over om weer nieuwe producten te ontwikkelen	
ROI	+	**SRE**	*With public funding, you can do basic research, but it will not deliver sufficient funding for the full clinical research program that is needed to bring the product to market*	Met publieke gelden kan je het basale onderzoek wel doen, maar daaruit kan niet de investering geleverd worden voor het volledige klinische onderzoek dat nodig is om het product op de markt te brengen	**CH**
ROI	+	**SRE**	*And yes, that is why you should be happy with the system the way it is. That basic research is funded by government money, but that when large amounts of money are needed, the commerce can continue. Otherwise the eco-system will not work*	En ja, daarom moet je eigenlijk heel blij mee zijn dat het systeem zo bestaat, dat het vroeg academisch onderzoek vanuit de overheid gefinancierd wordt, maar dat wanneer er stevig geld tegenaan gegooid moet worden dat de commercie dat op kan pikken. Anders werkt dat ecosysteem niet meer	**CH**
ROI	++	**SRE**	*Drug revenue is important for pharma companies. It is thé incentive. In case of IITs sponsored with public money, financial revenues are not important, only publications*	Drug revenu van belang voor pharma, is dé incentive. Voor IIT met publiek geld is dat niet van belang, alleen publicatie is dan belangrijk	**EP**
ROI			*That is what is strange in the discussion on expensive medications. I think about that a lot. Do you still see possibilities in the system?*	Dat maakt de discussie over dure geneesmiddelen ook wel vreemd. Daar denk ik ook vaak over na, zie je nog ruimte in het systeem?	**CH**
ROI			*Though I think medicines are less than 10% of total health care, and then people are complaining about a pharmaceutical profit of 17%, but every service provider calculates with this margin (that's what a guy on television said the other day, so I suppose he did some research on that)*	Volgens mij zijn medicijnen minder dan 10% van de totale gezondheidszorg, dan wordt geklaagd over een winstmarge van pharmaceuten van 17%, maar iedere dienstverlener houdt deze marge aan (dat zei die beste man laatst op teevee, dus die zal dat wel uitgezocht hebben dan)	**CH**
ROI			*Suppose we would decrease the profit with 10%, that would spare the entire healthcare less than 1%. That is an important amount, however not substantial in total*	Stel dat we daar dan toch 10% korting gaan geven, dat scheelt de totale gezondheidszorg uiteindelijk minder dan 1%, dat is wel belangrijk, maar een druppel op de gloeiende plaat	**CH**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
ROI			*And yes, if you need 15 years of development for one drug, it is not possible to do that for 10 euro's*	En ja, als je 15 jaar aan het ontwikkelen bent, dat gaat niet voor een tientje	**CH**
SPC	-	**IMO**	*If there are very clumsy systems, for example an e-diary, if it continuously dysfunctions, or something like that, then both the patient and the investigator will be demotivated to perform a study with you, and you can't turn that back*	Of je moet hele erge clumsy systemen hebben, bijvoorbeeld een e-diary, als die continu uitvalt of kapot gaat, of noem maar iets, dan is zowel de patient als de investigator gedemotiveerd om bij jou dat te doen, je draait dat dan niet meer terug	**AD**
SPC	-	**IMO**	*When many study specific assessments have to be done, that can be a limiting factor for both the patient and for the site. The site usually has little time, and then is not capable of to perform these additional assessments*	Wanneer er veel studie specifieke handelingen verricht moeten worden, dan kan dat zeker een beperkende factor zijn zowel voor de patient als de site. De site heeft vaak al weinig tijd en die extra handelingen lukt dan niet	**AJ**
SPC	-	**IMO**	*The difference between protocol writer and practice is sometimes very large and that may influence recruitment*	Verschil tussen protocol writer en praktijk soms erg groot en dan kan invloed hebben op de recrutering	**KV**
SPC	-	**IMO**	*It is important to keep the study protocol as simple as possible, for example frequent scanning is limiting*	Protocol zo simpel mogelijk houden, bijv. frequente scans is niet goed	**NS**
SPC	-	**IMO**	*I consider the content, which experimental arm, and then the design, fuss and finances*	Afweging op inhoud, welke experimentele arm, en dan op design rompslomp, financiën	**NS**
SPC	--	**IMO**	*The most important factors in slow recruitment are in my opinion: the study design, more realistic design is needed, and the site's capacity*	De belangrijkste factoren bij een slechte recruitment zijn mijns inziens: het studie design, meer realistisch design en vaak de capaciteit op de site	**AJ**
SPC	--	**IMO**	*All the fuss that is extra. Less patients are being asked because of that*	Gedoe dat er extra bijkomt. Daardoor worden patienten minder gevraagd	**BT**
SPC	--	**IMO**	*Easier to execute, easier eCRF*	Meer in andere trial geldt, eenvoudiger uit te voeren, eenvoudiger CRF	**JS**
SPC	--	**IMO**	*A study protocol nowadays is like a too abundant Christmas tree*	Een studieprotocol is tegenwoordig vaak een teveel versierde kerstboom.	**KV**
SPC	--	**IMO/ PMO**	*Study complexity is definitely of influence, for example when the trial design cannot be explained to the patient,*	Complexiteit van de trial is zeker wel van invloed, voorbeeld is een trial waarbij het design niet uit te	**EP**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
			for example when both the drug and the schedule are randomized	leggen is aan een patient, bijvoorbeeld zowel moment van behandelen als compound onbekend	
SPC	-	**PMO**	*Sometimes the patient wants to participate, but then has to participate for half a year and cannot go on a vacation or to work, etc.*	Soms wil die patient wel, maar dan moet die een half jaar meedoen en dat kan niet want die gaat dan op vakantie, of moet werken, ed	**AD**
SPC	-	**PMO**	*Protocols become more complex all the time and what is asked of patients is more and more. Not being able to do things, attend the clinic more often, get medication that hasn't been tested thoroughly yet*	De protocollen worden steeds complexer en dat wat er van de patient wordt gevraagd steeds meer wordt. Dingen laten, vaker komen, middelen die nog niet goed onderzocht zijn	**AD**
SPC	-	**PMO**	*Even an easy to understand Informed Consent Form is still difficult*	Zelfs begrijpelijk ICF is nog moeilijk	**KV**
SPC	-	**PMO**	*Intellectually difficult material is hard to understand for patients. Also, that can vary in different countries*	Intellectueel moeilijke materie lastig om te begrijpen voor patienten. Kan er ook weer anders uitzien in verschillende landen	**KV**
SPC	-	**PMO**	*The investment asked from a patient can be very high at times*	De investering die gevraagd wordt aan de patient kan soms zeer hoog zijn	**KV**
