TALLINN UNIVERSITY OF TECHNOLOGY
Faculty of Information Technology

Sille Kima 153403YVEM

UPDATE OF THE EUROPEAN UNION REQUIREMENTS FOR CLINICAL EVALUATION OF MEDICAL DEVICES: PROCESS MAPPING ON THE EXAMPLE OF FETAL HEART RATE MONITORING SOFTWARE

Masters thesis

Supervisor: Martin Daumer
Prof. Dr. rer. nat.
Dipl. Phys

Co-supervisor: Peeter Ross
MD PhD

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TALLINNA TEHNIKAÜLIKOOL
Infotehnoloogia teaduskond

Sille Kima 153403YVEM

MUUDATUSED EUROOPA LIIDU NÕUETES MEDITSIINISEADMETE KLIINILISE HINDAMISE OSAS: PROTSESSI KAARDISTAMINE LOOTE SÜDAME LÖÖGISAGEDUSE SEIRETARKVARA NÄITEL

Magistritöö

Juhendaja: Martin Daumer
Prof. Dr. rer. nat.
Dipl. Phys

Kaasjuhendaja: Peeter Ross
MD PhD

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Author’s declaration of originality

I hereby certify that I am the sole author of this thesis. All the used materials, references to the literature and the work of others have been referred to. This thesis has not been presented for examination anywhere else.

Author: Sille Kima

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Abstract

The recent and upcoming changes of the EU medical device policy regarding clinical evaluation of medical devices have stirred confusion and increased the amount of resources needed for compliance with the requirements, while the EU medical technology industry comprises mainly of small and medium sized enterprises that have less financial flexibility for coping with the changes than bigger companies.

The comparison of the current (revision 4) and previous (revision 4) versions of the MEDDEV 2.7/1 guidelines revealed multiple major changes in the content, structure and format of the guideline. The future EU Medical Device Regulation (MDR) further adds upon the requirements of the clinical evaluation.

The process of conducting the clinical evaluation in accordance with the current version of MEDDEV 2.7/1 (revision 4) guidelines was mapped using the flowchart method, but as the process presented in the guidelines is generic, its use is limited in real-life situations. Consequently, a case study-based clinical evaluation report-oriented process map was drafted, also adding relevant requirements from the MDR. It is based on the needs of a small medical device manufacturer specializing on fetal heart rate monitoring software. This case specific process map has, in addition, received feedback by in-depth semi-structured interviews with members of the device manufacturer's clinical evaluation team and an expert of the field.

The generic and the specific process are meant to improve the understanding of MEDDEV 2.7/1 revision 4 (which describes the clinical evaluation process in a prosaic form) and thus lower implementation barriers and simplify the process of conducting a clinical evaluation. The usability of the proposed clinical evaluation report-oriented approach and the process map need to be tested and refined by further research.

This thesis is written in English and is 64 pages long, including 6 chapters, 12 figures and 1 table.

Annotatsioon

Muudatused Euroopa Liidu nõuetes meditsiiniseadmete kliinilise hindamise osas: protsessi kaardistamine loote südame löögisageduse seiretarkvara näitel

Hiljutised ja tulevased muudatused ELi nõuetes meditsiiniseadmete kliinilise hindamise osas on tekitanud segadust ja suurendanud nõuetele vastamiseks vajalike ressursside mahtu, samas kui ELi meditsiinitehnoloogia tööstus koosneb peamiselt väikese ja keskmise suurusega ettevõtjatest, kelle rahalised vahendid muudatustega toimetulekuks võrreldes suuremate ettevõtetega on piiratud.

MEDDEV 2.7 / 1 suuniste praeguse (version 4) ja eelmise versiooni (versioon 3) võrdluses ilmnes suuri muutusi juhiste sisus, struktuuris ja vormingus. Lisaks muudab kliinilise hindamise nõudeid tulevane ELi meditsiiniseadmete määrus.

Universaalne protsess kliinilise hindamise läbiviimiseks vastavalt MEDDEV 2.7/1 suuniste praegu kehtivale versioonile kaardistati voogdiagrammi meetodil, kuid kuna suunistes esitatud protsess on üldine, on selle kasutamine elulistes olukordades piiratud. Sellest tulenevalt koostati juhtumianalüüsil põhinev kliinilise hindamise aruandele orienteeritud protsessi kaart, mis põhineb loote südame löögisageduse seiretarkvarale spetsialiseerunud väikese meditsiiniseadme tootja vajadustel. Kaardi koostamisel arvestati ka meditsiiniseadmete määruse asjakohaseid nõudeid. Lähenemisviisi ja juhtumipõhise protsessikaardi kasutatavuse hindamiseks kasutati poolstruktureeritud intervjuusid seadme tootja kliinilise hindamise meeskonna liikmetega. Täiendavalt andis lähenemisviisile tagasisidet valdkonna ekspert.

Nii üldise kui juhtumipõhise protsessi kaardistamise eesmärgiks on lihtsustada MEDDEV 2.7/1 4. versiooni (mis kirjeldab kliinilise hindamise protsessi proosalises vormis) nõuete mõistmist ja seega vähendada rakendusbarjääre ja lihtsustada kliinilise hindamise läbiviimist. Pakutud kliinilise hindamise aruandele orienteeritud lähenemisviisi ja protsessikaardi kasutatavust tuleb täiendavalt uurida ja täiustada.

Lõputöö on kirjutatud inglise keeles ning sisaldab teksti 64 leheküljel, 6 peatükki, 12 joonist ning 1 tabelit.

List of abbreviations and terms

MDM	Medical Device Manufacturer
NB	Notified Body
TUT	Tallinn University of Technology
EU	European Union
EC	European Commission
MDR	Medical Device Regulation
GHTF	Global Harmonization Task Force
IMDRF	International Medical Device Regulators Forum
MDEG	Medical Device Expert Group
UDI	Unique Device Identification
ER	Essential Requirement
SME	Small and Medium sized Enterprises
TOC	Table of Contents
PMS	Post Market Surveillance
PMCF	Post Market Clinical Follow-up
PSUR	Periodic Safety Update Report
CTG	cardiotocography
SOP	Standard Operating Procedure
FIGO	International Federation of Gynaecology and Obstetrics
MHRA	Medicines and Healthcare Products Regulatory Agency (UK)
MoM	Metal-on-Metal (hip implants)
PIP	Poly Implant Prothèse
CE	Clinical Evaluation
CER	Clinical Evaluation Report
IFU	Instructions for Use
PSUR	Periodic Safety Update Report

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1 INTRODUCTION

This chapter gives an insight into the current changes in the European Union framework for medical device regulation, specifically in the context of the clinical evaluation. Firstly, an overview of medical device regulatory environment in the EU is given and put into the global context. Subsequently, an overview of MEDDEV 2.7/1 revision 4 - the current version of the European Union guidelines for medical device manufacturers on conducting a clinical evaluation - is presented. Finally, the implications of the changes in the regulatory framework are discussed from the perspective of the medical device manufacturers on the European Union market.

1.1 Overview of the medical device regulatory environment

1.1.1 Medical device regulatory environment in the EU

The regulatory environment for medical devices in the European Union (EU) is currently in the midst of great changes. The policy currently in force, divided in three separate directives and accompanied by a framework of implementation guides known under the common denominator MEDDEV, date back to 1991 when the EU Commission first proposed a framework for harmonization of medical device management in the EU, followed by acceptance of three directives governing the medical device field in 1993 [7]. Before that, a consolidated legislation regarding medicinal products covered only pharmaceuticals, adopted in 1965 after the thalidomide crisis [6]. The directives were updated to meet the needs of the changing field in 2007 and scheduled to undergo another amendment in 2012 [8]. However, in 2010 a French company producing silicone breast implants - Poly Implant Prothèse (PIP) - was found to be using silicone not conforming to the type specified in the design and manufacturing files after an increasing number of implant ruptures. The certification of the implants was suspended and global backlash of patients and national authorities followed [9]. In 2010, the United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA) released an alert for patients with metal-on-metal (MoM)

hip implants as the revision rate was considerably higher than in conventional metal-on-polyethylene implants. Healthcare vigilance authorities in other countries soon followed [44]. The wear or the joint surfaces against each other would cause meal debris to chip off over time which created adverse reactions in the soft tissues and and in some cases, a systemic contamination of blood with metal ions [45]. In the light of these incidences, the European Commission (EC) called for amendment of the medical device directives in order to make sure that the legislation would not allow events such as the steps leading to the PIP scandal or controversy surrounding the MoM hip implants to occur in the future. This was followed by a swift action from the EC, who proposed for new medical device regulation in 2012 [26]. After four years of discussions on the expert level, and after an agreement with the ministers of the member states of the EU, the draft regulations were agreed upon by the European Parliament and Council in 2016, following the adoption of the new regulations in April 2017.

The entry of the new medical device regulation (MDR) into force in May 2017, that will along with the regulation on in vitro medical devices replace the current legislation on medical devices, marks the inception of a transition period from current fragmented system of legislative documents to a more consolidated and transparent environment based on two thorough regulation documents. The new rules will apply with all force in 2020 for medical devices and in 2022 for *in vitro* medical devices [1]. A directive is a legislative act applicable to all member states that obliges them to reach certain goals not by direct overhead law, but with internal legislation the way the member states see fit. Whereas a regulation is a binding legislative act, meaning that it is enforced by law directly and immediately from the date of adoption. The new policy on medical devices will be in the form of regulations, meaning that after the transition period specified in the MDR, all EU member states should have made (as good practice) necessary specifications in their respective legislation to be in accordance with the active regulations [5]. The end of the transition period will not mark a point when the regulatory environment for medical devices is complete, for managing such a large and vast field as medical devices will always be work in progress, but it will nevertheless introduce a considerably higher level of quality to the management of medical devices in the EU than ever before.

1.1.2 Global policy as the background for the EU policy

In order to understand the complex implications of a change of such a vast scale in the regulatory environment in the EU for medical devices, it is of utmost importance to get a clear understanding of how the regulations have been developed and which players are responsible for the development of the legislation framework in use today. As a field of global impact, any regulations in effect in the EU are immensely influenced by the state of the art in global policy as well as the legal frameworks in other countries. The global policymaking organisation in the field of medical devices is currently the International Medical Device Regulators Forum (IMDRF), preceded by Global Harmonization Task Force (GHTF) until 2011. The IMDRF brings together the representatives of medical device authorization organisations from Australia, Brazil, Canada, China, Europe (EU), Japan, Russia, Singapore, South Korea and the United States of America. [14]

Furthermore, through a two-way interplay, the global policy gives input for the local policy, accommodating to the needs and specificities of the region, while still being compatible with the global consensus regarding the governance of the field of medical devices. Yet, as much as the global regulatory environment influences the local, the local frameworks provide input for instating changes in the global policy, for example in the case of the global unique device identifiers (UDI) system that has been developed (but not yet implemented) by the IMDRF [13]. This system of giving each medical device a unique code for identification and tracking purposes under a unified system was developed under the lead of the EU which is also one of the first members of the IMDRF to be implementing a local UDI system and a database called EUDAMED with the adoption of the MDR [1]. The development of the EU UDI system has been one of the case study examples for the development of the global system [13].

The global policy affects the regional policy – such as is the case with the EU – and the EU sets the policy for its 27 member states. The EU policy in turn affects the changes in the global policy. Tapping into this process with their input are various international and regional actors such as the medical device manufacturers (MDMs), notified bodies (NBs) and organisations that congregate other parties with a vested interest like patients' associations, societies of medical professionals and manufacturers' organisations. The system is neither a bottom-up or top down hierarchy but rather a network of multiple actors that reaches for a common goal through a complex interplay of stakeholders.

1.2 MEDDEV 2.7/1

1.2.1 Clinical evaluation

According to the current (revision 4) MEDDEV 2.7/1 guidelines:

> *"the clinical evaluation is a methodologically sound ongoing procedure to collect, appraise and analyse clinical data pertaining to a medical device and to evaluate whether there is sufficient clinical evidence to confirm compliance with relevant essential requirements for safety and performance when using the device according to the manufacturer's instructions for use"* [12].

The essential requirements (ERs) are a set of base criteria that all medical devices have to comply with in order to be allowed to enter the EU market. The relevant ERs for clinical evaluation are concerned with safety, acceptability of the benefit/risk profile, device performance and acceptability of undesired side-effects [7]. The ERs are laid out in the EU medical device directives.

The clinical evaluation is usually first undertaken when applying for a CE-marking for the first time [12]. CE-marking is a declaration from the manufacturer that the product with the marking has been assessed to meet all the essential requirements of the directives that apply to it in the European Economic Area and the CE-marking is mandatory for all products that are on this market [17]. In order to keep the CE-marking, the manufacturer has to actively update the clinical evaluation throughout the whole lifecycle of the device [12].

With each clinical evaluation, certain risks related to the medical device will emerge, even as the device is used in a way the manufacturer has intended and described in the device documentation. The core objective of the clinical evaluation is to identify these risks and give justification to demonstrate that the potential benefits of the device outweigh the risks. The clinical evaluation has to be based on sound methods and be comprehensive in showing both the risks and benefits to the patient, as well as risks for users or other persons who have anything to do with the said device. Importantly, the benefits for anyone else but the patient are not relevant. The resulting benefit/risk

profile is the basis for demonstrating conformity with the essential requirements laid down in the EU policy. The written documentation of the clinical evaluation is the clinical evaluation report (CER) which documents all the steps of the clinical evaluation and conclusions made during the process. [12]

The clinical evaluation has to be viewed as an ongoing process that at any point of time takes into account all the possible available information that is relevant to the safety of the device to show conformity with the EU policy. The CER can be seen as a snapshot of the current status of the clinical evaluation and is a mandatory part of the device documentation portfolio that in turn is needed for applying for an access to the European market via the CE-marking.

1.2.2 Guidance MEDDEVs

Under the European Union framework for management of medical devices, the European Commission (EC) provides guidance documents for implementing the EU law. For the field of medical devices, these guidance documents are MEDDEVs. The MEDDEVs are especially addressed to notified bodies and medical device manufacturers to help with the procedures of conformity assessment with the EU law. Conformity assessment is a procedure in which the MDM and NB check conformance of the device documentation with the ERs set up in the relevant legislative policies. The MEDDEVs provide a common approach on how to implement the EU law regarding medical devices. [10]

The input for drafting the MEDDEVs comes from authorities who are concerned with safety of public health, with inclusion of all the relevant stakeholders such as industry associations, health professionals' associations, NBs, European Standardisation Organisations and other interested parties. Once a draft is in place, the guidelines are evaluated and eventually endorsed by the Medical Device Expert Group (MDEG) at the European Commission [10]. The MDEG is a consultative body, the aim of which is to give competent advice for the Commission, and that is set up by the EC and consist of experts in medical device field from both private and public domains [11]. The drafting authorities along with MDEG make sure that the content of the guidelines is in accordance with the EU law on medical devices. Though the guidelines are not legally binding, it is expected that the guidelines are followed by the MDMs and NBs alike, to

make sure the approach taken to follow the EU law is consistent and harmonised within the industry. [10] The current guideline, adopted in 2016, is the 4th revision of the document.

