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An EU 2017/745 Medical Device Regulation Compliant Decision Support System for Trial Design of a Clinical Investigation for a Medical Device

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Master's Thesis
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Synopsis:

The European Union (EU) Medical Device Regulation (MDR) 2017/745 sets stringent requirements for clinical data required in a clinical evaluation, which affects manufacturers of medical devices in getting their device approved and with that enter the EU market. Clinical data can be obtained by conducting a clinical investigation, which involves a clinical trial on human subjects. A sponsor has the responsibility for planning and conducting a clinical investigation, which comes with 14 challenges identified through a literature search. Currently, no tool which can assist in planning a trial design for a clinical investigation is available to sponsors.

To accommodate this, an initial analytical basis for a MDR compliant decision support system, ACIT, is developed, aiming to assist sponsors in planning and accommodating challenges at a clinical investigation. Unified Modeling Language is applied to develop diagrams which serves as the fundamental elements of ACIT. The analysis supports an object oriented methodology and results in user requirements, a use case diagram along with use case descriptions, activity diagrams, functional requirements, and analysis class diagrams. Additionally, two notes are created and included as a part of ACIT to give sponsors clarity about specific methods and real-world examples.
Of the 14 identified challenges, ACIT addresses 11. The remaining three challenges are not addressed by ACIT, as they are too specific to the device under investigation. By asking questions, ACIT prompts sponsors to be aware of and reflect on challenges, thus providing a stronger foundation for designing a clinical investigation. The assistance also includes references to methods and guidance for planning and handling challenges. ACIT needs further development, as it currently is in the initial stages of a software system development life cycle.

Resumé

Forordningen for medicinsk udstyr (MDR) gældende i Den Europæiske Union (EU) er MDR 2017/745. MDR omfatter strenge krav for kliniske data der skal indgå i en klinisk evaluering af det medicinske udstyr, hvilket påvirker fabrikanter i at få udstyret godkendt til at komme på det europæiske marked. En kilde til at opnå klinisk data er ved at udføre en kliniske afprøvning af det medicinske udstyr, som er et klinisk forsøg der involverer forsøgspersoner. Gennem en litteratursøgning er der identificeret 14 udfordringer ved kliniske afprøvninger af medicinsk udstyr. Disse udfordringer påvirker en sponsor, der er ansvarlig for en klinisk afprøvning. På nuværende tidspunkt er der intet eksisterende værktøj tilgængeligt for sponsorer, der kan assistere i at planlægge designet af en klinisk afprøvning.

For at adressere udfordringerne relateret til planlægningsfasen i en klinisk afprøvning udarbejdes et initierende analysegrundlag for et beslutningsstøttesystem, navngivet ACIT, som er i overensstemmelse med MDR. I analysen af ACIT er Unified Modeling Language anvendt til at udarbejde forskellige typer af diagrammer, som fungerer som centrale elementer i beslutningsstøttesystemet. Analysen omfatter definition af brugerkrav, udarbejdelsen af et use case diagram der indeholder use cases hvis hændelsesforløb præsenteres i use case beskrivelser, aktivitetsdiagrammer, definition af funktionelle krav samt analyseklassediagrammer. Analysen understøtter en objektorienteret tilgang, som sætter retningen for den videre systemudvikling af ACIT. Yderligere er der udarbejdet to dokumenter som er tiltænkt værende en del af ACIT, med det formål at give sponsorer klarhed omkring specifikke metoder og virkelige eksempler.

ACIT kan adressere 11 af de identificerede udfordringer i relation til klinisk afprøvninger. De resterende tre af identificerede udfordringer er ikke adresseret, grundet at disse udfordringer er for specifikke for det enkelte medicinske udstyr. Ved at stille spørgsmål får ACIT sponsorer til at bliver opmærksomme på og reflektere over udfordringer, hvilket giver et stærkere grundlag for at designe en klinisk afprøvning. Assistancen består også af referencer til metoder og vejledning til planlægning og håndtering af udfordringer. Eftersom ACIT på nuværende tidspunkt er i de indledende faser af systemudviklingen, er der behov for at fortsætte udviklingen af ACIT.

Preface

This report is the result of a master's thesis in the 4th semester of the master's program in Biomedical Engineering and Informatics at the Department of Health Science and Technology at Aalborg University. The thesis is carried out in the period 01th of February 2024 to 31th of May 2024.

The main topics of the thesis addresses challenges for manufacturers and sponsors with clinical investigations of medical devices under the EU Medical Device Regulation 2017/745 as well as the development of an initial analytical basis for a decision support system aiming to assist in the trial design choices and address challenges when planning a clinical investigation. The thesis also covers two developed notes "Calculation of sample size" and "Handle learning curve" which can be found in the zip file "External appendix".

Special thanks to the supervisor Ulrike Sabine Pielmeier for good and constructive guidance and collaboration.

Reading Guide

This master's thesis consists of a main report with associated appendices and a portfolio in the last appendix that addresses two problem-based learning objectives. The main report consists of the essential findings and methodologies, while further information appears in the appendices.

Chapters 1-3 introduce the thesis and address the initiating problem statement and the thesis statement. Chapter 4 presents and argues for the chosen methods and the methodical approach. Chapters 5-7 cover the findings and results obtained using the methodology as well as a discussion of use of the decision support system and its future development.

The Harvard method is used as a reference system. References are cited actively 'Last name/organisation [Published year]' or passively [Last name/organisation, published year], and with page number if refereed to a book. If a reference is cited within a sentence, it refers to the specific sentence, whereas if a reference is cited after the stop of a sentence, it refers to the section of sentences. The references appear in the bibliography, which is listed in alphabetically order by the last name of the first author. Abbreviations and acronyms are applied, and an overview appears from the "List of Acronyms" on the following page. References to the documents in the external appendix are provided by footnotes. Chapters in the main report are numbered and appendices are indicated with a capital letter. Figures and tables are referred to by chapter number in the main report or capital letter in the appendix and then sequential numbers.

List of Acronyms

AIMDD	Active Implantable Medical Devices Directive 90/385/EEC
CTMS	Clinical trial management system
DSMC	Data safety monitoring committee
DSS	Decision support system
EDC	Electronic data capture
EU	European Union
EUDAMED	The European database on medical devices
GSPR	General safety and performance requirements
MDCG	Medical Device Coordination Group
MDD	Medical Devices Directive 93/42/EEC
MDR	Medical Device Regulation 2017/745
OOA	Object oriented analysis
RCT	Randomised controlled trial
SCED	Single case experimental design
SDLC	Software development life cycle
SME	Small and medium enterprises

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1 Introduction

Prior to placing a medical device on the European Union (EU) market, the device must demonstrate conformity with the requirements outlined in the relevant legislation and thus obtain a Conformité Européenne (CE) marking clearance [The European Parliament and the Council of the European Union, 2017]. The legislation governing medical devices in the EU is the Medical Device Regulation (MDR) 2017/745, which supersedes two former directives: The Council Directive 93/42/EEC for general medical devices (MDD) and the Council Directive 90/385/EEC for active implantable medical devices (AIMDD). The former directives consist of general rules that each member state in the EU were responsible for incorporating into national legislation, which consequently led to a lack of consistency in legislation across the different nations. [Rahi and Rana, 2020] At the beginning of the 2010s, several major incidents involving medical devices causing harm to patients unfolded, encompassing metal-on-metal hip replacements, breast implants, and surgical meshes. These incidents stem from poor design, lack of clinical testing, and insufficient clinical evidence of the device, necessitating the formulation of a new legislation for medical devices. [Fraser et al., 2021; Bretthauer et al., 2023a] One of the primary objectives of the MDR is to mitigate risks associated with medical devices, ensuring they offer benefits, and are safe for use [The European Parliament and the Council of the European Union, 2017]. The MDR imposes more comprehensive requirements on the regulatory process, particularly impacting medical device manufacturers [Rahi and Rana, 2020].

A key change from the directives to the MDR is the heightened requirements imposed on medical device manufacturers for collecting, assessing, and analysing clinical data as part of the mandatory clinical evaluation process [Kearney and McDermott, 2023]. A clinical evaluation aims to verify that the medical device, during its intended use, demonstrates conformity with the general safety and performance requirements (GSPR) based on clinical data that provide sufficient clinical evidence [The European Parliament and the Council of the European Union, 2017]. However, specifying and assessing the amount of clinical evidence required poses challenges to manufacturers [Kearney and McDermott, 2023], as no detailed guideline exist due to the considerable variability among medical devices [The Medical Device Coordination Group, 2020c].

One of the sources of clinical data is clinical investigations, which entail conducting clinical trials on human subjects to gather clinical data on the medical device under investigation. A clinical investigation is planned, conducted, and financed by a sponsor which is responsible for the overall management of all aspects of the investigation process, which include creating and updating mandatory documents, maintaining stakeholder communication, and ensuring compliance with applicable legislation. [The European Parliament and the Council of the European Union, 2017] Planning and conducting a clinical trial involving a medical device presents a multitude of challenges for the sponsor, potentiality impacting the quality of the clinical data, and thereby affecting the content in the clinical evaluation [Zannad et al., 2014].

Based on the above, the following initiating problem statement is posed:

What are the challenges for manufacturers and sponsors with planning and conducting a clinical investigation under MDR for a medical device, and are there tools that can support sponsors in facilitating a clinical investigation?

2 Problem Analysis

This chapter clarifies what a clinical investigation is, including the challenges for manufacturers and sponsors along with the consequences the challenges imply. Additionally, tools applicable for facilitating a clinical investigation are presented.

2.1 Clinical Investigation under MDR

Under the MDD and AIMDD, conducting clinical investigations was not prescribed, even for high-risk medical devices. It was sufficient that manufacturers could demonstrate equivalence with a corresponding CE-marked device on the market. [Saia et al., 2023] This entailed that several medical devices were evaluated through a literature review of similar devices instead of data from a clinical trial of the device under investigation [Hulstaert et al., 2023]. The MDD and AMIDD primarily focused on ensuring that the medical device possessed the specified material qualities outlined by the manufacturer and did not require a detailed risk-benefit analysis for a large proportion of the devices [Bretthauer et al., 2023b]. Consequently, numerous medical devices entered the EU market with a negligible amount of or no clinical data directly associated with the devices themselves [Fraser et al., 2021]. This generated uncertainties about whether medical devices may be harmful or not, as the effectiveness and safety of the actual device has not been demonstrated by clinical trial data [Hulstaert et al., 2023]. A need for a new legislation, which was to be directly applicable across all member states of the EU, arose [Bretthauer et al., 2023a].

The motivation behind the MDR is to modernise and increase the robustness of the legislation for medical devices in response to technological and scientific advancements, strengthen patient safety, and ensure the efficacy of a free market [The European Parliament and the Council of the European Union, 2017]. Ideally, the MDR leads to increased safety and performance of medical devices which benefits patients without inhibiting innovation and entrepreneurship, as well as the possibility of entering the EU market with new and existing devices. However, many manufactures fear that the MDR will hinder innovation, increase the cost for the development and approval of devices, and complicate EU market entry. [White et al., 2023; Bretthauer et al., 2023a]

MDR, passed in 2017, was planned to come into force on 26$^{\text{th}}$ of May 2020, but was postponed to 26$^{\text{th}}$ of May 2021 due to the Covid-19 pandemic [Rahi and Rana, 2020]. The transition period for enterprises to certify their medical devices, initially set to conclude on 26$^{\text{th}}$ of May 2024, was postponed at the beginning of 2023. The new deadlines are 31$^{\text{th}}$ of December 2027 for high-risk class devices, i.e class III and implantable class IIb devices, and 31$^{\text{th}}$ of December 2028 for lower risk class devices. If the deadlines are not kept within, it has major consequences for enterprises since both existing and new medical devices which do not manage to be recertified, and thereby obtain a CE marking, under the new and stricter rules can no longer have the device on the EU market. [Bretthauer et al., 2023b; Kearney and McDermott, 2023] It is uncertain whether manufacturers can meet the new requirements before the deadlines, as it is assumed that the MDR in general has many major consequences, especially for manufacturers [Bretthauer et al., 2023a; Ben-Menahem et al., 2020]. Numerous manufacturers now encounter

more stringent requirements compared to the MDD and AIMDD, which include the necessity of conducting new clinical investigation(s) for medical devices already available on the EU market, primarily because of absence of a grandfathering clause from the MDD and AIMDD to the MDR [Bretthauer et al., 2023a].

A clinical investigation is defined in MDR, Article 2(45) as: *'any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device'* [The European Parliament and the Council of the European Union, 2017]. This means that a clinical trial of the medical device under investigation performed on human subject(s) must be conducted with the aim of assessing if the device complies with the GSPRs under the defined intended use. A clinical investigation is an essential component of an ongoing clinical evaluation process, encompassing the collection, assessment, and analysis of clinical data pertinent to the medical device. Results from the clinical evaluation and the clinical data, of a sufficient amount and quality, yields clinical evidence that the medical device, when used as intended, is safe and provides the intended clinical benefit(s). The clinical evaluation is conducted throughout the life cycle of the medical device to ensure sustained safety and performance of the device under its intended use. Before commencing the clinical evaluation, the claims of the medical device must be declared by the manufacturer, its intended purpose must be defined, its risk class must be determined, and a risk-benefit analysis must be initiated.

Clinical investigations are mandatory for many class IIb medical devices, implantable medical devices, and class III medical devices, all representing the highest risk class. Article 61(6) outlines two exceptions where a clinical investigation may not be required for these devices. The first exception applies if the device is an updated version, can demonstrate equivalence to prior market versions, and has received legal approval under the MDD or AIMDD with sufficient clinical data. The second exception arises when the device is classified as *'sutures, staples, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips and connectors'* (MDR, Article 61(6)) [The European Parliament and the Council of the European Union, 2017]. Clinical investigations are not required for medical devices with a lower risk class. For these devices, it is sufficient to establish compliance through other sources of clinical data. The different sources of clinical data are given in Figure 2.1.

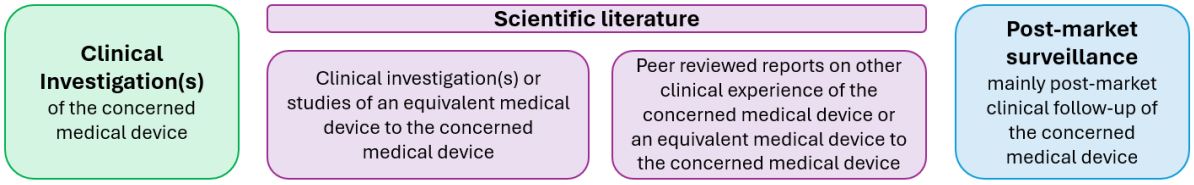

Figure 2.1: Sources of clinical data applicable in a clinical evaluation under the MDR.

2.1.1 Demonstrating Clinical Benefit

A new element introduced in the MDR is the term 'clinical benefit', defined in the MDR, Article 2(48) as *'the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health'* [The European Parliament and the Council of the European Union, 2017]. This tightening of what must be demonstrated, despite increasing safety for the patient, places additional demands on the

manufacturer [Wilkinson and van Boxtel, 2020; Hulstaert et al., 2023]. Requiring a medical device under clinical investigation to demonstrate clinical benefit endpoints aims to prevent the entry of devices into the EU market that, though not harmful, provide either limited benefits or lack any clinical benefit for patients. In general, this will improve the available devices and procedures in European healthcare. [Bretthauer et al., 2023a] Notably, the MDR states that endpoints of a clinical investigation must be 'clinically relevant' to the patient (MDR, Annex XV, Chapter I(2.6)) [The European Parliament and the Council of the European Union, 2017]. Debates may arise regarding the feasibility of collecting endpoints that are genuinely clinically relevant to the patient, given the discrepancies that often exist between clinical trials and the real-world clinical practice where the medical device is intended to be used. In addition, 'clinical benefit' is a broad and abstract term susceptible to interpretation. Wilkinson and van Boxtel [2020] criticises the need for defining clinical benefit prior to a clinical investigation, noting that the question of clinical utility often arises after the medical device has been deployed, i.e. it is not possible to predict all clinical benefits. Additionally, there is ambiguity regarding what qualifies as evidence that the medical device truly provides clinical benefit for patients [Ben-Menahem et al., 2020]. Understanding what is really meant by clinical benefit and how to collect such evidence is one of the challenges for manufacturers [Saia et al., 2023]. However, one of the biggest challenges for all stakeholders involved in clinical investigations is to determine what compose sufficient clinical data to meet the requirements in the MDR. Although it is a known challenge, no detailed guidance exist. [Kearney and McDermott, 2023] Wilkinson and van Boxtel [2020] predicts that demonstrating clinical benefit on old lower-risk devices that have never undergone a clinical investigation may lead to disappointment for manufacturers if the claimed clinical benefit(s) cannot be validated.

2.1.2 Demonstrating Equivalence with a Similar Medical Device

Clinical data can originate from the medical device under evaluation or from a device proven to be 'equivalent' to the one being assessed. The requirements for demonstrating equivalence were not clearly defined in the MDD and AIMDD, but are strengthen in the MDR which state that equivalence must be proven across clinical, technical, and biological characteristics, ensuring no significant difference in the safety and performance of the evaluated medical device compared to the similar device (MDR, Annex XIV, Part A(3)) [The European Parliament and the Council of the European Union, 2017; The Council of the European Communities, 1990, 1993]. Proving equivalence requires a manufacturer to collect sufficient evidence regarding every feature claimed as equivalent in the similar device. This task is particularly challenging without the cooperation of the enterprise that owns the other equivalent device, and most enterprises are hesitant to share such information. [Saia et al., 2023] The required information includes comprehensive access to the technical documentation of the device which is claimed as equivalent, encompassing device trial results. [Rahi and Rana, 2020; Hulstaert et al., 2023]

As the MDR imposes significantly stricter requirements for establishing equivalence compared to the MDD and AIMDD, this leads to substantial implications for manufacturers. In situations where the manufacturer cannot procure sufficient data to demonstrate compliance with the MDR, they are barred from using an equivalence case and must instead produce new clinical data to support their CE marking application. Manufacturers are forced to conduct a clinical investigation to generate the necessary clinical data for some high-risk and existing medical devices which came on the EU market under the MDD and AIMDD where they relied on

demonstrating equivalence. In some instances, the expense associated with generating the new required clinical data may surpass the potential return on investment, potentially resulting in the withdrawal of medical devices from the EU market and subsequent device shortages. [Kearney and McDermott, 2023; Wilkinson and van Boxtel, 2020]

2.1.3 Adherence to Standards

Clinical investigations must adhere to ethical principles outlined in The World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. This standard aims to ensure that clinical trials do not expose subjects to unwarranted risks and burdens, irrespective of any other positive effects they may possess. [Hulstaert et al., 2023] Furthermore, it is stated in the MDR that clinical investigations must comply with the requirements specified in the ISO 14155:2020 - Clinical investigation of medical devices for human subjects - Good clinical practice. Some of the fundamental requirements in this standard includes informed consent from subjects, communication with the ethics committee, and responsibilities of different stakeholders. [International Standardization Organisation, 2020] Furthermore, depending on the type of medical device to be tested in a clinical investigation, other relevant standards must be complied with. Some of the most widely used standards are provided in Table 2.1, though not exhaustive.

Table 2.1: Potentially relevant standards and a brief description of their content.

Standard	Description
ISO 14971:2019 Medical devices - Application of risk management to medical devices	Supports manufacturers in managing risks associated with a medical device across all phases of its life cycle. This assistance includes identifying hazards, estimating and evaluating risks, implementing risk control measures, and monitoring the effectiveness of these controls. [International Standardization Organisation, 2019]
IEC 62304:2006 Medical device software - Software life cycle processes	Establishes the framework for the life cycle of medical device software, including requirements for activities involving development and maintenance. [International Standardization Organisation, 2006]
IEC 81001-5-1:2022 Health software and health IT systems safety, effectiveness and security - Part 5-1 Security - Activities in the product life cycle	Is a supplement to the IEC 62304:2006 with a focus on IT security in the life cycle of a medical device software [International Standardization Organisation, 2021].
ISO 14708-(part 1-7): Implants for surgery - Active implantable medical devices	Specifies the requirements for active implantable medical devices. The first part covers general requirements. The remaining six parts addresses requirements and testing for various types of active implantable medical devices, divided by specific characteristics and objectives. [International Standardization Organisation, 2014]

The ISO 14971:2019 is an essential standard which must be followed by manufacturers for all types of medical devices according to the GSRPs in the MDR, where it is stated that a risk management system is required. The IEC 62304:2006 and IEC 81001-5-1:2022 are applicable to medical device software and the ISO 14708 part 1 to 7 are applicable to active implantable medical devices. In addition to the listed standards, various national and international guidelines may be applicable. It can be overwhelming to correctly identify, understand, and apply all relevant standards.

2.1.4 The Variety of Stakeholders and Required Documents

Different roles and responsibilities are assigned to several stakeholders involved in a clinical investigation. Figure 2.2 provides an overview of these stakeholders and how they interrelate.

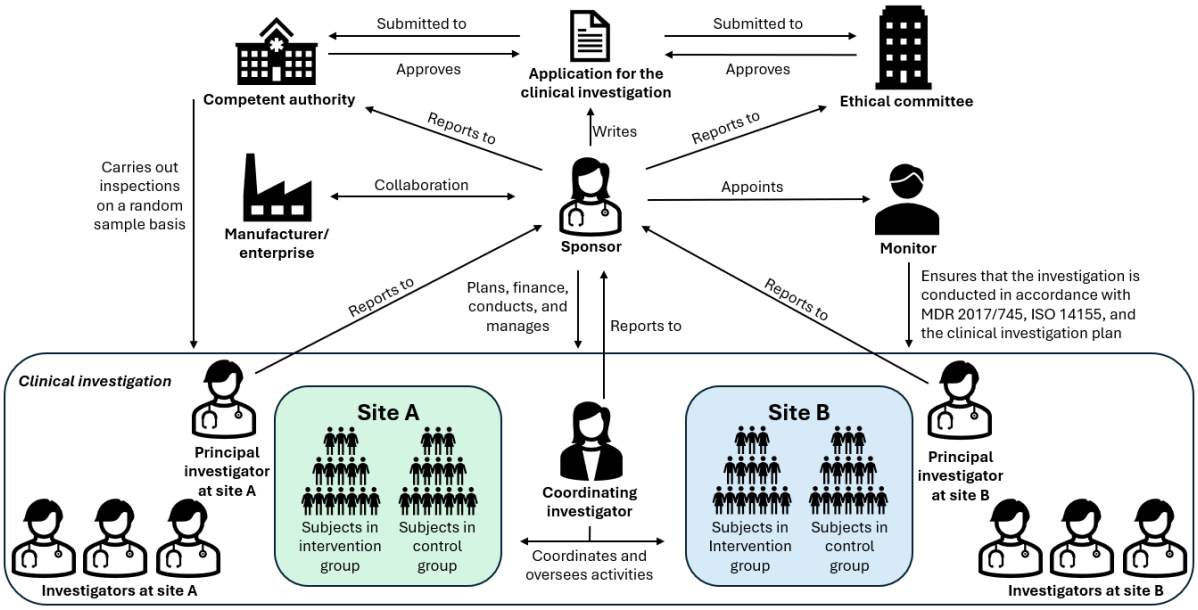

Figure 2.2: The relationship among stakeholders involved in a clinical investigation with two sites.