SPC	-	**PMO**	*Patients don't like these additional logistics, for some that is really a limitation, less freedom, they have to ask before they can go on a holiday*	Patienten vinden extra logistiek wel lastig, is voor een aantal patienten zeker een beperking, minder vrijheid, vakantie eerst vragen	**NS**
SPC	+	**PMO**	*I know that people have participated, because then they would be checked more regularly, than in standard treatment*	Ik heb ook wel meegemaakt dat mensen meededen omdat ze dan vaker werden gecontroleerd dan met de reguliere behandeling	**AD**
SRE	0	**IMO**	*The investigator fee is on the hospitals account*	Investigator fee komt op een grote rekening van het ziekenhuis,	**JS**
SRE	0	**IMO**	*No idea if the financial aspect is different for regional hospitals, where specialists work together in their own organization*	Regionaal ziekenhuis, vrijgevestigde specialisten. Maatschap van specialisten. Geen idee of financiën een argument is	**JS**
SRE	+	**IMO**	*The investigator fees and contracts are gaining importance, not so much from the investigator point of view, but mainly because of other disciplines that need to calculate their efforts. Therefore, they request to see the lab manual, or wait for board permissions*	Investigator fees en contracten worden steeds belangrijker, niet zozeer vanuit de investigator, maar vooral ook vanuit andere disciplines die in kaart willen brengen hoeveel inspanning dat gaat	**AJ**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
				zijn, dus willen eerst een labmanual zien of de lokale goedkeuring	
SRE	+	**IMO**	*I mainly work in many investigator initiated studies*	Werk met name met veel investigator initiated studies	**BT**
SRE	+	**IMO**	*For smaller, regional hospitals an investigator fee may be important*	Voor STZ-ziekenhuizen is een investigator fee heel belangrijk. (Pieter van der Berg in Tergooi)	**BT**
SRE	+	**IMO**	*i would like to contribute to new developments. For example, with a DNA/PK inhibitor study I was asked for input by the sponsor, but then it is unclear what status I get*	Graag bijdrage leveren aan ontwikkelingen. Bij DNA/PK inhibitor study bijvoorbeeld, heeft deze sponsor gevraagd om input, maar dan is het onduidelijk welke status je hebt	**BT**
SRE	+	**IMO**	*Also, no feedback to the Safety and Monitoring Committee, however credits are important*	Ook geen feedback over safety and monitoring committee - credits belangrijk	**BT**
SRE	+	**IMO**	*When you contributed and gained your position you should be added to the writing committee*	Bij verworven positie in de loop van het protocol nog toevoegen in bijv writing committee	**BT**
SRE	+	**IMO**	*The only direct financial incentive you may give in regards of recruitment is the investigator fee, that is however fairly standardized, so therefore, as I see it, is it not really an incentive*	De enige financiële impuls die je kunt geven ten behoeve van de recruitment is de investigator fee, maar die is redelijk standaard vastgelegd, dus dat is, zoals ik ernaar kijk, niet echt een stimulans	**CH**
SRE	+	**IMO**	*You cannot pay exorbitant amounts, because then you get a distorted and unethical incentive, therefore you always pay a reasonable amount, comparable to other studies, because otherwise you will enforce unethical behaviour*	Je kunt geen exorbitante bedragen betalen, want dan krijg je een scheve en onethische insteek, dus je betaald altijd een redelijk bedrag dat in vergelijking is met andere studies, want anders krijg je ongewenst gedrag	**CH**
SRE	+	**IMO**	*And that is ethically unacceptable, there is no way you may trigger a physician to include a patient in a clinical trial, while this patient may be better of in another study or standard treatment. Your financial input, because of this, is relatively limited*	En dat kan ethisch natuurlijk ook niet, want je kunt niet een arts op die manier triggeren om een patient in een studie te includeren, terwijl die misschien beter in een andere studie past. Je financiële input hier is dus al vrij beperkt	**CH**
SRE	+	**IMO**	*In Western Europe, the investigator usually doesn't see anything of the investigator fee, in Eastern European countries they do, but also there you cannot give any extreme triggers*	In de West-Europese ziet de investigator vaak zelf niets van de investigator fee, in Oost-Europese landen wel, maar ook daar kun je geen perverse prikkels geven	**CH**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
SRE	+	**IMO**	*Publications is a relevant incentive, agreements on this are made in most contracts*	Publicaties is wel een relevante incentive, dat staat ook eigenlijk altijd wel in de contracten	**CH**
SRE	+	**IMO**	*As far as I know, nothing is written in the contract about the minimum number of patients to be able to co-publish. If it would, there would be the same unethical drive to include patients. If it is either a financial trigger or an academic trigger, it would still generate the wrong motivation to include a patient*	Voor zover ik weet staat daar eigenlijk niets over een minimumaantal patienten dat de site geincludeerd moet hebben. Ja anders krijg je toch weer die onethische drive om patienten te includeren. Of het nu een financiele of academische prikkel is, dan zou je toch nog een verkeerde motivatie hebben om een patient in een studie te includeren	**CH**
SRE	+	**IMO**	*My experience with investigator fees is that it can be either a limiting or a primary force. Sometimes they get paid extra to cooperate*	Ervaring met investigator fees? Ja, dat kan zowel belemmerend zijn of de primaire drijfveer. Of extra betaald krijgen.	**EM**
SRE	+	**IMO**	*It has a business structure, when the trial consumes more time than a standard treatment, it is only natural that this will be reimbursed*	Bedrijfsmatige structuur, als de trial meer tijd kost dan een standaardbehandeling is dat niet meer dan reëel dat daar een financiële vergoeding tegenover staat	**JS**
SRE	+	**IMO**	*And the opportunity for investigators to link in some way their own research*	De mogelijkheid dat investigator ook hun eigen onderzoek eraan kunnen knopen	**KV**
SRE	+	**IMO**	*Hospitals become more and more business-like institutions. When more time and money is spent on recruitment and the execution of the trial, then choices are easily made*	Ook ziekenhuizen worden steeds meer een bedrijfsmatige instelling. Wanneer meer tijd en geld gestoken wordt in de recruitment en uitvoering dan vergoed wordt, dan is de keuze snel gemaakt.	**KV**
SRE	+	**IMO**	*Investigators have to put many things together to know and constantly have to consider who gets what*	Nodig om veel zaken samen te voegen om te weten wat wie waarvoor krijgt. Constante afweging door investigator.	**KV**
SRE	+	**IMO**	*A study could be financially beneficial, so the investigator may spend some money on own studies. Other studies could be financially less attractive, however have a high academic interest, with which the investigator could co-publish*	Een studie kan financieel gunstig zijn, waardoor de arts geld overhoudt om zelf ook studies te kunnen doen, andere studies kunnen financieel minder aantrekkelijk zijn, maar weer een groot academisch belang hebben, waar de arts kan mee publiceren	**KV**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