1.2.3 MEDDEV 2.7/1 revision 4 guidelines on clinical evaluation

The currently active European Commission guideline on clinical evaluation under Directives 93/42/EEC and 90/385/EEC, MEDDEV 2.7/1 is a guidance document that explains the common ground rules set by the EC for the NBs and MDMs on how to see through the clinical evaluation process and how to put together the CER, a document with a high weight in the device document portfolio required to bring and keep a medical device on the market and active use. The MEDDEV 2.7/1 revision 4 is an iteration in a series of updates and is a thorough revision of the previously published revisions of the MEDDEV 2.7/1 guidance regarding clinical evaluation. However, as the changes are mostly clarifying and specifying of the concepts already existent in the previous - revision 3 - of the guideline, there is no transitional period instated, meaning that the MDMs are expected to follow the guideline immediately [18]. Nevertheless, the step from revision 3 to revision 4 is rather steep as the amount of detail that has been added is massive. Also, due to the enormous changes the EU medical device management framework is currently going through, it is unclear, yet very likely that the current MEDDEV 2.7/1 guideline will undergo another update in the near future.

MEDDEV 2.7/1 revision 4 is based on and is in reference to European Union directives and regulations, international and harmonised standards, as well as European and international guidance documents. It gives detailed, but not device-specific information about the various aspects of clinical evaluation in the form of a comprehensive guide [12]. As the MEDDEV 2.7/1 revision 4 is in most but not all aspects in line with the future of EU medical device policy – the MDR – it is a good starting point for MDMs to prepare for the requirements of the new legislation [18].

Firstly, the general principles of clinical evaluation, such as the definition, importance, how and who should perform it and update principles are covered. Then a roadmap for the process of the clinical evaluation is laid down via setting the scope. The evaluation is divided into four stages (Figure 1) – the scoping of the evaluation itself (0), the

identification (1) and appraisal (2) of pertinent data, the analysis of the data (3) and the documenting of the whole process as well as the outcomes in the CER (4) [12].

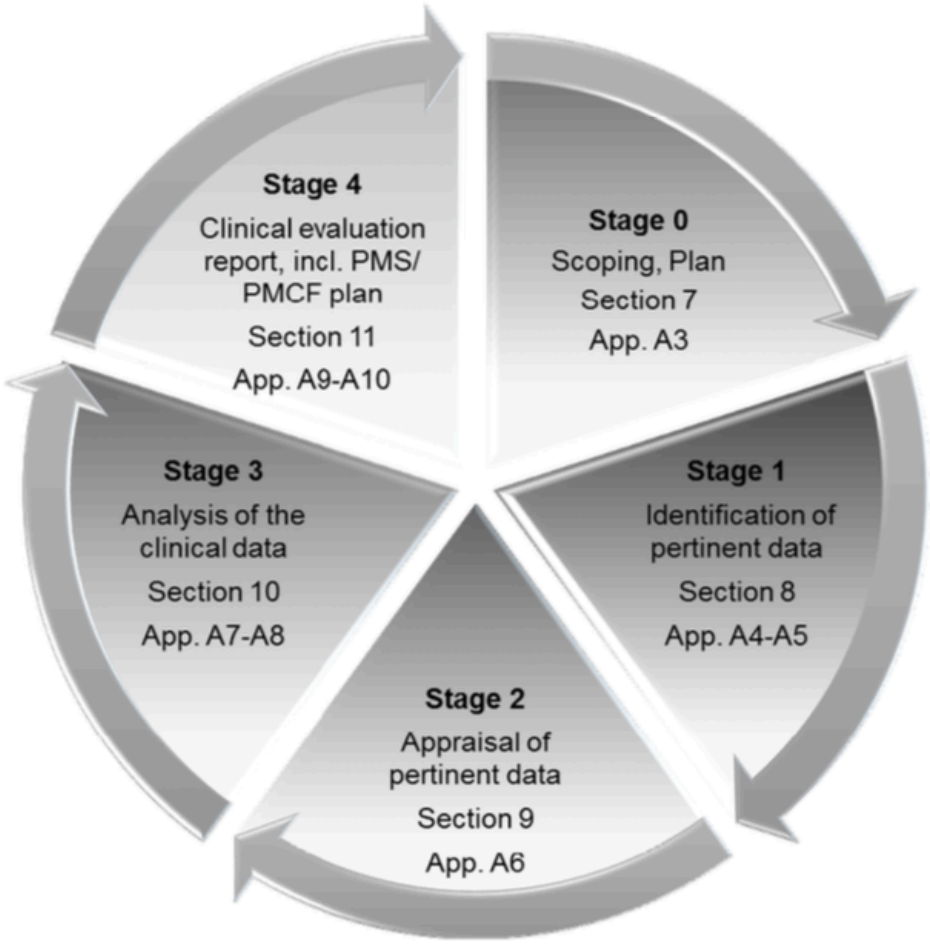

Figure 1. Stages of the clinical evaluation according to MEDDEV 2.7/1 revision 4 with references to relevant sections and appendices [12].

A significant portion of the MEDDEV 2.7/1 revision 4 is concerned with the sources of data and the suggested ways of how to identify the the data (stage 1) that is relevant and of sufficient quality (stage 2) for the clinical evaluation out of the mass of all the data on the subject. The MEDDEV 2.7/1 revision 4 distinguishes between data generated by the manufacturer, either by a clinical investigation which can be pre-market or post-market, or post market surveillance (PMS) documentation about the device; and data gained from literature, including studies about other similar devices where it is possible to show sufficient resemblance to the device that is being evaluated. It also lays down the way of how to demonstrate said equivalence by taking into account each of the three types of characteristics of the devices that are being compared for equivalence. If a

justified resemblance is shown, the data about the equivalent device can be used to draw conclusions on the device that is being evaluated [12].

Analysis of the data (stage 3) that has been gathered and evaluated follows, bearing in mind that the outcome of the analysis is to determine whether the device under evaluation is in line with the ERs described in the base documents of the EU medical device law, thereby ascertaining that the legislation laid by the EC with regards to the needs of the various interested parties – most importantly device performance and patient safety – is successfully followed, which is the prime reason for why the clinical evaluation is undertaken. This demonstration of conformity with the ERs is in most situations mainly to be based on clinical data. However, the MEDDEV 2.7/1 revision 4 also describes how to act in the rare situations in which the demonstration of conformity with the EU policy is not appropriate or possible based solely on the clinical data. In that case, other, non-clinical measures, such as performance evaluation, bench testing and pre-clinical evaluation can be used to demonstrate conformity with the EU policy, but that does not eliminate the need for a thorough clinical investigation to show why the clinical data that has been gathered is not enough for demonstrating conformity with the EU policy [12].

The MEDDEV 2.7/1 revision 4 gives a description for the MDM on how to see the clinical evaluation process through and how to document its outcomes (stage 4) in a Clinical Evaluation Report (CER). It also describes the role of the NB that is responsible for the assessment of the CER. The various appendices of the guideline give in-depth information on the processes that are laid down in general terms within the main part of the MEDDEV 2.7/1 revision 4 [12].

1.3 Implications of the regulatory changes for medical device manufacturers

Balancing patient safety with functioning of the market

The new policies of the EU for regulation of medical devices are an output of a complex network of actors, including both regional and international bodies, all of which comprise of professionals with multiple interests, among which personal interest cannot be marginalised. Therefore, the multi-actor symbiotic network of development is in the risk of being non-transparent in its actions. Care must be taken to keep in mind the desired value – optimal and safe healthcare for patients - that the regulators are aiming to create in the field. The new MDR lists two main objectives that are to be simultaneously pursued without superiority of one to the other:

- *"This Regulation aims to ensure the smooth functioning of the internal market as regards medical devices, taking as a base a high level of protection of health for patients and users, and taking into account the small- and medium-sized enterprises that are active in this sector.*
- *... this Regulation sets high standards of quality and safety for medical devices in order to meet common safety concerns as regards such products.[1]*"

Considering the changes in the EU medical device legislative environment regarding clinical evaluation procedures as described in the MEDDEV 2.7/1 revision 4 and the MDR, these two objectives are of high importance from two somewhat contradictory perspectives. Though the interest of all the stakeholders with the evaluation is first and foremost to make sure that the safety of the patient and the users of the device is guaranteed, for the manufacturer the outcome of the clinical evaluation can be a question of staying in business. That is especially true for the small and medium sized MDMs for whom the long and resource-heavy process of bringing a medical device on the market is associated with high risks. In the light of the revision 4 or the MEDDEV 2.7/1, this process has only become more arduous as the requirements to be met have been revised towards much stricter end than ever before. Adding to that, the change has been steep in a relatively small timeframe – something that large manufacturers with dedicated quality assessment and personnel training departments can cope with – but

may turn out to be a tough blow for small and medium sized MDMs. Although patient safety is and must stay the priority in the case of validating medical devices for the market, and that is what the latest revision of the MEDDEV 2.7/1 is rightfully aiming to secure, there is the delicate question of how to refrain from creating a disadvantage for the smaller MDMs to be considered.

SMEs and innovation

Small and medium sized enterprises (SMEs) are currently defined as enterprises that employ no more than 250 persons and have an annual turnover under 50 million euros. In Europe, SMEs form 95% of the medical device manufacturers. The whole medical technology field in Europe is responsible for more European Patent applications than any other business field, with 41 % of the applications coming from the countries of the European economic area, making medical technology in the EU a field of high importance for both European and global economy. The field is also characterised by high affinity to innovation - the product lifecycle before an updated version of the product is released is 18-24 months on average. Furthermore, the number or patent filings from medical technology field in Europe has doubled over the last decade [20], demonstrating that successful research activities are will continue to be ever more crucial for the livelihood and competitiveness of the manufacturers on the field, especially in the case of SMEs [24].

Software as medical device under the MDR

The new MDR does not resolve on how to classify and hence how much resources to plan for market approval in the case when the device a manufacturer is hoping to bring on the market is an IT solution [1]. Very often, companies providing such software applications are small sized and work with a limited budget and their product poses a relatively low risk on the patient. With the adoption of the new MDR, it has been voiced that almost any software solution will fall under class II medical device, meaning that a clinical evaluation is needed and the device will be audited by notified body. So far, most medical software producers with low risk products have been able to classify their products under the lowest class that makes reaching the market much easier. The adoption of stringent control over all types of software solutions that the update of the MDR suggests will increase patient safety and effectively regulate the current grey area

of medical software applications for smartphones, but also make the cost of healthcare higher for the patients and leave the field open for bigger companies to buy up the small innovative medical IT enterprises that are under financial pressure [40].

Changing business priorities

As the step from current situation to that described in the new MDR, and more imminently, the change to already adopted revision 4 or the MEDDEV 2.7/1, is rather steep, the transition has introduced much confusion within the field [2][3] and the changes themselves are poorly understood [15]. It is noteworthy that more than half of MDMs on the market today have reported to have only a basic understanding of the upcoming changes, according to a survey held by a global medical device consultancy company Emergo. The global trend has so far been that regulatory requirements are cited as the key challenges for their business by large MDMs, whereas the small and medium sized MDMs have traditionally been more concerned with funding and capital. The reason being that large companies usually have a bigger number of medical devices certified in multiple markets and must therefore work with many regulators. However, with the changes in the EU medical device regulatory framework, in the beginning of 2018, MDMs of all sizes, including companies with under 10 employees see regulatory requirements as the biggest business challenge for the year. [15]

Clinical investigation

Under the future MDR that will apply into force in 2020, the number of medical devices that will require a clinical trial in order to enter the market will surge up greatly. However, the research infrastructure of the EU expected not to be ready to handle the increased need, possibly leaving the products of smaller MDMs and manufacturers of highly specialized devices for care of rare conditions unavailable for the patients, hence undermining the underlying the patient-oriented goal of safe and quality healthcare [46]. The MEDDEV 2.7/1 revision 4 introduces increased requirements on the conduct of clinical trials which affect not only the EU, but the global market as well. With the lack of sufficient clinical trial infrastructure in the EU, it is likely that in the near future, many clinical trials will be outsourced from other countries. As policies in different countries vary greatly, the outcome of this will place serious challenges to the policymakers and the industry alike. Against the backdrop of a globalizing clinical

investigation field, the FDA has already responded with a level-up of the policy and a clarification guideline on good clinical practice in clinical investigations on medical devices [47]. To avoid uncontrollable increase in clinical trials with questionable quality, the EC is expected to mitigate the risks arising from the MEDDEV 2.7/1 revision 4 and MDR with the help of thorough implementation guides [46].

New needs of resource use

This change is creating new opportunities as well, a good example being the industry of medical consulting. In terms of readability, the guidelines have changed from a document that was fairly easily comprehendible by any MDM representative to a jargon heavy document that requires expert knowledge on the regulatory background of the EU medical device policy and experience in working with EU legislative documents. This is a clear sign from the European Commission that the clinical evaluation process should not be taken lightly by the MDMs and a significant addition to the skillset of the enterprise is due, as most MDMs have to choose between levelling up their knowledge of the MDR by 2020 or use the help of external consultants [15]. Another industry for which new opportunities have emerged, is the field of medical writing that has been traditionally concerned with producing documentation for pharmacological industry. The 2018 spring conference symposium of the European Medical Writers Association was focused on the topic of introducing the field of writing about medical devices with focus of writing clinical evaluation reports under the new requirements of the MEDDEV 2.7/1 and MDR [16]. As SMEs typically struggle with the lack of financial resources and qualified personnel when developing new products because of strict regulations in the field [20], it is to be expected that the MDMs who previously produced the CER without outside help, are now likely to outsource the skills (such as detailed knowledge of the regulatory needs, literature research skills and medical writing skills) needed for performing the clinical evaluation and documenting it in the CER [18]. As clinical evaluation is defined as an ongoing process in both the MEDDEV 2.7/1 revision 4 and the future MDR, the SMEs in the medical field are facing a heavy and permanent increase of financial burden in the coming years. As SMEs need to prioritize their limited resources to their key competences for the purpose of efficiency [20], this increased demand to allocate time and finances to dealing with regulatory matters could substantially hinder their competitiveness with large companies by eating

up resources that could be otherwise dedicated to research and development of new medical devices that are potentially more effective and safer for the patients. An additional obstacle to successful innovation, as the current number of EU NBs is deemed insufficient to handle the load of re-certifications of already marketed devices that the MDR and revision 4 guidelines make a necessity, the certification needs of novel devices are bound to receive considerably less attention than before [46]

2 AIMS

The new revision 4 of the EU medical device guidelines for clinical evaluations MEDDEV2.7/2, that are active since 2016, have stirred up confusion in the field. This is expected to be ever more intensified by the upcoming MDR which will be adopted starting from 2020. Even though the goal of the change – securing the safety of patients using medical devices and instating the best possible care - is laudable and was long due in the light of the scandals that rocked the field in 2010s, the change has been steep for most players of the market. Even though the guideline is officially an update and therefore there is no transition period for coping with the changes, considering the sheer amount of detail that is added, it could be well seen as a novel and much higher level of standard. For a field that is primarily saturated by small and medium sized medical device manufacturers who are always vulnerable to new needs of allocation resources, the guidelines have become a subject of criticism as it they raise more questions than they can answer.
The aim of this thesis is to alleviate the confusion by answering the following questions:

> What are the main changes regarding clinical evaluation that the medical device manufacturers have to cope with currently and in the coming years?
>
> How should the medical device manufacturer approach the task of the clinical evaluation to reach compliance with the MEDDEV 2.7/1 revision 4 requirements?