The most central stakeholder is a sponsor who is responsible for planning, conducting, and managing the clinical investigation, ensuring compliance with regulatory and ethical standards while also financing the clinical investigation. The MDR offers a broad definition of a sponsor, encompassing hospitals, doctors, manufacturers, research institutions, academic organisations, or any other entity. The sponsor bears overall responsibility in a clinical investigation and thus has numerous obligations. If not the same person, collaborating between the sponsor and the manufacturer involves communication on e.g. information about the medical device and occurrence of adverse events and device deficiencies. Investigators are individuals with knowledge in patient care. They play a crucial role in conducting the clinical investigation at the investigational site, e.g. a department of a hospital, where they follow a predefined study protocol describing how to conduct the investigation. The number of investigators dependent on the number of sites where the clinical investigation is conducted and the scope of the trial. In case of a large clinical trial, a principal investigator is appointed. If the clinical investigation is conducted at multiple sites, one principal investigator is appointed per site. Furthermore, one coordinating investigator is responsible for coordinating and overseeing activities across

the multiple sites. An independent monitor is appointed by the sponsor, who must assure that the clinical investigation meets the requirements of the MDR, ISO 14155:2020, and the clinical investigation plan. [The European Parliament and the Council of the European Union, 2017]

As part of planning the application for the clinical investigation, a sponsor is required to create various documents. The clinical investigation plan is one of the most important documents as it outlines the objectives, design, methodology, and statistical considerations of the trial. Another essential document included in the application is the investigator's brochure, which contains information regarding the medical device under investigation. The application form along with all required documents must be submitted to the competent authority and relevant ethics committees for approval. As stated in the MDR Article 71, it is the competent authority who has the responsibility of assessing the application. The competent authority must review several aspects, but most importantly the reliability and robustness of the clinical data, considering statistical approaches, trial design, and methodological aspects such as sample size, comparator, and endpoints. [The European Parliament and the Council of the European Union, 2017] Although the MDR contains more details and general principles regarding clinical investigations compared to the MDD and AIMDD, there are no specific requirements regarding the methodology for how a clinical investigation must be carried out due to the great diversity of medical devices, which poses a challenge for the stakeholders involved [Ben-Menahem et al., 2020; Fraser et al., 2021; White et al., 2023].

A clinical investigation can only be carried out if it is authorised by a competent authority and if the ethics committee has not issued a negative opinion. The results of the clinical investigation, recorded in the clinical investigation report, contribute to the clinical evaluation report, a comprehensive document that summaries all clinical data and supports the medical device's conformity with the essential requirements. The clinical evaluation report is a part of the exhaustive technical documentation which the manufacturer must establish to obtain a CE marking on the medical device. [The European Parliament and the Council of the European Union, 2017]

2.1.5 Consequences for Manufacturers

Before the MDR came into force, placing a medical device on the EU market was comparably easier and faster than in the United States of America, but now manufacturers fear that the reverse applies, as meeting the stringent requirements of the MDR proves more challenging and time-consuming [Fraser et al., 2021]. A possible concern due to the MDR, is that it will become unattractive to conduct clinical trials in the EU [Pazart et al., 2021]. Enterprises are already showing a trend toward scaling back new device development or prioritising markets outside the EU which have a less restrictive legislation [Bretthauer et al., 2023a; Kearney and McDermott, 2023]. A survey conducted in April 2022 revealed that out of more than 500,000 medical devices used in the EU, previously certified under the MDD and AMIDD, only around 6,000 new medical devices have been certified under the MDR. Furthermore, it is noteworthy that more than 85% of the 500,000 medical devices certified under the MDD or AMIDD have yet to undergo certification under the MDR. [MedTech Europe, 2022]

Only now, a few years after the MDR came into effect, are manufacturers truly realising the magnitude of the regulation [Bretthauer et al., 2023a]. The complexity of the regulation can be daunting and hard to interpret, particularly for start-ups [Ben-Menahem et al., 2020; Bretthauer

et al., 2023a]. Comprising around 25,000 companies and constituting approximately 95% of the MedTech sector in the EU, start-ups and small and medium-sized enterprises (SMEs) are the ones most affected by the regulation. These enterprises face substantial challenges, primarily due to constrained resources for regulatory compliance and financial limitations. The regulation imposes heightened costs for manufacturers, including additional personnel, more extensive clinical trials, and certification expenses. [Saia et al., 2023; Ben-Menahem et al., 2020; Pazart et al., 2021] This poses a significant obstacle to the advancement of medical devices, given that most of the innovation occurs in SMEs [Bretthauer et al., 2023a]. There is a concern that a reduction in SMEs due to difficult market access affects how many new innovative medical devices are developed in the EU [Saia et al., 2023].

2.2 Challenges with Clinical Trials of Medical Devices

Before a high-risk medical device comes on the market, it must be clinically tested on patients under controlled conditions to gather sufficient evidence about the benefits and harms of using the device [Charlesworth and van Zundert, 2019; Ben-Menahem et al., 2020]. Existing clinical trials of medical devices have been criticised for generally having low evidence and poor quality. This also applies to randomised controlled trials (RCTs) which are otherwise considered to be a very reliable trial design to assess clinical efficacy and yield a great extent of scientific evidence. Identified shortcomings for RCT mainly concern lack of clearly defined endpoints, short study period of implants in conjunction with the device having a long duration of use, and small sample sizes. [Hulstaert et al., 2023; Pazart et al., 2021; Ceelen, 2014] Regulators prefer clinical evidence obtained through a double-blind RCT due to its high level of internal validity. However, gathering such evidence is challenging, time-consuming, and requires a lot of financial resources, posing challenges for startups and SMEs in particular [Pazart et al., 2021; Tarricone et al., 2016].

Some aspects of medical devices pose challenges, making it difficult, impossible, and/or unethical to conduct experimental clinical trials, unlike pharmaceuticals. Therefore, a one-to-one methodological approach cannot always be applied. [Fraser et al., 2021; Zannad et al., 2014; Tarricone et al., 2016] When planning a clinical investigation, it is not always appropriate to merely reuse design choices from past clinical trials, as each medical device's characteristics, risk class, and intended purpose are highly influential on the specific clinical investigation.

The list below presents the most central challenges in clinical trials of medical devices, which have been identified through the first literature search, described in Section 4.1.

1. **Defining endpoints:** Defining appropriate and relevant endpoints for medical device trials presents a challenging and complex task. The endpoints must be clear, measurable, and reflect the safety, effectiveness, and/or clinical benefit of the medical device. Despite the relevance to patients, hermeneutic outcomes such as quality of life, discomfort, and disability are underutilised in favour of traditional outcomes such as survival and complication rates, commonly employed in pharmaceutical trials but not always aligning with the unique considerations of medical device trials. [Neugebauer et al., 2017; White et al., 2023; Zannad et al., 2014; Hulstaert et al., 2023]
2. **Regulatory compliance:** It is difficult to fully understand the regulatory framework and to handle the strict regulations for large clinical trials, complicating market entry. [Ben-Menahem et al., 2020; Bretthauer et al., 2023a] The comprehensive requirements in

the MDR complicate the process of obtaining approval for a clinical trial. Any missing information necessitates additional time to acquire, leading to delays in commencing the trial. [Rêgo et al., 2023]

3. **Subject recruitment and retention:** Identifying, recruiting, and retaining subjects from the appropriate target group pose challenges [White et al., 2023; Hulstaert et al., 2023]. The comprehension of patient selection may not be comprehensive during planning of a trial design. In general, medical device trials recruit fewer patients than pharmaceutical trials, increasing the likelihood of being under-powered for significant mortality and morbidity outcomes. [Zannad et al., 2014] Additionally, the limited number of potential subjects is a further constraint, as recruitment often relies on the investigator's own list of subjects [Rêgo et al., 2023].
4. **Selecting the control group:** Determining an appropriate control group can be complex. Identifying a suitable comparator, especially when a device under investigation is innovative or no equivalent device on the market exist, can be challenging. Placebo-controlled trials such as RCTs may not always be feasible or ethical. For example, it is unethical to offer an invasive shame procedure since the patients does not receive any benefit, only potential risks. [Wilkinson and van Boxtel, 2020; Neugebauer et al., 2017; Pazart et al., 2021]
5. **Blinding and use of comparator:** Although it is an important action to reduce bias, achieving blinding in medical device trials can be more challenging for practical or ethical reasons than in pharmaceutical trials [Neugebauer et al., 2017; Haute Authorité de Santé, 2021]. Implementing blinding in a medical device trial may involve using a sham procedure (e.g., simulating device implantation), a sham device (which often raises ethical concerns due to the absence of potential individual benefit, although both sham procedures and devices can elicit a notable placebo effect that may balance potential benefits and risks), or implanting a device without activating it [Zannad et al., 2014]. Creating a convincing comparator or maintaining blinding when the device is visible to both subjects and investigators may be difficult. [Neugebauer et al., 2017; Ceelen, 2014] According to Ceelen [2014], it is impossible to blind investigators in a surgical intervention, but outcome assessors and subjects can still be blinded.
6. **Handling device changes:** Medical devices often undergo iterative improvements in design, which may occur even during trials involving human subjects. Determining the optimal timing for assessments becomes challenging, particularly in the context of lengthy RCTs. [Tarricone et al., 2016; Neugebauer et al., 2017; Zannad et al., 2014] Additionally, there are no established guidelines or rules specifying the threshold for changes deemed significant enough to necessitate new clinical trials [Zannad et al., 2014].
7. **Determination of the sample size:** Estimating an appropriate sample size is critical for statistical validity. However, the sample size of the target population is often too small, making randomisation in RCT difficult and thus the results of doubtful quality. [Pazart et al., 2021; Iglesias, 2015; Hulstaert et al., 2023]
8. **Real-world applicability:** Ensuring the relevance of trial results to real-world clinical settings presents challenges. Factors like the skill of the operator, patient variability, and variations in device use can influence the generalisability of trial findings. In particular, study protocols for RCTs pose challenges in adhering to real-world clinical practice, leading to low external validity. Challenges may arise due to atypical healthcare professionals or treatments. For example, clinical investigation results from a procedure exclusively performed by expert surgeons may be short of external validity. [Tarricone et al., 2016; Iglesias, 2015; Ceelen, 2014]

9. **Long-term follow-up:** A crucial aspect of medical device trials is the choice of an appropriate stratified follow-up. The ideal duration of follow-up varies depending on the specific device and can be difficult to determine during the trial design phase. [Zannad et al., 2014] Many studies face limitations in follow-up duration, making it challenging to capture all relevant outcomes comprehensively. This issue is particularly pronounced conducting clinical investigations for patients with implants, as the manifestation of all effects may take a considerable amount of time. [Neugebauer et al., 2017; Hulstaert et al., 2023; Pazart et al., 2021]
10. **Costly and time-consuming:** It is costly to generate the required evidence through a comprehensive clinical trial [Charlesworth and van Zundert, 2019]. This cost is, in part, attributed to the heightened requirements for clinical trials, contributing to an overall increase in the development and pre-market approval expenses for a medical device [Bretthauer et al., 2023b]. Moreover, the MDR mandates an insurance policy for clinical trials which is estimated to amount in €15 600 for a class IIa medical device [Rêgo et al., 2023]. Additionally, navigating and comprehending the legislation, as well as executing a trial, are time-consuming processes that present further obstacles [Saia et al., 2023].
11. **Randomisation:** When possible, randomisation is the preferred approach [Zannad et al., 2014]. The absence of randomisation in certain trials can be attributed to various factors. Firstly, the cost of conducting a randomised trial is a significant consideration. Secondly, the feasibility of randomisation may be deemed impractical from the outset, often due to practical reasons such as healthcare professional or patient preference for a potentially effective new treatment. [Haute Authorité de Santé, 2021] Thirdly, randomisation may not be feasible in certain medical device trials, such as when having a small target population [Zannad et al., 2014]. Additionally, situations where randomisation can be considered unethical exist [Iglesias, 2015]. An example is cases of invasive surgery, where the comparator is a non-invasive treatment [Tarricone et al., 2016].
12. **Devices that cannot be evaluated alone:** A medical device is frequently employed alongside other interventions such as surgical or diagnostic procedures or monitoring, posing challenges in assessing the reel efficacy of a device during a clinical investigation. Surgical interventions, in particular, present a complex scenario where factors beyond the surgeon's expertise come into play, including practices at the individual hospital, the influence and actions of other team members, and the care provided before and after the intervention. [Haute Authorité de Santé, 2021; Neugebauer et al., 2017]
13. **Expertise and learning curve:** The expertise and experience of operators, e.g. surgeons, significantly influence the trial results and must be carefully considered. Varied levels of experience can impact the execution of procedures or interventions. Performance bias can arise when there is a lack of experience which influences trial outcomes by penalising the new tested medical device. [Haute Authorité de Santé, 2021; Neugebauer et al., 2017] Operator skills typically improve over time due to the learning curve effect, which can be difficult to manage [Motte et al., 2017; Ceelen, 2014]. Initiating a RCT prematurely, before adequate training and experience are acquired, may not accurately reflect the true performance of the investigated device. Conversely, conducting an RCT too late poses other challenges, such as potential deviations from the study protocol. [Neugebauer et al., 2017]
14. **Sufficient high-quality data:** Collecting the right amount and kind of reliable and robust clinical data to generate sufficient clinical evidence is essential. However, the term 'sufficient' is not clear which present a major challenge for all types of medical devices,

irrespective of risk class. [Hulstaert et al., 2023; Wilkinson and van Boxtel, 2020; Kearney and McDermott, 2023]

The list highlights numerous challenges in conducting clinical trials for medical devices. There is a demand for more targeted guidance, particularly for trial designs involving high-risk medical devices, and for using other appropriate trial designs that may not strictly adhere to the RCT design. Addressing and mitigating these challenges is crucial while upholding a high level of clinical evidence and ensuring compliance with standards and regulations.

2.3 Guidance Documents for Clinical Investigations

As a result of the release of the MDR, the Medical Device Coordination Group (MDCG) were established. One of their purposes is to prepare guidance documents. [The European Parliament and the Council of the European Union, 2017] All the guidelines from the MDCG are not legally binding but can help interpret the MDR and provide general advice. Guidelines identified as relevant for clinical investigations are:

- **MDCG 2020-1: Guidance on Clinical Evaluation (MDR) / Performance Evaluation (IVDR) of Medical Device Software**
  [The Medical Device Coordination Group, 2020a]
- **MDCG 2020-6: Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC. A guide for manufacturers and notified bodies**
  [The Medical Device Coordination Group, 2020c]
- **MDCG 2020-10/1: Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745**
  [The Medical Device Coordination Group, 2020b]
- **MDCG 2021-08: Clinical investigation application/notification documents**
  [The Medical Device Coordination Group, 2021a]
- **MDCG 2021-20: Instructions for generating CIV-ID for MDR Clinical Investigations**
  [The Medical Device Coordination Group, 2021b]
- **MDCG 2021-28: Substantial modification of clinical investigation under Medical Device Regulation**
  [The Medical Device Coordination Group, 2021c]
- **MDCG 2024-3: Guidance on content of the Clinical Investigation Plan for clinical investigations of medical devices**
  [The Medical Device Coordination Group, 2024]
- **Commission Guidance on the content and structure of the summary of the clinical investigation report**
  [The European Commission, 2024]

Some of these guidelines are temporary guidelines established due to the incomplete implementation of the European database on medical devices (EUDAMED), and they will be revoked once EUDAMED is fully operational. This includes MDCG 2020-10/1, MDCG 2021-08, and MDCG 2021-28. [The Medical Device Coordination Group, 2020b, 2021a,c]

Although primarily addressed to clinical evaluations, MDCG 2020-1 and MDCG 2020-6 include

elements pertinent to clinical investigations. MDCG 2020-1 has a small section on clinical investigations of medical device software, highlighting suitable trial design based on the type of medical device software [The Medical Device Coordination Group, 2020a]. In MDCG 2020-6, Appendix III outlines a hierarchy of clinical evidence for demonstrating conformity with the relevant GSPRs, accompanied by relevant considerations and comments. Moreover, it includes references to specific tools that can aid in the appraisal of clinical data. [The Medical Device Coordination Group, 2020c]

MDCG 2021-20 provides detailed instructions for creating a Clinical Investigation ID within the former European Database on Medical Devices, Eudamed2, to enable communication between competent authorities and sponsors [The Medical Device Coordination Group, 2021b]. MDCG 2024-3 outlines the purpose and content of the clinical investigation plan, specifying section titles, required information, and presentation order [The Medical Device Coordination Group, 2024]. The Commission Guidance aims to ensure that the clinical investigation report contains all essential information, employs accurate terminology, and is presented in a clear and organised manner [The European Commission, 2024].

The listed guidelines, particularly MDCG 2024-3 and the Commission Guidance, are deemed more accessible compared to the MDR, aiding in translating the general requirements of the regulation into specific specifications on how to e.g. write the required documents. Nevertheless, they offer general advice, requiring sponsors and manufacturers to extract relevant parts and interpret their application in each clinical investigation for the specific medical device. It is, however, noteworthy that MDCG 2024-3 and the Commission Guidance were published approximately seven years after implementation of the MDR. Pazart et al. [2021] states that there is still a need for guidance, as the existing guidelines describe very vaguely and imprecisely how clinical investigations must be conducted. The manufacturer is thus responsible for improving the process of evaluating the medical device, albeit without the right tools and knowledge to do so. Furthermore, a burden is placed on the manufacturer and sponsor to navigate through the MDR, guidance documents, and standards, while understanding how they interrelate. This increases the complexity of regulatory compliance.

2.4 Assisting Tools for Clinical Trials

In addition to the guidance documents aiming to help interpret clinical investigations under the MDR, various tools and frameworks have been developed to assist in the process of a clinical trial. These tools and frameworks were identified through the second literature search as described in Section 4.1.

The IDEAL Framework and Recommendations, developed by an expert consensus group and initially introduced in 2009, has created a new paradigm in the way surgical innovations are evaluated through the five stages: Idea (1), Development (2a), Exploration (2b), Assessment (3), and Long-term follow-up (4) [Pennell et al., 2016]. The recommended trial designs from stages 1 to 4 are as follows: 'first in human' study (case report), prospective development study (cohort study), prospective exploratory study (collaborative cohort study), RCT, and database or register study [Sedrakyan et al., 2016]. The stages ensure evaluation with a high degree of transparency throughout the life cycle of the medical device. At each stage, it is advised to adhere to a standardised trial template for presenting the evidence that is most pertinent

to that particular stage, aiming for early identification of safety problems. [McCulloch, 2020] The work conducted by Pennell et al. [2016] aimed to modify the IDEAL for medical device evaluation through a Delphi expert consensus exercise, resulting in the IDEAL-D Framework and Recommendations. Key modifications included the addition of a new pre-clinical stage denoted as Stage 0 and consensus on the appropriateness of registry use at each stage. [Pennell et al., 2016] Additionally, a checklist is developed for each stage to aid in various aspects of the clinical trial process [Hirst et al., 2019].

A study by Páez et al. [2022] has devised a principles-based framework grounded in ethical considerations concerning RCTs, along with a concise sequential decision-making algorithm which aims to determine when conducting an RCT study for a new therapeutic device is unnecessary and what the alternatives entail. However, this approach is not tailored specifically to the MDR and is a highly simplified tool that requires answering a maximum of three questions to arrive at a final decision.

A clinical trial management system (CTMS) is a software platform designed to assist in the process of a clinical trial, such as scheduling, tracking, and management [Iusov, 2024]. Its advantages include providing access to accurate and current trial information, fostering collaboration between sponsors and sites, and ensuring transparent oversight of trial management components. Furthermore, essential documents generated during the clinical investigation can be managed electronically [SimpleTrials, 2024]. Most CTMS platforms also integrate with electronic data capture (EDC) systems, facilitating data collection, management, monitoring, and storage processes. EDC replaces conventional paper-based data collection methods, offering increased efficiency, accuracy, and security. [Iusov, 2024] Several CTMS and EDC systems are available. One example of an EDC system integrated in CTMS is EasyTrial which supports medical device enterprises to fulfil the requirements of the MDR. Easytrial can be used to collect clinical data, built electronically case report forms, and assist in structuring and documenting trials, including preclinical trials, clinical trials, and post-market clinical trials. [EasyTrial, 2024] An example of an EDC system is Greenlight Guru Clinical, designed specifically for the MedTech industry. It ensures compliance with ISO 14155:2020, the EU MDR, and the United States Food and Drug Administration regulations, and offers templates for various documents, including informed consent forms. [Greenlight Guru, 2023]

3 Problem Definition

The MDR imposes many challenges to medical device manufacturers due to its stringent requirements regarding proving safety, performance, and clinical benefit of the medical device compared to the previous medical device directives the MDD and AIMDD. These requirements in the MDR demand high-quality and quantity of clinically relevant data, posing numerous obstacles for manufacturers comprising raising concerns about the ability of market entry in the EU. In the worst-case scenario, this could lead to enterprises either succumb or seeking markets outside the EU with less strict regulations, potentially resulting in a shortage of medical devices and reduced innovation in the EU MedTech sector.

For many medical devices, collecting sufficient clinical data through clinical investigations on human subjects are mandatory. A manufacturer relies on a sponsor to conduct, manage, and finance a clinical investigation. A sponsor has many areas of responsibility, including designing the trial, ensure compliance with standards, prepare documentation before, during and after the trial, and ensuring efficient and timely reporting to various stakeholders. Clinical trials for medical devices face their own set of challenges complicating the planning and execution. The challenges include regulatory compliance, obtaining sufficient high-quality data, ensuring real-world applicability, handling expertise and learning curve, handling changes to the device, and testing devices that cannot be evaluated alone. Furthermore, challenges closely related to the trial design includes defining endpoints, recruitment and retention of subjects, determination of sample size, selecting the control group, blinding and use of comparator, randomisation, long-term follow-up, and given that trials are often costly and time-consuming. Most of these challenges are attributed to the unique aspects of medical devices sometimes making clinical trials difficult, impossible, and/or unethical. Consequently, there is a demand for more guidelines addressing the identified challenges.

Several guidance documents aiming to help interpret clinical investigations under the MDR are developed. Although these guidance documents are deemed more accessible compared to the MDR, they primarily assist in how to prepare the required documentation and offer limited guidance on making design choices. Furthermore, various tools have been developed to facilitate clinical trials, including Clinical Trial Management Systems and the IDEAL-D Framework and Recommendations. However, none of these guidance documents or tools can assist sponsors in making decisions regarding the challenges of medical device trial design. Therefore, the following thesis statement is outlined:

Which challenges, faced by the sponsor of the trial design of a clinical investigation for a medical device, can be accommodated by an EU MDR 2017/745 compliant decision support system?

4 Methods

This chapter describes the methods utilised in this master's thesis. Two literature searches are conducted which creates the basis for the problem analysis leading to the thesis statement. The main method used to answer the theses statement revolves around an analytical basis for a decision support system.

4.1 Literature Searches

This master's thesis examines challenges at clinical investigations in compliance with the MDR and identifies existing tools to assist sponsors with the clinical investigation. To address the initial problem statement, two research questions are formulated, serving as the foundation for a systematic literature search.

1. What are the challenges for manufacturers and sponsors with planning and conducting a clinical investigation under MDR for a medical device?
2. Which, if any, tools can support sponsors in facilitating a clinical investigation in compliance with MDR?

For each research question, a search protocol is made. The two search protocols are available in Appendix A, Tables A.1 and A.2. The search protocols encompass the research question, chosen databases, inclusion and exclusion criteria, and the search strategy. Several health science and technology databases are selected to facilitate a comprehensive list of publications addressing the two research questions. Initially, 16 health technology databases are identified through Aalborg University Library's 'Databases' section on their website [Aalborg University, 2024]. Subsequently, five databases are chosen based on the descriptions provided on the website about the content of the databases. Inclusion and exclusion criteria are defined to refine search results and provide a focused direction for the search.

The first part of the search strategy involves the method block search. The block searches for the two research questions can be found in Appendix A, Tables A.3 and A.4. Since all databases are built on the basis of boolean operators, the block search is structured with these. The block search is based on three focus areas found in each research question from which synonyms are drawn up. The boolean operator AND is used between the columns in the block search table and the boolean operator OR is used between the individual synonyms. The boolean operator NOT is not used as there is a risk of relevant sources being wrongly sorted out. Truncation with an asterisk (*), which aims to expand the search, is used after words that can have different suffixes. Phrase searching with putting the search terms in quotation marks (" ") is used when the terms must be read together in a specific order and aims to clarify the search.

The block searches for the two research questions are documented in the search documentation forms, available in Appendix A, Tables A.5 and A.6. The purpose of the two search documentation forms is to consistently provide an overview and facilitate the identification of potential typing errors during the search. The search strings for the two searches are available in Appendix A.