SRE	+	**IMO**	*As a sponsor/CRO you may choose between key opinion leaders and East-European countries. In East-European countries physicians earn less than CRAs. Earning a part of the patient fee, is therefore interesting*	Kiezen tussen key opinion leaders en Oost-Europese landen. In Oost-Europese landen verdienen artsen minder dan de CRAs. Ontvangen een deel van fee, is dus interessant om extra patienten te recruteren	**KV**
SRE	+	**IMO**	*To author articles is important to academic hospitals, for other hospitals considerations are mainly budgetary*	Zeker bij academische ziekenhuizen is het belangrijk om te publiceren. Bij andere ziekenhuizen is de overweging meer budgettair	**KV**
SRE	+	**IMO**	*You can influence this by publication, appraisal, scientific achievement*	Invloed op geven, door publicatie, schouderklop, wetenschappelijke prestatie	**NS**
SRE	+	**IMO**	*An investigator fee may help as well*	Investigator fee kan ook helpen om zelf dan ook nog iets te doen	**NS**
SRE	+	**IMO**	*When there is only coverage of costs it may not be so interesting, just for the patient*	Bij alleen dekkende kosten niet interessant, alleen voor de patient	**NS**
SRE	+	**IMO**	*And interesting for the site investigator, however not for colleagues*	Alleen voor de PI, niet voor collega's	**NS**
SRE	+	**IMO**	*Then there is always the consideration for the physician: what do I think is important?*	Dan altijd afweging voor de arts wat vind ik belangrijk	**NS**
SRE	+	**IMO**	*And almost always: what is in it for me? It is usually not a patient consideration, because I have to choose anyway*	Bijna altijd: wat heb ik eraan? Niet de patient. Moet toch kiezen	**NS**
SRE	+	**IMO**	*For example, investigator fees that cost too much for the sponsor, but are still insufficient for hospitals to cover the costs*	Bijvoorbeeld investigator fees die een grote kostenpost zijn voor de sponsor, maar voor het ziekenhuis nog onvoldoende om de kosten te dekken	**NS**
SRE	+	**IMO**	*Sometimes the investigator fee is for the hospital*	Vaak komt de investigator fees ook ten goede van het hele ziekenhuis	**RZ**
SRE	++	**IMO**	*Although it is my experience that in East-Europe the physician often does do all the work him/herself, because they earn much more that way. I have seen physicians become a CRA because they would earn so much more, you can hardly imagine…*	Maar toch is mijn ervaring in Oost-Europa dat de arts vaak wel alles zelf doet, omdat ze daar meer mee verdienen. Artsen daar werden ook wel CRA omdat ze dan zoveel meer verdienden, dat kun je je bijna niet voorstellen	**EM**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
SRE	++	**IMO**	*Money is an important incentive, especially in Eastern Europe, where one patient fee is as much as multiple months salaries*	Geld is een belangrijke incentive, met name in Oost-Europa; patientfee is een aantal maandsalarissen	**EP**
SRE	++	**IMO**	*To co-publish is very important to investigators*	Welke rol krijgt de investigator? Mee publiceren is belangrijke factor voor investigators. Als dat wel kan bij studie 1, maar niet bij studie 2 geeft dat al een belangrijke schifting aan	**JS**
SRE	+	**OUT**	*When parameters change in the course of the study, you start adding up costs for the sponsor, therefore the risk of the CRO is not so big*	Als er parameters veranderen in de studie, dan ga je gewoon herrekenen naar de sponsor toe, dus het risico als CRO is redelijk beperkt	**CH**
SRE	+	**OUT**	*If you would count the costs and add an additional 40%, then you may take all the risk as a CRO, that would benefit everyone. Now CRO's are not so bothered*	Als je uitrekent wat het kost en je doet er 40% bovenop, dan kun je als CRO al het risico op je nemen, daar zou iedereen mee gebaat zijn. Nu maakt het voor een CRO vaak niet zoveel uit	**CH**
SRE	+	**OUT**	*The problem is now that if something changes, the sponsor doesn't want to pay extra, they prefer to take the risk themselves, because they want to earn as much as possible*	Het probleem is nu dat als er iets verandert de sponsor daar niet extra voor wil betalen, dus die nemen dan liever zelf het risico, omdat ze voor een dubbeltje op de eerste rang willen zitten	**CH**
SRE	+	**OUT**	*The CRO is not accounted for that*	De CRO wordt daar uiteindelijk niet financieel op afgerekend	**CH**
SRE	+	**OUT**	*Actually, you should leave full responsibility with the CRO, and agree that if the trial runs on time you will receive a bonus, but if the trial runs late, you pay less. That is what I would say*	Eigenlijk zou je dus de verantwoordelijkheid helemaal bij de CRO moeten neerleggen, en dan als je op tijd bent krijg je een bonus en als je te laat bent gaat er iets vanaf, zou ik zeggen	**CH**
SRE	+	**OUT**	*Freedom to negotiate as a CRO is difficult now, because you are tied by the budget*	Vrijheid om te handelen is u lastig omdat je budget gebonden bent	**CH**
SRE	+	**OUT**	*Often this is a discussion with the sponsor, we would like to call sites every month, just for small talk. But the sponsor doesn't want to pay for that. So that complicates things*	Hierover heb ik met de sponsor vaak een discussie, dat wij de sites willen bellen iedere maand, alleen maar voor een kletspraatje. Maar daar wil de sponsor niet voor betalen, en dan wordt het lastig natuurlijk.	**CH**
SRE	+	**OUT**	*Time necessary for small talk is hard to quantify*	Tijd die nodig is, is een moeilijk te kwantificeren getal	**CH**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
SRE	+	**OUT**	*All starts with a good qualified project manager. But we had once that our qualified project manager could not get along with the sponsors project manager, so even if you have very good people, if they do not get along things don't work out*	Het begint met een goed gekwalificeerde projectmanager. Maar we hebben weleens gehad dat de projectmanager van de sponsor niet overeen kon met onze projectmanager, dus dan heb je nog zulke goed mensen, als ze niet met elkaar overweg kunnen wordt het niks	**CH**
SRE	+	**OUT**	*If there are people you can count on for regulatory affairs, of course you will outsource*	Mensen waarop je kunt terugvallen om regulatoire zaken ed kunt brengen dan ga je daar natuurlijk naartoe	**KV**
SRE	+	**OUT**	*Big pharma usually hires some CRO*	Grote farma, vast weer een CRO ingehuurd	**NS**
SRE	+	**PMQ**	*It is sometimes hard to get sufficient funding for trials you want to do yourself. It is unclear how to go about it. Cooperation within the hospital could raise opportunities*	Het is soms moeilijk om voldoende funding te krijgen voor onderzoeken die je op wilt starten. Het is niet duidelijk hoe je dit kan aanpakken. Samenwerkingen binnen het ziekenhuis kunnen de kans groter maken	**BT**
