Tampere University

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RISK MANAGEMENT IN ACADEMIC MEDICAL DEVICE RESEARCH ENVIRONMENT

Case mTMS prototype

M. Sc. (Tech) Thesis
Faculty of Medicine and Health Technology
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January 2022

ABSTRACT

Viivi Lankinen: “Risk Management in Academic Medical Device Research Environment: Case mTMS Prototype”
M. Sc. (Tech) Thesis
Tampere University
Master’s Degree Programme in Biotechnology and Biomedical Engineering
January 2022

Universities are places for learning and education but importantly also hubs for innovation and arising technologies. The know-how and expertise of several sciences collaborate and form a great base for, *e.g.,* medical device research and development. The field of medical devices is highly regulated by national legislation and ruling to ensure the safety and effectiveness of the devices available on the market. The new Medical Device Regulation came to force in May 2021 which sets the requirements for medical device manufacturers for obtaining a CE (Conformité Européenne) label that allows free marketing and selling of the devices in European market. The regulatory body in the United States is the Food and Drug Administration which requirements slightly differ from the MDR. The regulatory environment is a jungle that the manufacturers must conquer and accomplish. However, there is a long list of internationally recognized state-of-art standards that assist the manufacturers in doing so.

Risk management, guided by the ISO 14971 standard, is one of the most crucial parts in medical device development. The aim of this thesis was to produce a preliminary risk management system according to ISO 14971, for a novel multi-locus transcranial magnetic stimulation (mTMS) prototype developed in Aalto University in Espoo. mTMS is advanced technology from the traditional transcranial magnetic stimulation (TMS) where high currents are passed through electromagnetic coil adjacent to subject’s head. The current in the coil generates a magnetic field which penetrates the skull and induces and electric field in the underlying brain tissue. The electric field can either excite or inhibit the neurons and thus affect brain signalling. mTMS allows electrical adjusting of the stimulation parameters (*i.e.,* location, intensity, orientation) instead of physically moving the traditional TMS coil.

The preliminary risk management system was produced by studying the regulatory requirements, especially ISO 14971, and participating a training on the functional prototype in its operating environment. In addition, discussions with different stakeholders concerning the technology were a great data source in the risk management process. Overall, 35 hazards leading to 74 different hazardous situations and 112 harms, of which 59 were unacceptable and 53 acceptable, were identified in the risk management process. After appropriate risk mitigation, the residual risks were all acceptable. Some risk control measures, and risk control verification methods were suggestions for future design whereas some of them were already existing in the current prototype design.

Another aim of this thesis was to study the organization of risk management, and quality and regulatory (Q&R) awareness among other similar academic medical device commercialization projects. To create a general view of the proposed topics, three other Aalto University researchers were interviewed. Generally, the risk management was organized very similarly in the projects. The researchers’ awareness regarding Q&R issues before starting the project was not very high and commonly, they were facing similar kind of challenges in the risk management process. The challenges were mainly related to the low maturity of the project, the lack of clinical data or other important information regarding the features of the device, and difficulties in the communication within the project.

The risk management system was produced for internal purposes of mTMS commercialization project and to serve as a base for later purposes of obtaining a regulatory approval.

Keywords: medical device, research and development, regulation, risk management, ISO 14971, multi-locus transcranial magnetic stimulation

TIIVISTELMÄ

Viivi Lankinen: Riskienhallinta lääkinnällisten laitteiden akateemisessa tutkimusympäristössä: mTMS-prototyypin tapaus
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Tammikuu 2022

Yliopistot ovat sekä oppimiskeskuksia että paikkoja uusille innovaatioille ja kehitystyölle. Monen eri alan tietämys ja ammattitaito yhdistyvät yliopistoissa, luoden hyvän pohjan esimerkiksi lääkinnällisten laitteiden tutkimus- ja kehitystyölle. Lääkinnällisten laitteiden ala on tarkoin säännelty. Säännöksillä ja lainsäädännöllä varmistetaan markkinoitavien laitteiden turvallisuus sekä kliininen tehokkuus. Uusi lääkinnällisten laitteiden regulaatio astui voimaan Euroopan Unionissa toukokuussa 2021. Siinä asetetaan vaatimukset, jotka valmistajien tulee täyttää saadakseen laitteellensa CE-merkinnän. Lääkinnällisiä laitteita valvova viranomainen Yhdysvalloissa on elintarvike- ja lääkevirasto (Food and Drug Administration), jonka vaatimukset poikkeavat joiltain osin Euroopan säätelystä. Monimutkaisten ja vaativien regulatoristen vaatimusten täyttämistä avustavat lukuisat kansainvälisesti hyväksytyt standardit.

Lääkinnällisten laitteiden riskienhallintaa ohjaa ISO 14971 -standardi. Riskienhallintaa voidaan pitää yhtenä tärkeimmistä osa-alueista lääkinnällisten laitteiden tuotekehityksessä. Tämän diplomityön tarkoituksena oli tuottaa alustava riskienhallintajärjestelmä Aalto-yliopistossa kehitetylle uudelle monipaikkaiselle transkraniaaliselle magneettistimulaatiolaitteelle (mTMS). Transkraniaalisessa magneettistimulaatiossa aivokudokseen luodaan sähkökenttä ajamalla voimakas virtapulssi pään läheisyydessä olevan kelan läpi. Sähkövirta luo magneettikentän, joka puolestaan indusoi aivoihin sähkökentän, jonka avulla voidaan vaikuttaa hermoratoihin joko eksitoivasti tai inhiboivasti. mTMS eroaa perinteisestä TMS:sta siten, että sillä voidaan sähköisesti muuttaa stimulaation sijaintia ja orientaatiota.