After the systematic literature search is performed using the block searches, the method backward

snowballing is applied as a second step in the search strategy to find additional relevant sources and thereby to extend the systematic literature search. Backward snowballing uses the reference lists from the included sources in the block search. The second search protocol involves an additional search on the internet using the search engine Google as it is anticipated that limited amount of sources are available regarding existing tools used in practice. The online tool Rayyan is utilised to organise and manage the all identified sources from the two searches [Rayyan, 2024].

The selection process is illustrated by the two Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagrams at Figures 4.1 and 4.2. The selection process is divided in identification, screening, eligibility, and included.

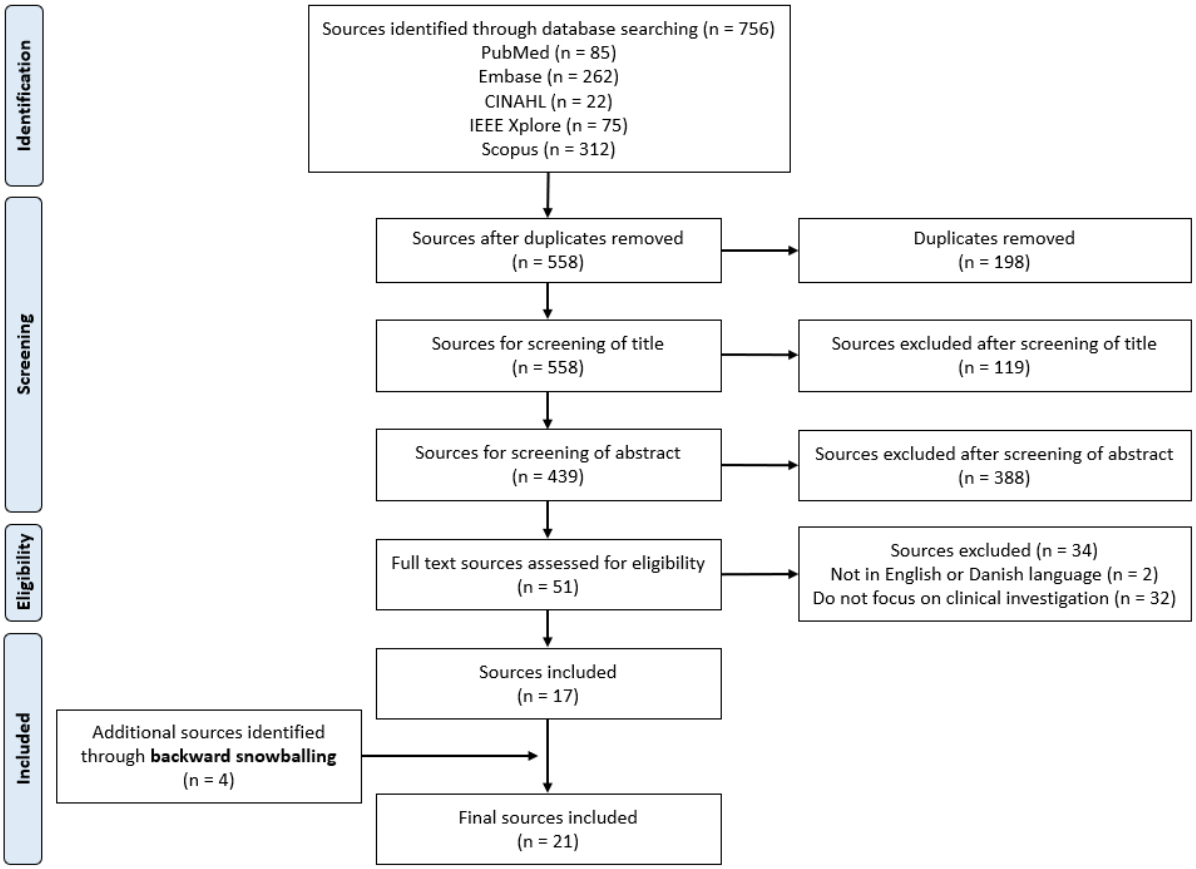

Figure 4.1: PRISMA flow diagram of the source selection process for the search addressing the first research question.

For the search relating to the first research question, 756 sources were identified, of which 17 met the inclusion criteria. Utilising the backward snowballing method, an additional four sources were included, bringing the total to 21 sources to address the first research question.

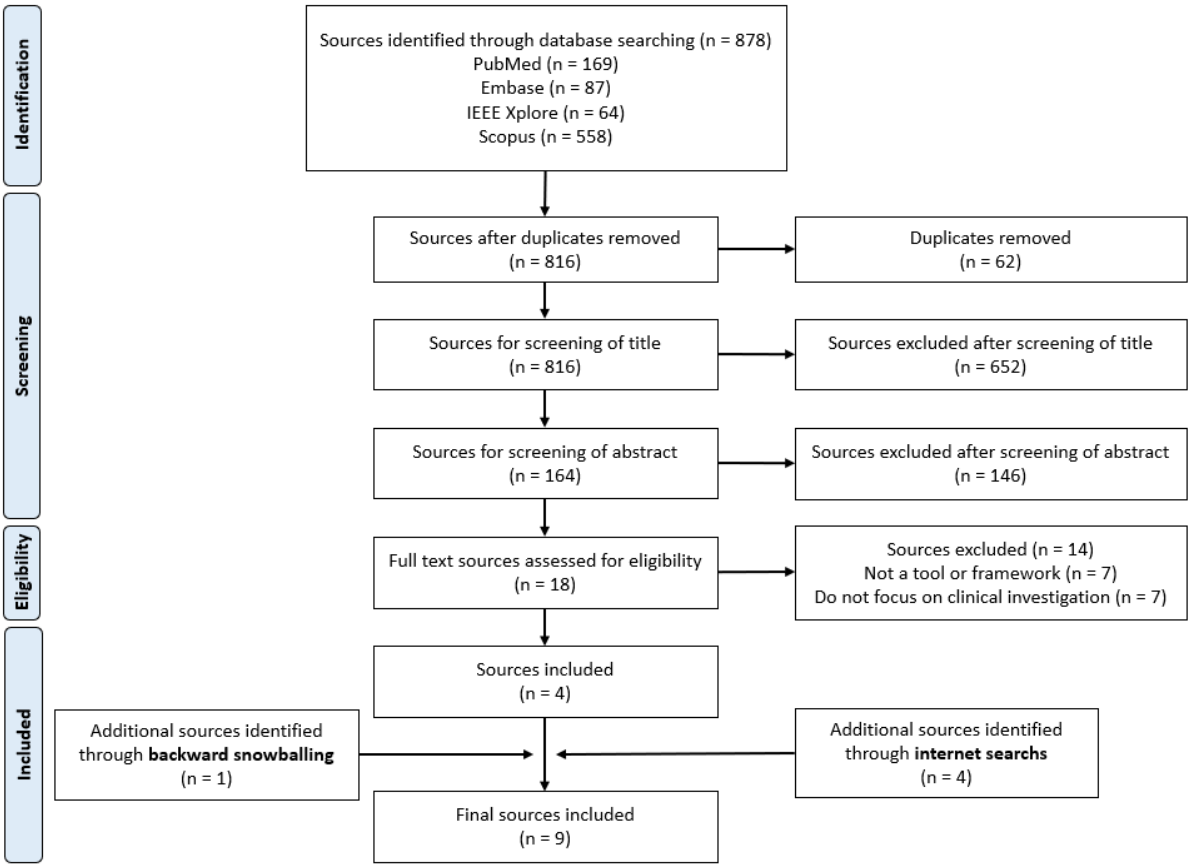

Figure 4.2: PRISMA flow diagram of the source selection process for the search addressing the second research question.

For the search relating to the second research question, 878 sources were identified, of which four met the inclusion criteria. Utilising the backward snowballing method, one additional source was included, bringing the total to five sources to address the second research question.

4.2 Decision Support System

Making a decision is to take action within a scenario with numerous alternatives, representing a selection from various possibilities. Decision making involves a decision-maker and a set of alternatives aimed at achieving an objective. Making decisions is challenging, as they often need to meet various specific criteria, rendering the decision making process complex and resource intensive. A DSS is defined by Power [2021] as *"an interactive computer-based system or subsystem intended to help decision makers use communications technologies, data, documents, knowledge and/or models to identify and solve problems, complete decision process tasks, and make decisions".* A DDS is a computerised system involving one or more technologies designed to aid individuals, groups, or organisations in decision making within a specific task. When well-designed, a DSS can facilitate fact-based decisions with a high level of quality, thereby enhancing decision making processes in terms of efficiency and effectiveness. The demand for decision support arises from the vast amount of information that needs to be processed, often leading to information overload, which generally complicates decision making. [Power and Heavin, 2016, p. 2-3]

4.2.1 Types of Decision Support Systems

DSSs are classified into five generic types based on a specific technology component: model-driven, data-driven, communications-driven, document-driven, and knowledge-driven [Power and Heavin, 2016, p. 38]. The main principle in a model-driven DSS is accessing and manipulating a quantitative model. The model can e.g. be a mathematical model or an algorithm aiming to optimise or simulate different scenarios. [Power and Heavin, 2016, p. 39]. It employs limited data and parameters provided by decision makers to assist them in analysing a situation. These DSS typically do not require large databases, as they are not inherently data-intensive. [Burstein and Holsapple, 2008, p. 126] Data-driven DSS can handle substantial amounts of data from both internal and external real-time data sources, presenting it in a comprehensible and accessible format. The main functionality is access to and manipulation of data. Core functionality entails accessing files via query and retrieval tools, while advanced data-driven DSS involves analytical processing of data. [Burstein and Holsapple, 2008, p. 127] Communications-driven DSS facilitate collaborative decision making and communication among two or more individuals, allowing them to interact, synchronise their activities, and exchange information [Power and Heavin, 2016, p. 38]. Document-driven DSS employs processing and computer storage technologies to enable comprehensive retrieval and analysis of documents relevant to the decision making process. These documents are stored in a massive database, encompassing various formats such as procedures or product specifications. [Burstein and Holsapple, 2008, p. 130] The purpose of knowledge-driven DSS is to assist users in determining appropriate courses of action. The system acts as an expert in problem solving within a defined domain. The main element is a knowledge base which can consist of facts, rules, and procedures. [Power, 2021]

Depending on the decision making problem to be solved, different methods can be employed. The rule-based method comprises rules presented in a logical format, often in the form of if-then statements [Burstein and Holsapple, 2008, p. 514]. Fuzzy logic, grounded in set theory principles, is applied to problems involving uncertainty [Berner, 2016, p. 23]. Another method, the Bayesian network, deals with uncertainty by considering conditional probabilities of events. An example of a DSS where managing uncertainty is crucial is in a clinical DSS, such as those used to provide diagnoses based on symptoms. [Berner, 2016, p. 34]

The latest development within the area of DSSs is the integration of artificial intelligence, machine learning, and deep learning techniques [Kose et al., 2020, p. 3-4]. It is the learning capabilities of these techniques which makes it possible to solve advanced problems which requires a deep analysis of data [Kose et al., 2020, p. 8-10]

Choice of Decision Support System

The most suitable type for the DSS to be developed is a knowledge-driven DSS, as its primary function is to offer advises on trial design for a medical device, essentially serving as an expert system. A knowledge-driven DSS is illustrated through a generic representation in Figure 4.3 with the main components: input, knowledge base, reasoning engine, and output. The user of the DSS shall provide inputs to the DSS typically through a user interface. The knowledge base stores domain-specific knowledge. It provides the reasoning inference engine with knowledge to enhance decision making. [Burstein and Holsapple, 2008, p. 513] The reasoning inference engine is the logic that combines the input with the knowledge to generate output for the user

[Berner, 2016, p. 32]. Output examples include ranked lists of possibilities presented through a user interface.

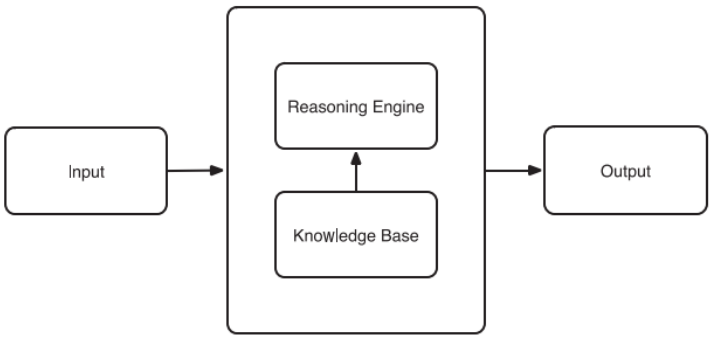

Figure 4.3: A general representation of the components in a knowledge-driven DSS [Berner, 2016, p. 32].

The DSS to be developed will not encounter problems with uncertainty involved, so the methods Fuzzy logic and Bayesian network are deselected. Despite advancements in artificial intelligence techniques, the DSS to be developed will rely on fundamental principles of rule-based logic. The advantage of using rule-based is that it offers full transparency in decision making, which is crucial in this DSS as it must comply with regulations mandating traceability. Artificial intelligence, in this context, is deemed overly opaque, as the DSS will appear as a black box.

With a restricted timeframe, emphasis is placed on developing the knowledge base in the DSS, while components like the reasoning engine and user interface are not developed.

4.2.2 Software Development Life Cycle

Generally, a DSS is developed by using a software development life cycle model, which defines the processes in the development procedure. One type of the various SDLC models is the structured V-model, depicted in Figure 4.4.

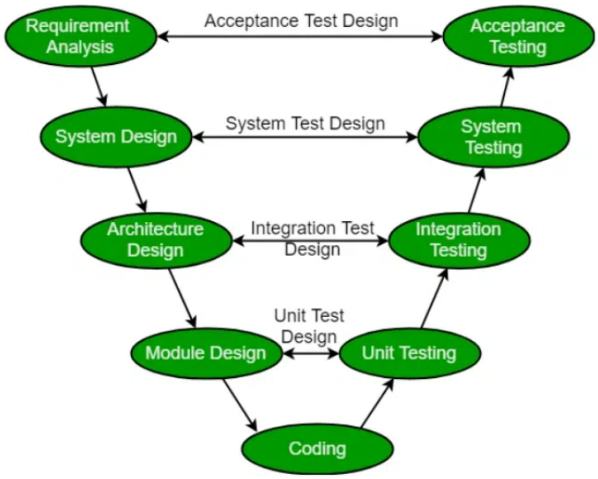

Figure 4.4: The V-model, consisting of several development processes within the verification part at the left side of the V and test processes at the validation part on the right side of the V. The test to a process in the development phase is defined along with or right after the process is completed. [GeeksforGeeks, 2024]

The V-model consist of a verification and a validation part. The verification part consists of several development processes, each linked to a corresponding test in the validation part. These processes proceed sequentially, starting with requirements analysis and progressively becoming more refined through software design until the coding phase of the software development. The V-model offers several advantages, including traceability between requirements and software, early testing to ensure alignment between development and testing, and the detection of defects in early stages before coding. [GeeksforGeeks, 2024] The DSS to be developed includes the two phases requirement analysis and system design. The activities within these two phases are elaborated in the following section.

4.3 Unified Modeling Language & Object Oriented Methodology

It is common practice to develop models to represent a software system as they can serve as simplifications of reality and improve comprehension of the complexity of the system. Unified Modeling Language (UML) can be used in software development for constructing models that facilitate visualisation of the system under development, specification of its structure and behaviour, system construction, and continual documentation of decisions. [Scott, 2002, p. 17] UML serves as both a notation and a conceptual framework, dictating how diagrams and text are conducted and how symbols are applied and interpreted [Vendelhaven, 2002, p. 20]. Its primary benefits lie in facilitating communication among diverse stakeholders and to foster a mutual understanding [Scott, 2002, p. 18]. UML supports an object oriented methodology, which centre on structuring and utilising reusable modules. A well-structured system is easy to maintain, enabling quick and cost-effective system changes. Furthermore, high flexibility in the structure is essential, allowing the system to adapt to changing requirements and needs that frequently occur during the development process. [Vendelhaven, 2002, p. 20-21]

The methodological approach for developing the DSS is presented in Figure 4.5, where the approach is divided into steps. The initial step involves making a pre-analysis of the clinical investigation process, spanning from writing the required documents to submitting the clinical investigation report. The information is acquired by screening MDCG 2021-8 [The Medical Device Coordination Group, 2021a] and Article 62-82 and Annex XV of the MDR [The European Parliament and the Council of the European Union, 2017] with a focus on required documents, deadlines, and actors. Furthermore, an application form Lægemiddelstyrelsen [2024] provided by the competent authority in Denmark, the Danish Medicines Agency, is applied to identify the required documents in the clinical investigation application. The result from the pre-analysis is an activity diagram, illustrating the flow within the activities and actions defined in the MDR.

The remaining steps in the methodological approach is divided the requirement analysis and system design processes from the V-model. The activities involved in these processes of the software development of the DSS are performed in line with an object oriented analysis (OOA) aiming to model the behaviour, function, and structure of the DSS.

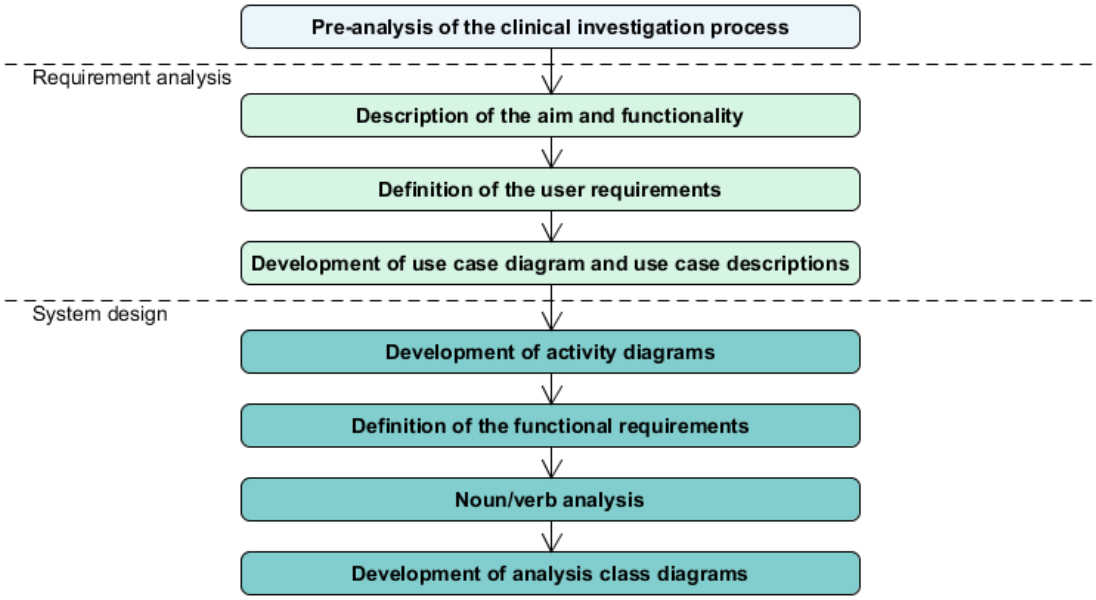

Figure 4.5: The methodology applied through the development of the DSS. The dashed lines indicate the relation with the phases requirement analysis and system design from the V-model.

The first step in the requirement analysis process is to describe the aim and functionality of the DSS. The description of the DSS provides a vision for the development. The second step in the requirement analysis process is to define the user requirements of the DSS. The user requirements are identified through the two literature searches, the pre-analysis, and the description of the aim and functionality of the DSS. The user requirements reflect the function of the DSS defined in a simple language. The third step in the requirement analysis process is the development of a use case diagram and use case descriptions. The use case diagram is based on the user requirements and aims to specify the context of the DSS, where it illustrate the use cases within the DSS, their internal relationship, and their relationship to the identified actors outside of the DSS. The content of each use case is elaborated by a descriptive text to clarify whom the case involves, the main scenario, potential alternative scenarios, and guarantees.

The first step in the system design process is the development of activity diagrams. An activity diagram is developed for each of the use cases, illustrating the flow of activities in the DSS. The use cases and activity diagrams are all developed by screening Article 62-82 and Annex XV of the MDR [The European Parliament and the Council of the European Union, 2017] and the ISO 14155:2020 [International Standardization Organisation, 2020], providing the requirements that the DSS must comply with. Additional articles, books, and guidance documents are used to develop the use cases and activity diagrams, as these sources contain specific methods and design choices. The activity diagrams serves as the knowledge base in the DSS to be developed. The second step in the system design process is the definition of the functional requirements for the DSS. These requirements, written with a high level of details, clarifies what the DSS must do in relation to function to achieve the user requirements. The third step in the system design process is a noun/verb analysis, where the nouns and verbs from the preceding analysis of the DSS are screened and recorded aiming to find candidates to the classes and relationships in the analysis class diagrams, which is the last step in the system design process of the DSS. The analysis class diagrams act as a stepping stone for the next process in the software development, object oriented design.

5 Initial Analytical Basis for ACIT

This chapter covers the pre-analysis of the clinical investigation process and the initial analytical basis for an EU MDR 2017/745 compliant decision support system, named ACIT, which stands for Assisting Clinical Investigation Tool.

5.1 Pre-analysis of the Clinical Investigation Process

A pre-analysis of the clinical investigation process is performed to provide a context for the DSS and to identify the user requirements. The process for a clinical investigation is illustrated in Figure 5.1, which focus on activities performed by a sponsor. Initially, a sponsor shall write the 14 required documents. This process of writing these documents occurs in parallel, except for the informed consents form(s) which is written after the patient information sheet(s) and the clinical investigation plan synopsis which is written after the clinical investigation plan. The MDCG 2024-3 can be followed for assistance in writing the clinical investigation plan. A general outline of the monitoring plan must be included in the clinical investigation plan or be a independent document in the application for a clinical investigation. A note connected to the parallel process of writing the documents provides additional documents that must be written if relevant to the clinical investigation. After the documents are written, an application form is written and the application is submitted the competent authority through either the web form via EUDAMED or by filling in the template in MDCG 2021-08, depending on whether EUDAMED is available and fully functional. When submitted, a unique single identification number is assigned to the clinical investigation. Indicated by the time signal, the competent authority must notify the sponsor within 10 days whether the application falls within the scope of the MDR and whether it is complete. A note is attached to this time signal, as the sponsor must be aware of that the deadline can be extended with five days if more time is needed for the competent authority. If the application is approved, the clinical investigation can begin. If the application is denied, the sponsor needs to provide comments or complete the application within the timeframe and submit the application again. Three possible outcomes exist, where the first is that the competent authority approved the new application, the second is that the application is rejected at which the sponsor needs to undergo an appeal procedure, and the third is that the application is stated as lapsed at which the sponsor must review the documents. Before the clinical investigation can begin, the ethics committee needs to provide an opinion.

The risk class of the medical device determines when the clinical investigation can begin. This is illustrated by the box in the lower right corner of the figure. When begun, five processes run in parallel which are processes that the sponsor needs to be aware of and manage if they require actions. After the end of the clinical investigation, the sponsor needs to write a clinical investigation report and submit this to the competent authority within the required deadlines. Within 15 days after the end of the clinical investigation, the sponsor shall notify the competent authority that the clinical investigation has ended. The sponsor needs to keep the documentation related to the clinical investigation for 10 to 15 years, depending on whether the device is implantable or not.

From this pre-analysis it appears that the documents submitted with the clinical investigation

application must be comprehensive to prevent unnecessary delays and deviations. To expedite the approval process of the clinical investigation, it is essential to have a firm grasp on the design choices and ensure they are thoroughly described and substantiated with arguments in the required documents of the application. Additionally, the sponsor must manage numerous concurrent tasks during a clinical investigation, where unexpected delays and events can escalate costs and complicate proceedings rapidly.