The thesis seeks to achieve the goal of answering these questions by:

- giving a comprehensive insight to the current and upcoming EU guidelines and policy regarding clinical evaluation for medical devices
- mapping the process that is described with the MEDDEV 2.7/1 revision 4 guidelines in detail
- proposing an optimized process map for conducting a clinical evaluation in compliance with the revision 4 guidelines, using real-life insight from a case study.

3 METHODS

3.1 Phase one - comparative analysis and process mapping

As a way to alleviate confusion about the regulatory changes among MDMs, firstly a comparative analysis of MEDDEV 2.7/1 revision 3, revision 4 and MDR is conducted, identifying:

- the aspects of revision 4 that are extending on the content of revision 3
- the aspects of revision 4 that were not present in revision 3 and are thus novel additions
- the notable changes related to clinical evaluation that are introduced in the MDR, extending the requirements of MEDDEV 2.7/1 revision 4

The comparative analysis is based on Table of Contents (TOC) comparisons (Appendix 2) and analysis of the content of the documents. The changes between the documents are described in the results.

Process mapping is a qualitative method that is widely used in business, clinical and health promotion contexts to deconstruct, logically order and visualize the path of the steps needed for conducting a process in order to optimize the process and increase efficiency [41]. Often used to create a plan for action for health promotion programs, process analysis and mapping is also a way to add a practical dimension to the planning of a process, mainly to give all stakeholders the opportunity to identify and clarify each function that needs completing to achieve program outcomes [41]. It is especially useful when the process under evaluation is poorly understood [42] and acts as way to visually depict the current state of the process, draft an ideal process and analyse the differences of the two to avoid the use of resources for redundant activities.
Here, the process mapping method uses common flowchart symbols to depict activities, decisions, added data or documents within the process. For visualizing sub-processes, colour grading is used. Besides the map itself, a narrative is introduced to describe the processes illustrated on the map in more detail, especially in the case of additional information that was difficult to represent visually [43].

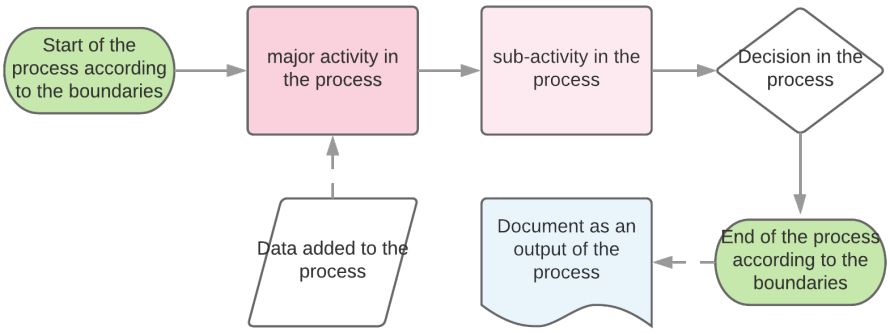

Figure 2. Method and common symbols used for common flowchart mapping. Adapted from [41] [Author].

The clinical evaluation according to the new EU guidelines is a resource demanding process that is yet not well-understood by the industry it is directed to. Although process maps are usually created and feedback for it gathered based on group-interviews [43], in this case study, a document (MEDDEV 2.7/1 revision 4) already proposes a process that any manufacturer of medical devices has to conform to, yet this process is in broad terms. Therefore, the stage by stage process presented in the guideline was taken as a base for mapping the general process of conducting a clinical evaluation to give a clear overview of what is needed to be done when seeking compliance with the new requirements and avoid unnecessary use of resources. The process boundaries were set according to the MEDDEV 2.7/1 revision 4 guidelines (Figure 2).

3.2 Phase two - case study on the example of Trium CTG Online

3.2.1 Description of the case study subject

Trium Analysis Online is an internationally operating medium sized medical device manufacturer based in Munich, Germany. The company specializes on medical software solutions and services for healthcare and life sciences. For clinical research, the company collaborates with Sylvia Lawry Center for Multiple Sclerosis Research.

The company serves as an example of a SME whose device is globally distributed and well-established on the market. The device is a software solution and it is used in obstetrics departments globally to monitor the well-being of unborn babies in order to prevent instances that can be life-threatening or seriously debilitating for both the

mother and the baby. Yet this field of utmost importance to public health is in imminent need for innovative research [25] in order to keep up with the increasing demand of patient safety, thereby making the enterprise especially vulnerable to the implications of the regulatory changes underway in the EU and also analogous to the situation of SMEs dealing with medical devices in other fields. These aspects prove the case of "CTG Online" suitable for as a case study subject on the implementation of the European Union guidelines for clinical evaluation of medical devices.

Description of the device

Trium CTG Online is a web-browser based surveillance system for monitoring fetal heart rate, uterine contractions of the mother, fetal movement and other parameters detected by fetal montors. The system is designed for use in obstetric departments, is compatible with common fetal monitors providing cardiotocography (CTG) traces and gathers the data via the network infrastructure of the hospital (Figure 3).

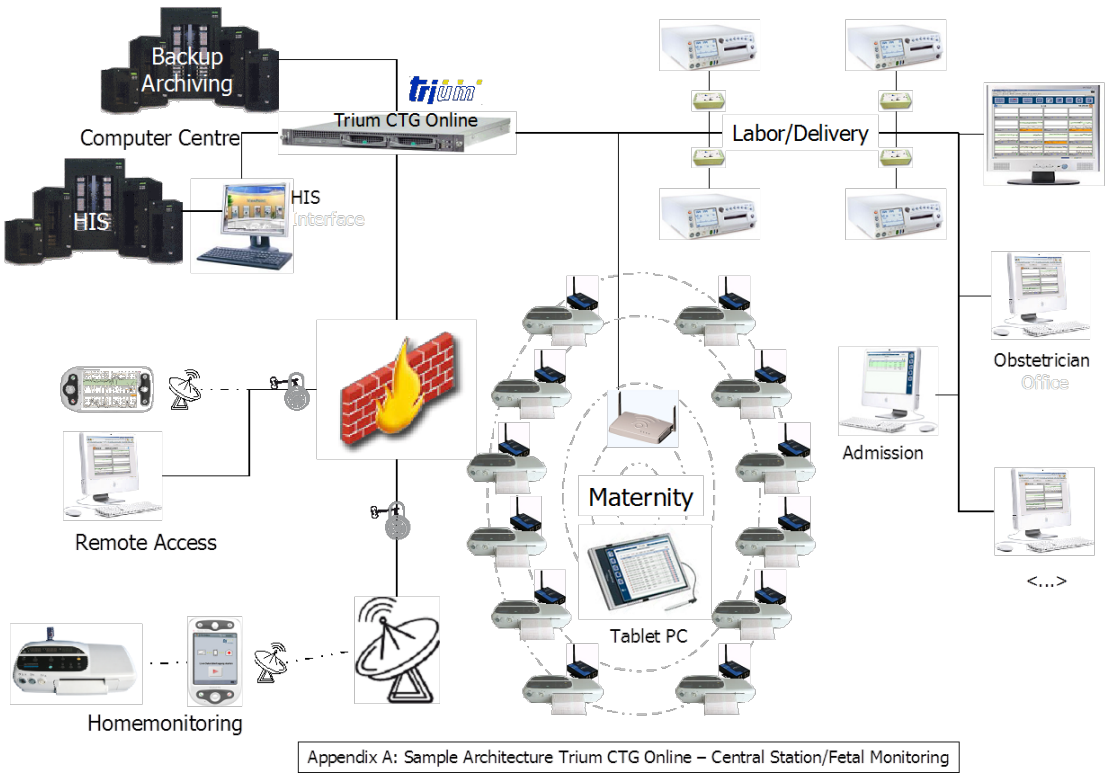

Figure 3. Sample architecture of Trium CTG Online in a hospital setting [50].

The system is designed to acquire, transfer, store, process and display CTG signals in real time. The system processes the data and classifies it according to the standard

classification of International Federation of Gynaecology and Obstetrics (FIGO) (Figure 1).

Figure 4. Single view of CTG Online showing fetal heart rate (FHR1), accelerations, decelerations, fetal movements (TOCO) and alert history based of FIGO guidelines [50].

The system provides visual and audible alarms based on various parameters of the fetal heart rate signals. The system is not an automated diagnosis tool, but supports decision making.

Trium CTG Online is a class IIb classified medical device that is marketed in the EU and in various countries internationally. The device is available in the EU since market clearance in 2001. The device is distributed globally by GE Electronics.

3.2.2 Background on fetal heart rate monitoring

The field of widely used commercial fetal monitoring dates back to late 1960s when fetal monitors became small and practical enough to be comfortably used in the obstetrics wards [28]. Today, monitoring of the fetal heart rate (FHR) using cardiotocography is a routine procedure in ante- and intrapartum care. Even though FHR monitoring is a widely accepted and used tool for determining the status and well-being of the unborn baby, there is controversy about the basic principles of how to read the FHR traces and connect the findings of the traces to meaningful parameters and outcomes of the fetal status [27].

The common way to interpret the CTG trace is to determine a baseline rate and evaluate the presence and nature of deviations from that baseline, such as accelerations and

decelerations. The core of the controversy is the circular definition of baseline fetal heart rate and those periodic changes as baseline is defined as FHR regions lacking accelerations or decelerations, yet accelerations and decelerations are defined as deviations from the baseline rate [34].
There is also well-documented evidence that the interobserver reproducibility is poor when the traces are interpreted in a common visual way by experts [33] and when using a computerized analysis of the FHR traces, this issue is alleviated [29].

Although the technology of FHR monitoring is extremely well-established and widely used, its' use does not yield better outcomes for reducing perinatal fetal mortality or have a correlation to higher Apgar scores of the newborns than using no CTG monitoring altogether [25]. Undergoing the procedure at admittance to the obstetrics department however increases the rate of deliveries via caesarean section by approximately 20% [30].

The use of generalised fetal monitoring is not improving the fetal outcome and puts the mothers in a higher risk of undergoing an invasive procedure that poses a high risk for the health of both the mother and the newborn. However, in high-risk pregnancies, the use of computerized analysis as opposed to common visual analysis of the CTG traces has been shown to have significant benefits for the fetal outcome [25]. Unfortunately and rather surprisingly, there is currently insufficient high-quality and up to date evidence to back this claim, but several attempts have been made and are underway to bridge this gap, especially with the emergence of more efficient ways of processing the data such as machine learning technologies[31][32].

3.2.3 Methods of the case study

The general process map drafted in previous phase was expected to be refined to match the specific process of the enterprise based on the observations of clinical evaluation team meetings during the case study period from October 2017 to May 2018. However, the process determined by the guideline turned out to be too unspecific and general to be of help for the enterprise with understanding the task of updating the CER. Consequently, for the enterprise-specific set of process maps, a new approach in terms of how to structure the process map was drafted based on critique to the process presented by the guideline and input from external experts during observations of the

meetings of the clinical evaluation team. The start boundary of the process is defined as the first meeting of the clinical evaluation team with an external advisor present. The end-boundary of the process is defined as the approval of the finalized CER.

The company did not have a standard operating process (SOP), an internal document with step-by step set of instructions for a specific task, in place for conducting a clinical evaluation for compliance with MEDDEV 2.7/1 revision 3 or revision 4. An SOP [37] that is compliant with revision 4 was obtained via consulting service from Johner Institute along with templates for clinical evaluation plan and clinical evaluation report [36]. Unlike the ambiguous stage by stage approach taken in the clinical evaluation guidelines, the SOP proposes an activity based approach and specifies the actors responsible for each task along with input and output documents [37].
As the end boundary of CER update process is the completion of the CER, the approach for the mapping is adapted from the structure of the CER template [36] itself and the approach of the SOP. Input form chapter 4.1 was added to make the process map compliant with the upcoming MDR.
As the CER update process for CTG Online is not finalized by the end of the case study period, the process map is drafted as a proposal and presented to the clinical evaluation team of the enterprise.

Feedback to the process proposal is gathered in the form of a semi-structured in-depth personal interviews with the team members that are electronically recorded. Additionally, an in-depth personal interview is conducted with an expert of the field on the usability of the CER-oriented approach of the case specific process map and the implications of the legislative changes to the EU medical device industry. All of the interviewees sign a release form for the use of the information they provided (see appendices 3 and 4, Interview Release Form and Interview Protocol). The interview protocol is adapted from a template provided by Stanford Institute of Higher Education Research [48] and the interview release form is adapted from one provided by University of Illinois Press [49].
The feedback section would benefit from a higher number expert inputs, but as the main objective is to gather feedback on the the case specific process map that only the team members of the enterprise can be interviewed for, this is not a serious limitation.

4 RESULTS

4.1 Changes between MEDDEV 2.7/1 revision 3, revision 4 and MDR

The revision 4 of the MEDDEV2.7/1 is a substantial revision of the previous revision 3 in terms of enhancement on the detail. The emphasis on added detail is evident already when comparing how clinical evaluation is defined in the two documents.

Revision 3:	Revision 4:
Clinical evaluation is the assessment and analysis of clinical data pertaining to a medical device in order to verify the clinical safety and performance of the device	*Clinical evaluation is* ***a methodologically sound ongoing procedure to collect, appraise and analyse clinical*** *data pertaining to a medical device* ***and to evaluate whether there is sufficient clinical evidence to confirm compliance with relevant essential requirements for*** *safety and performance* ***when using the device according to the manufacturer's instructions for use***

Firstly, the revision 4 definition emphasises the ongoing nature of the clinical evaluation and the need for it to be based on stringent methods. Secondly, how exactly to collect and appraise the data on which the evaluation is based, is brought to focus. Thirdly, revision 4 explicitly marks the need to be thorough on collecting enough and quality evidence in order to show accordance to the EU policy in the form of essential requirements. Finally, the manufacturer is required to base the instructions for use (IFU) on the conclusions of the clinical evaluation.