SRE	+	**PMQ**	*And yes, of course you can try to manage that, you could make your study cheaper or more expensive with this, but I don't believe in cheap, because cheap is usually expensive in the end, because there is always the full length of the trial that counts*	Ja en daar kun je natuurlijk wel op managen, je kunt je studie er duurder of goedkoper mee maken, maar ik geloof niet in goedkoop, want goedkoop is meestal duurkoop, want je zit altijd met je studie lengte	**CH**
SRE	+	**PMQ**	*That makes project management quality a very important factor. If you don't assure that well enough and you don't pay for it, then nothing will come out*	Daarmee is de project management kwaliteit een hele belangrijke factor, als je dat niet goed regelt en je betaald daar niet voor, dan komt er niets uit	**CH**
SRE	+	**PMQ**	*For a CRO that is sometimes difficult. You are talking about million dollar studies, for which billions are earned. The patient recruitment could cause such a delay, that you lose maybe 2-3 years of patent in the end*	Als CRO is dat weleens lastig. Je praat over miljoenen studies, waar uiteindelijk miljarden vanaf komen. Die patient recruitement kan een dermate grote vertraging opleveren, dat je misschien wel 2-3 jaar aan patent verliest, uiteindelijk	**CH**
SRE	+	**PMQ**	*You cannot solve that just by sending money to a hospital, so you have to spend money in things that matter*	Je kunt dat niet oplossen door zomaar geld naar het ziekenhuis te sturen, dus je moet geld besteden aan zaken die iets opleveren	**CH**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
SRE	+	**PMQ**	*The difficult thing when I talk to sponsors, is that I have to explain it is not a standardized process. It is not like you put in money and out comes the data. It doesn't work that way, because much of the deal is in the soft side*	Het lastige vind ik altijd als je met sponsors praat, het is geen standaard proces. Het is niet zo dat als je er geld in stopt dat de data er vanzelf uitkomt. Zo werkt het niet. Want heel veel in het verhaal zit in de softe kant	**CH**
SRE	+	**PMQ**	*The costs for these (investigator) meetings are often too high for the sponsor, therefore these are teleconferences now, but that is less adequate*	De kosten voor deze (investigator) meetings zijn vaak te hoog, dus nu zijn dat vaak teleconferences, maar dat werkt minder goed	**CH**
SRE	+	**PMQ**	*Sufficient finances are important for progressing the trial. Many public funded trials quit prematurely, because the costs are not calculated correctly*	Financing is van belang voor voortgang van trial. Veel publiek gesponsorde trials stoppen voortijdig, omdat er niet voldoende rekening is gehouden met kosten	**EP**
SRE	+	**PMQ**	*Incorrect calculation of recruitment (maybe because of wishful thinking), that is why halfway during the trial the budget runs out, for including additional centres for example*	Geen juiste berekening recruitment rate (door wishfull thinking?), daardoor blijkt halverwege dat er te weinig budget is voor toevoegen centra oid	**EP**
SRE	+	**PMQ**	*An example is an investigator initiated trial in which recruitment was slow and including extra centres was too expensive. As a result of the delay in recruitment the research question was outdated*	Voorbeeld investigator initiated trial waarbij recruitment te langzaam verliep en nieuwe centra aansluiten te kostbaar was en vervolgens ook de onderzoeksvraag outdated	**EP**
SRE	+	**PMQ**	*For biotech, it is important to open the trials quickly, because of limited financing, however this may lead to protocol adaptions that may lead up to 80% delay at study end*	Voor biotech is het snel open belangrijk voor financiering, kan bij opstarten nog weer aanpassingen geven die In eigen praktijk 80% delay in studie einde geven	**KV**
SRE	+	**PMQ**	*Sponsor then includes additional centres, to speed up recruitment. But then afterwards is appears that 80 centres have been included instead of 40, of these 80, 30 have included only 1 or 2 patients*	Sponsor er alleen maar centra bijhaalt om de inclusie te versnellen, maar achteraf blijkt dan je 80 centra in plaats van 40, waar van die 80 er 30 maar 1 of 2 patienten hebben geïncludeerd	**RZ**
SRE	+	**PMQ**	*And then you have to discuss with the sponsor why you are running out of budget, because when there are only 2 or 3 patients included, especially in case of an Investigator Initiated Trial (IIT), you cannot commit and*	En dan ga je in discussie waarom opeens het budget oploopt, omdat als er 2-3 patienten bij een IIT dan kun je dat niet meer nakomen en zeggen dan ga ik een paar keer daar naartoe om te monitoren	**RZ**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
			say not to go there. You have to have several monitoring visits		
SRE			*Insurances could maybe play a more active role in all of this. The more people are treated within clinical research, it would mean a decrease in costs for the insurance companies, because they do not pay for the care and treatment then. However, if for example the insurance company would reimburse the care, then some of the study costs would not be for the pharma, and will not be included in the medication costs*	Verzekeringen zouden misschien ook een rol in het geheel kunnen spelen. Hoe meer mensen behandeld worden in onderzoek, betekent een ontlasting van kosten voor de verzekering, aangezien deze dan niet voor de zorg en de behandeling betalen. Als nu de verzekeraar wel de zorg voor rekening neemt, dan heb je in ieder geval een deel van de studiekosten die niet in het potje van de farmaceut terecht komen, wat ook niet terug belast wordt in de kosten van de medicatie	**CH**
SRE			*Then there may be a shift of costs from pharma towards the insurer, only then there will be less profit, which we will spare, all of us, and I think, well yes fine for me*	Dan verschuift er wat van de kosten van de farmaceut naar de verzekeraar, alleen dan zit er wat minder winst op. Nou ja, die bespaar je dan met z'n allen in die hele supply chain, dan denk ik nou ja prima	**CH**
SRE			*You also give more space and means to perform studies. If I look at those small pilot companies, when you look at a study, almost 40% is investigator fees, so if you could spare that, almost 2 studies can be done. And then there will be more research*	En je geeft ook meer ruimte en mogelijkheden om studies te doen. Als ik kijk naar die pilot bedrijfjes, als je naar een studie kijkt, bijna 40% zijn investigator fees, dus als je die eruit zou halen, kan je bijna 2 studies doen. En dan kan je weer meer onderzoek doen	**CH**
SSA	+	**SPC**	*Then extra labs etc. are requested, because they need to know if a product doesn't work. "How quickly can we kill a product?" That is why they try to get as much information right from the beginning*	Dan willen ze graag nog extra labs ed. Willen zo snel mogelijk weten of het product niet werkt. "How quickly can we kill a product" Daarom proberen ze zoveel mogelijk informatie vanaf het begin erbij te krijgen	**KV**