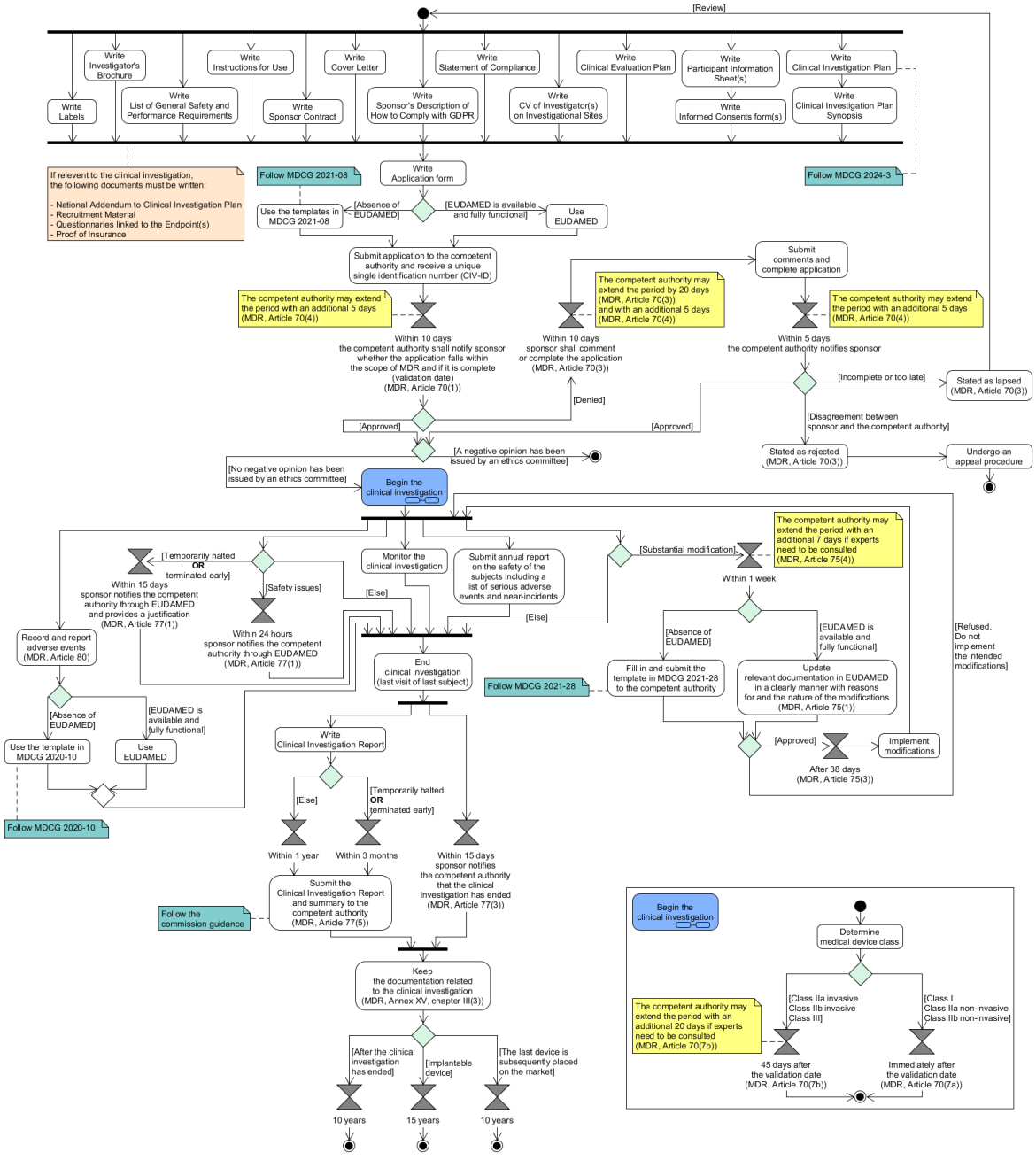

Figure 5.1: Activity diagram for the process of a clinical investigation.

5.2 Aim and Functionality

The purpose of ACIT is to assist sponsors in planning trial designs and addressing challenges in pre-market clinical investigations of medical devices. ACIT must comply with the EU MDR 2017/745, the guidance documents with relation to the planning of a clinical investigation, and ISO 14155:2020. ACIT is a knowledge-driven DSS build on rule-based logic. The format of ACIT is a dynamic questionnaire that follows a flow path based on the inputs provided by the sponsor. ACIT asks questions related to planning of the trial design. The responses, along with information from relevant questions, are compiled into a file. This file is the output from ACIT and serves as the foundation for filling out some of the required documents for the clinical investigation application, including the clinical investigation plan, clinical evaluation plan, and the application form. By asking questions, ACIT prompts sponsors to be aware of and reflect on challenges, thus providing a stronger foundation for designing a clinical investigation. ACIT also provide the sponsor with references to methods and guidance for handling challenges.

ACIT is intended for use in the early planning stages of a clinical investigation, particularly when preparing documents for the application of a clinical investigation. ACIT is indented to be applicable for clinical investigations of all types of medical devices across all risk classes.

Ideally, ACIT shall address all 14 identified challenges. However, it is chosen to focus on those challenges in the planning phase which are concrete and possible to provide assistance to. These challenges include defining endpoints, selecting control group, blinding and use of comparator, handling device changes, calculating sample size, long term follow-up, randomisation, and expertise and learning curve. Challenges regarding regulatory compliance, high cost and time-consumption, and collection of sufficient high-quality data are broad and vague and therefore more difficult to accommodate. However, these three challenges all relate in some way to the eight challenges listed above and will therefore also be addressed. The remaining three challenges are identification, recruitment, and retention of subjects; real-world applicability; and cases where a medical device cannot be evaluated alone. These challenges are currently beyond the scope of ACIT, as these challenges are highly dependent on the characteristic of the specific medical device.

Based on the pre-analysis, it is chosen that ACIT should also assist in planning the monitoring of the clinical investigation, including handling adverse events, as this is a crucial part of a clinical investigation.

ACIT is justified as planning of a clinical investigation involves several challenges which the sponsor may not be fully aware of. Additionally, it may prompt the sponsor to enhance confidence in their role, gain a better understanding of the clinical investigation process, and initiate reflections on how to effectively communicate with other involved stakeholders.

5.3 User Requirements

The user requirements for ACIT are identified through the two literature searches, the pre-analysis, and the description of the aim and functionality of ACIT. Every user requirement can be identified through an ID. The user requirements are listed in Table 5.1.

Table 5.1: User requirements for ACIT.

ID	User requirement
UR-1	ACIT must be consistent with the requirements in: a) MDR 2017/745, Article 62-82 and Annex XV b) MDCG 2020-1: Guidance on Clinical Evaluation (MDR) / Performance Evaluation (IVDR) of Medical Device Software c) MDCG 2020-6: Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC. A guide for manufacturers and notified bodies d) MDCG 2024-3: Guidance on content of the Clinical Investigation Plan for clinical investigations of medical devices e) MDCG 2020-10/1: Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 f) Commission Guidance on the content and structure of the summary of the clinical investigation report g) ISO 14155:2020 - Clinical investigation of medical devices for human subjects - Good clinical practice
UR-2	ACIT must show references to the requirements in: a) MDR 2017/745, Article 62-82 and Annex XV b) MDCG 2020-1: Guidance on Clinical Evaluation (MDR) / Performance Evaluation (IVDR) of Medical Device Software c) MDCG 2020-6: Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC. A guide for manufacturers and notified bodies d) MDCG 2024-3: Guidance on content of the Clinical Investigation Plan for clinical investigations of medical devices e) MDCG 2020-10/1: Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 f) Commission Guidance on the content and structure of the summary of the clinical investigation report g) ISO 14155:2020 - Clinical investigation of medical devices for human subjects - Good clinical practice
UR-3	ACIT requires that the risk class, the intended purpose, and the claimed clinical benefit(s) of the medical device under investigation are established
UR-4	ACIT must assist in the design choices of the clinical investigation
UR-5	ACIT must assist in the determination of endpoints
UR-6	ACIT must assist in the determination of choosing the trial design
UR-7	ACIT must assist in blinding and use of comparator
UR-8	ACIT must provide a method to calculate sample size along with the equation(s)
UR-9	ACIT must assist in the determination of the trial duration and the criteria and procedures for the follow-up of the subjects
UR-10	ACIT must assist in how to handle the learning curve effect when the clinical investigation involves a surgical or interventional technique
UR-11	ACIT must assist in planning how to monitor the clinical investigation

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UR-12	ACIT must provide a method for handling device changes and assist in the recording procedure for handling a device change
UR-13	ACIT must assist in defining a strategy of how to handle adverse events and assist in how to register a reportable event to the manufacturer and the competent authority
UR-14	ACIT must create a file and save the decisions in it

5.4 Use Cases

Based on the pre-analysis, the description of the aim and functionality, and the user requirements, a use case diagram is developed which appears in Figure 5.2. A use case diagram is a behaviour diagram that illustrates the actors and use cases involved in the system. Each use case represents a series of actions performed by an actor to achieve a specific goal, outlining what the system should do without specifying how it should act. [Scott, 2002, p. 54] The include relationship is applied when the behaviour of the included use case is always included to the base use case, while the extend relationship is applied when the behaviour of the extended use case is optional. The developed use case diagram comprises nine use cases within ACIT. The primary actor, which is the user of ACIT, is the sponsor of the clinical investigation. The secondary actors are the competent authority and the manufacturer, neither of which can interact with ACIT. Furthermore, different entities including the ISO 14155:2020, the MDR 2017/745, and the guidance documents are outside ACIT. These entities are incorporated into the use case diagram, as the MDR states that the sponsor needs to report statement of compliance with all relevant legislation.

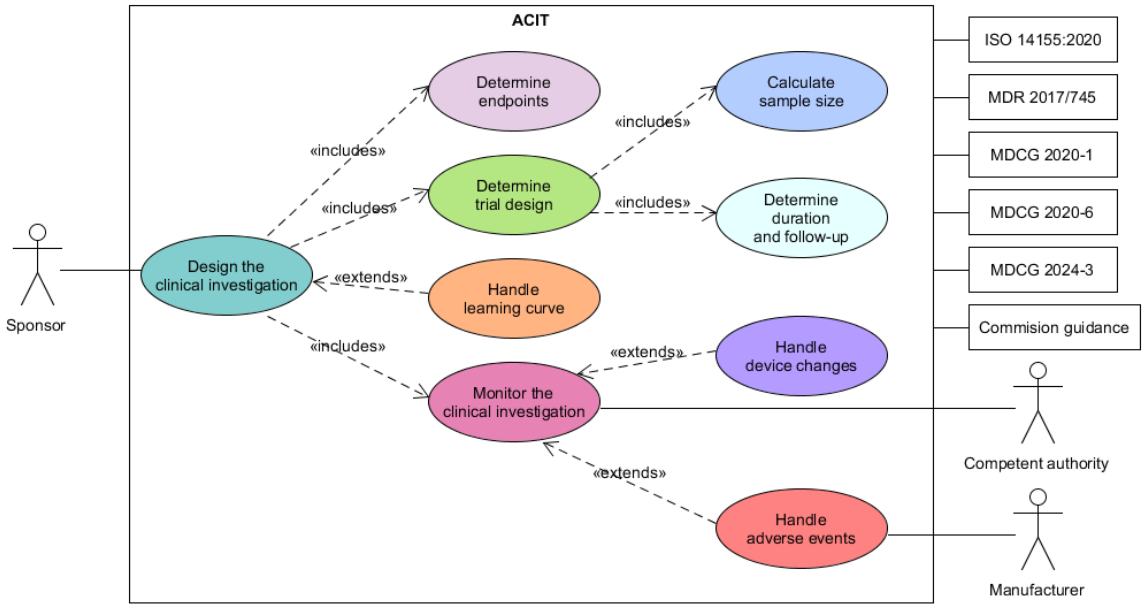

Figure 5.2: Use case diagram for ACIT.

Each of the nine use cases from the use case diagram are elaborated by a descriptive text outlining the flow, both ideal main paths and alternative paths, as well as the actions performed by actors and the system's response to those actions. The use case descriptions appears in Tables 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, and 5.10. The individual use cases will be referred to through an ID, defined in the tables.

Table 5.2: Use case 1 - Design the clinical investigation.

Use case: Design the clinical investigation
ID: UC1
Brief description: The sponsor receives assistance in making design choices when planning the clinical investigation. ACIT creates the file ”User inputs” and updates it each time the user has entered an answer to a question provided by ACIT. ACIT generates the file ”Clinical Investigation Planning Draft” using the answers stored in the file ”User inputs”.
Primary actor: Sponsor
Pre-condition: The risk class, intended purpose, and claimed clinical benefit for the medical device under investigation are established
Trigger: The sponsor needs assistance in determining design choices for the clinical investigation
Main success scenario: 1. ACIT must create the file ”User inputs” 2. The sponsor enters the risk class, intended purpose, and claimed clinical benefit(s) 3. ACIT updates the file ”User inputs” with the risk class, intended purpose, and claimed clinical benefit(s) 4. ACIT provides assistance to the sponsor on how to determine the endpoints. *Includes UC2.* 5. ACIT provides assistance to the sponsor on how to determine the trial design. *Includes UC3.* 6. ACIT proposes a method for calculating sample size and the sponsor calculates the sample size. *Includes UC4.* 7. ACIT provides assistance to the sponsor on how to determine the duration of the clinical investigation as well as the criteria and procedures for the follow-up of the subjects. *Includes UC5.* 8. The sponsor can determine how to handle the learning curve effect in case of a surgical or interventional technique is to be assessed. *Extends UC6.* 9. ACIT provides assistance to the sponsor on how to monitor the clinical investigation. *Includes UC7.* 10. The sponsor can receive assistance in how to handle device changes prior to the beginning of the clinical investigation. *Extends UC8.* 11. The sponsor can receives assistance in how to handle adverse events. *Extends UC9.* 12. ACIT generates the file ”Clinical Investigation Planning Draft” using the answers stored in the file ”User inputs”
Success guarantees: The clinical investigation is designed, and the file ”Clinical Investigation Planning Draft” is generated.
Minimal guarantees: The file ”User inputs” is updated with the answers from the user.

Table 5.3: Use case 2 - Determine endpoints.

Use case: Determine endpoints
ID: UC2
Brief description: The sponsor determines the endpoints in the clinical investigation and substantiates these endpoints with rationale for the selection and how these will be measured. ACIT updates the file ”User inputs” with the answers from the user.
Primary actor: Sponsor
Trigger: The manufacturer wants to document the safety, performance, and/or clinical benefit of the device under investigation on human subjects
Main success scenario: 1. The sponsor defines a primary endpoint 2. ACIT updates the file ”User inputs” with the primary endpoint 3. The sponsor substantiates the primary endpoint with rationale for the selection and measurement 4. ACIT updates the file ”User inputs” with the substantiation of the primary endpoint 5. The sponsor defines one or more secondary endpoint(s) 6. ACIT updates the file ”User inputs” with a list of the secondary endpoint(s) 7. The sponsor substantiates the secondary endpoint(s) with rationale for the selection and measurement 8. ACIT updates the file ”User inputs” with the substantiation of the secondary endpoint(s) 9. The sponsor has the opportunity to define composite endpoint(s) *The sponsor wants to define composite endpoint(s)* 10. The sponsor defines one or more composite endpoint(s) 11. ACIT updates the file ”User inputs” with a list of the composite endpoint(s) 12. The sponsor substantiates the composite endpoint(s) with rationale for the selection and measurement 13. ACIT updates the file ”User inputs” with the substantiation of the secondary endpoint(s) 14. The sponsor continues to point 5 in the main success scenario in UC1 *The sponsor does not want to define composite endpoint(s)* 10. The sponsor continues to point 5 in the main success scenario in UC1
Alternative scenarios: 1a. The sponsor has already defined a primary endpoint 1b. Return to point 2 in the main success scenario *OR* 1a. ACIT notifies that the primary endpoint has not been determined correctly 1b. ACIT allows the sponsor to rewrite the primary endpoint 1c. Return to point 1 in the main success scenario *AND/OR* 5a. The sponsor has already defined one or more secondary endpoint(s) 5b. Return to point 6 in the main success scenario *OR*

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Alternative scenarios:
5a. ACIT notifies that the secondary endpoint has not been determined correctly
5b. ACIT allows the sponsor to rewrite the secondary endpoint
5c. Return to point 5 in the main success scenario
AND/OR (under the headline *The sponsor wants to define composite endpoint(s)*)
10a. The sponsor has already defined one or more composite endpoint(s)
10b. Return to point 11 in the main success scenario
OR (under the headline *The sponsor wants to define composite endpoint(s)*)
10a. ACIT notifies that the composite endpoint has not been determined correctly
10b. ACIT allows the sponsor to rewrite the composite endpoint
10c. Return to point 10 in the main success scenario
Success guarantees: One primary endpoint and one or more secondary endpoints are determined. The file ”User inputs” is updated with the answers.
Minimal guarantees: ACIT saves the file ”User inputs” with the latest update. ACIT displays an error message if one of the endpoints is not properly defined.

Table 5.4: Use case 3 - Determine trial design.

Use case: Determine trial design
ID: UC3
Brief description: The sponsor chooses the trial design for the clinical investigation including the level of blinding. ACIT updates the file ”User inputs” with the answers from the user.
Primary actor: Sponsor
Pre-condition: The sponsor has determined a primary endpoint
Trigger: The manufacturer is planning a clinical investigation involving human subjects
Main success scenario:
1. The sponsor chooses if it is possible to have a control group
2. The sponsor chooses whether the control group can be blinded, and which comparator(s) is the most applicable
3. ACIT updates the file ”User inputs” with the type of control group and the comparator
4. The sponsor chooses the trial design
5. ACIT updates the file ”User inputs” with the trial design
6. The sponsor chooses whom, if any, to blind and how to achieve the blinding
7. ACIT updates the file ”User inputs” with the choices of blinding
8. The sponsor continues to point 6 in the main success scenario in UC1
Alternative scenarios:
1a. The sponsor chooses that it is impossible to have a control group
1b. ACIT updates the file ”User inputs” with the choice not to have a control group
1c. Return to point 4 in the main success scenario
OR
4a. The sponsor has already chosen a trial design
4b. Return to point 5 in the main success scenario
Success guarantees: Trial and blinding type are chosen. The file ”User inputs” is updated.
Minimal guarantees: ACIT saves the file ”User inputs” with the latest update.

Table 5.5: Use case 4 - Calculate sample size.

Use case: Calculate sample size
ID: UC4
Brief description: The sponsor chooses a method to calculate the sample size to be used in the clinical investigation and calculates the sample size. ACIT updates the file ”User inputs” with the answers from the user.
Primary actor: Sponsor
Pre-condition: The sponsor has determined a primary endpoint and a trial design
Trigger: The manufacturer is planning a clinical investigation involving human subjects
Main success scenario: 1. The sponsor chooses the method to calculate the sample size that is most suitable for the clinical investigation *The following steps must be reviewed if the method requires several design choices to be made* 1.1 The sponsor accesses the introduction of the note ”Calculation of sample size” and chooses a level of power and a significance level 1.2 ACIT updates the file ”User inputs” with the level of power and the significance level 2. The sponsor accesses the section of the note ”Calculation of sample size” that describes the chosen method 3. ACIT updates the file ”User inputs” with the method to calculate the sample size 4. The sponsor calculates the sample size 5. ACIT updates the file ”User inputs” with the calculated sample size 6. The sponsor estimates the expected drop-out rate 7. ACIT updates the file ”User inputs” with the drop-out rate 8. The sponsor calculates an adjusted sample size which takes the drop-out rate into account 9. ACIT updates the file ”User inputs” with the adjusted sample size 10. The sponsor continues to point 7 in the main success scenario in UC1
Alternative scenarios: 1a. The sponsor has already chosen a method to calculate the sample size 1b. Return to point 3 in the main success scenario
Success guarantees: The note ”Calculation of sample size” is available for the user. A method for calculating the sample size is chosen and the sample size is calculated. The file ”User inputs” is updated.
Minimal guarantees: ACIT saves the file ”User inputs” with the latest update. ACIT displays an error message if the level of power and/or the significance level is not selected by the user.

The note ”Calculation of sample size”[1] is a document that can be accessed by the sponsor and applied to increase the level of assistance by elaborate the methods and equations of calculating the sample size. The note is developed due to the lack of specific methods in the MDR and ISO 14155:2020. Thus the note is prepared by screening scientific literature.

[1] See External appendix

Table 5.6: Use case 5 - Determine duration and follow-up.

Use case: Determine duration and follow-up
ID: UC5
Brief description: The sponsor receives assistance in how to determine the duration of the clinical investigation, and the criteria and procedures for the follow-up of the subjects. ACIT updates the file ”User inputs” with the answers from the user.
Primary actor: Sponsor
Pre-condition: The sponsor has calculated the sample size
Trigger: The manufacturer is planning a clinical investigation involving human subjects
Main success scenario: 1. The sponsor chooses the duration of the clinical investigation 2. ACIT updates the file ”User inputs” with the duration of the clinical investigation 3. The sponsor defines criteria and procedures for the follow-up of the subjects 4. ACIT updates the file ”User inputs” with a list of criteria and procedures for the follow-up of the subjects 5. The sponsor continues to point 8 in the main success scenario in UC1
Alternative scenarios: 1a. The sponsor has already chosen the duration of the clinical investigation 1b. The sponsor keeps the chosen duration 1c. Return to point 2 in the main success scenario *OR* 1a. The sponsor has already chosen the duration of the clinical investigation 1b. The sponsor chooses another duration 1c. Return to point 1 in the main success scenario *AND/OR* 3a. The sponsor has already defined criteria and procedures for the follow-up of the subjects 3b. The sponsor keeps the criteria and procedures for the follow-up of the subjects 3c. Return to point 4 in the main success scenario *OR* 3a. The sponsor has already defined criteria and procedures for the follow-up of the subjects 3b. The sponsor rewrites the criteria and procedures for the follow-up of the subjects 3c. Return to point 3 in the main success scenario
Success guarantees: The duration of the clinical investigation and the criteria and procedures for the follow-up of the subjects are defined. The file ”User inputs” is updated.
Minimal guarantees: ACIT saves the file ”User inputs” with the latest update.

Table 5.7: Use case 6 - Handle learning curve.

Use case: Handle learning curve
ID: UC6
Brief description: The sponsor receives assistance in how to handle the learning curve effect. ACIT updates the file ”User inputs” with the answers from the user.

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Primary actor: Sponsor
Trigger: The clinical investigation involves a surgical or interventional technique
Main success scenario: 1. The sponsor accesses section 1.0 in the note ”Handle learning curve” and defines the variable(s) to measure the learning curve 2. ACIT updates the file ”User inputs” with a list of the variable(s) 3. The sponsor accesses section 2.0 in the note ”Handle learning curve” and defines the confounding factor(s) 4. ACIT updates the file ”User inputs” with a list of the confounding factor(s) 5. The sponsor plans how to report the confounding factors 6. ACIT updates the file ”User inputs” with the plan 7. The sponsor chooses a method to quantify the learning curve 8. ACIT updates the file ”User inputs” with a method to quantify the learning curve 9. The sponsor quantifies the operators existing level of expertise 10. ACIT updates the file ”User inputs” with the operators existing level of expertise 11. The sponsor chooses the type of training of the operators 12. ACIT updates the file ”User inputs” with the type of training of the operator(s) 13. The sponsor chooses a method to assess the competences of the operator(s) acquired through the training 14. ACIT updates the file ”User inputs” with the method to assess the competences acquired through the training 15. The sponsor defines the learning plateau for the operator(s) 16. ACIT updates the file ”User inputs” with the learning plateau 17. The sponsor continues to point 9 in the main success scenario in UC1
Alternative scenarios: 7a. ACIT gives an error message if no method is chosen 7b. Return to point 7 in the main success scenario *AND/OR* 11a. ACIT gives an error message if no type of training is chosen 11b. Return to point 11 in the main success scenario *AND/OR* 13a. ACIT gives an error message if no method is chosen 13b. Return to point 13 in the main success scenario
Success guarantees: The note ”Handle learning curve” is available for the user. ACIT provided assistance to the sponsor in how to handle the learning curve effect. The file ”User inputs” is updated.
Minimal guarantees: ACIT saves the file ”User inputs” with the latest update.

The note ”Handle learning curve”[1] is a document that can be accessed by the sponsor and applied to increase the level of assistance by giving examples on how to define variables and confounding factors in relation to handling the learning curve effect. The note is developed due to the lack of specific methods in the MDR and ISO 14155:2020. Thus the note is prepared by screening scientific literature.