Though revision 4 is a thorough update, it builds upon the revision 3 rather than deprecating what has been stated in the previous revision. When comparing the tables of contents of the two documents, it is evident that the content remains similar, but a lot of detail has been added. The enhancements have brought about a restructuring of the table of contents where some of the topics that were discussed briefly in the main body of the revision 3, are covered in a detailed appendix in the revision 4 (see appendix 2, TOC

comparison). Structurally, the revision 4 makes a stricter separation between information in general terms in the main body and specific guidance in appendices than revision 3. Also in terms of content, the revision 4 includes little completely novel concepts but concentrates on substantially specifying the concepts covered in revision 3.

More detail has been added about post-market surveillance, determining the risk/benefit profile, appraisal and analysis of data (9, 10, A6, A7), establishing the state of the art (7, 8.2), contents of the device description (A3), contents of the CER and the table of contents of the CER (A9), literature search and review protocol (A5), demonstration of conformity with the essential requirements (6.1, A7), demonstration of equivalence with the ERs (A1), when to perform a clinical investigation (A2) and also the checklist for CER (A10) (Appendix 1, TOC comparison). The additions clarify and explain the various aspects already present in revision 3 in more detail. The key changes that do not concern the checklists and description of table of contents of the CER are presented in the following table (Table 1) and discussed in detail in Appendix 1 of this thesis. The results also cover the aspects of the upcoming MDR that add to the clinical evaluation.

Table 1. Comparison of main changes between MEDDEV revision 3, MEDDEV revision 4 and MDR.

	MEDDEV 2.7/1 revision 3	*MEDDEV 2.7/1 revision 4*	*MDR*
Frequency of updates	First evaluation before marketing and then periodical updates. *Chapter 1*	Revision 3 requirements + MDM has to set and justify an update frequency. *Chapter 6.2.3*	-
Establishing the state of the art	Current standard of care and other treatment/diagnostics options. *Appendix F, 3.3.3, 3.4.12*	Revision 3 requirements + specific patient populations, medical conditions the device is used for managing, SOA information on claimed equivalent and benchmark devices. safety and performance endpoints for the literature review must be set and justified. Throughout the document	-
Scientific validity of data	General requirements of needing to scientifically validate the data. Throughout the document	Revision 3 requirements + details on: evaluating methodological quality of data, connecting endpoints of literature search to device performance, searching, analysing and appraising datasets, linking data to ERs. *Chapter 8,9,10 & Appendices 5,6,7.*	-
Equivalent devices	Equivalence is shown in clinical, biological and technical terms. *Footnote of Appendix F*	Revision 3 requirements + each equivalent device has to cover all three terms on its own. Equivalent devices must be CE-marked. Detail on demonstrating equivalence. Need for access to technical data of equivalent devices. *Appendix 1*	In specific cases, contractual agreement between manufacturers for access to technical data on equivalent device. *Art 61 §4-5*
Clinical investigations	General requirements of how to conduct a clinical investigation. *Throughout the document*	Revision 3 requirements + establishing when a clinical investigation is needed, examples include: implantable, high-risk, class III devices, new/unproven technology, new clinical use based on existing technology, high invasiveness, emergence of new risks, emergence of alternatives with lower risk. *Appendix 2*	-
Risk/benefit analysis	Benefits to patient have to be weighted against risks and tied to risk management of the MDM.	Revision 3 requirements + benefits and risks quantifiable. Need to document: measurable improvements of clinical outcome & severity, rates, duration, probability of benefits and harmful events. *Appendix 7.2*	-
PMS and PMCF	CE must consider PMS and PMCF. Throughout the document	Revision 3 requirements + need to establish: acceptable PMS plan, need for PMCF. Data from PMS and PMCF is fed into CE continually and documented in CER. *Appendix 12*	Proactive approach to PMS and need for PMS plan. *Annex XIV, part A & B.*
Evaluator qualifications	Writing - person suitably qualified in the relevant field Approval - objective expert, knowledgeable in SOA *Appendix F, 3.4.1*	Need for declaration of interests from all evaluators Individual or team possessing: relevant higher education, degree or 5 yrs of experience OR no degree and 10 yrs of experience, deep understanding of the device technology and use, scientific research skills, information management skills, medical writing skills, knowledge on regulatory requirements. *Chapter 6.4*	-
Periodic safety update Report	-	-	Need to add PSUR - a summary of results and conclusions of PMS data based on PMS plan to technical documentation. Updated: Class III and implantable devices - every yr class IIa - every 2 yrs *Art 86, art 61 §11*
Summary of safety and clinical performance	-	-	For class III and implantable devices: device overview for the upcoming public EUDAMED database, written in plain language. *Art 32*

4.2 General process map – mapping the CER conduct process according to MEDDEV 2.7/1 revision 4

The MEDDEV 2.7/1 revision 4 contains a general process on how to conduct a clinical evaluation for any device (Figure 1). Although there is a clear stage by stage approach to the process described, what exactly is the content of each stage and how does the content translate into specific tasks that the clinical evaluation team has to perform under each stage is unclear. In order to get an an unambiguous overview of the process proposed in the guideline, the activities required under each stage was mapped by using the common flowchart method as described in chapter 3.1.

The stages of the clinical evaluation according to MEDDEV 2.7/1 revision 4 are (Figure 1):

- Stage I – scoping
- Stage II – identification of pertinent data
- Stage III – appraisal of pertinent data
- Stage IV – analysis of clinical data
- Stage V – compiling the clinical evaluation report

In stage I (Figure 5), the main task is creating a plan for the clinical evaluation, as the process undertaken by an enterprise that aims for a first-time CE-marking for a new device is undoubtedly different from the process of an enterprise with a goal of updating the CER for an already marketed device, as the latter can use the clinical evaluation plan from a previous update as a draft for the new one. Other factors play a role in drafting the clinical evaluation plan as well, such as the nature of the device and the medical condition the device is to be used for managing.

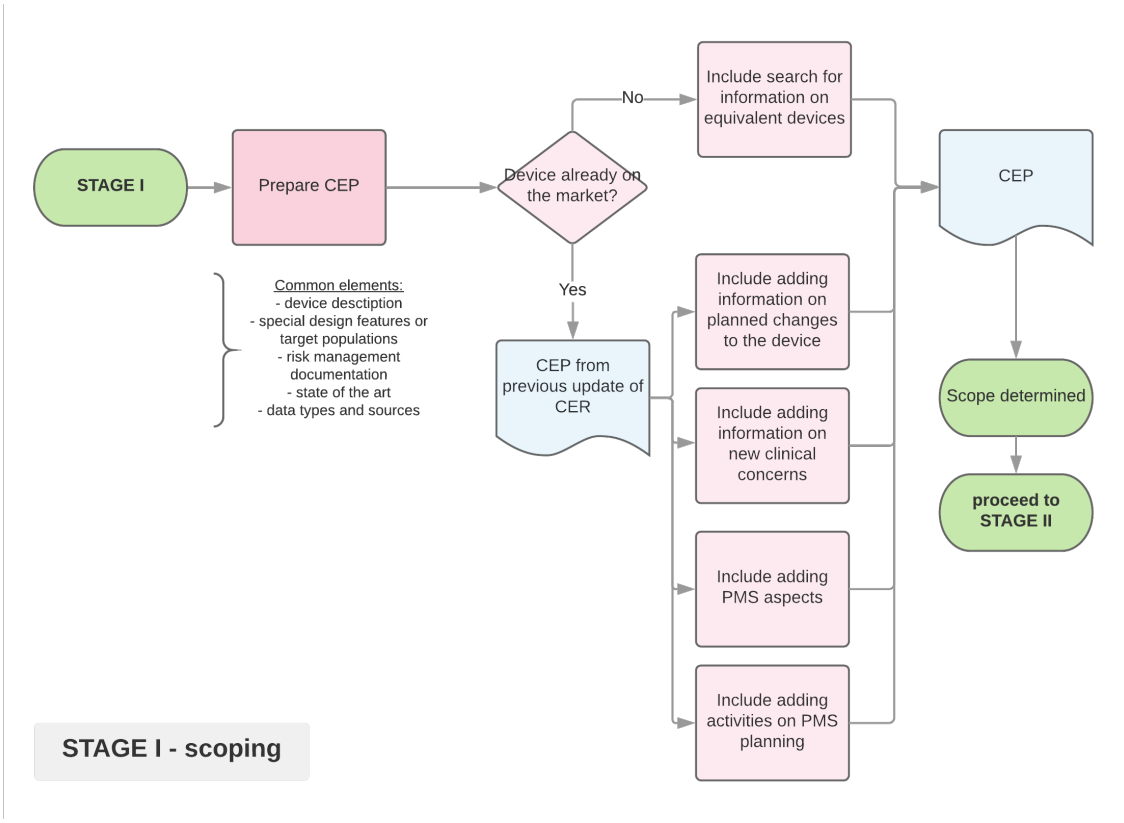

Figure 5. General process map of stage I of the clinical evaluation according to MEDDEV 2.7/1 revision 4. CEP – clinical evaluation plan, CE – clinical evaluation [Author].

In stage II (Figure 6), pertinent data is identified. Important output here is the literature search protocol, to be compiled keeping in mind that all available and relevant data that has to do with the device that is being evaluated or the device to which the manufacturer wishes to draw parallels to as an equivalent device. The selection of the search terms and inclusion/exclusion criteria is crucial, as insufficient attention to keeping the selection unbiased can make or break the literature review. The evaluation team must take care to avoid setting search terms and inclusion and exclusion criteria so that the outcome is a convenience sample or otherwise biased. The main outputs in this stage are the literature search protocol and the literature search report.

Stage III (Figure 7) deals with appraisal of the data. The important output here is the data appraisal plan. In this stage the criteria for appraising the data are set.

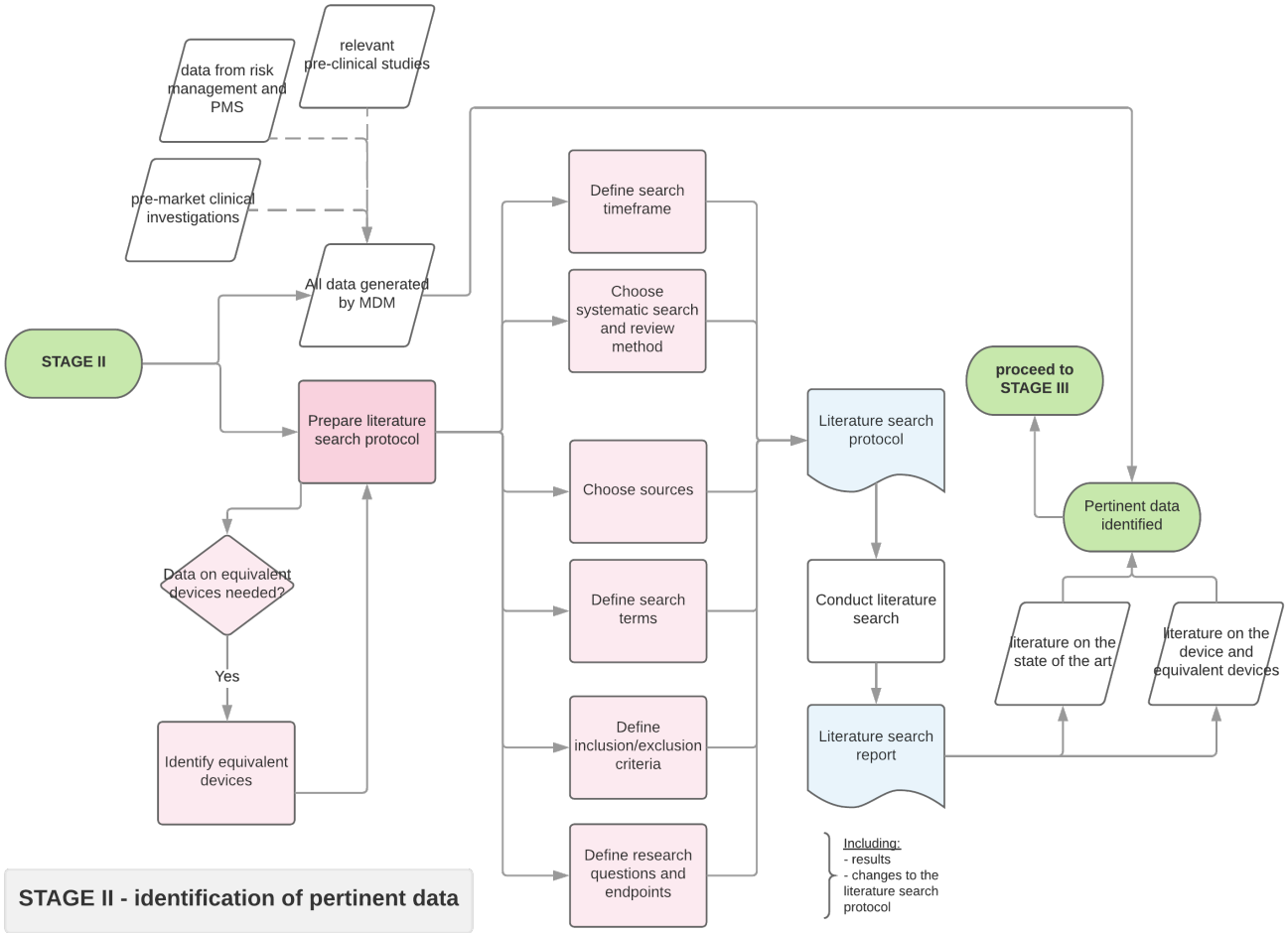

Figure 6. General process map of stage II of the clinical evaluation according to MEDDEV 2.7/1 revision 4 MDM - medical device manufacturer [Author].

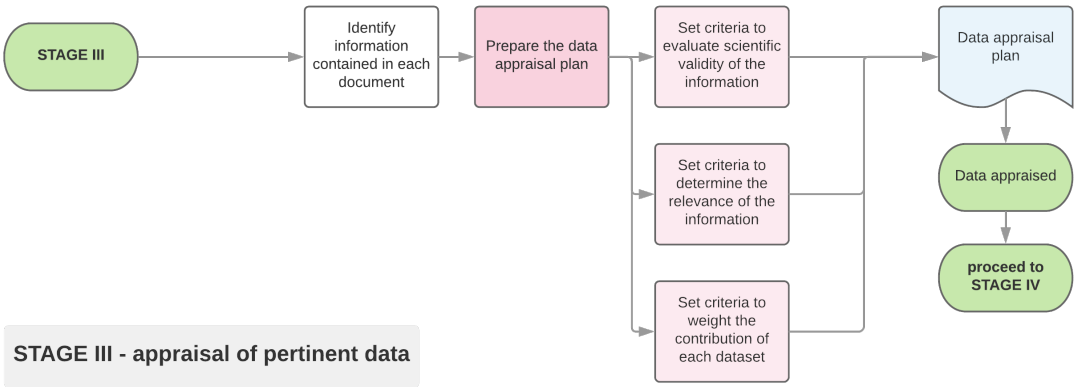

Figure 7. General process map of stage III of the clinical evaluation according to MEDDEV 2.7/1 revision 4 [Author].