SUP	+	**IMO**	*Our CRA's have very good relationships with the hospitals. They even receive wish cards from the hospitals they visit, in case of festivities or illness*	Onze CRA's hebben hele goede relaties met de ziekenhuizen. De ziekenhuizen waar zij komen, sturen zelfs een kaartje naar ze bij verlof of ziekte o.i.d.	**AD**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
SUP	+	**IMO**	*And sometimes it doesn't even matter who the pharma company is, except when materials don't function well*	En soms maakt het niet eens uit welke farmaceut het is, alleen als materialen niet werken	**AD**
SUP	+	**IMO**	*You will have to support very much and make sure you have good equipment. And professionals who know what it is about, that really engage*	Je zal heel erg moeten supporten daarin en zorgen dat je goede spullen hebt. En vakmensen die weten waar het over gaat, die echt in gesprek gaan	**AD**
SUP	+	**IMO**	*Support, I think, is very important in general*	Support is denk ik wel heel belangrijk in het geheel	**AD**
SUP	+	**IMO**	*And you always have to be there for your investigator*	En daarnaast altijd klaar staan voor je investigator	**AD**
SUP	+	**IMO**	*If you invest in visiting the site in the beginning, that is very important for the commitment of a site*	Als je in het begin veel naar een site toegaat is dat heel belangrijk voor de commitment	**AJ**
SUP	+	**IMO**	*It is also important who will come. If there is a CRA that is corrective about every small aspect, or there is someone who says 'come on, let's find a solution together', that will make a huge difference. Also in recruitment*	Het is ook heel belangrijk wie er komt. Als je een CRA krijgt die op iedere slak zout legt, of iemand die zegt 'kom we gaan het samen even oplossen', dan maakt dat een heel groot verschil. Ook op de recruitment	**AJ**
SUP	+	**IMO**	*It is the way you communicate with the site*	Het gaat om de manier van gesprek voeren.	**AJ**
SUP	+	**IMO**	*My expectations of a CRO is that it has to be practical. For example, one time they did not want to provide a stock at the pharmacy. They assumed a 3-week delivery period, but that is not always right. That was a problem*	Voor een CRO moet het praktisch zijn. Vb zij wilden niet dat er een voorraad was in de apotheek. Zij gingen uit van een wachttijd van 3 weken, maar dat is niet altijd. Wel probleem geweest.	**BT**
SUP	+	**IMO**	*I need flexibility from a CRO, otherwise it is a limitation*	Verwacht flexibiliteit van CRO. Is zeker belemmering	**BT**
SUP	+	**IMO**	*That is why you have to make sure the investigator is sufficiently managed, you have to put in time and energy. And not even so the investigator, but the research coordinators/ nurses that play a big role*	Daarom moet je zorgen dat die arts voldoende gemanaged wordt, daar moet je heel veel tijd en aandacht aan besteden. En eigenlijk niet die arts, maar meer nog de research coordinator/verpleegkundige die daar een rol in spelen	**CH**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
SUP	+	**IMO**	*I can imagine that a physician doesn't know or think about a project , when busy with a patient. But you can work on that, eliminate that factor*	Ik kan me voorstellen dat een arts niet weet of zich niet herinnert dat er een project loopt, want die is druk met die patient, maar daar kun je aan werken, die factor kun je uitschakelen	**CH**
SUP	+	**IMO**	*Another problem is the capacity of the investigators. What we do then sometimes is to engage a 'flying study nurse' at a site. When an enormous administrative burden bothers the site, it can make a difference up to 2 patients a day*	Een ander probleem is dan de capaciteit van de investigators, en wat we dan weleens doen is bijvoorbeeld een 'flying study nurse' op een site zetten. Als er een enorme administratieve last ligt, dan kan dat zomaar 2 patienten per dag schelen	**CH**
SUP	+	**IMO**	*Sites are happy with this, so these are things you can do as well. The day to day stuff*	Daar zijn sites blij mee, dus dat zijn ook dingen die je kunt doen. Dat zijn wel de dag to dag dingen	**CH**
SUP	+	**IMO**	*Support from a study nurse is important in identifying eligible patients, they usually bring this to the doctor's attention*	Ondersteuning studienurse is wel van belang in herkennen van patienten, brengt vaak onder de aandacht	**EP**
SUP	+	**IMO**	*You could ask: may we be in contact with your study coordinator? Local coordinators are very important, much easier to reach then the investigators*	Vragen: mogen wij af en toe met de coordinator van het onderzoek contact hebben? Lokale coordinatoren zijn belangrijk, veel meer benaderbaar dan lokale specialisten	**JS**
SUP	+	**IMO**	*That is what we did in one of our studies, have contact with the local coordinators, and not bother the investigators. Service as much as possible*	bij de Candy study ook gedaan, contact via lokale coordinatoren, niet lastig vallen, zoveel mogelijk servicen	**JS**
SUP	+	**IMO**	*This person has to be able to make his/herself invisible, take the interest of the study first. It depends al lot on who you send, before you know it things get messed up*	Persoon moet zichzelf kunnen wegcijferen, belang van de studie eerst, hangt enorm af van degene die daar naartoe gaat, voor je het weet is het weer mis	**JS**
SUP	+	**IMO**	*Frequent visits from a monitor don't really have a positive effect on recruiting patients, asking them in the outpatient clinic, but maybe if you look upon the monitor as a kind of trial manager, the it may help*	Frequente visites van monitor niet echt positief effect op vragen van patienten op de poli, misschien als je de monitor als trial manager ziet	**NS**
SUP	+	**IMO**	*It helps a lot when you can easily contact het monitor for questions etc.*	Laagdrempelig contact bij dingen, bij vragen ed helpt heel erg	**NS**
SUP	+	**IMO**	*When there is someone in start-up that cooperates, and says what is and what is not essential and you can mail with questions*	Als je iemand in het voortraject hebt die ook meewerkt en die zegt dat en dat is niet nodig en als je vragen hebt mail me dan	**NS**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
SUP	+	**IMO**	*Someone who can think constructive, that helps*	Iemand die inhoudelijk meedenkt, daar heb je wat aan	**NS**
SUP	+	**IMO**	*no' as an answer may also be fine, as long as you get an answer*	Soms is een antwoord nee ook prima, als je maar een antwoord krijgt	**NS**
SUP	+	**IMO**	*What we want is almost impossible of course. That is an experienced person, who responds at the right time, without bothering to much and asking too much attention. Of course, that doesn't exist*	Wat wij willen is natuurlijk bijna onmogelijk. Dat is een heel ervaren iemand, die precies op het goede moment reageert, zonder hier teveel te zijn en te veel van ons te vragen. Dat bestaat natuurlijk niet echt	**NS**
SUP	+	**IMO**	*Centers may use these materials, but they don't have to. They choose what suites them best*	Centra kunnen daar gebruik van maken, maar dat hoeft niet. Ze kunnen kiezen wat voor hen het beste past	**RZ**