[1] See External appendix

Table 5.8: Use case 7 - Monitor the clinical investigation.

Use case: Monitor the clinical investigation
ID: UC7
Brief description: The sponsor receives assistance in how to plan the monitoring of the clinical investigation. ACIT updates the file ”User inputs” with the answers from the user.
Primary actor: Sponsor
Secondary actor: Competent authority
Pre-condition: The duration of the clinical trial and the criteria and procedures for the follow-up of the subjects are determined
Main success scenario: 1. The sponsor chooses to plan the monitoring activities 2. The sponsor appoints the monitor 3. ACIT updates the file ”User inputs” with the choice of the monitor 4. The sponsor collects information about the monitor 5. ACIT updates the file ”User inputs” with the information about the monitor 6. The sponsor specifies the qualification of and the required training for the monitor 7. ACIT updates the file ”User inputs” with the qualification of the monitor and the required training for the monitor 8. The sponsor chooses if a data safety monitoring committee (DSMC) is needed. If needed, the sponsor provides information regarding the DSMC. If not needed, the sponsor provides a explanation of why a DSMC is not needed. 9. ACIT updates the file ”User inputs” with the information of the DSMC 10. The sponsor defines a strategy for keeping documentation and records along with a detailed description of the strategy 11. ACIT updates the file ”User inputs” with the strategy 12. The sponsor provides a detailed description of which data and documents that will be monitored and to which extent 13. ACIT updates the file ”User inputs” with the description 14. The sponsor describes the investigation site(s) facilities and the rationale for the selection(s) 15. ACIT updates the file ”User inputs” with the information and the rationale 16. The sponsor plans the site(s) selection visit 17. ACIT updates the file ”User inputs” with the plan of the site(s) selection visit 18. The sponsor plans the site(s) initiation visit 19. ACIT updates the file ”User inputs” with the plan of the site(s) initiation visit 20. The sponsor plans the interim monitoring visits and chooses the type of monitoring 21. ACIT updates the file ”User inputs” with the plan of the interim monitoring visits and the type of monitoring 22. The sponsor describes procedures to review the monitoring visit reports, follow-up on monitoring findings, and corrective actions 23. ACIT updates the file ”User inputs” with the procedures 24. The sponsor plans the site(s) close-out visit 25. ACIT updates the file ”User inputs” with the plan of the site(s) close-out visit

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Main success scenario:
26. The sponsor plans when to report to the competent authority
27. ACIT updates the file ”User inputs” with the reporting plan
28. The sponsor continues to point 10 in the main success scenario in UC1
Alternative scenarios:
1a. The sponsor has already written a general outline of the monitoring plan
1b. ACIT updates the file ”User inputs” with the general outline of the monitoring plan
1c. Return to point 28 in main success scenario
OR
2a. ACIT gives an error message if no monitor is appointed
2b. Return to point 2 in the main success scenario
AND/OR
10a. ACIT gives an error message if no strategy is chosen
10b. Return to point 10 in the main success scenario
AND/OR
20a. ACIT gives an error message if no monitoring type is chosen
20b. Return to point 21 in the main success scenario
Success guarantees: ACIT provided assistance to the sponsor in planning the activities related to monitoring the clinical investigation. The file ”User inputs” is updated.
Minimal guarantees: ACIT saves the file ”User inputs” with the latest update.

Table 5.9: Use case 8 - Handle device changes.

Use case: Handle device changes
ID: UC8
Brief description: The sponsor receives assistance in how to handle device changes prior to the beginning of the clinical investigation. ACIT updates the file ”User inputs” with the answers from the user.
Primary actor: Sponsor
Pre-condition: The sponsor has planned how to monitor the clinical investigation
Main success scenario:
1. The sponsor chooses a method which can help in assisting on the timing of assessment of the medical device
2. ACIT updates the file ”User inputs” with the method
3. The sponsor can view the procedure for recording and handling a device change during the clinical investigation
4. The sponsor continues to point 11 in the main success scenario in UC1
Alternative scenarios:
3a. The sponsor chooses not to view the procedure for recording and handling a device change
3b. Return to point 4 in the main success scenario
Success guarantees: ACIT provided assistance to the sponsor in how to handle device changes prior to the beginning of the clinical investigation. The file ”User inputs” is updated.
Minimal guarantees: ACIT saves the file ”User inputs” with the latest update.

Table 5.10: Use case 9 - Handle adverse events.

Use case: Handle adverse events
ID: UC9
Brief description: The sponsor receives assistance in how to handle adverse events during the clinical investigation. ACIT updates the file ”User inputs” with the answers from the user.
Primary actor: Sponsor
Secondary actor: Manufacturer and competent authority
Pre-condition: The sponsor has planned how to monitor the clinical investigation
Main success scenario: 1. The sponsor defines method(s) to record adverse events, device deficiencies, and new findings in relation to adverse events and device deficiencies 2. ACIT updates the file ”User inputs” with a list of the method(s) 3. The sponsor defines how to inform the investigator(s) about adverse events, device deficiencies, and new findings in relation to adverse events and device deficiencies 4. ACIT updates the file ”User inputs” with the strategy to inform the investigator(s) 5. The sponsor defines how to inform the subjects in the trial about the adverse events 6. ACIT updates the file ”User inputs” with the strategy to inform the subjects in the trial 7. The sponsor chooses the format of the reporting 8. ACIT updates the file ”User inputs” with the format of the reporting 9. The sponsor can view the reporting procedure for when a reportable event occurs 10. The sponsor continues to point 12 in the main success scenario in UC1
Alternative scenarios: 1a. The sponsor has already written a strategy for handling adverse events 1b. ACIT updates the file ”User inputs” with the strategy 1c. Return to point 7 in the main success scenario *AND/OR* 9a. The sponsor chooses not to view the reporting procedure 9b. Return to point 10 in the main success scenario
Success guarantees: ACIT provided assistance to the sponsor in how to handle adverse events. The file ”User inputs” is updated.
Minimal guarantees: ACIT saves the file ”User inputs” with the latest update.

5.5 Activity Diagrams

The flow of activities in ACIT, from start to finish, is illustrated through activity diagrams. To simplify the flow, each use case is represented by its own activity diagram. Activities with a chain symbol in the lower right corner indicate hidden subactivities. Activities updating the file ”User inputs” have a grey background and decisions have a pale green background. In each activity diagram, the title of the use case appears in the top left corner.

Figure 5.3 illustrates the main flow in ACIT, defined in UC1 ”Design the clinical investigation” showing the activation sequence of the following use cases. ”Determine endpoints” is the first activity, as it establish the clinically relevant outcome parameters for the trial. The sample size

is calculated based on the primary endpoint, why the activity ”Determine endpoints” is required prior to ”Calculate sample size”. Additionally, ”Determine trial design” precedes ”Calculate sample size” because the design affects the number of subjects involved in the trial. The activity ”Determine duration and follow-up” is closely related to the activity ”Determine trial design”, why this activity is activated early in the flow. The activity ”Handle learning curve” includes pre-monitoring actions, why is it activated just before the activity ”Monitor the clinical investigation”. The final two activities, both related to ”Monitor the clinical investigation”, are positioned before generating the ”Clinical Investigation Planning Draft” file. These two activities do not need to be activated in a specific order.

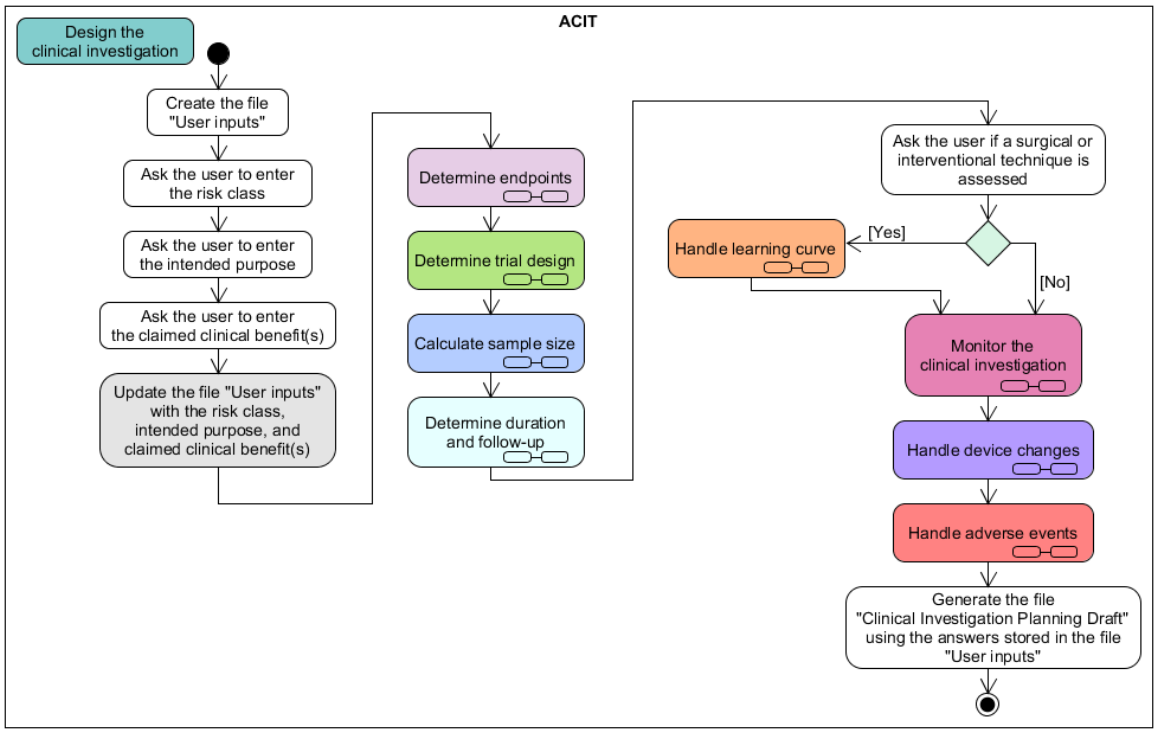

Figure 5.3: Activity diagram for UC1.

The following activity diagrams are developed by screening the MDR [The European Parliament and the Council of the European Union, 2017] and the ISO 14155:2020 [International Standardization Organisation, 2020]. Additional sources for each specific activity diagram will be mentioned as needed. References to the MDR, ISO 14155:2020, guidance documents, and notes are highlighted in bold within the specific activity. Text inside an activity written in italic provides explanations or clarifications to the activity.

The activity diagram for UC2 ”Determine endpoints” is shown in Figure 5.4. The article by Johner Institute [2023] is applied to prepare this diagram. Initially, the primary endpoint of the clinical investigation needs to be defined, as it is directly related to the objective of the investigation. It is essential as the primary endpoint is used to formulate the primary hypothesis, if applicable to the investigation, and thus used to calculate the sample size. After defining the primary endpoint and providing a rationale for its selection and describing how it will be measured, the secondary endpoint(s) must be defined. Defining composite endpoint(s) is optional, so activities related to composite endpoint(s) are placed at the end of the flow.

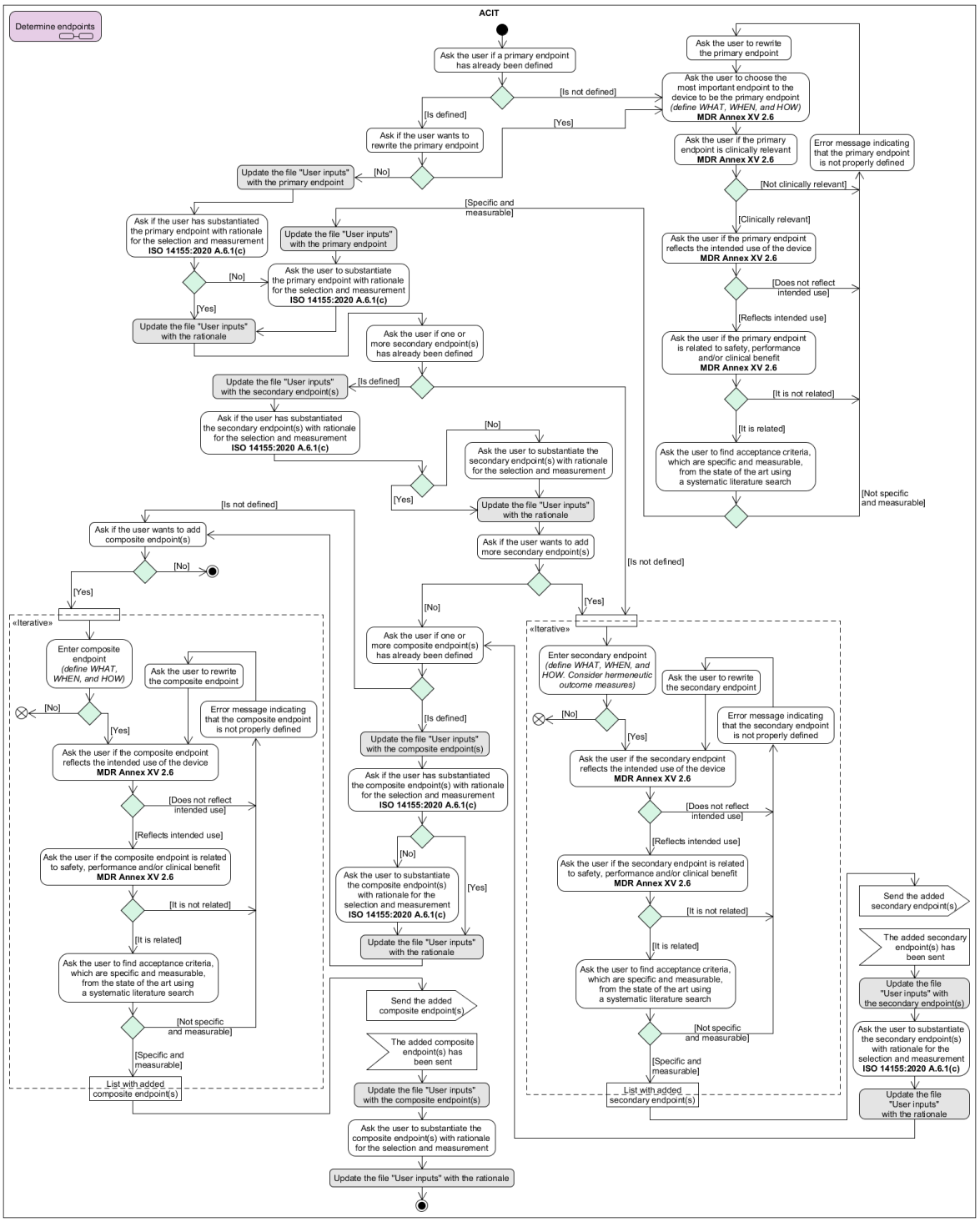

Figure 5.4: Activity diagram for UC2. By ”define WHAT, WHEN, and HOW”, the following structure of the formulation of the endpoint is meant: Specify the endpoint (WHAT), the timing (WHEN), the method, the survey instrument, or device, etc. (HOW) it will be recorded.

The activity diagram for UC3 ”Determine trial design” is shown in Figure 5.5. This diagram is prepared using articles by Haute Authorité de Santé [2021], Neugebauer et al. [2017], and Zannad et al. [2014] as the main sources, since the MDR does not provide specific examples of trial designs. The ISO 14155:2020 briefly lists a few examples of the design, but only in general terms such as crossover, randomised, and blinded. The flow for determining the trial design

begins by asking the user if it is possible to have a control group in the clinical investigation. If a control group is feasible, the next step is to determine whether blinding of the control group is possible, followed by the selection of the comparator(s). The flow continues with a series of questions on the trial design, which helps narrow down the options to identify the most applicable design for the trial. The flow concludes with questions about blinding other participants involved in the trial.

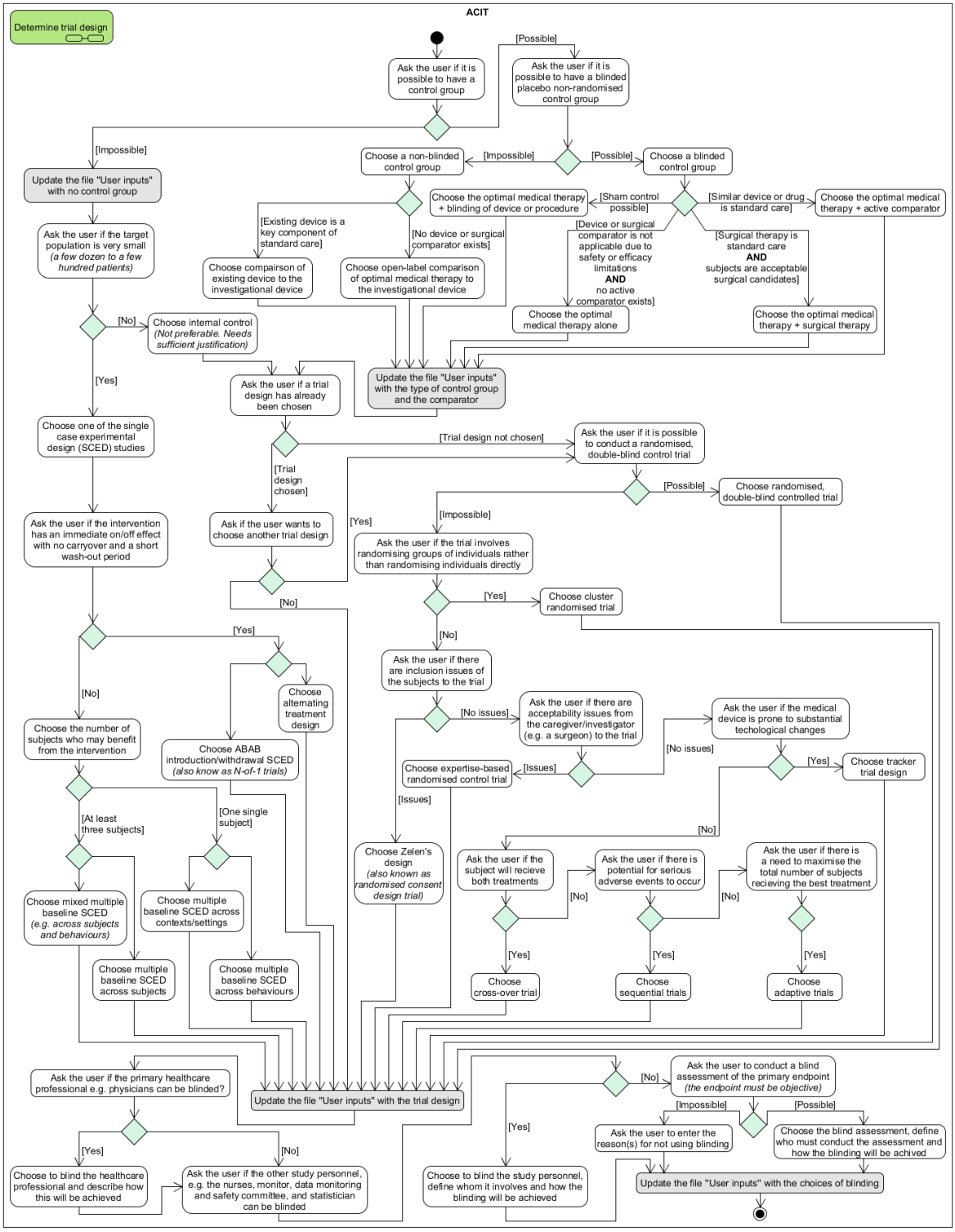

Figure 5.5: Activity diagram for UC3.

The activity diagram for UC4 ”Calculate sample size” is shown in Figure 5.6. The sources used to prepare this diagram are the article by In et al. [2020] and the books by Bland [2000] and Zar [2016]. The flow leads to one of eight methods, as only one method is necessary for calculating the sample size. The note ”Calculation of sample size”[1] can be applied by the user to assist in a method for calculating the sample size. Even though the MDR and ISO 14155:2020 do not specify methods, they mandate that the clinical investigation plan must incorporate statistical considerations, including sample size, based on power calculation if applicable. Therefore, the provided methods are sourced from additional literature. Given the phrase ’if applicable’, the methods for population mean and population proportion are included. Activities related to the drop-out rate are also included, as considerations of drop-out rate are essential in designing the statistical analysis, as outlined in ISO 14155:2020 Annex A7.

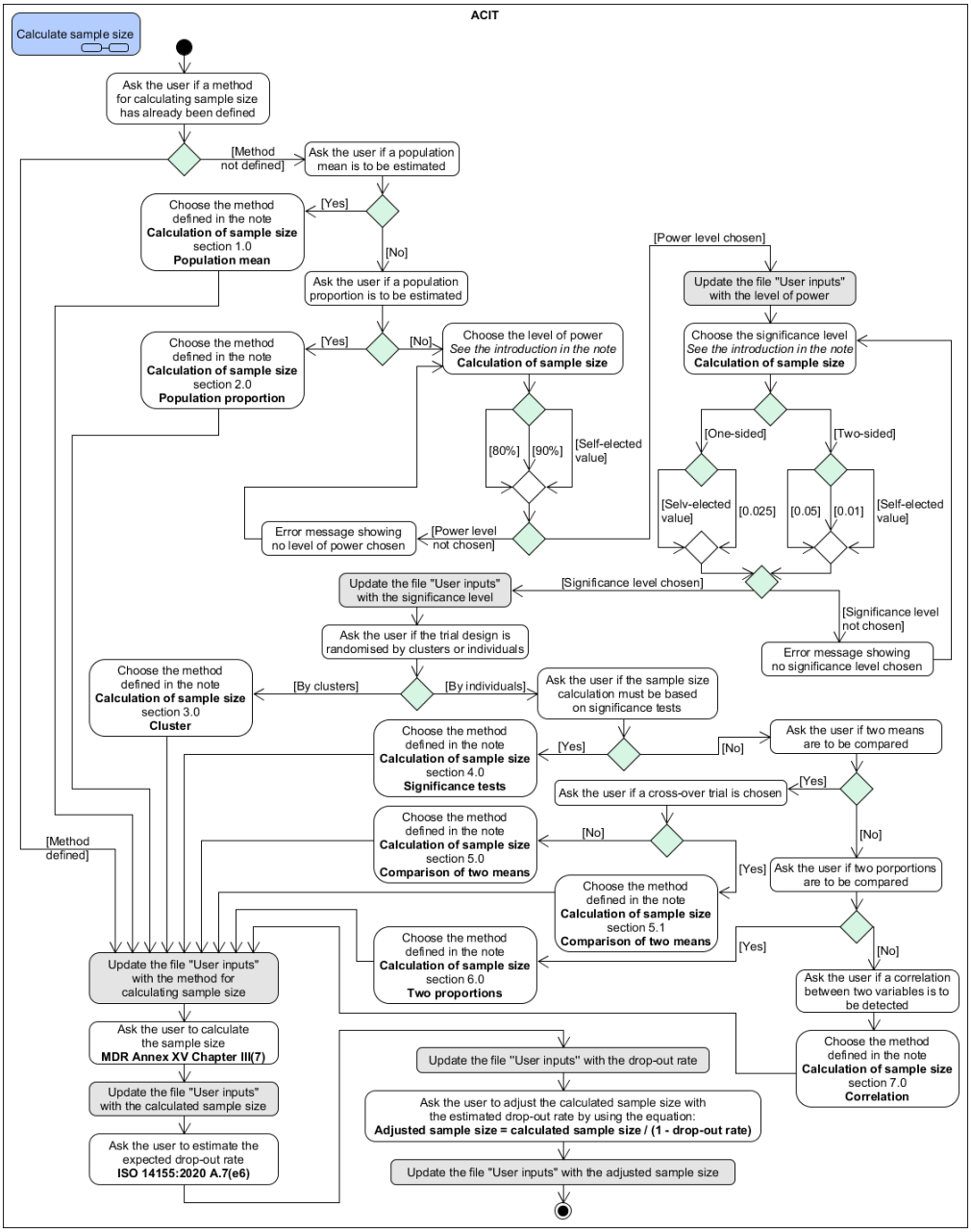

Figure 5.6: Activity diagram for UC4.