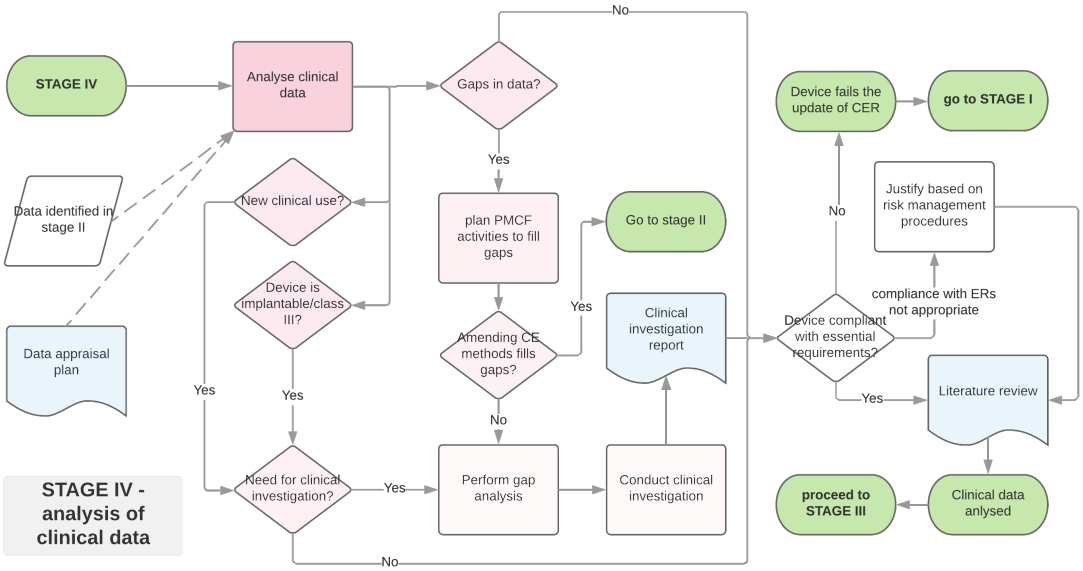

Figure 8. General process map of stage IV of the clinical evaluation according to MEDDEV 2.7/1 revision 4 [Author].

Stage IV (Figure 8) is concerned with the analysis of the data that has been identified in stage II using the data appraisal criteria developed in stage III. The analysis is directed towards determining whether the device is compliant with the essential requirements. This stage also briefly touches the conduct of clinical investigation, a separate process that is not always necessary and not described in detail in the MEDDEV 2.7/1 revision 4 guidelines, hence it was not included in the general process map for conducting a clinical evaluation. The output of stage IV is the literature review.

The final stage of the general clinical evaluation process as proposed by the MEDDEV 2.7/1 revision 4 guidelines is about conglomerating all the information generated in the previous stages into a clinical evaluation report. To help with that the guideline contains a proposed table of contents in the appendix 9 and a checklist for re-evaluating the CER in appendix 10.

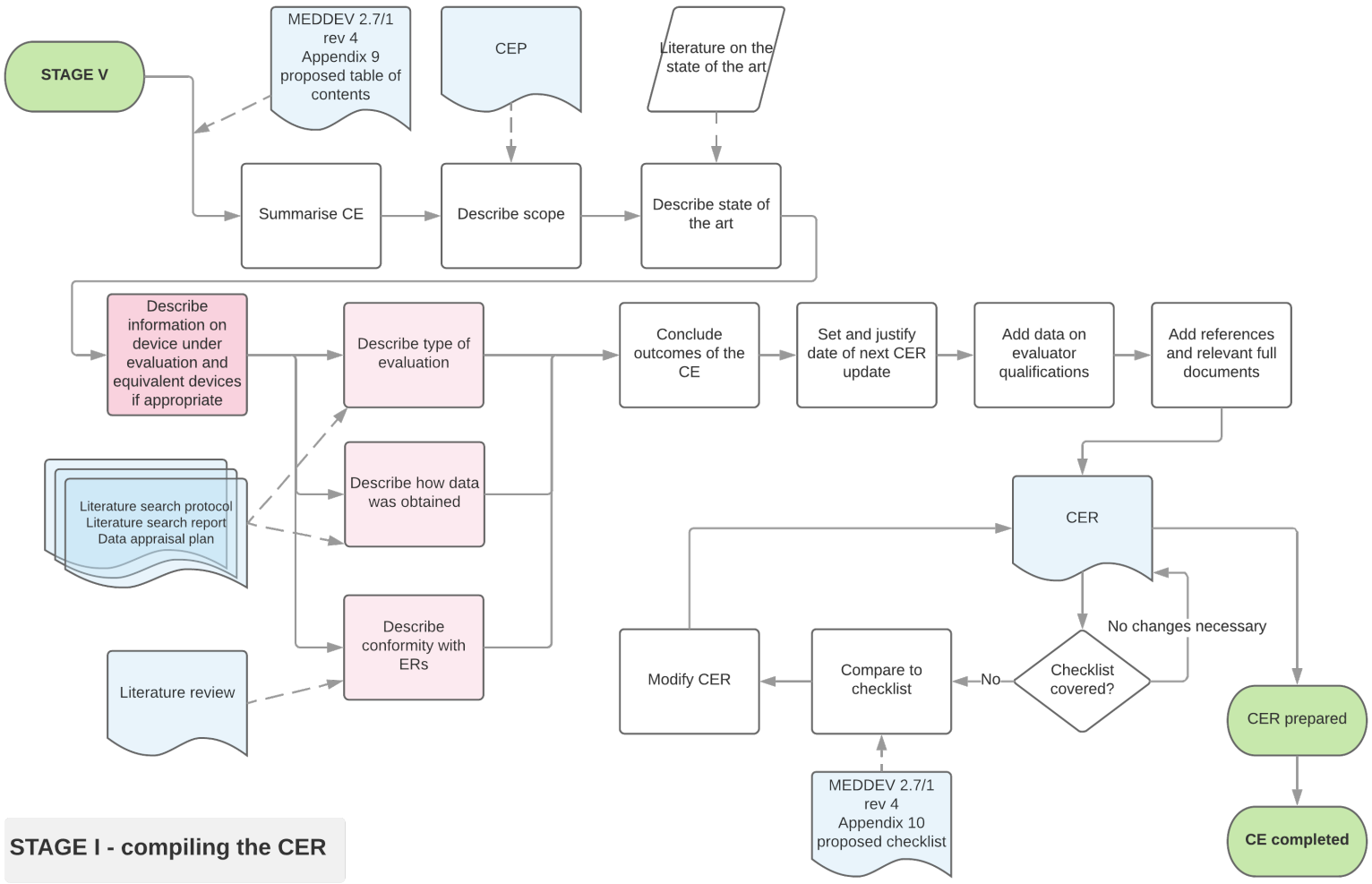

Figure 9. General process map of stage V of the clinical evaluation according to MEDDEV 2.7/1 revision 4. CE – clinical evaluation [Author].

4.3 Case specific process map – mapping the CER conduct process according to MEDDEV 2.7/1 revision 4 and MDR on the example of Trium CTG Online

Though clinical evaluation is defined as an ongoing process, it is the appraisement of the clinical evaluation report by the notified body that determines the market-status of the device. Therefore, for any manufacturer, the update of the report becomes the primary goal. To grasp the practical nature of the process from a manufacturers point of view, it is helpful to distinguish between the update of the clinical evaluation and the update of the clinical evaluation report. The MEDDEV 2.7/1 revision 4 guideline proposes the first part of this duality - the process for a clinical evaluation which was mapped in the previous phase. In this chapter, the latter – a proposed process for the update of the clinical evaluation report on the example of Trium CTG Online is presented as described in chapter 3.2.3 with input from chapter 4.1 on compliance with MDR.

The update of the clinical evaluation for CTG Online was initiated by a regular audit by the notified body that identified shortcomings in the risk management documentation, an issue with labelling of the accessory of the device and the fact the clinical evaluation itself did not comply to the updated guideline – revision 4 – requirements.
The main aspects that are potentially influencing the process of the clinical evaluation for Trium CTG Online are:

- The company producing the medical device is an SME
- the medical device is a software solution
- the device is relevant in the field of fetal heart rate monitoring
- the clinical evaluation is an update, not a first-time venture
- the shortcomings identified by the notified body need to be resolved

The steps of the clinical evaluation according to the proposed process of the clinical evaluation in line with the MEDDEV 2.7/1 revision 4 guidelines are:

- Step 1 - plan update of the clinical evaluation report
- Step 2 - collect internal data
- Step 3 - collect and evaluate data on equivalent devices
- Step 4 - collect clinical data
- Step 5 - systematic literature search
- Step 6 - evaluate collected clinical data
- Step 7 - assess risk/benefit
- Step 8 - plan PMS activities
- Step 9 - finalize CER
- Step 10 - approve CER

Step 1 – plan update of the clinical evaluation report

In step 1 (Figure 10), the scope of the update was planned during a meeting of the clinical evaluation team. The template for the CER was worked through and the content of each section was discussed. In was decided that unlike in the previous CER, with this time equivalent devices will be left out of the CER as there are no other online fetal heart rate surveillance systems that utilise the FIGO guidelines for displaying alarms. The output of this step is the clinical evaluation plan which is to be annexed in the final CER.

Step 2 – collect internal data

The first step after the initial meeting is to collect all internal data (Figure 1, step 2) about the device and fill in the parts covering the general info about the device. The intended use, indications, precautions and warnings are to be filled using the instructions for use from the technical documentation of the device. A question was raised about changing the precautions so that it would cover a notice to avoid the use of fetal heart rate surveillance for low-risk pregnancies as the false-alarm rate of the technology is high [27], hence generalised use in low-risk cases would result in a heightened caesarean section rate, meaning that many of these operative interventions would be in fact unnecessary. As adding the precaution would result in needing to change the technical documentation of the device which was deemed inappropriate

because of the general nature of the issue, it is to be validated as a risk via literature review and balanced with the benefits of the device.

CTG Online has two product variations on the market. For Japanese market, the alarms are produced using a 5-tier color coded system and for rest of the world, a conventional 3-tier red, yellow and green system is used. The existence of different product versions, even with slight changes, influences the terms set for collection of internal and external data and data from literature. It was decided to set the search terms accordingly so that data from both versions would be covered. Compliance with other devices is in this case compliance with fetal heart rate monitors that provide the raw signals that the software gathers, processes and visualizes. It is crucial to demonstrate the unaltered and adequate transfer of raw data from the monitors to the central surveillance system.

For summarising risks and benefits of the device, it is helpful at this point to list all probable benefits and risks, validate the relevance and existence of enough evidence for each proposal and adjust the lists accordingly after assessing the risk/benefit profile. The claims in marketing materials should be cross-referenced with the performance, safety and benefit/risk assessment of the device in order to avoid discrepancies. The parts of the previous clinical evaluation report that are still relevant can be used for filling in various chapters of the CER under update.

Step 3 – collect and evaluate data on equivalent devices

According to the decision made when planning the evaluation, in step 3 (Figure 11) no equivalent devices are claimed, yet a list of similar devices based of the list of equivalent devices from previous CER is presented along with the justification of this decision. The list of similar devices is necessary as a base for scouring the safety databases to establish the safety of the technology in step 4 (Figure 11) as data on recalls and events from the device under evaluation only might in this case not be sufficient according to MEDDEV 2.7/1 revision 4 guidelines [12].

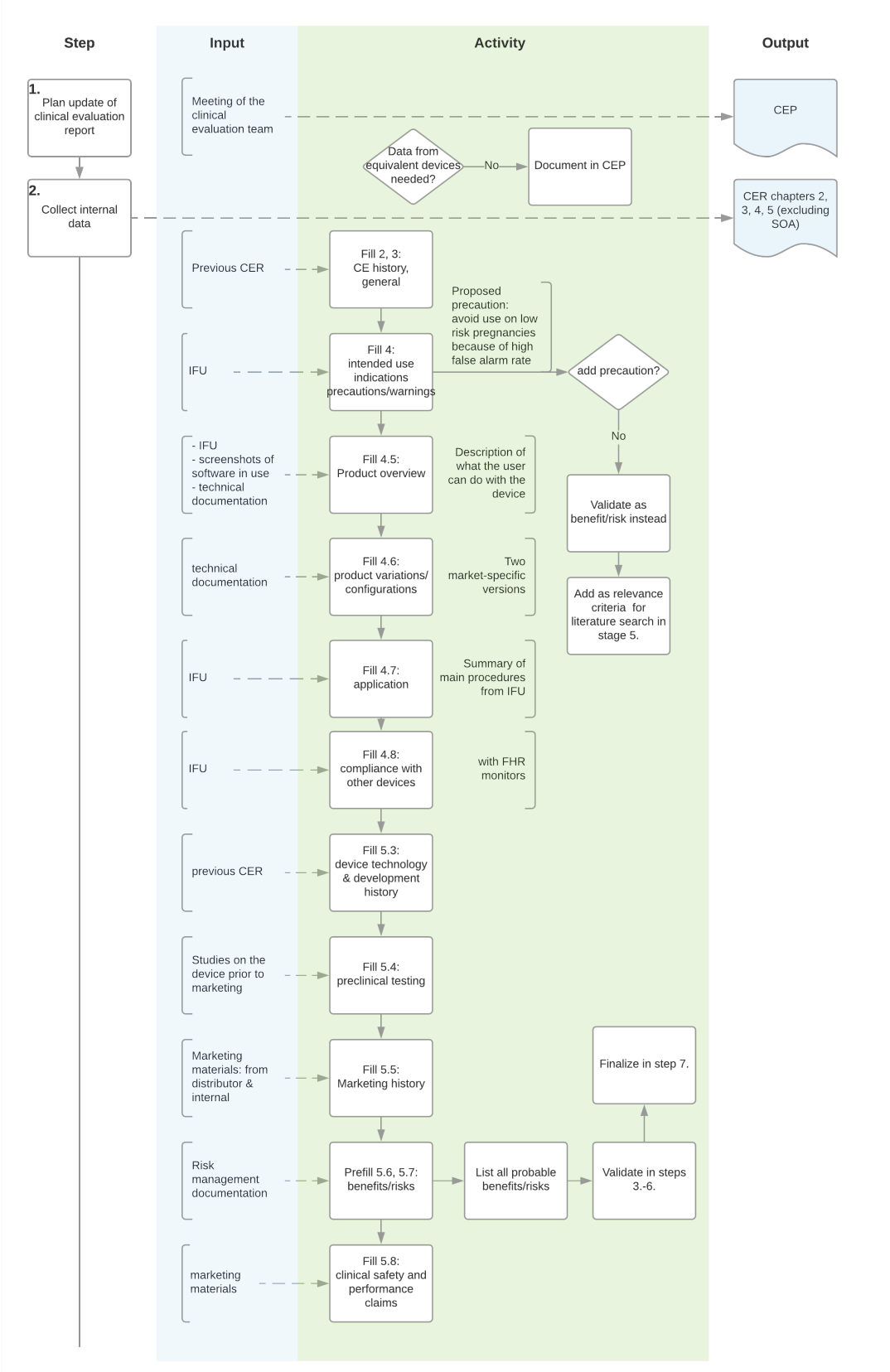

Figure 10. Steps 1-2 of the case specific clinical evaluation report update process of CTG Online. CEP – clinical evaluation plan, CER – clinical evaluation report, CE – clinical evaluation, IFU – instructions for use, FHR – fetal heart rate, SOA – state of the art [Author].