SUP	++	**IMO**	*Without a good relationship you get nowhere, things will not work out, because it is all goodwill.*	Zonder goede relatie kom je helemaal nergens, dan gaat het niet lukken, want het blijft een gun-factor	**AD**
SUP	++	**IMO**	*I always say: TLC, Tender Loving Care for the investigator. Make sure they have all the materials, make sure they are trained, and make sure that there are not too many vendors. And if you do provide materials, make sure they work well*	Ik zeg altijd TLC voor de investigator, Tender Loving Care, zorg dat ze alle middelen hebben, zorg dat ze getraind zijn, zorg dat je niet teveel vendors hebt en als je middelen geeft, zorg dat ze werken	**AD**
SUP	++	**IMO**	*It is important to have one contact person at a CRO. Not be slow in responding, but be supportive*	CRO. Persoonlijk aanspreekpunt. Traag, ondersteunen	**JS**
SUP	++	**IMO**	*Absolutely it can help when you reach the right persons. You have to take care which character you send, the person has to be amiable, be service minded*	Kan absoluut helpen als je de juiste personen weet te benaderen, erg opletten welke karakterstructuur je stuurt, amabel persoon sturen, service gerichte opstelling	**JS**
SUP	++	**IMO**	*The CRA is much more important, it can help a site to identify patients*	CRA veel belangrijker, kan een centrum helpen om patienten te identificeren	**KV**
SUP	++	**IMO**	*In oncology, you must try to understand the disciplines. In specific cancer centers knowledge is fairly high level. What is needed? Support. And help to prioritize.*	In de oncologie proberen de diensten te begrijpen. In specifieke kankercentra is de kennis van zaken vrij hoog. Wat is nodig?	**KV**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
SUP	++	**IMO**	*If you support sites they feel more comfortable to execute the study. Consider the data you really need. For example, if you need to now every minute of every admission, you have to consider carefully where they should really focus their time and effort*	Als je steun verleent aan de centra voelen ze zich ook meer op hun gemak om de studie uit te voeren. Goed kijken naar welke data je echt nodig hebt. Bijvoorbeeld als je iedere minuut wil weten van de toediening. Goed kijken naar waar zij de beschikbare tijd aan moeten spenderen	**KV**
SUP	++	**IMO**	*You can help sites to prioritize, what we can live with and what is really important*	Je kunt de centra helpen prioriteiten op te stellen, waar kunnen we mee leven enwat is echt nodig	**KV**
SUP	++	**IMO**	*To make the sites feel comfortable is most important. If there is no money to do that, then it will become a cascade of triggering events*	Het centrum op zn gemak te laten voelen is belangrijkst. Als daar geen geld voor is, dan is het wel een cascade die het ene triggert na het andere	**KV**
SUP	++	**IMO**	*The most important is personal contact, all the other factors you may influence, however yes, the biggest impact has personal contact*	Het allerbelangrijkste is persoonlijk contact. Andere punten kan je invloed op hebben. De grootste impact factor is ja, persoonlijk contact	**KV**
SUP	++	**IMO**	*That personal contact must make sure that you can influence the investigator in the best way possible, and also to find out why a site doesn't recruit. From simple stupid things like persons who do not work well together to problems with the study protocol design. Everything depends on the information you are able to acquire*	Dat persoonlijk contact moet ervoor zorgen dat je de investigator op de beste manier kan beinvloeden of dat je te weten komt waarom een site niet gaat recruteren. Van simpele domme dingen als mensen die niet goed met elkaar samenwerken tot problemen met het studieprotocol. Alles staat of valt met de informatie die je kunnen inwinnen	**KV**
TOT	+	**XSC**	*Recruitment in a clinical trial is one of the most relevant factors. In regards of the timelines maybe even the most relevant*	Recruitment is in een klinische trial een van de meest relevante factoren. Zeker gezien de tijdlijn misschien wel de meest relevante	**CH**
TOT			*Although the system threatens to fail, and indeed, patient recruitment is an essential part*	Maar dat systeem dreigt al niet meer te lukken, en dan inderdaad, daar maakt patient recruitment een wezenlijk onderdeel van uit	**CH**
TTR			*The 'time to register the drug' is shortening, the FDA and EMA have short trajectories*	De time to register the drug die wordt steeds korter, en de FDA en EMA hebben verkorte trajecten	**AD**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
TTR			*They have improved in trajectories for target populations, which is good. That is why more research should be performed in elderly. Usually medications that are indicated for elderly, are not being tested in elderly*	Ze gaan steeds sneller in de targeted population, wat ook goed is, want daarom moet er eigenlijk ook meer onderzoek komen voor ouderen. Meestal worden medicijnen die bij veel ouderen worden toegepast, worden nu eigenlijk niet getest bij ouderen	**AD**
	feasibility		*Everything needs to go fast nowadays, from pharma's perspective, that piece of work is a somewhat out of sight. They use a global view*	Alles moet tegenwoordig snel, vanuit de farma, dat stukje is inderdaad een ondergeschoven kindje bij de farma. Er wordt globaal gekeken	**AJ**
	feasibility		*A pharma company has little time and the site has little time, therefore both spend little time on feasibility*	En bij de farma is er weinig tijd en bij de site is er weinig tijd, beide besteden weinig tijd aan de feasibility	**AJ**
	feasibility		*The result is that inaccurate information is generated and used. A lot could be gained there.*	Het gevolg is dat er inaccurate informatie wordt gegenereert en gebruikt, daar is nog wel een stukje winst te behalen	**AJ**
	feasibility		*My idea is that sites do not realize how important feasibility really is, especially in the start-up phase, because it has no use for including in a study for which you are unable to recruit patients, then all it takes is time*	Ik heb het idee dat bij sites niet het besef heerst hoe belangrijk een feasibility is, juist in die start-up fase, omdat je niets hebt aan een studie waar je geen patient voor kunt leveren, want dat kost alleen maar tijd	**AJ**
	feasibility		*Only when patients are recruited, you exploit what you invested in the start-up*	Pas als patienten in de studie komen, dan krijg je eruit wat je er in de start-up in hebt gestoken	**AJ**
	feasibility		*I doubt if a start-up fee covers all expenses, and if you do not recruit any patient it is a waste of time anyway*	Ik vraag me af in hoeverre een start-up fee dekkend is, en als je er geen patient in krijgt is het zowieso zonde van de tijd	**AJ**
	feasibility		*It is better to carefully consider feasibility*	Beter om goed naar de feasibility te kijken	**AJ**