[1]See External appendix

The activity diagram for UC5 ”Determine duration and follow-up” is shown in Figure 5.7. The sources used to prepare this diagram are the Commission Guidance [The European Commission, 2024], the MDCG 2020-6 [The Medical Device Coordination Group, 2020c] and the MDCG 2024-3 [The Medical Device Coordination Group, 2024]. The flow involves two parts. The first part is choosing a duration. There is limited literature describing how to determine a trial duration, as it depends on various factors. Therefore, ACIT asks the user to draw on existing clinical experience from similar devices and provides examples of factors that influence the duration. The second part is choosing criteria and procedures for the follow-up on subjects. Due to the lack of well-defined criteria and procedures in scientific literature, ACIT similarly asks the user to draw on existing clinical experience from similar devices.

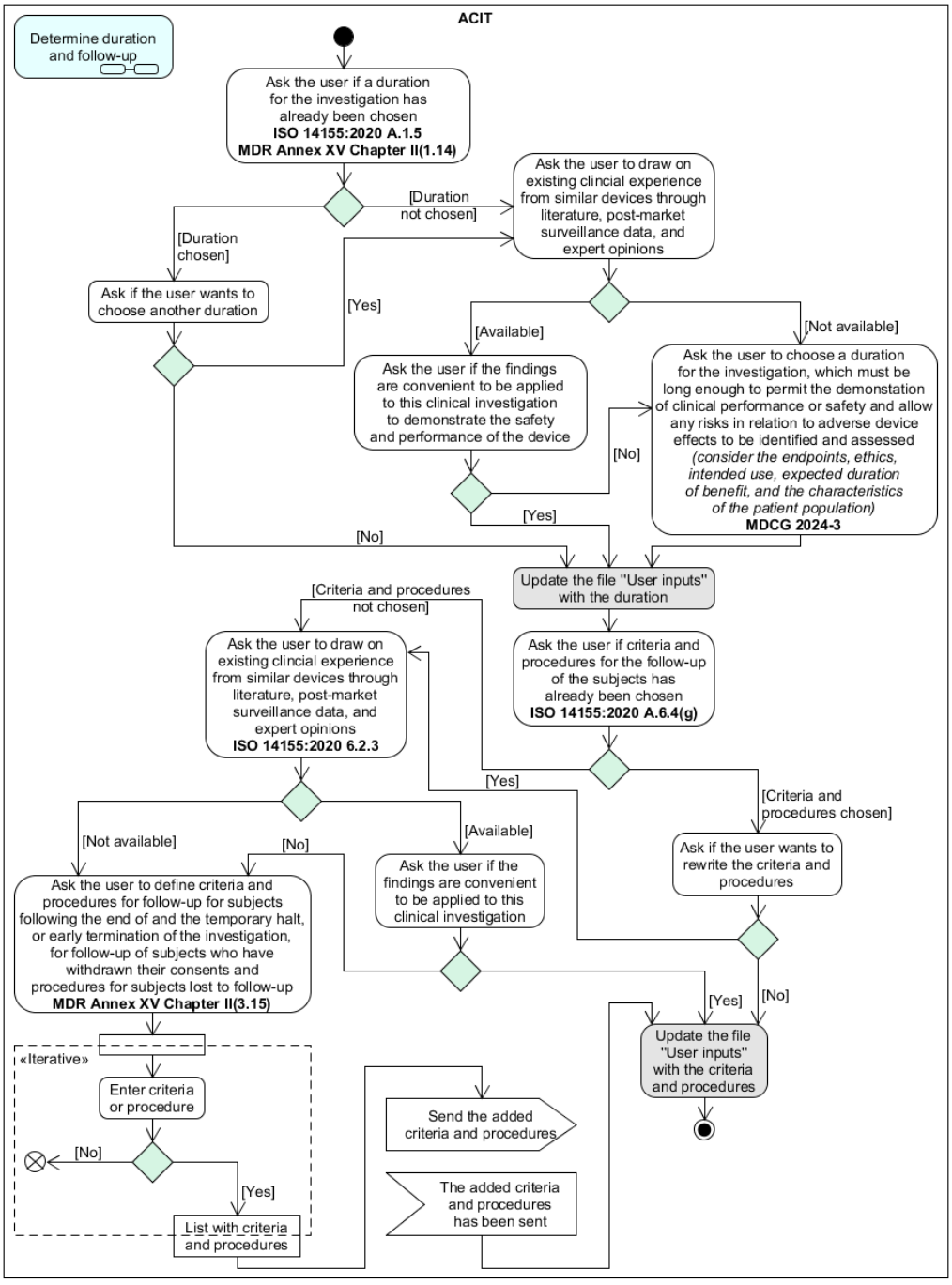

Figure 5.7: Activity diagram for UC5.

The activity diagram for UC6 ”Handle learning curve” is shown in Figure 5.8. This diagram is prepared using the articles by Khan et al. [2014], Haute Authorité de Santé [2021], Motte et al. [2017], and Neugebauer et al. [2017]. The flow starts with the user defining variables and confounding factors. The user can seek assistance in the note ”Handle learning curve”[1]. Next, the user must plan how to report the confounding factors. The remaining activities focus on the operator. For three of these activities, specific methods and types of training identified through the articles are provided.

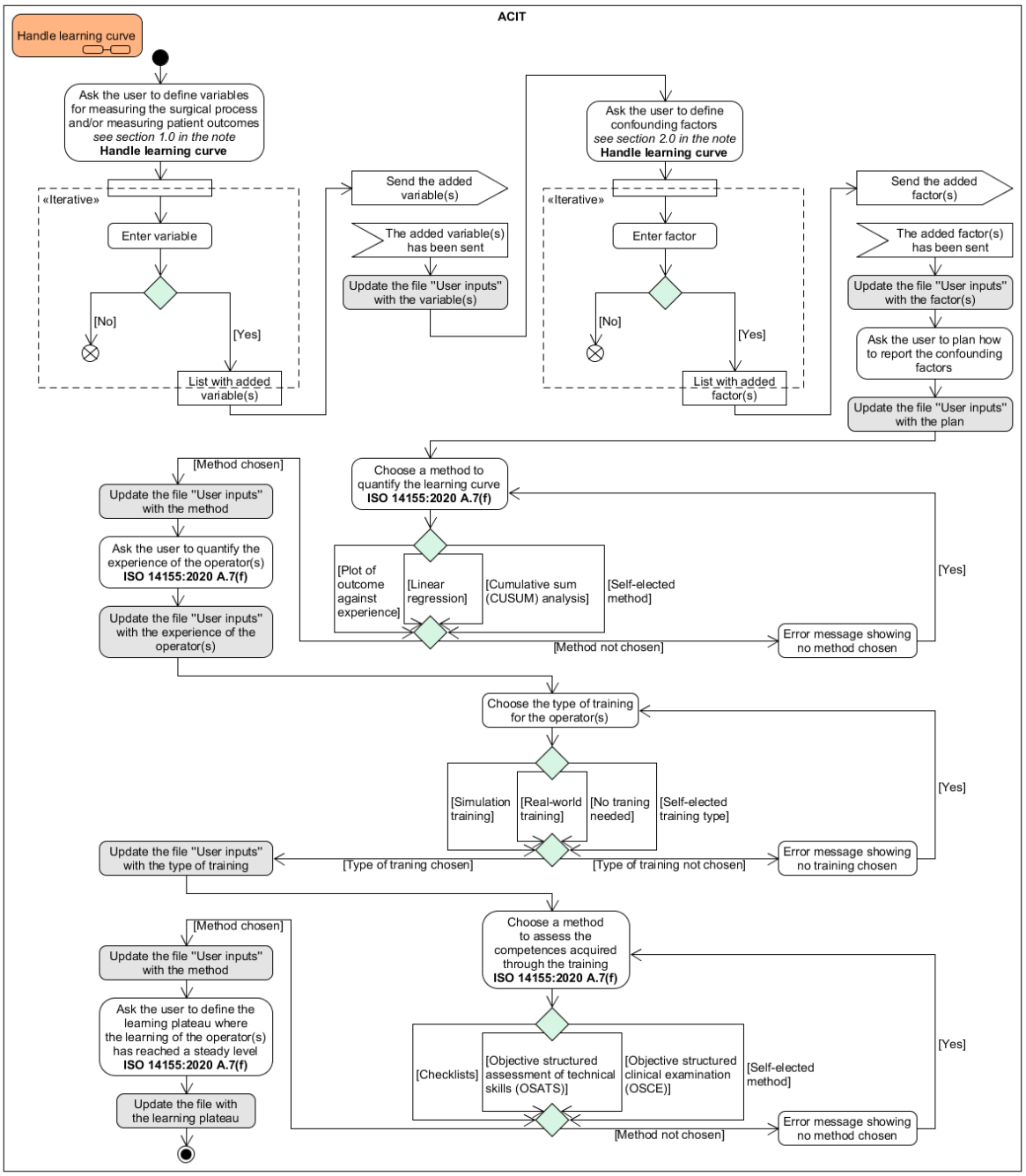

Figure 5.8: Activity diagram for UC6.

[1]See External appendix

The activity diagram for UC7 ”Monitor the clinical investigation” is shown in Figure 5.9. The sources used to prepare this diagram are the MDCG 2024-3 [The Medical Device Coordination Group, 2024], the Clinical Investigation Plan template by Swissethics [2022], the application form for the authorisation for clinical investigations of medical devices by Lægemiddelstyrelsen [2024] and the article by Qserve CRO [2023]. The activity diagram encompasses several elements required in the application of the clinical investigation. First, the monitor must be appointed, and relevant information of the monitor collected. Second, the user must determine whether a DSMC is needed and enter the necessary information based on the decision. The subsequent activities involve data and document management, followed by planning various types of visits and outlining how to report to the competent authority.

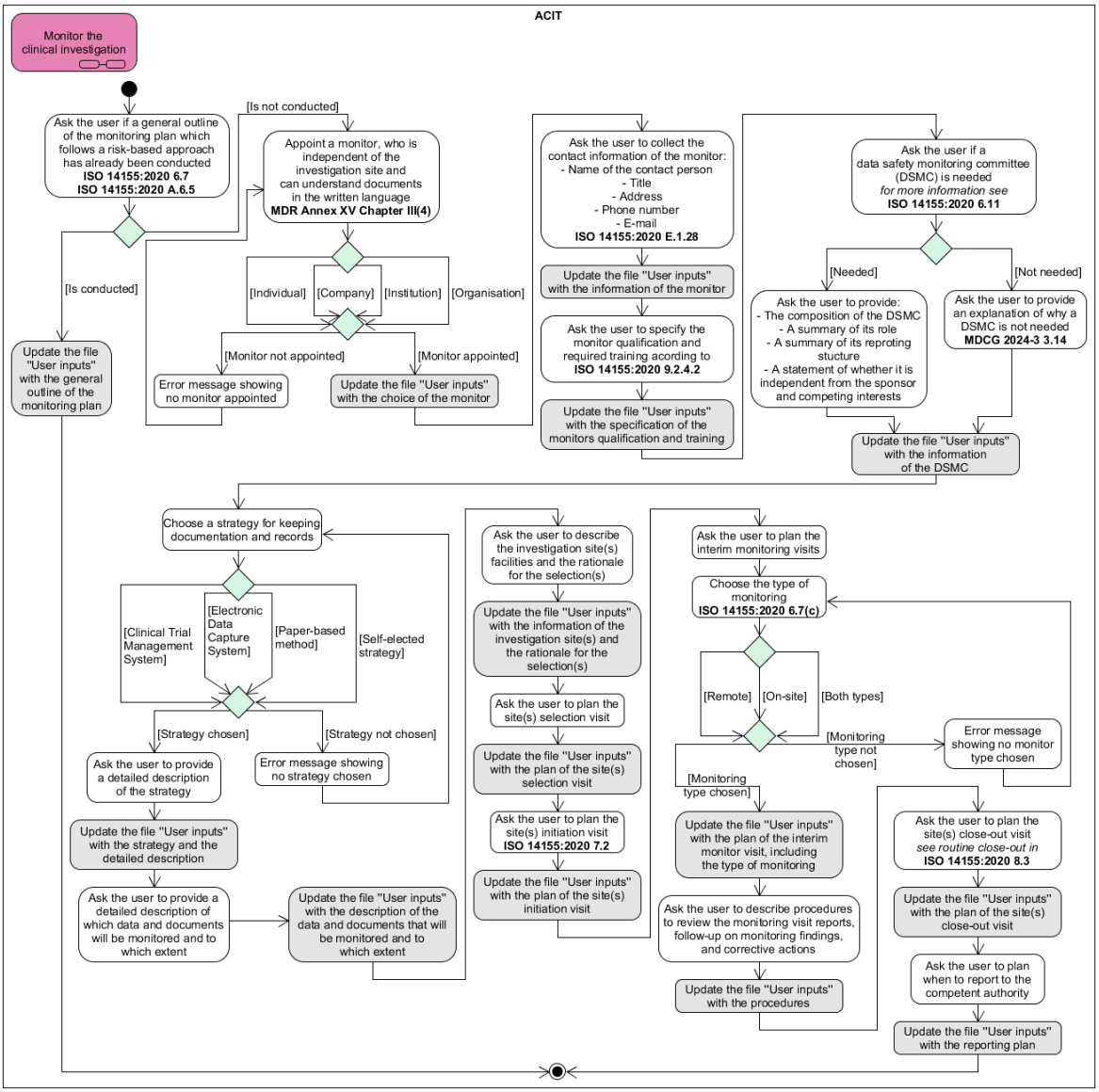

Figure 5.9: Activity diagram for UC7.

The activity diagram for UC8 ”Handle device changes” is shown in Figure 5.10. The sources used to prepare this diagram are the MDCG 2021-6 revision 1 [The Medical Device Coordination Group, 2023], the MDCG 2020-1 [The Medical Device Coordination Group, 2020a], and the articles by Haute Authorité de Santé [2021] and Neugebauer et al. [2017]. The activity diagram outlines various methods for determining the timing of assessment of the medical device for a clinical investigation. Only one method can be applied. The methods are prioritised as follows: first, follow the IDEAL-D Framework and Recommendations; second, change the trial design to a tracker trial design; and third, follow recommendations from the expert panel. Additionally, the diagram includes the activity ”Record a device change” which is meant to serve as an image for the user. This image is useful to the user when an actual change in the device occurs during the clinical investigation, as it depicts the procedure and provides references to relevant guidance documents.

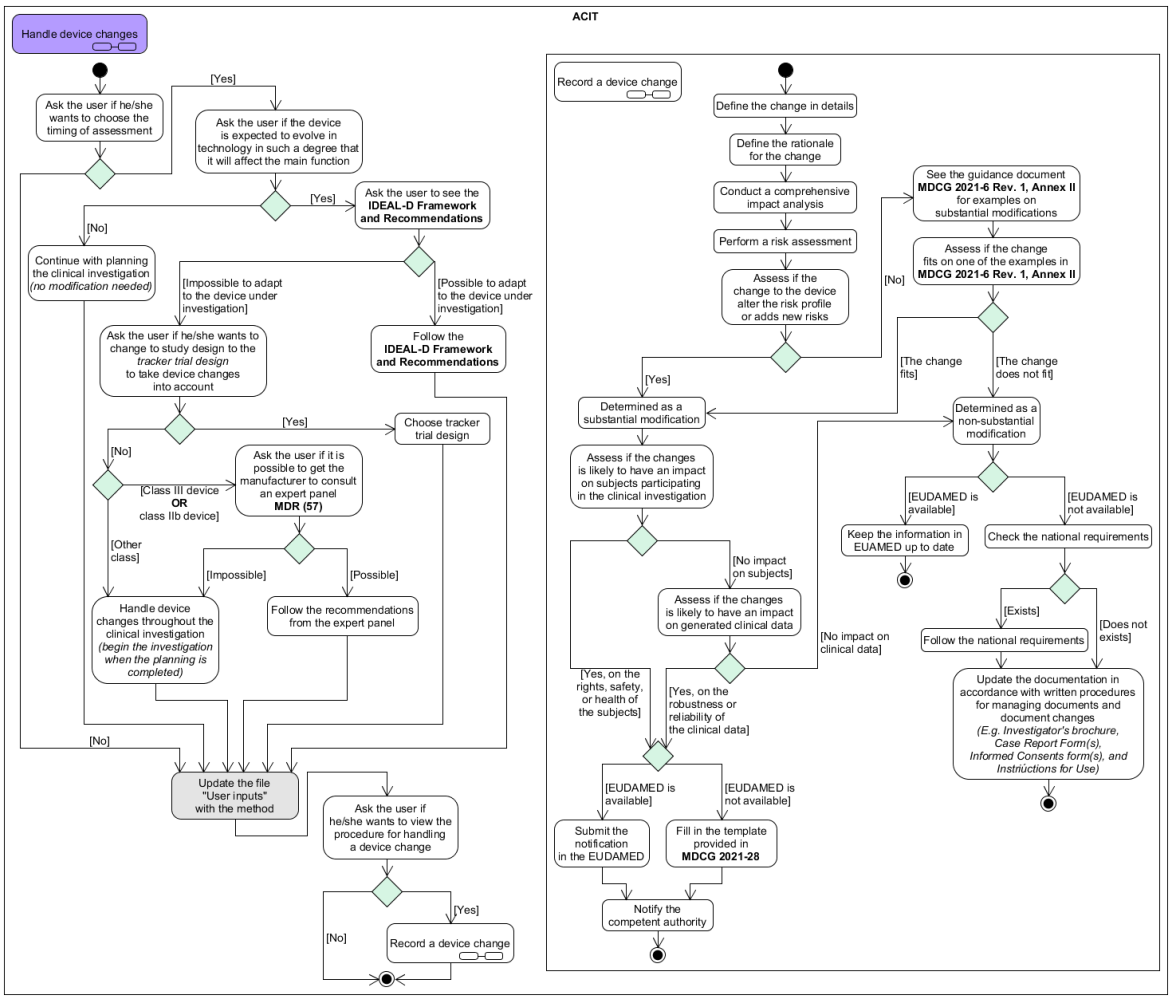

Figure 5.10: Activity diagram for UC8.

The activity diagram for UC9 ”Handle adverse events” is shown in Figure 5.11. The MDCG 2020-10/1 [The Medical Device Coordination Group, 2020b] is applied to prepare this activity diagram. The diagram outlines several of the elements involved in a strategy for handling adverse events. First, the user needs to define how the record the events. Second, the user must define how information about the events will be communicated to the investigator(s) and the subjects in the trial. Third, the reporting format must be determined. Lastly, the diagram

includes the activity ”Register when a reportable event occurred” which is meant to serve as an image for the user. This image is useful to the user during the clinical investigation as it illustrates the required information that needs to be reported and all the important deadlines. Furthermore, the image includes references to relevant guidance documents, an article in the MDR and an annex in the ISO 14155:2020.

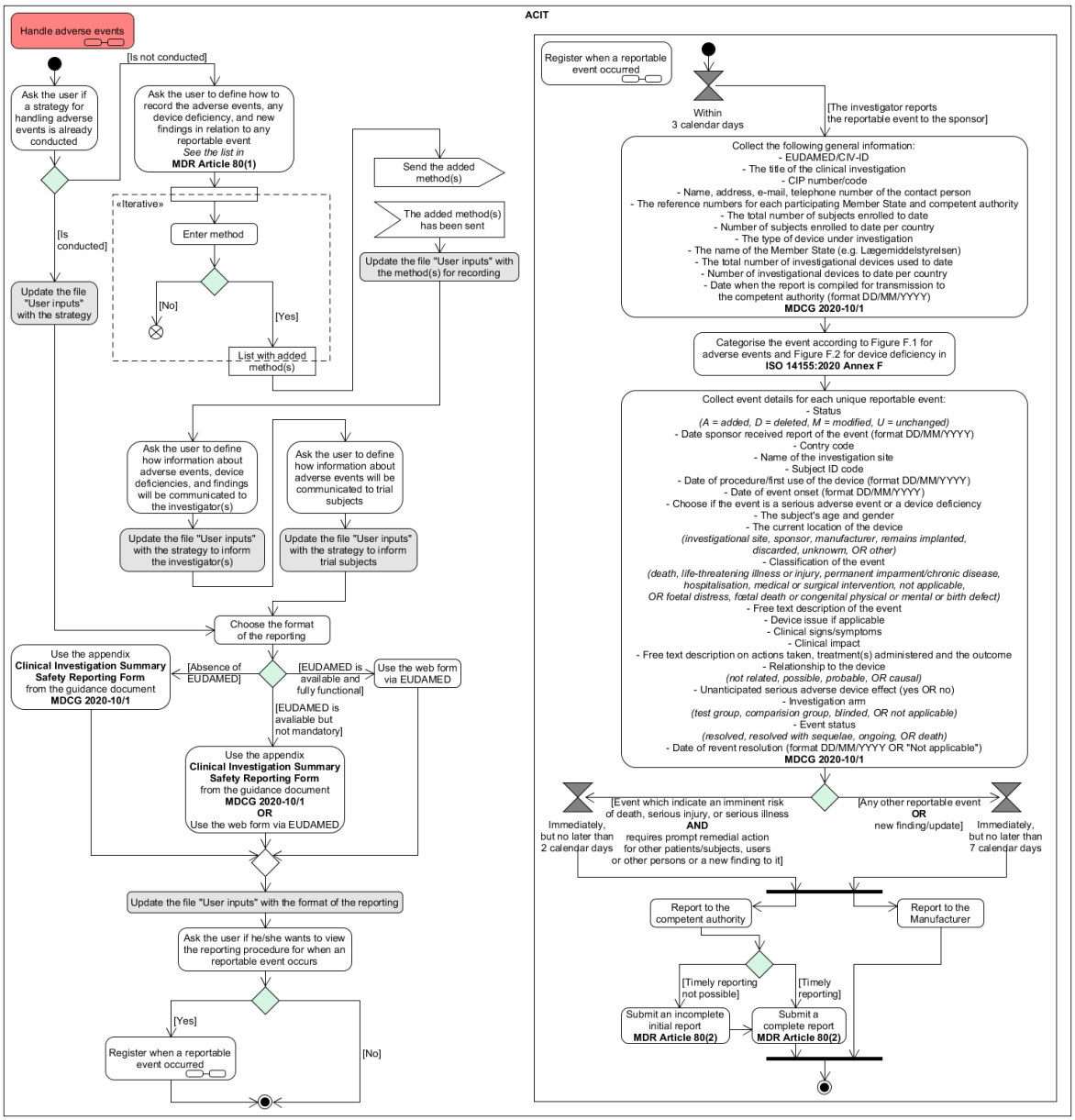

Figure 5.11: Activity diagram for UC9.

5.6 Functional Requirements

Based on the description of the aim and functionality, the use case diagram, the use case descriptions, and the activity diagrams, the must have functional requirements for ACIT are formulated. These requirements are listed in Table 5.11.

Table 5.11: Functional requirements for ACIT.

ID	Functional requirement
FR-1	ACIT must create an electronic file called ”User inputs” for storing inputs given by the user.
FR-2	ACIT must update the file ”User inputs” every time the user has provided an input.
FR-3	ACIT must have a user interface serving as a dynamic questionnaire which follows a flow path depended on the inputs provided by the user. The interface must enable the user to write free text and choose a predefined option, depending on the question.
FR-4	ACIT must generate the file ”Clinical Investigation Planning draft” and make this available to the user. This is a document that contains questions from the ACIT questionnaire along with corresponding answers. The document only contains the questions and answers relevant to the flow path the user has completed.
FR-5	ACIT must receive the risk class, intended purpose, and claimed clinical benefit(s) for the device under investigation, and must only allow the user to design the clinical investigation if they are received.
FR-6	ACIT must follow the flow to design the clinical investigation: 1. Create the file ”User inputs” 2. The user enters the risk class, intended purpose, and claimed clinical benefits for the medical device under investigation 3. Determine endpoints 4. Determine trial design 5. Calculate sample size 6. Determine duration and follow-up 7. If the trial involves a surgical or interventional technique to be assessed, continue to handle learning curve. If not, continue directly to monitor clinical investigation 8. Handle device changes 9. Handle adverse events 10. Generate the file ”Clinical Investigation Planning draft” using the answers stored in the file ”User inputs”
FR-7	ACIT must assist in the content and formulation of the primary endpoint, the secondary endpoint(s), and, if applicable to the clinical investigation, the composite endpoint(s). If the user has already composed the endpoints, then ACIT must allow the user to enter these endpoints. ACIT must allow the user to rewrite the primary endpoint, the secondary endpoint(s), and the composite endpoint(s).
FR-8	ACIT must list the secondary endpoint(s) and the composite endpoint(s) in individual lists. These lists must be sent to the file ”User inputs”.
FR-9	ACIT must receive the rationale for the selection and measurement of the primary endpoint, the secondary endpoint(s), and, if applicable to the clinical investigation, the composite endpoint(s).
FR-10	ACIT must provide an error message if the primary endpoint, one of the secondary endpoints, and/or one of the composite endpoints is not properly defined. An endpoint is properly defined if it follows the structure WHAT, WHEN and HOW, is clinically relevant, reflects the intended use of the device, is related to safety, performance and/or clinical benefit, and has specific and measurable acceptance criteria. The primary endpoint must be the most important endpoint to the device.