Step 4 – collect clinical data

Step 4 concentrates of collecting various clinical data that is not appropriate to be searched for in the systematic literature review, such as data on recalls and events from internal sources and safety databases, feedback from users, mentions in guidelines and research that is underway. A research paper on the relevance of FIGO guidelines utilising the experience of Trium CTG Online is referenced in the guideline of German Society of Gynaecology and Obstetrics [35], deeming the use of FIGO guidelines appropriate. As Trium CTG Online is the only device on the market using the FIGO guidelines, this reference can be used as a data on clinical experience along with comments from expert users of the device, such as heads of obstetrics departments in hospitals using the device. Trium Analysis Online and Sylvia Lawry Center for Multiple Sclerosis Research are currently in the initial steps of an international research project aiming to find ways to improve the predictive power of automated CTG analysis using a large multicentre dataset from populations in Japan, Germany, USA and Israel. Information on this study is useful in the CER as clinical investigation data.

Step 5 – systematic literature search

At this point, any data that is relevant and has not been collected yet should come up with the literature search in step 5 (Figure 11). The timeframe of the search should be set from 2015 (time of the last CER update) to present and the search terms from the previous CER should be reused to ensure continuation while any deviations should be documented and justified. A hand search should be added to include Cochrane reviews on FHR monitoring as the meta-analysis strategies of Cochrane are generally seen by the scientific community as the benchmark for systematic literature reviews and the problematics of the FHR monitoring field are highlighted in a recent meta-review [25].

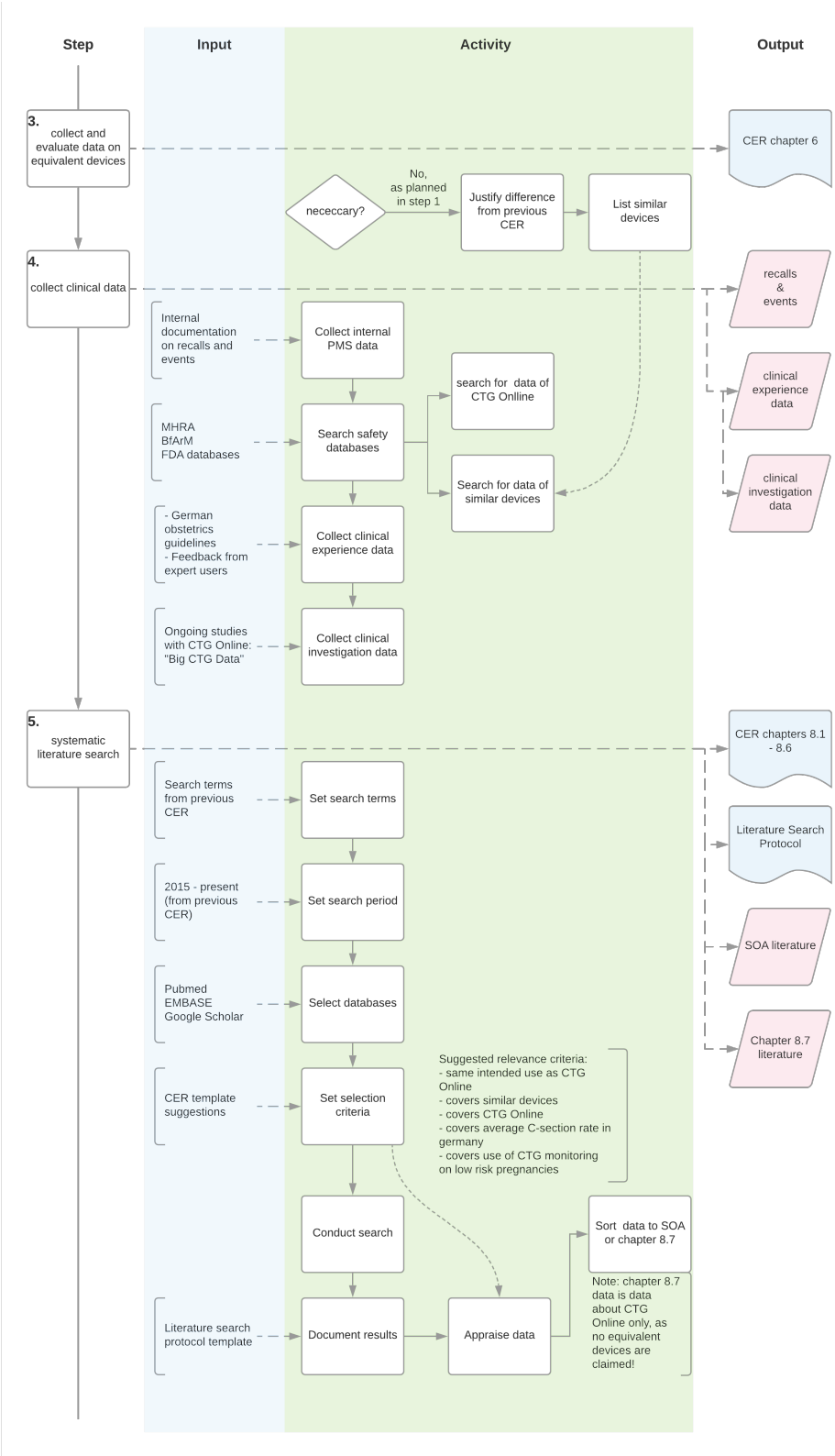

Figure 11. Steps 3-5 of the case specific clinical evaluation report update process of CTG Online. CER – clinical evaluation report, SOA – state of the art, PMS – post-market surveillance, MHRA – Medicines and Healthcare products Regulatory Agency, BfArM - Bundesinstitut für Arzneimittel und Medizinprodukte, FDA – Food and Drug Administration, CTG – cardiotocography [Author].

The review also highlights the lack of good quality research on the topic of electronic fetal heart rate monitoring, which further justifies the use of it in the CER update as a source with significant weight and quality. The MEDDEV 2.7/1 revision 4 states that multiple databases should be used for the search [12] so it is suggested that PubMed, EMBASE and Google Scholar can be used to ensure no relevant publications are left out. Appraisal can be done via relevance criteria or based on study design. [36] Journal Impact Factor is proposed in the MEDDEV 2.7/1 revision 4 as a method for appraisal but as this has been widely criticised as not being an appropriate indication for evaluating the quality of a scientific journal [38], a method proposed in the guideline for clinical evaluation by GHTF [39] might be more appropriate. Special interests like information of use of FHR monitoring in low-risk pregnancies and its correlation with caesarean section rates should be listed in relevance criteria.

The results are documented in a literature search protocol, appraised using the methods and criteria set earlier and then sorted to categories of relevance to discussing the state of the art and relevance for literature review. As it was decided that no devices are deemed equivalent, the data that can be used for literature review covers only studies where the device - CTG Online - is used, with the addition of relevant Cochrane reviews.

Step 6 – evaluate collected clinical data

All clinical data that has been collected is evaluated in this step and the results summarised in various parts of the CER. The chapters on the state of the art and the literature review are filled. The conduct of the data collection and the strategy for it are summarized.

Step 7 – assess risk and benefit

With the data gathered and evaluated until this point, the risks and benefits of the device and the technology it uses should clear and can be consolidated into a benefit/risk profile. Benefit/risk profile is also the focal point in the appraisement by the notified body due to the outcomes of the audit of Trium CTG Online. The prefilled lists of risks and benefits of the device in the general chapters of the CER should be adjusted in the light of the risk/benefit profile.

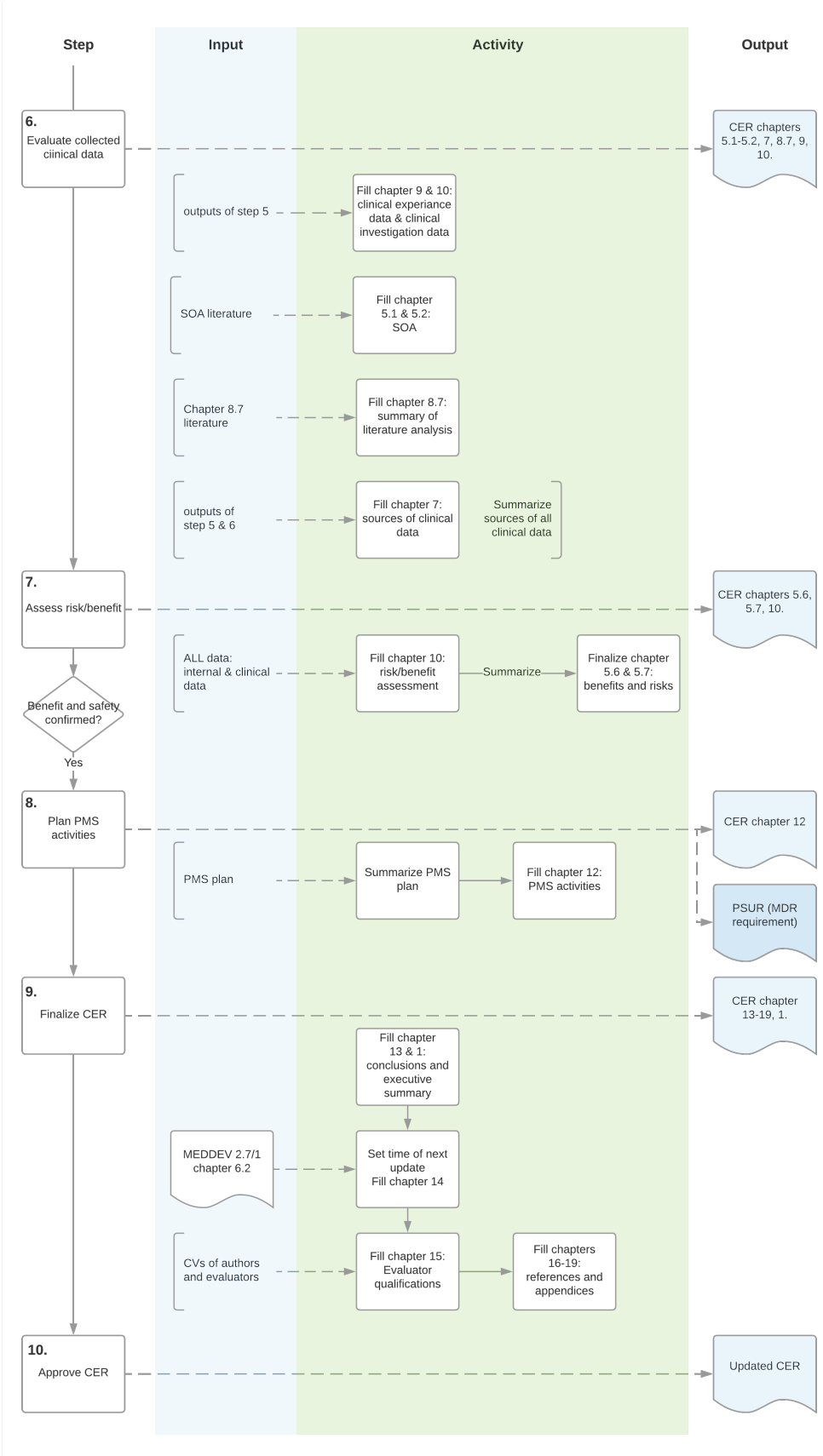

Figure 12. Steps 6-10 of the case specific clinical evaluation report update process of CTG Online. CER – clinical evaluation report, SOA – state of the art, PMS – post-market surveillance, SOA – state of the art, PSUR – periodic safety update report [Author].

Steps 8 – plan PMS activities

As the device is well-established and the company participates actively in research, it is unlikely that the benefit/risk profile will be unbalanced towards the risks. It can be assumed that there will be no need for a post market clinical follow-up study. Once the benefit and safety can be confirmed, the post market surveillance activities for Trium CTG Online should be adjusted, a PMS plan made and summarized in the CER. As stemming from MDR, the PMS plan should also be summarized in the device technical documentation in the form of periodic safety update report (PSUR).

Step 9 and 10 – finalize and approve CER

All unfinished chapters of the CER should be filled, conclusions made and a plain language executive summary should be written for publication in the EUDAMED database once it is launched. The CVs of the clinical evaluation team are gathered and summarized. As CTG Online is a class IIb medical device, the default update interval of 1 year that has been followed from the first version of the CER is appropriate also under the requirements of MEDDEV 2.7/1 revision 4. References to full documents are added. The finalized CER shall be approved by a meeting of the clinical evaluation team.

4.3.1 Feedback on the case specific process map

The proposal of a case specific process for updating the CER was gained through in-depth interviews with the members of the clinical evaluation team. The input from an interview with a freelance medical writer with over 15 years of experience in consultancy and writing services for the pharmaceutical, biotechnology and medical devices industry, was also added as expert feedback. The interview covered topics such as the implications of the policy changes to the industry and the viability of the process mapping approach as a tool to bring more clarity into the process. The results of the interviews are presented in this chapter.

Three members of the clinical evaluation team of CTG online were interviewed – the quality manager, the manager of engineering and the product manager of CTG Online. At the beginning of each interview, the case specific process map was shown to the team member, followed with questions regarding the usability and comprehensiveness of the process. In the second block of questions, the case-specific influences presented in chapter 3.3 were discussed.

None of the team members found any shortcomings or redundancies in the process and confirmed that the shortcomings of the notified body would be adequately covered by the process proposed in chapter 3.3. Furthermore, the team members expressed that a functional process map would simplify the work related to clinical evaluation considerably:

> *"The challenge is to decide how the process will be in the end. (...) We could benefit from fixing this process and finding a solution that works in a proper way for us." (...) if the process map is stabile, we could achieve a robust process and I would hope that in the future these updates wouldn't be so painful."*

The format of the guidelines was deemed confusing to an unskilled reader by the experts which implies the need for manufacturers to accumulate novel expertise for conducting the clinical evaluation:

> "(…) *the way the guideline is written, that fact that it's written out in these different stages, means that for somebody that has to work out what they have to do, they have to look at several places in the guideline. It's not a case of just*

logically following it through, you've got to jump about the guideline a lot. So you can't do that unless you're very familiar with what you are doing."