	feasibility		*A start-up fee in my experience doesn't decrease the incentive to recruit patients, centres genuinely do want to participate in the study*	De start-up fee vermindert naar mijn ervaring niet de incentive om patienten te recruteren, centra willen toch graag met de studie meedoen	**AJ**
			My two 'hats', first as a representative of a pharma company, that perform the operational work itself, and secondly as a patient	Mijn twee petten, ten eerste als een vertegenwoordiging van een farma bedrijf die zelf	**AD**

Causing variable / stock	Influence	Using variable / stock	Quotes in English	Quotes in Dutch	Interviewee
				nog het operationele (CRO) werk doet en ten tweede als patient	
			I worked 17 years as a CRA, of which the last 5 years as a start-up, and now 3 years in patient recruitment	17 jaar als CRA, laatste 5 jaar als start up, nu 3 jaar in patient recruitment	**AJ**
			I like this job, it's more out-of-the-box thinking in patient recruitment	Deze baan vind ik erg leuk, meer out-of-the-box denken nu in patient recruitment	**AJ**
			We work together with sites, but are being paid by pharma. We get reimbursed when patients are included. And sometimes we even reimburse the sites for cooperating with us. However we are still quite unknown. And yes, we are again another vendor...	Wij werken samen met sites, maar worden betaald door de farmaceuten. Wij worden vergoed als er patienten worden geincludeerd. En soms betalen wij zelfs sites om mee te kunnen helpen. Maar dat isnog onwetendheid en weer een vendor	**AJ**
			In the US this concept has proven its function, but here we need to get known. A few success stories would help	In Amerika werkt dat al heel goed, maar hier moet dat nog meer bekendheid krijgen. En een paar succesverhalen	**AJ**
			There is development of our business towards oncology, however the trust bond between doctor and patient could become an issue	Er zijn wel ontwikkelingen richting de oncologie, maar daar zou de vertrouwensrelatie met de arts nog wel een issue kunnen worden	**AJ**
			However, something has to change in drug development, it isn't much longer feasible this way…	Maar er moet iets veranderen, zo kan het niet langer…	**AJ**
			The model you made seems very impressive, however I do recognize this is the way it works!	Het model dat je gemaakt hebt ziet er indrukwekkend uit, maar ik herken wel dat dit is hoe het werkt	**BT**
			And if we continue to consider three phases as necessary…	En zolang we het met z'n allen nodig vinden om 3 studiefasen te hanteren, tja…	**CH**
			It is very easy to blame the pharmaceutical industry	Het is heel makkelijk om een boeman te vinden in de farmaceutische industrie	**CH**

Appendix 4: List of equations

Variable Type	*Abbre-viation*	*Parameters/ variables*	*Description*	*Unit*	*Base value*	*Min/max variety*	*Equation*
		Results					
Rate	PRR	Patient recruitment rate	Number of patients recruited per month, based on the study population and determined by Patient motivation and the Number of participating sites	Patients/month			Potential patients*(PMO out)*DELAY3I(Number of participating sites , 9 , 30) *Project is done
Auxilliary	PSC	D Deviation from planned study closure	Any deviation from planned study closure that results from an increased or decreased patient recruitment rate and total recruitment	Months			DELAY FIXED(Study Lateness, 6 , 1)
Stock	ROI	Estimated Return of Investment	Expected Return on Investment (ROI) based on remaining market time within the drugs patented lifetime, after registration for commercial use	€/month	0		ROI in-ROI out
Auxilliary	ROI in	ROI in	Inflow Expected Return of Investment	€/month			(Expected ROI/Expected market time to patent expiration)*(Expected market time to patent expiration-IF THEN ELSE(D Deviation from planned study duration >36 , 36 , D Deviation from planned study duration))
Auxilliary	ROI out	ROI in	Outflow Expected Return of Investment	€/month			Estimated Return of Investment
Auxilliary	STL	Study Lateness	The additional time from planned study closure that results from a slow patient recruitment rate and total recruitment	Months			MAX(Time + X time till study closure under current rate,Planned study duration) -Planned study duration

Variable Type	*Abbre-viation*	*Parameters/ variables*	*Description*	*Unit*	*Base value*	*Min/max variety*	*Equation*
Stock	TOT	Total recruitment	Cumulative number of patients entered in a clinical study, originating from the potential patients and speed defined by the Patient recruitment rate	Patients	0	max 1000	+ Patient recruitment rate
Auxilliary	TPE	Expected market time to patent expiration	Time before expiration of patent, after the drug has been registered, i.e. time left to market the drug and get revenues.	Months			Patent duration-Planned time to drug registration
Auxilliary	XSC	X time till study closure under current rate	The time left for achieving the planned number of patients under the current Patient recruitment rate	Months			IF THEN ELSE((Total patients needed - MIN(Total patients needed,Total recruitment))/(0.001 + Patient recruitment rate)>200 , 1 , (Total patients needed - MIN(Total patients needed,Total recruitment))/(0.001 + Patient recruitment rate))
		Protocol Design Factors					
Constant	CLR	Clinical relevance	Clinical relevance of the investigative drug, based on novelty and/or expected benefit	Dimensionless	1	1-2	Value
Constant	COT	Competing treatments	Number of competing treatments; this includes other clinical trials targeting the same patient population or emerging new (standard) treatments	Dimensionless	1	1-2	Value
Auxilliary	DEN	Density	Density of population in combination with the number of participating sites	Dimensionless			1*Number of participating sites

Variable Type	*Abbre-viation*	*Parameters/ variables*	*Description*	*Unit*	*Base value*	*Min/max variety*	*Equation*
Constant	ELI	Eligibility criteria specificity	Specificity of eligibility criteria which defines the study population of the clinical trial, in order to include a comparable group of patients and to reduce confounding factors. A higher specificity results in a smaller number of potential patients.	Dimensionless (specificity; high-normal-low)	1	1-2	Value
Constant	INC	Incidence	Incidence of the specific disease, number of patients/1000 inhabitants	Patients/months	45000/12		Value
Constant	NPS	Number of participating sites	The number of sites that are planned to be included in the clinical trial	Number	80	60-100	Value
Auxilliary	POD	Project is done	Variable supporting simulation stops when total recruitment is reached	Dimensionless			IF THEN ELSE(Total recruitment>1000 , 0 , 1)
Stock	POP	Potential patients	Number of patients available based upon incidence and density of the population in combination with the study eligibility criteria	Patients	3750		(Incidence/Density)*IF THEN ELSE(Eligibility criteria specificity>1 , 0.95 , 1)-Patient recruitment rate