Continued on next page

FR-11	ACIT must ask the user whether it is possible to have a control group and whether blinding of the control group is possible.
FR-12	If the user has chosen to have a control group in the clinical investigation, ACIT must assist in the determination of the comparator(s) for the control group. The comparator(s) can be one or more of the following options: Optimal medical therapy, blinding of device or procedure, surgical therapy, and active comparator.
FR-13	ACIT must provide applicable trial designs for the clinical investigation by asking the user questions related to the trial design. The trial design that ACIT must propose first is a randomised double-blind control trial. The remaining trial designs are cluster randomised trial, Zelen's design, expertise-based randomised control trial, cross-over trial, tracker trial design, sequential trials, and adaptive trials. If the target population is very small, one of the following single case experimental design (SCED) studies is applicable: Mixed multiple baseline SCED, multiple baseline SCED across subjects, multiple baseline SCED across contexts/settings, multiple baseline SCED across behaviours, ABAB introduction/withdrawal SCED, and alternating treatment design. If the user has already chosen a trial design, then ACIT must allow the user to enter the trial design. ACIT must allow the user to choose another trial design than the one the user had chosen in advance.
FR-14	ACIT must assist the user in choosing alternative blinding for the primary healthcare professional and/or other study personnel. The user must define whom it involves and how blinding will be achieved. If neither is chosen, ACIT must ask the user if a blind assessment of the primary endpoint is possible. If a blind assessment is possible, the user must define who must conduct the assessment and how blinding will be achieved. If a blind assessment is impossible, ACIT must ask the user to enter the reason(s) for not using blinding.
FR-15	ACIT must define methods to calculate the sample size. The methods are population mean, population proportion, cluster, significance tests, comparison of two means, two proportions, and correlation. All methods are defined in the note: "Calculation of sample size" (reference number ACIT-N-CoSS). This note must be available to the user.
FR-16	ACIT must assist in choosing the level of power and the significance level based on the note: "Calculation of sample size" (reference number ACIT-N-CoSS). If the user does not want to choose one of the recommended values of power and/or significance level from the note, the user can enter a self-elected value. ACIT must provide an error message if the level of power and/or the significance level is not chosen.
FR-17	If the user has already chosen a method for calculating the sample size then ACIT must allow the user to enter the method.
FR-18	ACIT must ask the user to calculate the sample size based on the chosen method and to enter the calculated sample size as a number of subjects.
FR-19	ACIT must ask the user to estimate the expected drop-out rate, and to calculate an adjusted sample size which take the drop-out rate into account. The equation for calculating the adjusted sample size is: Adjusted sample size = Calculated sample size / (1 - drop-out rate)
FR-20	ACIT must assist the user in the duration of the trial. The duration must be provided as a number with one of the following units: days, months, years. If the user has already chosen the duration of the trial, then ACIT must allow the user to enter the duration as a number with one of the following units: days, months, years.

Continued on next page

FR-21	ACIT must assist the user in how to define the criteria and procedures for the follow-up of the subjects. If the user has already chosen the criteria and procedures for the follow-up of the subjects, then ACIT must allow the user to enter these. ACIT must allow the user to rewrite the criteria and procedures.
FR-22	ACIT must list the criteria and procedures for the follow-up of the subjects in a list, which must be sent to the file ”User inputs”.
FR-23	ACIT must enable the user to receive assistance in how to handle the learning curve effect only if a surgical or interventional technique is assessed.
FR-24	ACIT must refer to examples on variables for measuring the surgical process and/or measuring patient outcomes, and confounding factors in the note: ”Handle learning curve” (reference number ACIT-N-HLC). This note must be available to the user.
FR-25	ACIT must list the variables for measuring the learning curve, which includes variables for measuring the surgical process and/or measuring patient outcomes. These variables must be entered in a list, which must be sent to the file ”User inputs”.
FR-26	ACIT must list the confounding factors to the learning curve in a list, which must be sent to the file ”User inputs”.
FR-27	ACIT must provide the following methods to quantify the learning curve: Plot of outcome against experience, linear regression, and cumulative sum analysis. If the user does not want to choose one of the provided methods, the user can enter a self-elected method. ACIT must provide an error message if a method to quantify the learning curve is not chosen.
FR-28	ACIT must provide the following options of the training type for the operator(s): Simulation training, real-world training, and no training needed. If the user does not want to choose one of the provided training types, the user can enter a self-elected training type. ACIT must provide an error message if a type of training is not chosen.
FR-29	ACIT must provide the following methods to assess the competences of the operator(s) acquired through the training: Checklists, objective structured assessment of technical skills, and objective structured clinical examination. If the user does not want to choose one of the provided methods, the user can enter a self-elected method. ACIT must provide an error message if a method is not chosen.
FR-30	ACIT must ask the user to define the learning plateau of the operator(s).
FR-31	ACIT must assist the user in defining activities within the monitoring plan. If the user has already defined a general outline of the monitoring plan, ACIT must allow the user to enter this outline.
FR-32	ACIT must ask the user to appoint a monitor of the clinical investigation and must provide the following options: Individual, company, institution, and organisation. ACIT must provide an error message if no monitor is appointed.
FR-33	ACIT must ask the user to collect contact information of the monitor including name of the contact person, title, address, phone number and e-mail, and to specify the monitor qualification and required training needed before the beginning of the trial.
FR-34	ACIT must ask the user if a data safety monitoring committee (DSMC) is needed. If a DSMC is needed, the user must provide information of the DSMC. If a DSMC is not needed, the user must provide an explanation of why a DSMC is not needed.

Continued on next page

FR-35	ACIT must provide the following strategies for keeping documentation and records: CTMS, EDC system, and paper-based method. If the user does not want to choose one of the provided strategies, the user can enter a self-elected strategy. ACIT must provide an error message if no strategy is chosen. ACIT must ask the user to provide a detailed description of the strategy as well as which data and documents will be monitored and to which extent.
FR-36	ACIT must ask the user to describe the investigation site(s) facilities and the rationale for the selection(s).
FR-37	ACIT must ask the user to plan the site(s) selection visits, the site(s) initiation visit, the interim monitoring visits, the site(s) close-out visit, and the reporting plan to the competent authority.
FR-38	ACIT must provide the following options on the type of monitoring at the interim monitoring visits: Remote, on-site, and both types. ACIT must provide an error message if no monitoring type is chosen.
FR-39	ACIT must ask the user to describe procedures to review the monitoring visit reports, follow-up on monitoring findings, and corrective actions.
FR-40	ACIT must provide the following methods for determining the timing of assessment: follow the IDEAL-D Framework and Recommendations, choose the tracker trial design, and consult an expert panel. If the user does not want to determine the timing of assessment, then ACIT must allow the user to enter the decision.
FR-41	ACIT must enable the user to see an image of the process regarding how to record a change in the medical device under investigation.
FR-42	ACIT must assist the user in defining a strategy for handling adverse events. If the user has already defined a strategy, then ACIT must allow the user to enter the strategy.
FR-43	ACIT must list the methods defining how to record the adverse events, any device deficiency, and any new finding in relation to any reportable event in a list, which must be sent to the file ”User inputs”.
FR-44	ACIT must provide methods to report events depending on the stage of EUDAMED.
FR-45	ACIT must enable the user to see an image of the process regarding how to register a reportable event under the clinical investigation.

In addition to the list with the functional requirements for ACIT, a requirement traceability matrix is conducted with the aim of documenting consistency among the use cases and the functional requirements. The requirement traceability matrix is found in Appendix B.

5.7 Analysis Class Diagrams

Initially, a noun/verb analysis is performed by screening Chapter 5 for relevant nouns and verbs related to ACIT. The analysis forms the basis for the analysis class diagram. The result of the noun/verb analysis is arbitrary listed in Table 5.12.

Table 5.12: Noun/verb analysis. The words marked in bold are the relationships and classes used in the analysis class diagram.

Nouns			**Verbs**	
Sponsor	**User**	**Clinical investigation**	Ask	Must
MDR 2017/745	**Note**	File	Show	Allow
MDCG 2020-1	Application	Requirement	**Apply**	Provide
MDCG 2020-6	Risk class	Intended purpose	Advise	Determine
MDCG 2024-3	**Endpoint(s)**	Clinical benefit(s)	Report	Handle
MDCG 2020-10	**Trial design**	**Sample size**	Create	Conducting
Commission Guidance	Criteria	**Duration**	**Generate**	Receive
ISO 14155:2020	Procedures	Subjects	Assist	**Update**
Learning curve	Technique	Manufacturer	Define	Save
Competent authority	**Input**	Substantiation	Enable	Calculate
Rationale	**Monitor**	Qualification	Monitor	Register
Training	Information	**DSMC**	Choose	Rewrite
Site	Visit	Strategy	Display	Appoint
Adverse event	Finding	Device deficiencies	Collect	Specify
Medical device	Decision	**Device change**	**Plan**	Describe
Challenges	Image	Comparator	Record	Inform
Control group	Equation	Drop-out rate		
Description	**Draft**	**Follow-up**		
Operator				

The analysis class diagram illustrates the relationships between classes which forms the basis of the structure of the system [Scott, 2002, p. 45]. Three analysis class diagrams are developed to illustrate the classes and relationships within ACIT at varying levels of detail. Figure 5.12 depicts the first version of the analysis class diagram, offering a simple overview. Some classes and relationships are elucidated below. The unidirectional association labelled ”plans” between the class `User` and the class `ClinicalInvestigation`, with the specified multiplicity, signifies that one to many user(s) plans one to many clinical investigation(s). The composition relationship between the class `ClinicalInvestigation` and the class `MedicalDevice`, with the specified multiplicity, indicates that one to many clinical investigation(s) cannot exist without a medical device.

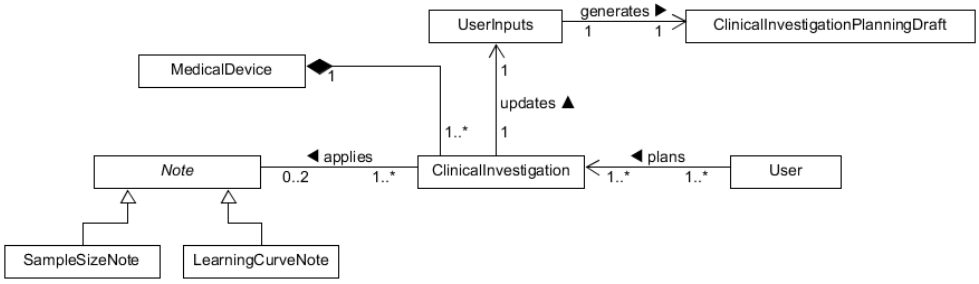

Figure 5.12: Analysis class diagram for ACIT version 1.

In Figure 5.13, the analysis class diagram is detailed with attributes to each class. The abstract class `Note` is a generalisation of the non-abstract classes `SampleSizeNote` and `LearningCurveNote`, which both inherit the attributes of the abstract class `Note`. These two classes include one attribute which is the note document.

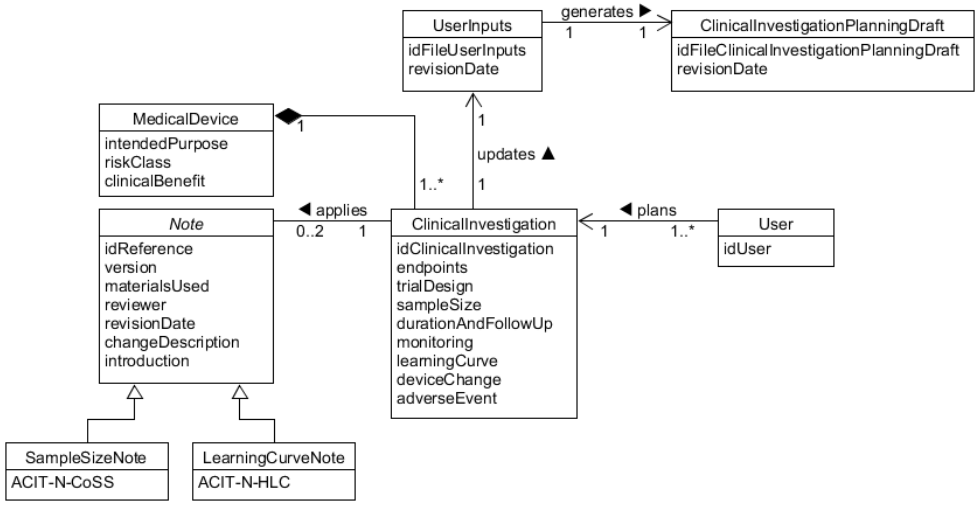

Figure 5.13: Analysis class diagram for ACIT version 2.

In the third and most detailed version of the analysis class diagram, depicted in Figure 5.14, attributes two to nine of the class `ClinicalInvestigation` are represented as eight separate classes with individual attributes. Conversely, the first attribute to the class `ClinicalInvestigation`, ”idClinicalInvestigation”, is a primitive type, meaning it contains only a single value. The classes `Operator`, `Monitor`, and `DataSafetyMonitoringCommittee` are created, as they represents a person or committee needed in the clinical investigation.

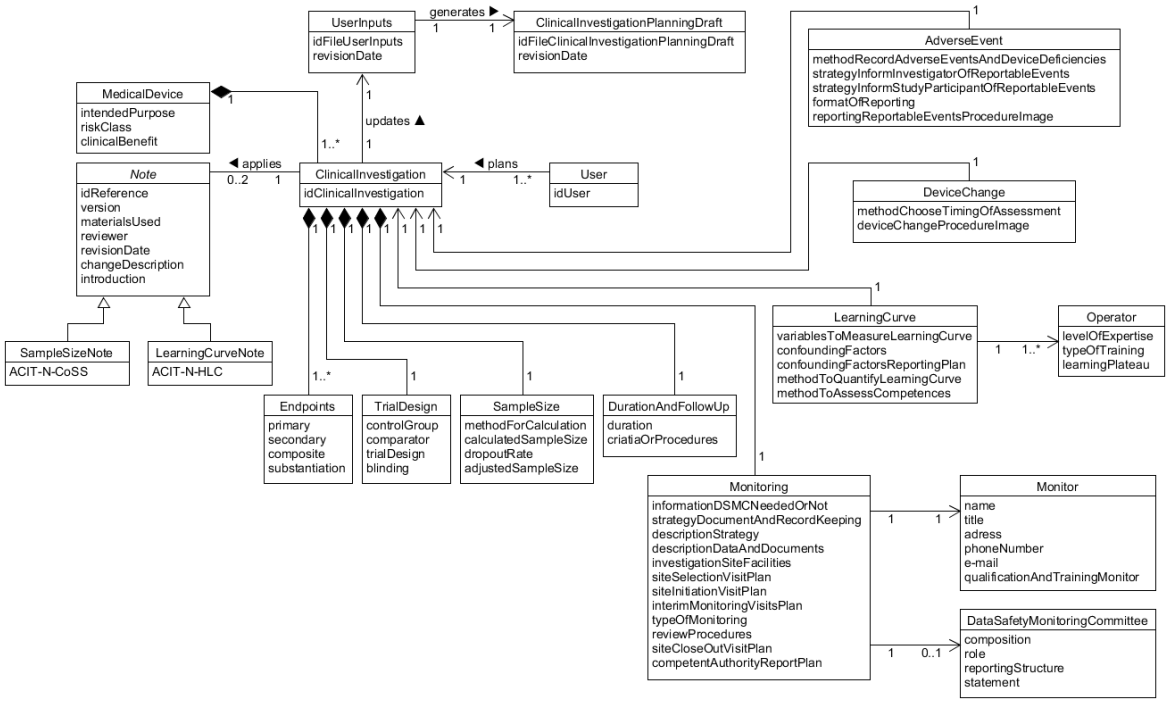

Figure 5.14: Analysis class diagram for ACIT version 3.

6 Discussion

6.1 Identified Challenges Addressed by ACIT

An initial analytical basis for the DSS ACIT is made, which, besides planning of the monitoring and handling adverse events, centres around addressing the challenges with clinical trials of medical devices listed in Section 2.2. The analysis shows that the following 11 challenges can be addressed by ACIT: defining endpoints (1), regulatory compliance (2), selecting control group (4), blinding and use of comparator (5), handling device changes (6), calculating sample size (7), long term follow-up (9), high cost and time-consuming (10), randomisation (11), expertise and learning curve (13), and collection of sufficient high-quality data (14). Some challenges are addressed in more detail than others. Each challenge is not necessarily addressed adequately, but a direction has been set for how the challenges can be addressed.

ACIT addresses the challenges by asking the sponsor targeted questions. It is deemed easier to relate to questions, rather than reviewing the legislation and guidance documents from beginning to end to identify relevant material, which aid the use of ACIT. The questions that ACIT asks are general as they must apply to all types of medical devices. It can thus be debated whether the generic formulation constitutes obstacles which results in a way too vague review of planning a clinical investigation and handling associated challenges. Some questions are closely related to the MDR and ISO 14155:2020, such as those in UC1 ”Determine endpoints” which involves several specific requirements of what the endpoints must contain. Some challenges can be addressed so concretely that ACIT can assist in specific options for methods, variables, and factors, as seen in UC6 ”Handle learning curve”. Other challenges, such as those in UC5 ”Determine duration and follow-up”, are more vaguely addressed by ACIT since these challenges are highly influenced by the medical device under investigation. In these cases, ACIT encourages the sponsor to consider what must be taking into account, serving as a starting point for initiating reflections.

The challenge regarding regulatory compliance is addressed by providing references to the requirements in the MDR and ISO 14155:2020. When sponsors use ACIT, it may help alleviate challenges related to interpreting legislation involving a clinical investigation, potentially saving both time and money during the planning phase. Ideally, by using ACIT early in the planning phase, the content within the clinical investigation application could be of sufficient quality to achieve a quick approval, as sponsors would have received guidance on challenging aspects. Furthermore, the time used for planning the trial may be reduced, as using ACIT early in the process provides a foundation for the further planning activities. The challenge regarding obtaining sufficient high-quality data is multifaceted, depending on factors such as trial methodology, including the use of blinding, randomisation, sample size, and endpoint definition, all which ACIT provides assistance with. The adequacy of clinical data required varies depending on the specific medical device, its characteristic, risk class, and the amount and severity of the potential risks. In order to obtain sufficient high-quality data incorporating other sources of clinical data into the clinical evaluation may be necessary to enhance the level of clinical evidence, why ACIT can only address the challenge in part.

6.1.1 Identified Challenges ACIT does not Address

Three of the 14 identified challenges are not address by the use of ACIT. The first unaddressed challenge is challenge number 3, concerning subject identification, recruitment, and retention. Subject identification depends on how well-defined the intended use is written by the manufacturer, as the intended target group should be evident from this. The difficulty in subject recruitment lies in getting enough subjects to accept participating in the trial within the allocated time frame. Retaining subjects is challenging as it depend on several factors including their motivation, the arm of the trial they are assign to, the amount of time and energy required, and whether they understand the aim of and how to use the device. Furthermore, they have the right to withdraw their consent and leave the trial at any time. Thus, it is assessed that ACIT cannot assist in any of these three aspects within challenge number 3.

Challenge number 8, regarding real-world applicability, is a broad aspect that is difficult to assist in, as it depends on various factors. To some extent, ACIT assists sponsors to consider certain aspects, such as the skill of the operators. However, not matter what, a clinical trial will almost always in some degree differ from real-world usage. Perhaps ACIT could ask the sponsor to contemplate initiatives on how to design the trial to resemble real-world scenarios more closely. However, these initiatives are very case-specific and depend on several factors, including available locations and the knowledge of the trial personnel, which may differ from the knowledge and competences of those who will use the medical device in real-world cases.

The last challenge that ACIT does not address is challenge number 12, concerning cases where a medical device cannot be evaluated alone. ACIT briefly assess the cases of surgical interventions, but the question is if that is adequately. The challenge is complex as it depends on the specific device. However, ACIT could be further developed to offer some guidance that may reduce the challenge or simply draw attention to the potential issue, thereby enhancing the applicability of the results obtained from the clinical investigation. This increased awareness will potentially trigger reflections on how to evaluate the device and enable the sponsor to address the challenge.

6.2 Advantages and Limitations of ACIT

The two developed notes, which ACIT refers to, can serve as helpful tools to enhance support for sponsors. Nevertheless, these notes are not comprehensive and needs to be further elaborated. The extent of this refinement should be evaluated in collaboration with intended users of ACIT. Moreover, it is essential to assess whether these notes provide value to the intended users and determine if additional notes need to be developed, and if so, what specific content is needed.

Relying solely on the MDR, ISO 14155:2020, and guidance documents pertaining to clinical investigations is insufficient for making the knowledge base of ACIT, as these sources did not provide concrete examples or guidance on specific design choices. Consequently, a range of articles, books, and frameworks for the clinical investigation application form were consulted to develop the use cases and activity diagrams. This raises questions about ACIT's conformity with the legislation. It is therefore necessary to carry out quality assurance. If possible, consulting a conformity authority with the aim of verifying that ACIT comply with the legislation shall be done.

Cardiovascular devices are often high-risk class devices and thus they must undergo a clinical

investigation. Zannad et al. [2014] states that no universal trial design applicable to all cardiovascular devices exist, as variables such as the type of trial, target population, and suitable comparator, if any, can all influence the design of a clinical investigation. This underscores the utility of ACIT, as it allows sponsors to choose from a range of different design options and thereby tailor the design of the clinical investigation to the specific circumstances. ACIT is intended to be applicable for planning of any clinical investigation involving a medical device, regardless of the type and risk class of the device. However, it is difficult to assess whether it is realistic at the current time. To assess which type of medical devices ACIT can provide assistance to, a comprehensive analysis of existing medical devices, their functionalities, and the methodologies employed in their clinical investigations can to be made. This analysis can offer insights into how ACIT may be adapted to accommodate as many devices as possible. However, given the rapid pace of innovation in the MedTech industry, with new devices and assessment methods frequently emerging, ACIT must undergo continuous updates to remain current with evolving knowledge.

Developing ACIT as a DSS is advantageous due to the complexity of planning a clinical investigation, which requires consideration of various aspects of trial design to obtain the right kind of clinical data with a high level of evidence which the manufacturer can use in the clinical evaluation. According to [Burstein and Holsapple, 2008, p. 180], a DSS of the type of a rule-based expert system offers benefits by emulating human expertise. Especially since sponsors must act as experts themselves, they may find some support and reassurance in using ACIT in the initial design phases of a clinical investigation. An additional benefit provided by [Burstein and Holsapple, 2008, p. 180], is the fact that an expert system is always accessible to the user. However, a drawback of expert systems is that the knowledge base must be updated when new knowledge becomes available [Berner, 2016, p. 32]. This knowledge can consist of changes in legislation such as the ISO 14155:2020, which is currently under development to a new version, or the release of new guidance documents.