Furthermore, the approach of mapping the detailed process of the clinical evaluation was regarded by the expert as something that will become more and more necessary in the near future.

A theme that was recurring throughout the interviews was the added workload and therefore, a need for more resources to cope with the requirements of the revision 4 of MEDDEV 2.7/1 guidelines. The team members linked this issue with the the enterprise being a small MDM, being therefore consequently under increased financial strain:

"It is difficult for small companies like Trium to cope with these requirements and have enough manpower to fulfil the requirements of revision 4. And so we need either external consultancy or to hire extra personnel just to cover all these tasks."

Main reasons for increased workload - as expressed by the team members - were issues of literature review, equivalent devices, formal documentation requirements and the the requirement for continuous documentation of the PMS activities:

"The data on the equivalent devices is insufficient, so we need to do more literature research. This is a big challenge"

"It's too much work, especially for a small company like Trium, to keep the clinical evaluation report continually updated, with all the changes that are underway – for example, risk assessment is also something that the new ISO 13485:2016 standard emphasizes."

"Doing the evaluation takes time already, but documenting it according to the requirements of the revision 4 takes at least twice as much. (...). Of course we also want to improve the literature research, but it shouldn't be the whole mission of the company. (...) it's something we have to do as an add-on to the software development. Currently the assumption is that the percentage of time we are spending on the topic of clinical evaluation is too high."

The expert interview also highlighted the difference of effect of the regulatory changes to large versus small companies:

> *"I think if you're are a global company (...) I don't think it will make any difference at all, because they already have their processes well established and I suspect they have been involved in developing these guidelines. (...). But I think for the smaller companies, it will have a huge effect. One, just having the resources and expertise to actually conduct the clinical evaluation. I think they often lack both of those and obviously the money that goes with that."*

The route to market using data from equivalent devices was considered by the expert as the main route for smaller companies with new devices. The expert noted that this route has become more difficult to take and might disappear completely because of the new requirements, which creates serious problems to smaller companies and a hindrance to innovation for the entire field.

Interestingly, the opinions of the clinical evaluation team members and the expert diverged in completely opposite directions about the effect of the changes for companies that need to update their clinical evaluation as opposed to tackling this as a first time venture. For the team members, not having to start from scratch was seen as an advantage:

> *"It would be much more difficult to prepare it from scratch for a new product for example, because in the past the requirements were not so high as they are now with this rev 4."*,

whereas by the expert opinion was that the changes would create backward-compliance issues for companies that need to update the CER:

> *"For manufacturers of longstanding devices, rules have changed over time so that the data that supported the initial CE-mark are old and don't meet current standards. The regulations that were in place when these devices were first marketed, were different from what they are now, so keeping up with the changes in hindsight is an issue for these companies."*

The nature of the device as fetal heart rate surveillance system also influences the CE, as the benefit of the technology is difficult to demonstrate and the field is so small that conflict of interest is inevitable:

"*We have to address some questions that shouldn't be on the shoulders of the manufacturer. Especially the topic of linking C-section rate with outcomes of fetal monitoring. That is something that has to be done on a real research basis, in universities for example."*

(...) if you see who's publishing papers in this field then most likely you will end up with a list of only, say 10-20 persons who are doing research in this field (...) so of course everybody has a conflict of interests."

The difficulties that the small manufacturers and the whole field have to cope with with the regulatory changes underway, can be summarized by the quote from the the manager of engineering:

"Its easy to write something in a MEDDEV document, but if the field doesn't do additional work, in the end the manufacturer ends up with this burden. And that's of course something that is difficult, especially for small companies."

5 DISCUSSION

The clinical evaluation according to MEDDEV 2.7/1 revision 4 is a hurdle for SMEs

The current and upcoming changes in the regulations for clinical evaluation of medical devices in the EU seem to have become a hurdle that has become especially difficult to tackle for small and medium sized enterprises in the medical technology industry who find their resources inevitably shifting towards coming to terms with regulatory changes instead of concentrating on their key competences such as innovation through research and development. The level of manufacturers' understanding about the changes is at the moment far from comprehensive, even though NBs are already expecting MDMs to comply with the requirements of the updated guidelines. For internal conduct of the clinical evaluation, the MDMs would need to create new competencies in regards of regulatory knowledge and clinical investigation related skills, despite the initial learning curve. Hence, the MDMs are expected to rely on the emerging field of consulting and medical writing to assist in the process of clinical evaluation for conducting the evaluation internally, both which are expected to require more resources than before. This in return implies that satisfying regulatory changes affects especially the competitiveness of SMEs as the medical device, as opposed to large companies that have more resources at hand and can either take care of MEDDEV 2.7/1 revision 4 compliance with the help of their internal resources or by their financial power in acquiring external expertise. SMEs or start-ups that are active in the field of digital health or provide software are especially vulnerable to these tendencies.

The one-size-fits-all approach of the guidelines is too general for use in practice

The MEDDEV 2.7/1 revision 4 guideline is intended to be used both by enterprises who are in the beginning of their journey towards CE-marking and entry to the market and enterprises that are already on the market. However, the difference between the main focus of the clinical evaluation for manufacturers of CE-marked and non-CE-marked devices is vast, as the latter already has a body of previous CER versions, clinical investigations, PMS and quality management data. In some cases, though, this might become a disadvantage because the issue of backward-compliance. The main purpose of the guidelines should be to help manufacturers to tackle the clinical evaluation process and CER creation or update process. However, it is currently not up to the task as the

one-size-fits-all design creates confusion because of the multitude of options and situations it covers. Issuing additional implementation guides with information on how to adapt the advice to the specific device and the situation of the enterprise could make the guidelines more approachable and more in line with the presumed main purpose of the document which is to help manufacturers to comply with the requirements of the medical device policies.

The format of the guideline if not user-friendly

The revision 4 guideline tries to simultaneously be a standard-like list of requirements and rules and a practical guide on the process of clinical evaluation. Unfortunately, the final revision 4 guideline is lacking in practicality and user-friendly process description, unlike the revision 3. The internal contradiction embedded in the revision 4 guideline is evident for example from the way the proposed stage by stage approach is conflicting with the format of the guideline, as information is partitioned between the main body and annexes in a manner which forces the reader to jump back and forth through the content, making it easy to lose the sense of the process in hand.

The guidelines are not matching the needs of the industry

The change in the content between revision 3 and revision 4 is significant, but nevertheless mostly add-ons to what has already been stated in previous revisions. Taking into account the confirmation of commitment to patient safety which the strict new requirements are ensuring, that has been under attack in the EU following the PIP scandal and controversy about metal-on-metal hip implants, the additions and particularizations, especially for providing the necessary evidence to prove the validity of the data, were long due. Yet the contrast of how the content is presented in revision 4 in comparison to revision 3 is disquieting. What should ideally be a jargon-light translation of the judicial language of the medial device directive and the medical device regulation is in fact a document that infers having skills to work with highly specialized language and format and implies, for most MDMs, the need for external advice. A look into the requirements for evaluator qualifications confirms this. The health of the internal market in regards of ensuring the continuation of innovation, prevention of monopolization and equal conditions to every enterprise, regardless of the size, seems to be under question for the manufacturers on the medical device field. The

guidelines represent the ideal framework and ideal standards of ethical integrity of the European community, yet it is unsure if in everyday practice this ideal indeed motivates or instead discourages the manufacturers to pursue the common goal to provide optimal, safe and quality care for the patients.

Mapping of the general process of the CE revealed redundancies

Regardless, to stay on the market, the MDMs have to be comply with the new requirements. The process map of the clinical evaluation process described in the MEDDEV 2.7/1 revision 4 guidelines was surprisingly just confirmative of the all too general nature and idealistic approach of the guidelines.

During the mapping of the general process, stage III (Figure 7) was found to be somewhat arbitrary because it converges in with stage (IV Figure 8) as the appraisal and analysis of data are interlinked. One cannot appraise data without analysing it and vice versa. The guideline calls this stage the appraisal of pertinent data, yet this is contradictory with the description of stage IV (analysis) that indicates using the criteria set in the data appraisal plan for analysing the data. Hence, if separating the guideline into stages for disclosing a process is sincerely the goal of the guideline, as suggested by the approach, it would be more appropriate and less confusing to designate stage III as the setting of the appraisal plan. In conclusion, stage III is about educating the evaluators about the guidelines' detailed description on how to appraise data and develop a strategy for an unbiased literature review. This communicates a strong message from the European Commission that the clinical evaluation should be taken much more seriously by the MDMs as until the latest update of the MEDDEV 2.7/1 revision 4.

Clinical evaluation versus clinical evaluation report as the orientation of the process

In every case, whether an update or a first-time endeavour, a crucial distinction clarifies the process considerably – while the guidelines speak about the clinical evaluation, medical device manufacturers and also the evaluating notified bodies concentrate on the clinical evaluation report. When looking at the process as the creation or update of the clinical evaluation report through the clinical evaluation as opposed to conducting a clinical evaluation and documenting it in the CER, the process is more in line with the

perspective of the manufacturers and hence the real-life implementation of these guidelines.

Mapping of the case specific process to match the needs of the industry

Redesigning the process to match the perspective of the industry does not imply making compromises on user and patient safety. On the contrary, it has the potential of creating a sincerer environment where the values embedded in the guidelines, medical device directives and the future medical device regulation can be openly followed. The proposed CER update process presented in the case study of this paper is an example of this industry-matching approach. By adopting this, the MEDDEV 2.7/1 revision 4 guidelines would be not be only a description of a tool, but a practical and useful instrument for complying with the upcoming medical device regulation.

6 CONCLUSIONS

The framework of the European Union regulations for clinical evaluation of medical devices is currently undergoing vast changes in order to bring the safety and performance of the medical devices on the EU market to a higher level of stringency, as a reaction to incidents of foul play and resulting adverse health effect by a few major companies in the last decade. The first, and steep step of the changes was brought on by enforcing of the MEDDEV 2.7/1 revision 4 guidelines for clinical evaluation of medical devices and will continue with the enforcement of the Medical Device Regulations in the near future. For manufacturers of medical devices on the European Union market, the update has and is continuing to pose a hurdle, as the increased amount of resources needed for conducting a clinical evaluation in compliance with the new guidelines is a challenge, especially for small and medium sized enterprises who see their priorities shifting from innovative research to coping with the increased regulatory burden.

The MEDDEV 2.7/1 revision 4 guideline mostly adds to the aspects already covered by the previous revision, but the amount of detail added is huge. The main changes cover the frequency of updates of the clinical evaluation report, establishing the state of the art, establishing the validity of the data, claiming equivalent devices, clinical investigations, risk/benefit analysis, post market surveillance and post market clinical follow-up, evaluator qualifications and the need for Periodic Safety Update Report and Summary of Safety and Clinical Performance. Moreover, the structure of the guideline has been thoroughly changed for the revision 4. Although the guideline proposes a generic process for manufacturers on how to conduct the clinical evaluation, this is unhelpful because of the generality of the approach. Furthermore, when following through the guidelines, it is extremely difficult to get a grasp of the whole process in detail from start to beginning without expert expert knowledge and previous experience in working with regulatory documents, because of the way the process meanders through the main part and appendices. The guidelines are more of a requirement list than a user-friendly walkthrough of the clinical evaluation.

A possible way to make the the clinical evaluation process according to the guideline more straightforward is visualize the process by mapping it using the common flow chart method. This approach does clarify the requirements but offers little help when the map is to be used in a real-life application as the generality of the process remains. The mapping highlighted the need for an approach that is more in line with the needs of the manufacturers for whom the main goal of the clinical evaluation is the completion of an acceptable clinical evaluation report that would enable the manufacturer to live up to the high standard of patient safety and thereby ensure the viability of the product.

The approach that is oriented towards clinical evaluation report and is hence more in line with the everyday functioning of the manufacturers of medical devices gives the manufacturer clear inputs and outputs and guides the manufacturer through the process while simultaneously giving precise instructions on when and which parts of the clinical evaluation report to fill in. The process presented in this thesis is mapping the clinical evaluation for a small manufacturer that is producing a software solution for surveillance on fetal heart rate. As the clinical evaluation process needs to be adapted to the needs of the enterprise, the nature and the point of time in the product lifecycle of the device, the proposed process map has to be modified for application on other devices.

The clinical evaluation report-oriented process has been deemed promising by experts and industry representatives as an approach that could facilitate the manufacturers in achieving compliance with the MEDDEV 2.7/1 revision 4 guidelines and MDR via conducting the clinical evaluation. Further research is needed to confirm the usability of the process map in action and for other types of enterprises and device types to make sure that patient safety and device performance is not compromised when using the process for the conduct of the clinical evaluation.

DECLARATION OF CONFLICTS OF INTEREST

The author was affiliated with the enterprise under analysis in the case study, Trium Analysis Online, with a master student contract for the duration of the case study period. No further conflicts of interests to declare.

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APPENDICES

Appendix 1 – detailed description of changes between MEDDEV 2.7/1 revision 3, revision 4 and MDR regarding clinical evaluation

Aspects of revision 4 that are extending on the content of revision 3

Frequency of updates

If the revision 3 generally states that the clinical evaluation process is to be first undertaken before the marketing of the device and must be repeated periodically, taking into account the emergence of new safety and performance information [22], then revision 4 expands on that significantly. When revision 3 talks about clinical evaluation process, the revision 4 is equally concerned with the outcome of that process – the CER. Revision 4 requires the manufacturer to specify a justified frequency of updates of the CER for the device under evaluation. In doing so, the MDM has to consider the overall risk the device carries for the users and patients, whether the device is well established and if the device itself or the field of use has or will undergo changes. For low-risk, well-established and unchanging devices (f.e thermometer), the proposed timeframe of CER update frequency is every 2 to 5 years. For devices carrying high risks (f.e implantable devices) or novel devices, the CER should be updated at least annually. In the case of emergence of new potentially game-changing information generated by post market surveillance activities of the manufacturer or when an audit by the NB has revealed shortcomings, the clinical evaluation is to be updated immediately. [12]

Establishing the state of the art

In revision 3, there are general notions about making sure that the literature review and evaluators knowledge reflects the current standard of care and other available diagnostic or treatment options for the condition the device is intended to be used in [22]. Chapter 8.2 of the revision 4 states that state of the art is to be established by literature searching as in revision 3, yet revision 4 is more detailed about how to do that and what to consider.