Auxilliary	SPC	Study protocol complexity	Complexity caused by study specific assessments and specificity of eligibility criteria. Least complex is a clinical trial that most resembles standard of care.	Dimensionless		1-2	(Eligibility criteria specificity+Study specific assessments)/2
Constant	SSA	Study specific assessments	Specific assessments required by study protocol, which are not a performed as standard of care. Therefore, this requires patients to undergo additional assessments and requires study specific coordination in the hospital.	Dimensionless	1	1-2	Value

Variable Type	*Abbre-viation*	*Parameters/ variables*	*Description*	*Unit*	*Base value*	*Min/max variety*	*Equation*
Constant	TPN	Total patients needed	Calculated number of patients needed in the clinical trial to obtain a statistically significant outcome	Patients	1000		Value
		System Factors					
Constant	ERU	Expected revenue	Revenue expected based on study feasibility	€	10		Value
Auxilliary	LFA	Local facilities	Facilities (infrastructure) available in the hospital for study specific investigations and support of clinical studies (e.g. study coordination, data management)	Dimensionless			DELAY1I(IMO out , 12 , 1)
Constant	PAD	Patent duration	Patented drug duration at time of study start	Months	120	80-180	Value
Constant	PSD	Planned study duration	Planned number of months from study start to closure	Months	36		Value
Constant	RAP	Extent of regulatory and administrative procedures	Extent of procedures necessary for obtaining approval of study conduct per country	Dimensionless	1	0.5-1.5	Value
Auxilliary	TDR	Planned time to drug registration	Planned time from study start until registration of the drug	Months			Planned study duration+Time to register drug
Constant	TTR	Time to register drug	Time needed for the authorities to review a registration file before registration of the drug for commercial use	Months	10	8-16	Value
		Project Management Factors					
Auxilliary	EDU	Education	Development of educational materials for patients and public, as well as (on-site) training for study personnel	Dimensionless			PMQ out

Variable Type	*Abbre-viation*	*Parameters/ variables*	*Description*	*Unit*	*Base value*	*Min/max variety*	*Equation*
Auxilliary	OUC	Outsourcing complexity	Complexity in study conduct correlated to number of vendors where activities are outsourced, increasing the level of bureaucracy (e.g. administrative burden, communication levels)	Dimensionless			IF THEN ELSE(Outsourcing*Number of vendors>3 , 0.5 , 1)
Auxilliary	OUT	Outsourcing	Activities for study conduct that are outsourced (i.e. CRO, lab, IPO)	Dimensionless			SRE out
Auxilliary	PIF	Publicity Impact Factor	The impact of clinical relevance on the awareness of the public	Dimensionless			DELAY3I(IF THEN ELSE(Clinical relevance>1 , 1.2 , 1) , 4 , 1)
Stock	PMQ	Project Management Quality	Project management needed for coordination of study operations. This may be provided by sponsor, outsourcing company and/or lead study investigator	Dimensionless	1		PMQ in-OMQ out
Auxilliary	PMQ in	PMQ in	Inflow Project Management Quality	Dimensionless			(Outsourcing+Outsourcing complexity+Experience+IMO out+(IF THEN ELSE(Study Lateness>6 , 2 , 1)))/5
Auxilliary	PMQ out	PMQ out	Outflow Project Management Quality	Dimensionless			Project management quality
Stock	PUA	Public awareness	Awareness created through media e.g. publications in newspapers, expert journals, internet, etc.	Dimensionless	1		PUA in-PUA out
Auxilliary	PUA in	PUA in	Inflow Public awareness	Dimensionless			(PMQ out+Publicity Impact Factor)/2
Auxilliary	PUA out	PUA out	Outflow Public awareness	Dimensionless			Public awareness
Stock	SRE	Sponsor resources	Financial or other resources (e.g. co-authorship) made available by sponsor as reimbursement of study activities in the participating hospitals (= investigator	Dimensionless	1		SRE in-SRE out

Variable Type	*Abbre-viation*	*Parameters/ variables*	*Description*	*Unit*	*Base value*	*Min/max variety*	*Equation*
			motivation) and for study operational/project management (through outsourcing)				
Auxilliary	SRE in	SRE in	Inflow Sponsor resources	Dimensionless			(IF THEN ELSE(ROI out>10 , 1 , 1)+IF THEN ELSE((D Deviation from planned study duration) > 4 , 3 , 1))/2
Auxilliary	SRE out	SRE out	Outflow Sponsor resources	Dimensionless			Sponsor resources
Auxilliary	SUP	Support	Project management support given to investigators during the conduct of the clinical trial	Dimensionless			PMQ out*2
Constant	VEN	Number of vendors	The number of vendors used for outsourcing	Number	1	1-3	Value
		Human Factors					
Stock	ATT	Attitude towards study drug	Attitudes towards the study drug are compiled of basic norms and beliefs, personal experience and may be influenced by education and peer opinion. A positive attitude towards the study drug would encourage a patients' and investigators' motivation to participate in the clinical trial	Dimensionless	1		ATT in-ATT out
Auxilliary	ATT in	ATT in	Inflow Attitude towards study drug	Dimensionless			(Norms and beliefs+Peer opinion+PUA out+Experience+Education)/5
Auxilliary	ATT out	ATT out	Outflow Attitude towards study drug	Dimensionless			Attitude towards study drug

Variable Type	*Abbre-viation*	*Parameters/ variables*	*Description*	*Unit*	*Base value*	*Min/max variety*	*Equation*
Auxilliary	EXP	Experience	The amount of experience with clinical trials, either in management, conduct or in participation, which is influenced by education	Dimensionless			Education
Stock	IMO	Investigator motivation	The motivation experienced by investigator to fully cooperate with the recruitment of patients in the clinical trial	Dimensionless	1		IMO in-IMO out
Auxilliary	IMO in	IMO in	Inflow Investigator motivation	Dimensionless			(IF THEN ELSE(Competing treatments>1 , -6 , 1)+ATT out+IF THEN ELSE(Clinical relevance>1 , 6 , 1)+Experience+Extent of regulatory and administrative procedures+Local facilities+Outsourcing complexity+SRE out+MIN(IF THEN ELSE(Study protocol complexity>1 , -1 , 1) , IF THEN ELSE(Study protocol complexity>1.5 , -2 , 1))+Support)/11
Auxilliary	IMO out	IMO out	Outflow Investigator motivation	Dimensionless			Investigator motivation
Constant	N&B	Norms and beliefs	Norms and beliefs are mainly determined by cultural aspects and personal nature	Dimensionless	1	0.5-1	Value
Auxilliary	PEO	Peer opinions	Peer opinions may influence the attitude towards the study drug under investigation; these peers can be academic colleagues, as well as relatives, friends, neighbors, etc.	Dimensionless			PUA out
Stock	PMO	Patient motivation	The motivation experienced by patients to decide whether or not to participate in the clinical trial	Dimensionless	0.01		PMO in/100-PMO out

Variable Type	*Abbre-viation*	*Parameters/ variables*	*Description*	*Unit*	*Base value*	*Min/max variety*	*Equation*
Auxilliary	PMO in	PMO in	Inflow Patient motivation	Dimensionless			(IMO out+ATT out+MAX(IF THEN ELSE(Study protocol complexity>1 , 0.9 , 1) , IF THEN ELSE(Study protocol complexity>1.5 , 0.8 , 1)))/3
Auxilliary	PMO out	PMO out	Outflow Patient motivation	Dimensionless			Patient motivation