It is interesting to investigate if and how the pre-analysis can be used elsewhere. Although the pre-analysis is not an integrated part of ACIT, it may still provide value in addressing the challenge of regulatory compliance by presenting a way of illustrating the process of a clinical investigation. It would be interesting to explore whether the pre-analysis can be applied as a standalone tool in the form of a flowchart which can be used by sponsors and competent authorities in the EU. Similarly, this concept could be extended to the ”Record a device change” activity in the activity diagram for UC8 and the ”Register when a reportable event occurred” activity in the activity diagram for UC9.

6.3 Future Work

An initiative to make ACIT more supportive to sponsors in decision-making actions could be to increase the level of the provided information. A interface could, beyond presenting the questions, feature an in-depth descriptions and explanation of advantages, disadvantages, and relevant considerations in relation to the question. To achieve a more complete system, ACIT could be expanded to assist in all parts within planning of a clinical investigation, and not just the challenging parts identified from the literature search along with planning of the monitoring and handling adverse events. This expansion could include assistance on subject selection, handling insurance, and handling the informed consent process. However, there is a risk of making ACIT

redundant if it assists with tasks the sponsor is already familiar with and has expertise in. The aim is to find an appropriate balance in how much ACIT shall assist in decision-making in a way that it will provide most value to the sponsor. ACIT should allow sponsors to leverage their existing knowledge and to make independent decisions. Therefore, some part of the flow in ACIT include options for self-elected values or entering pre-defined strategies, ensuring that sponsors remain responsible for selecting the most appropriate design choices based on the guidance provided by ACIT without being completely limited to the predefined options.

A path for the further development of ACIT is integration with existing systems. Integrating ACIT into a CTMS, which sponsors already commonly use, could be a logical next step. CTMS is typically utilised from the enrolment of the first subject, offering functionalities such as managing trial data, calendar planning, and ensuring that all information on e.g. sites, trial personnel, and subjects are updated. However, a CTMS does not address how to design the clinical investigation and do not provide assistance in the form of decision support during the planning phase. By integrating ACIT into a CTMS, sponsors would have all the necessary tools assembled at one place, which simplifies the process of planning and conducting a clinical investigation.

If not integrated with a CTMS, ACIT could instead be modified to create or update existing relevant documents within the clinical investigation directly rather than storing all the information in the file ”Clinical Investigation Planning draft”. The file serves more as a note rather than a formal document that could be directly applied in the clinical investigation application. If this approach is followed, the efficiency and effectiveness of ACIT could be enhanced.

Currently, as intended users of ACIT, i.e. sponsors, are not engaged in the development process, it is uncertain whether all user requirements have been obtained. Therefore, involving intended users in the requirements-gathering phase for ACIT is necessary. Furthermore, one or more competent authorities may contribute to gather further requirements. The process of gathering additional requirements will begin by elucidate the identified problems of clinical trials from the literature and present the initial analytical basis for ACIT and how it relates to the problem domain. Subsequently, the intended users will be asked to provide their inputs on whether ACIT can address the identified problems and how they envision its application in real-world scenarios. There is a chance that the intended users will present more challenges than those already identified through the literature, which then needs to be analysed to assess whether these challenges can be reduced by applying ACIT. After the new requirement analysis has been completed, the V-model can be effectively applied to the development of ACIT, continued with founding on the existing steps in the system design process. The OOA of ACIT facilitates object oriented design and programming, which will be used in the later processes of the system development. To ensure the completion of the system development through all processes of the V-model, it is crucial to establish a development team and perform a clear development and testing strategy as initial steps. To be in line with the V-model, the design of the acceptance testing must be planned first. This will include end-user testing where it is investigated whether the end-user finds that the requirements are accommodated and if the DSS can be accepted. There will be at least one test case for each use case, testing real-world scenarios. The test needs to be performed multiply times for various types of medical devices of different risk classes. The aim and expected result of the tests must be defined, followed by a step-by-step procedure for execution of the test and the criteria for when the test is passed.

7 Conclusion

One of the sources for generating clinical data is conducting a clinical investigation of the medical device under investigation, which is done by the sponsor. Through a literature search, 14 challenges regarding clinical trials of medical devices are identified. These challenges need to be addressed by the sponsor at an early stage of the planning process. Currently, no assisting tool exist that supports sponsors in decisions related to the planning process of a clinical investigation. A decision support system may serve as a tool to sponsors, assisting in the challenging aspects of planning a trial design of a clinical investigation. In this master's thesis, the initial analytical basis for an EU MDR 2017/745 compliant decision support system, ACIT, is developed.

The format of ACIT is a questionnaire, which follows a flow path. ACIT asks questions to the user related to the trial design. The answers along with information from the relevant question are presented in a file, serving as the foundation for filling out documents for the clinical investigation application.

The problem domain that ACIT is to address, is analysed to determine the desired behaviour, requirements, and structure of the decision support system. The analysis results in user requirements, a use case diagram along with use case descriptions, activity diagrams, functional requirements, and analysis class diagrams. This requirement analysis and system design compose the first two processes of the V-model. The results from these processes serve as a stepping stone for the remaining phases including the design, coding, and test phases which is outside the scope of this master's thesis.

By asking questions, ACIT forces the sponsor to be aware of and reflect on the challenges which provides a stronger foundation for designing a clinical investigation. ACIT also provides the sponsor with references to methods and guidance for handling challenges. Of the 14 identified challenges, ACIT is able to address the challenges regarding definition of endpoints, regulatory compliance, selection of control group, blinding and use of comparator, handling device changes, determination of the sample size, long term follow-up, high cost and time-consumption, randomisation, assessment of expertise and learning curve, and collection of sufficient high-quality data. ACIT does not address the challenges regarding identification, recruitment, and retention of subjects; real-world applicability; and cases where a medical device cannot be evaluated alone.

ACIT needs further development, as it is currently in the initial stages of a software system development life cycle with no technical elements developed. ACIT must undergo quality assurance to verify that the content of ACIT complies with the MDR and ISO 14155:2020 prior to further system development. Further development should include considerations from end-users of ACIT in order for ACIT to be a useful decision support system that will be accepted and applied in real-world cases.

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A Literature Search Documentation

This appendix covers the search protocols, the block searches, and the search documentation forms for the two literature searches that forms the basis of the problem analysis. Additionally,the two search strings, one for each research question are presented. Besides, deviations from the two search strategies are described.

Table A.1: Search protocol applied in the first systematic literature search.

First research question	What are the challenges for manufacturers and sponsors with planning and conducting a clinical investigation under MDR for a medical device?
Databases	PubMed, Embase, CINAHL, IEEE Xplore, and Scopus
Search strategy	1) Block search with truncation, phrase searching, and boolean operators (AND, OR) 2) Backward snowballing
Inclusion criteria	- Sources in Danish and English - Sources published from 01/01/2014 to 19/01/2024 - Sources of all kinds of publication types
Exclusion criteria	- No access to full text - Sources that focus on regulations or guidelines outside of the EU - Sources that focus exclusively on paediatrics - Sources with a different focus than a clinical investigation or clinical trial

Table A.2: Search protocol applied in the second systematic literature search.

Second research question	Which, if any, tools can support sponsors in facilitating a clinical investigation in compliance with MDR?
Databases	PubMed, Embase, IEEE Xplore, and Scopus
Search strategy	1) Block search with truncation, phrase searching, and boolean operators (AND, OR) 2) Backward snowballing 3) Search on the internet search engine Google
Inclusion criteria	- Sources in Danish and English - Sources published from 01/01/2014 to 19/01/2024 - Sources of all kinds of publication types
Exclusion criteria	- No access to full text - Sources that focus exclusively on regulations or guidelines outside of the EU - Sources that focus exclusively on paediatrics - Sources with a different focus than a clinical investigation or clinical trial - Sources that do not present a tool or framework

Table A.3: Block search applied in the first systematic literature search.

	AND		
OR	”clinical investigation*”	”medical device regulation*”	challenge*
	”clinical stud*”	”investigational medical device*”	barrier*
	”clinical trial*”	”european medical device regulation*”	problem*
	”systematic investigation*”	”medical device legislation*”	issue*
	”clinical research”	”regulation 2017/745”	effect*
	”research design*”	”EU medical device regulation 2017/745”	difficult*
	”study design*”		consequence*
	”clinical trial design*”		impact*
	”clinical protocol*”		innovation*
	”clinical evaluation*”		implication*
			requirement*
			”regulatory science”

Table A.4: Block search applied in the second systematic literature search.

	AND		
OR	”clinical investigation*”	”medical device regulation*”	”regulatory tool*”
	”clinical stud*”	”investigational medical device*”	”supporting tool*”
	”clinical trial*”	”european medical device regulation*”	”assisting tool*”
	”systematic investigation*”	”medical device legislation*”	”assessment tool*”
	”clinical research”	”regulation 2017/745”	”decision support system*”
	”research design*”	”EU medical device regulation 2017/745”	system*
	”study design*”		guidance*
	”clinical trial design*”		”decision support”
	”clinical protocol*”		”decision making”
	”clinical evaluation*”		protocol*
			framework*

Table A.5: Search documentation form applied in the first systematic literature search in the database PubMed. The search only includes sources published from 01/01/2014 to 19/01/2024.

Search No.	Search term	Hits: 19/02/2024
#1	”clinical investigation*”	13,005
#2	”clinical stud*”	97,544
#3	”clinical trial*”	452,123
#4	”systematic investigation*”	3,981
#5	”clinical research”	221,481
#6	”research design*”	68,859
#7	”study design*”	161,272
#8	”clinical trial design*”	3,746
#9	”clinical protocol*”	12,580

Continued on next page

Search No.	Search term	Hits: 19/02/2024
#10	”clinical evaluation*”	22,517
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	947,108
#12	”medical device regulation*”	295
#13	”investigational medical device*”	15
#14	”european medical device regulation*”	30
#15	”medical device legislation*”	312
#16	”regulation 2017/745”	15
#17	”EU medical device regulation 2017/745”	6
#18	#12 OR #13 OR #14 OR #15 OR #16 OR #17	534
#19	challenge*	620,847
#20	barrier*	268,478
#21	problem*	538,618
#22	issue*	412,876
#23	effect*	4,668,488
#24	difficult*	386,899
#25	consequence*	234,406
#26	impact*	1,152,971
#27	innovation*	416,900
#28	implication*	380,559
#29	requirement*	160,632
#30	”regulatory science”	3,320
#31	#19 OR #20 #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30	6,820,608
#32	#11 AND #18 AND #31	85

Search string applied in the first systematic literature search
(”clinical investigation*” OR ”clinical stud*” OR ”clinical trial*” OR ”systematic investigation*” OR ”clinical research” OR ”research design*” OR ”study design*” OR ”clinical trial design*” OR ”clinical protocol*” OR ”clinical evaluation*”) AND (”medical device regulation*” OR ”investigational medical device*” OR ”european medical device regulation*” OR ”medical device legislation*” OR ”regulation 2017/745” OR ”EU medical device regulation 2017/745”) AND (challenge* OR barrier* OR problem* OR issue* OR effect* OR difficult* OR consequence* OR impact* OR innovation* OR implication* OR requirement* OR ”regulatory science”)

Deviations from the search strategy of the first literature search
In the IEEE Xplore database, only a limited number of search terms can be entered. Therefore, the following search terms are not included: problem*, issue*, and "regulatory science".

The Scopus database yielded 1246 hits, significantly more than the other databases using the same search string. To refine the results, additional criteria were applied. The first criterion involved excluding the following specific subject areas: ”biochemistry, genetics, and molecular biology” and ”pharmacology, toxicology, and pharmaceutics”, resulting in 911 hits, still deemed excessive. A second criterion was applied, requiring the sources to contain the keyword ”medical

device regulation". This resulted in 312 hits, considered an appropriate number, and thus, these sources were included as the final identifications from the Scopus database.

Table A.6: Search documentation form applied in the second systematic literature search in the database PubMed. The search only includes sources published from 01/01/2014 to 19/01/2024.

Search No.	Search term	Hits: 19/02/2024
#1	"clinical investigation*"	13,005
#2	"clinical stud*"	97,544
#3	"clinical trial*"	452,123
#4	"systematic investigation*"	3,981
#5	"clinical research"	221,481
#6	"research design*"	68,859
#7	"study design*"	161,272
#8	"clinical trial design*"	3,746
#9	"clinical protocol*"	12,580
#10	"clinical evaluation*"	22,517
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	947,108
#12	"medical device regulation*"	295
#13	"investigational medical device*"	15
#14	"european medical device regulation*"	30
#15	"medical device legislation*"	312
#16	"regulation 2017/745"	15
#17	"EU medical device regulation 2017/745"	6
#18	#12 OR #13 OR #14 OR #15 OR #16 OR #17	534
#19	"regulatory tool*"	208
#20	"supporting tool*"	301
#21	"assisting tool*"	51
#22	"assessment tool*"	28,999
#23	guidance*	112,559
#24	"decision support"	27,363
#25	"decision making"	167,669
#26	framework*	302,310
#27	#19 OR #20 #21 OR #22 OR #23 OR #24 OR #25 OR #26	599,809
#28	#11 AND #18 AND #27	169

Search string applied in the second systematic literature search

("clinical investigation*" OR "clinical stud*" OR "clinical trial*" OR "systematic investigation*" OR "clinical research" OR "research design*" OR "study design*" OR "clinical trial design*" OR "clinical protocol*" OR "clinical evaluation*") AND ("medical device regulation*" OR "investigational medical device*" OR "european medical device regulation*" OR "medical device legislation*" OR "regulation 2017/745" OR "EU medical device regulation 2017/745") AND

(”regulatory tool*” OR ”supporting tool*” OR ”assisting tool*” OR ”assessment tool*” OR guidance* OR ”decision support” OR ”decision making” OR framework*)

Deviations from the search strategy of the second literature search

The Scopus database yielded 881 hits, significantly more than the other databases using the same search string. To refine the results, additional criteria were applied. The first criterion involved excluding the following specific subject areas: ”biochemistry, genetics, and molecular biology” and ”pharmacology, toxicology, and pharmaceutics”, resulting in 640 hits, still deemed excessive. A second criterion was applied, requiring the sources to be of the type ”Journal”. This resulted in 558 hits, considered an appropriate number, and thus, these sources were included as the final identifications from the Scopus database.

B Requirement Traceability Matrix

Table B.1: Requirement traceability matrix of the relationship between the functional requirements and the use cases.

		Use case								
		UC1	**UC2**	**UC3**	**UC4**	**UC5**	**UC6**	**UC7**	**UC8**	**UC9**
Functional requirement	**FR-1**	X								
	FR-2	X	X	X	X	X	X	X	X	X
	FR-3	X	X	X	X	X	X	X	X	X
	FR-4	X								
	FR-5	X								
	FR-6	X	X	X	X	X	X	X	X	X
	FR-7		X							
	FR-8		X							
	FR-9		X							
	FR-10		X							
	FR-11			X						
	FR-12			X						
	FR-13			X						
	FR-14			X						
	FR-15				X					
	FR-16				X					
	FR-17				X					
	FR-18				X					
	FR-19				X					
	FR-20					X				
	FR-21					X				
	FR-22					X				
	FR-23						X			
	FR-24						X			
	FR-25						X			
	FR-26						X			
	FR-27						X			
	FR-28						X			
	FR-29						X			
	FR-30						X			
	FR-31							X		
	FR-32							X		
	FR-33							X		
	FR-34							X		
	FR-35							X		
	FR-36							X		
	FR-37							X		
	FR-38							X		
	FR-39							X		
	FR-40								X	
	FR-41								X	
	FR-42									X
	FR-43									X
	FR-44									X
	FR-45									X

C Portfolio

Complex, long-term projects involve multiple facets and an increased understanding of the problem of interest is constantly achieved. Consequently, effective planning and learning demand the integration of diverse tools, methods, and reflections.

C.1 Activity Plan and Timetable

Essential components of a long-term project spanning several months is planning and management, given the inherent unpredictability and potential emergence of unforeseen tasks. To ensure that the thesis reaches its overarching goals within the allocated timeframe, an activity plan and timetable is established at the outset of the thesis. A tool for work organisation is a Gantt chart, composed using the software TeamGantt is applied [TeamGantt, 2024]. Moreover, the backcasting method is applied when preparing the Gantt chart since this method contributes to a more realistic timetable. This approach allocates more time for the busy periods, as these are placed earlier. In addition, previous experiences with planning a long-term project are used as a starting point. The Gantt chart is structured in blocks representing specific project phases, as illustrated by the grey bars in Figure C.1, and each block can have one to several subsidiary goals and/or deadlines depicted by yellow rhombus in Figure C.2. Activities are arranged vertically, and time progresses horizontally.

As it appears from the figures, the Gantt chart facilitates parallel execution of multiple tasks.

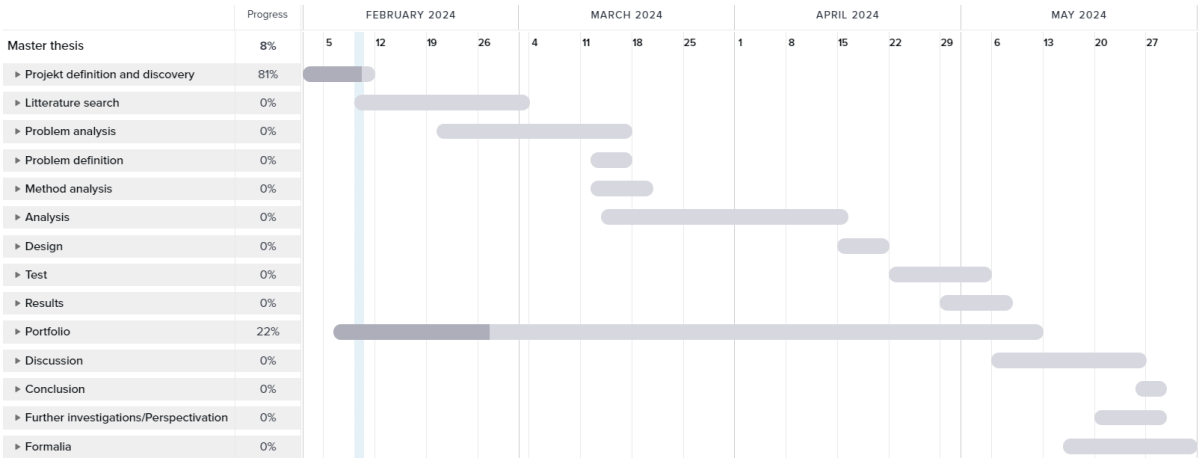

Figure C.1: Overview of the Gantt chart version 1.

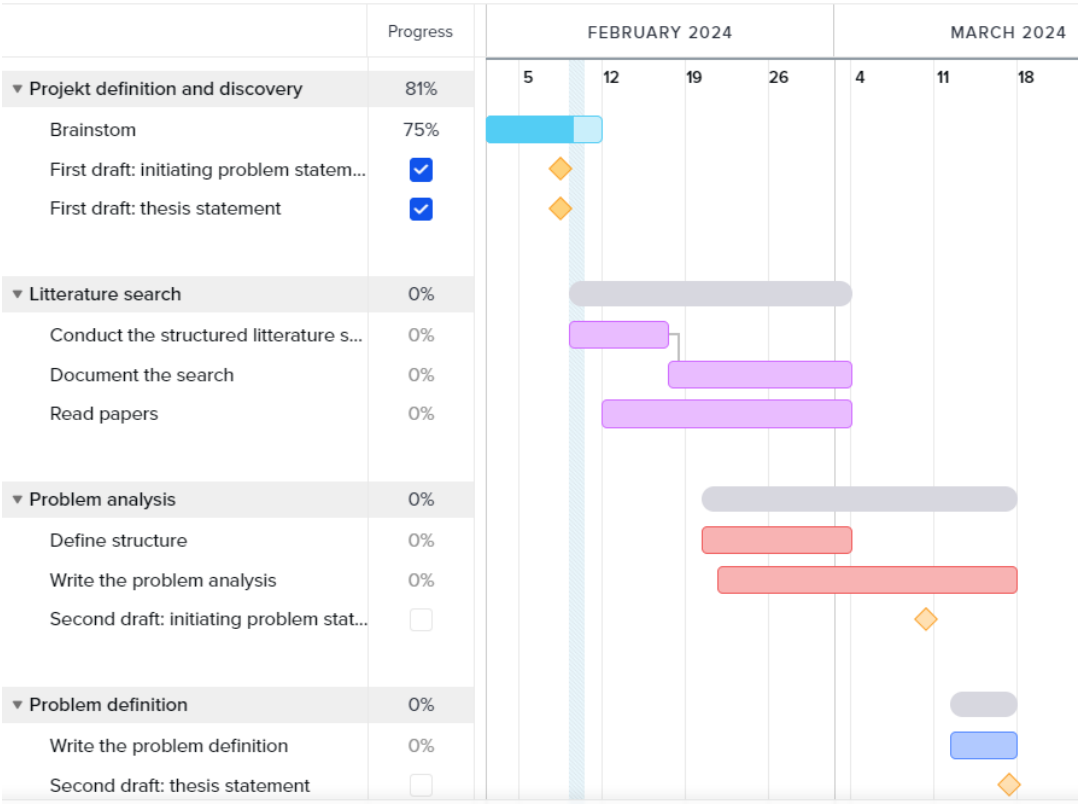

Figure C.2: A segment of the detailed Gantt chart version 1.

The Gantt chart is continuously revised to ensure that the overall goals and subsidiary goals are achieved within the established timeframe. Recognising that an overarching timetable may not suffice, a detailed document with weekly goals is created, functioning as a comprehensive to-do list. This document aids in visualising progress and enhances motivation throughout the thesis.

C.2 Learning Needs and Learning Process

I interpret learning needs as the knowledge and skills I require to successfully complete the thesis. Therefore, from the outset of the thesis, I have aimed to prioritise my own learning needs. I have achieved this by actively reflecting on what I need to learn during the period. Initially, I carefully examined the learning objectives and reflected on how these objectives could be fulfilled. After identifying the requirements and expectations, I further reflected on how I could steer the thesis in a direction that I find interesting, knowing from previous project work that the best results are achieved when motivation and engagement are high. Subsequently, I have framed the learning needs as challenges. Examples of these include: ”How can I critically evaluate sources from a systematic literature search as a sole individual?” and ”How can I make a complex activity diagram reader-friendly for an external person, and how can I convey the diagram in a clear manner?”

A good learning process helps to develop one’s own knowledge, skills, and competences. In this thesis, I am responsible for driving my own learning process. However, I have the opportunity for seeking guidance from my supervisor as well as to spar with fellow students. Understanding that the learning process is cyclical, I have been aware not to become entrenched in old or initial thoughts and ideas. Instead, I have continuously sought out new knowledge to deepen my

understanding of a given topic, revisiting initial idea phases such as brainstorming and freehand drawing. I have frequently jotted down probing questions, which I have then found answers to by either acquiring new knowledge or restructuring my existing knowledge in different ways, such as making a brainstorm or creating connections between various keywords using simple figures and diagrams. An example of this is the analysis phase of the system development of ACIT. While I had some prior knowledge, I needed to search for and acquire additional information before commencing the analysis. Subsequently, I had to comprehend and interpret this new knowledge before drafting various requirements and diagrams. At times, I received critical feedback on certain tasks, enabling me to revisit earlier phases. I have repeated this process several times, where possible, to optimise the system development. Another example where I have focused on the learning process is the textual understanding of sources from the systematic literature search and standards. I have revisited the same texts and standards multiple times, identifying sources I initially considered unimportant. With increased knowledge on the subject, I later recognised these sources as essential. Consequently, I have identified how this knowledge can be applied in the analysis or as part of ACIT. Broadly, the process has involved first seeking and learning, then identifying the need for more information to learn and understand further about a specific topic.

Personally, I enhance my learning by explaining concepts to others or verbalising a topic to myself. By verbalising my knowledge, I quickly identify gaps that need further investigation, thus acquiring new knowledge. I have particularly focused on this aspect as I write the thesis alone and therefore must perform all work processes and make all decisions primarily based on my own inputs. I have attempted to convey the essence of this thesis to various individuals, such as family members or peers from study activities studying different subjects, as well as fellow students from the same field of study, for example, through an activity such as status seminar. By being able to communicate to different target groups with different levels of knowledge within the subject, I learn to communicate scientific work on health technology problems and solutions.