The part of the literature review concerned with the state of the art should describe the clinical background and current knowledge, including specific patient populations and

medical conditions that are to be managed with the device. The safety and performance endpoints used for the clinical evaluation and the risks and benefits of the device have to be identified and justified. Other available treatment or management options and claimed equivalent devices or benchmark devices should also be covered to show that the practices or devices that have been claimed equivalent are indeed relevant in terms of embodying the current best knowledge and practice. Only then can the MDM make claims that its device is better or equal to the competitors' devices or other management options [23]. Establishing the state of the art is also important for positioning the device under evaluation within the treatment or management portfolio of the condition the device is used for. The state of the art is based on applicable standards and guidance documents, data about the clinical background and similar and benchmark devices. [12]

Scientific validity of the data

The current guideline puts far more emphasis on the scientific validity of the data used for clinical evaluation than the revision 3. With this update, the generation, validation and analysis of the different datasets becomes a key part of the evaluation. Throughout the document, explanations are given regarding the handling and gathering of data concerning each stage of the clinical evaluation, so that the ensuing CER would be based on comprehensive and objective data that has been used so that the weight of each piece of data is considered. Revision 4 clarifies how to evaluate the methodological quality of the data and to shows how the outcomes of that data can be aligned with the outcomes of the intervention with the device [23]. The guideline also discusses how to do a literature search including suggesting retrieval and appraisal methods, how to analyse the data and how to use data properly for demonstration of conformity with the essential requirements. Sections 8,9, 10 and appendices 5,6 and 7 of the revision 4 are concerned with scientific validity of data. [12]

Equivalent devices

In order to undertake a clinical evaluation, the MDM needs sufficient amount of clinical data about the device. As this is mostly not possible financially or time-wise, especially for small and medium sized enterprises (SMEs) and for novel devices, the MDM has the possibility to use data about a similar device. That is where the demonstration of equivalence is needed. In revision 3 a footnote comment to appendix F states that

equivalence is to be shown via clinical, technical and biological terms [22]. In revision 4 the criteria remain unchanged, but it introduces much more detail to this process with the requirements described in appendix 1 of the guideline.
Before revision 4, it was not uncommon for MDMs to interpret the guidelines so that equivalence could be demonstrated based on multiple devices, each fulfilling one of the criteria for equivalence. With revision 4, this is no longer accepted – MDMs may claim equivalence to multiple devices, but each device has to fulfil all three criteria on its own. The requirements for demonstrating equivalence are rather stringent. For example, the patient populations used for acquiring the data about equivalent devices have to be analogous to EU population. The equivalent device must be CE-marked.

Establishing the need for clinical investigation

Although revision 3 covers the topic of clinical investigation in the context of investigations carried out by the manufacturer or by other researchers [22], it is not specified when it is not sufficient to rely on clinical investigations found with literature research so that the MDM has to perform the clinical evaluation itself. Revision 4 amends that in appendix 2, where it is clarified that when gaps are found in the data about the device that cannot be filled in other ways, a clinical investigation is due [12].
Revision 3 interestingly does not reference the medical device directives about the requirement for MDMs of implantable, high-risk and class III devices to almost always carry out a clinical investigation. Revision 4 corrects that [12] and adds additional aspects that indicate the need for clinical investigation, such as whether the device harbouring a new or unproven technology, whether the device is intended to have a new clinical use based on existing technology, invasiveness, whether new risks have emerged or whether alternative devices or procedures with lower risk have become available, among others [12].

Risk / Benefit analysis

Revision 3 and revision 4 both call for the risks to the patient and other users to be analysed and weighted against the benefits of the device, cross-referencing the resulting risk/benefit profile with the risk management activities of the MDM, but revision 4 further ties the outcomes of the post market surveillance and post market clinical follow-up to the evaluation of the benefit/risk profile, making yet again a reference to

the ongoing nature of the clinical evaluation. Where revision 3 was general, revision 4 specifies with a requirement that the benefits and risk must be quantifiable in appendix 7.2. Measurable improvements of the clinical outcome and severity and rates of the possible harmful events probability must be documented, as well as the duration and probability of both benefits and harmful events. An acceptable risk/benefit profile is one of the essential requirements [12].

Post market activities

Besides the data found in literature, documentation of equivalent devices and data generated by clinical investigations, the clinical evaluation must consider information gained from post market surveillance (PMS) and post-market clinical follow-up (PMCF), both a crucial part of quality assurance of risk management activities of the MDM. Revision 3 was clear throughout the document about the role of that data, yet in practice the PMCF is oftentimes neglected and information gathered by PMS has little contact points with the clinical evaluation [21]. In revision 4, the connection of post market activities and the ongoing nature of clinical evaluation is strongly reinforced in multiple sections. More specifically, requirements in appendix 12 of the guideline are to make sure that the PMCF is indeed undertaken and that the MDMs PMCF plan is appropriate to fill the gaps on data identified through the clinical evaluation by requiring the NBs to take an active role for confirming the plan and ensuring that the outcomes of the PMCF are fed into the clinical evaluation process and properly documented in the CER [12].

Aspects of revision 4 that are to be considered novel additions to revision 3

Evaluator qualifications

Something that is covered with one sentence in the appendix F (checklist for the NBs) in revision 3, is the question of who should perform the clinical evaluation. In revision 4, subchapter 6.4 is dedicated to that.

The clinical evaluation can be performed by an individual or a team. The latter is though more likely, as the skill sets necessary can be represented within the team without the need for every member to possess all of the expertise and qualifications. The evaluator

(team) should have a relevant higher education degree plus five years of related professional experience or just ten years of professional experience on the field when degree is not deemed necessary for the task. The evaluator(s) should have a thorough understanding of the device technology and use, the management and diagnosis of the condition the device is intended to be used for, be acquainted with research methodology, have experience with information management and medical writing and understand the regulatory requirements. There is also an escape clause that allows any of the requirements to be unfilled in case it is justified. From all team members, a declaration of interests is needed to prevent bias rising from conflict of interest. [12]

Access to data of equivalent devices

Revision 4 also expects the MDM to have access to technical documentation of the equivalent devices - including information about how the device was manufactured and pre-clinical study reports [12]- meaning access to sensitive, confidential or unavailable data of competitors. Furthermore, the NBs are expected to challenge the MDMs attempts to obtain this data [12]. This is a clear step towards alignment with the MDR, which requires the MDM in specific cases to have a contractual agreement with the manufacturer of the equivalent device for access to this data [1].

Aspects of the MDR that add to the clinical evaluation process

Periodic Safety Update Report

The article 86 and article 61, paragraph 11 of MDR sets a requirement for the manufacturer to provide a Periodic Safety Update Report (PSUR) among the technical documentation of the device. For class III and implantable devices, the PSUR is to be updated at least annually and for class IIa devices, every two years. The PSUR summarises the results and conclusions of the Post Market Surveillance (PMS) data acquired according to the PMS plan set up by the manufacturer in the CER [1].

Summary of Safety and Clinical Performance

For class III and implantable devices, the MDR specifies in article 32 the need to submit a summary of safety and clinical performance. The main objective of this summary is to

give an overview of the device via the so far not yet launched public medical device database EUDAMED, hence the summary has to be written in a way that is understandable for the untrained reader [1].

Additions to conduct clinical evaluation and post market clinical follow-up

The Annex XIV, part A of the MDR reinforces and specifies the need for the MDM to set up a clinical evaluation plan and to document it in the CER. Part B of the same annex declares that the MDMs approach to post market clinical follow-up has to be proactive as opposed to reactive as it is usual at the moment [1].

Access to data of equivalent devices in specific cases

In specific cases, the MDM is required to have a contractual agreement with the manufacturer of the equivalent device to omit conducting a clinical evaluation. This applies when the device a manufacturer wants to bring on the market is based on a second device made by another manufacturer so that equivalence between the devices can be claimed and validated by the NB. Also, the clinical evaluation of the second device must be sufficient and the second device must be already on the market. Only in this case do the manufacturers of the two devices have to have a contract for accessing technical documents and the manufacturer of the second device must give evidence of the existence of this contract to the NB. This is specified in article 61, paragraphs 4 and 5 of the MDR [1].

Appendix 2 – TOC analysis between MEDDEV 2,7/1 revisions 3 and 4

Main body	
MEDDEV rev 3	MEDDEV rev 4
Preface	
1.0 Introduction	1.0 Introduction
2.0 Scope	2.0 Scope
3.0 References	3.0 References
4.0 definitions	4.0 definitions
	5.0 Abbreviations
5.0 general principles of clinival evaluation	6.0 general principles of clinival evaluation
	6.1 What is clinical evaluation?
	6.2. When is clinical evaluation undertaken and why is it important?
	6.2.1. Clinical evaluation undertaken for the development of a medical device
	6.2.2. Clinical evaluation for initial CE-marking
	6.2.3. Updating the clinical evaluation
	6.3. How is a clinical evaluation performed?
	6.4. Who should perform the clinical evaluation?
	7. Definition of the scope of the clinical evaluation (Stage 0)
6.0 Sources of data/documentation used in a clinical evaluation (Stage 1)	8. Identification of pertinent data (Stage 1)
6.1 Data generated through literature search	8.2. Data retrieved from literature
6.2 Data generated through clinical experience	8.1. Data generated and held by the manufacturer
6.3 Data from clinical investigations	
7.0 Appraisal of clinical data (Stage 2).	9. Appraisal of pertinent data (Stage 2)
	9.1. General considerations
	9.2. The appraisal plan
	9.3. Conduct of the appraisal
	9.3.1. How to evaluate methodological quality and scientific validity
	9.3.2. How to determine the relevance of a data set for the clinical evaluation
	9.3.3. How to weight the contribution of each data set
8.0 Analysis of the clinical data (Stage 3)	10. Analysis of the clinical data (Stage 3)
	10.1. General considerations
	10.2. Specific considerations
	10.3. Where demonstration of conformity based on clinical data is not deemed appropriate

9.0 The Clinical Evaluation Report 10 The role of the notified body in the assessment of clinical evaluation data 10.1 Examination of design dossier 10.2 Evaluation as part of the quality system procedure 10.3 Notified body specific procedure and expertise	11. The clinical evaluation report (CER, Stage 4) 12. The role of the notified body in the assessment of clinical evaluation reports
Appendix/main body overlappings	
10.3 Notified body specific procedure and expertise 10.1 Examination of design dossier 10.2 Evaluation as part of the quality system procedure 9.0 The Clinical Evaluation Report E: A possible format for a clinical evaluation report	A12.4. Notified body specific procedures and expertise A12.2. Examination of a design dossier (Annex II.4; Annex 2.4) or of a type examination dossier A12.3. Evaluation as part of quality system related procedures A9. Clinical evaluation report - proposed table of contents, examples of contents
Appendixes	
A: A possible format for the literature search report B: A possible methodology for documenting the screening and selection of literature within a literature search report C: Some examples to assist with the formulation of criteria D: A possible method of appraisal E: A possible format for a clinical evaluation report	A1. Demonstration of equivalence A2. When should additional clinical investigations be carried out? A3. Device description - typical content A4. Sources of literature A5. Literature search and literature review protocol, key elements A5.1. Background to the literature search and the literature review A5.2. Objective A5.3. Methods A6. Appraisal of clinical data - examples of studies that lack scientific validity for demonstration of adequate clinical performance and/or clinical safety A7. Analysis of the clinical data - compliance to specific Essential Requirements A7.1. Conformity assessment with requirement on safety (MDD ER1 / AIMDD ER1)

	A7.2. Conformity assessment with requirement on acceptable benefit/risk profile (MDD ER1 / AIMDD ER1) A7.3. Conformity assessment with requirement on performance (MDD ER3 / AIMDD ER2) A7.4. Conformity assessment with requirement on acceptability of undesirable side-effects A8. Devices for unmet medical needs - aspects to consider A9. Clinical evaluation report - proposed table of contents, examples of contents A10. Proposed checklist for the release of the clinical evaluation report A11. Information on declarations of interests. A12. Activities of notified bodies A12.1. Notified body assessment of clinical evaluation by conformity assessment route A12.2. Examination of a design dossier (Annex II.4; Annex 2.4) or of a type examination dossier A12.3. Evaluation as part of quality system related procedures
F: Clinical evaluation checklist for Notified Bodies	A12.4. Notified body specific procedures and expertise

Appendix 3 – Interview release form

Interview Release form

I understand that Sille Kima (the Author) is preparing, writing, and will publish a master thesis on the subject of the implications of the current and upcoming changes to the EU medical device regulatory framework to the medical device industry, which is currently titled "*Update of the European Union requirements for clinical evaluation of medical devices: a case study on the example of fetal heart rate surveillance software*" (the Work), to be published in the library of Tallinn University of Technology.

In order to assist the Author in the preparation of the Work, I have agreed to be interviewed and to provide information and other materials to be used in connection with the Work, including my personal experiences, remarks, and recollections.

I hereby grant permission to the Author to quote or paraphrase all or any portion of the interview in her Work. Permission granted is for World rights in all languages and versions of the Work, including electronic versions.

I acknowledge and agree that I am not entitled to receive any form of payment from the Author or the Technical University of Tallinn.

Agreed and confirmed:

_____ Date: _____

Signature

_____

Name (print)

Comments:

Appendix 4 – Interview protocol for feedback from clinical evaluation team

Feedback for case-specific process mapping of the clinical evaluation report update process of Trium CTG Online

Interviewee (Title and Name): _____

Interviewer: _____

Survey section used:

_____ A: Usability of the process map

_____ B: Influence of main case specific aspects

_____ C: Main challenges

Other topics discussed: _____

_____

Documents obtained: _____

_____

_____

Post Interview comments or leads:

_____

Introductory Protocol

To facilitate our note-taking, we would like to audio tape our conversations today. Please sign the release form. For your information, only researchers on the project will be privy to the tapes which will be eventually destroyed after they are transcribed. In addition, you must sign a form devised to meet our human subject requirements. Essentially, this document states that: (1) the information gathered with this interview will be anonymised to your position in the company, (2)

your participation is voluntary and you may stop at any time if you feel uncomfortable, and (3) we do not intend to inflict any harm. Thank you for agreeing to participate.

Introduction

This interview Is part of a master thesis that aims to bring more clarity into the clinical evaluation process as stated in the MEDDEV 2.7/1 revision 4 guidelines for clinical evaluation. For this purpose, as a part of the thesis, the process of updating the clinical evaluation report for an SME specializing on providing software for fetal heart rate surveillance was mapped. To gather feedback on the accurateness of this process map and identify the main challenges for the enterprise, personal interviews with the members of the clinical evaluation team are conducted.

A:

1. What is your position in the enterprise and your responsibilities in the clinical evaluation team?
2. Are any relevant step/s missing from the process map?
3. Do you see any step/s that seem redundant or that could be merged?
4. Do you think that the shortcomings identified by the notified body during the audit are sufficiently addressed in this process proposal?

B:

5. What is unique for your enterprise about the clinical evaluation (rev 4) from the perspective of a small medical device manufacturer?
6. What is unique for your enterprise about this clinical evaluation from the perspective of a provider of a software solution?
7. What is unique for your enterprise about the clinical evaluation from the perspective of an enterprise working in the field of fetal surveillance?
8. How do you think does your enterprise benefit from having an update of the CER instead of a first time clinical evaluation when complying with the new revision 4 guidelines? Or does it pose a disadvantage?

C:

9. What do you think are the main challenges for your enterprise regarding the clinical evaluation?