Alustava riskienhallintajärjestelmä tuotettiin opiskelemalla erityisesti ISO 14971:n vaatimukset ja osallistumalla prototyypin käyttöä koskevaan koulutukseen. Lisäksi projektin eri osapuolien kanssa käydyt keskustelut olivat hyvä tiedonlähde riskienhallintajärjestelmän muodostamista varten. mTMS-prototyypin riskienhallintaprosessissa identifioitiin 35 vaaraa, 74 vaarallista tilannetta ja 112 eri vahinkoa. Vahingoista 59 olivat hyväksymiskelvottomia, kun taas 53 olivat hyväksytyn rajoissa. Oikeanlaisten riskikontrollitoimenpiteiden jälkeen kaikki jäljelle jäävät riskit olivat hyväksyttäviä. Osa riskikontrolleista sekä tarkastustoimenpiteistä olivat mahdollisia ehdotuksia prototyypin kehittämiselle, kun taas osa kontrolleista oli jo käytössä tarkasteltavassa prototyypissä.

Diplomityön toinen tarkoitus oli perehtyä riskienhallinnan järjestämiseen sekä sen haasteisiin muissa samankaltaisissa akateemisissa lääkinnällisten laitteiden kaupallistamisprojekteissa. Lisäksi haluttiin perehtyä tutkijoiden yleiseen tietämykseen liittyen lääkinnällisten laitteiden laatu- ja regulatorisiin vaatimuksiin. Tätä varten haastateltiin kolme tutkijaa Aalto-yliopistosta, minkä avulla voitiin luoda yleinen käsitys edellä mainituista aiheista. Yleisesti ottaen riskienhallintaa järjestettiin kaikissa projekteissa hyvin samankaltaisesti. Riskienhallinnan haasteet liittyivät lähinnä projektin alhaiseen kehitysasteeseen sekä puutteelliseen tietoon lopullisesta laitteesta. Lisäksi kliinisen näytön ja muun tärkeän tiedon vähäisyys sekä projektin sisäisen kommunikoinnin haasteet hankaloittivat riskienhallintaa.

Tässä diplomityössä onnistuneesti tuotettu alustava riskienhallintajärjestelmä mTMS-laitteelle palvelee hyvin projektin sisäisiä tarpeita sekä voisi toimia pohjana mahdollista myöhempää kaupallistamista varten.

Avainsanat: lääkinnällinen laite, tutkimus- ja kehitystyö, säätely, riskienhallinta, ISO 14971, transkraniaalinen magneettistimulaatio, mTMS-laite

PREFACE

I want to thank Distinguished Professor Risto Ilmoniemi and the whole TMS-research group in Aalto University for the opportunity to complete my thesis as a continuum for a summer job position. Especially, I would like to thank my supervisor, Research Fellow Dubravko Kicic, for all the great and inspiring discussions during the thesis process. The discussions did not only guide me with the thesis but also gave me insight and advice concerning the future work life I am about to enter. I am thankful for having the opportunity to write my thesis about a topic that interests me and gives me a great basis concerning the topics I want to work with in the future.

I want to thank Research Fellow Jaakko Nieminen and Doctoral Candidates Heikki Sinisalo and Aino Tervo for teaching me about the mTMS technology and giving me valuable feedback during the process. I also want to thank the interviewees who participated and shared their experiences.

I want to thank Research Director Alpo Värri, my supervisor from the university, for the valuable feedback on my writing, thesis structure and contents as well as for the guidance concerning all the thesis practicalities.

Finally, I want to thank my family and friends for supporting me through my studies and helping me to believe in myself when times were challenging.

Tampere, 10th of December 2021

Viivi Lankinen

CONTENTS

LIST OF SYMBOLS AND ABBREVIATIONS

CAPA	Corrective and preventive actions
CE	Conformité Européenne
CNMPA	Chinese National Medical Products Association
C2B	ConnectToBrain
DoC	Declaration of conformity
EEA	European Economic Area
EEG	Electroencephalography
EMA	European Medicinal Agency
EMG	Electromyography
ETA	Event tree analysis
EUDAMED	European database on medical devices
EU	European Union
FDA	The U.S. Food and Drug Administration
fMRI	Functional magnetic resonance imaging
FMEA	Failure Mode and Effects Analysis
FTA	Failure Tree Analysis
FURLS	FDA's Unified Registration and Listing System
HACPP	Hazards Analysis Critical Control Point
HAZOP	Hazard and operability study
HTM	Hazard traceability matrix
HUS	Helsinki University Hospital
IFU	Instructions for use
IP	Intellectual property
IT	Information technology
IVDR	In vitro diagnostic device regulation
MAUDE	Manufacturer and User Facility Device Experience
MD(s)	Medical device(s)
MDD	Medical device directive
MDR	Medical device regulation (EU) 2017/745
MEE	Medical electrical equipment
MEP	Motor evoked potentials
MHRA	Medicines & Healthcare products Regulatory Agency
mTMS	Multi-locus transcranial magnetic stimulation
NB	Notified body
NBE	Department of neuroscience and biomedical engineering in Aalto University
PC	Personal computer
PHA	Preliminary hazard analysis
PMA	Premarket approval
PMCF	Post-market clinical follow up
PMS	Post-market surveillance
QMS	Quality management system
QSR	Quality System Regulation
Q&RA	Quality and regulatory affairs
Q&R	Quality and regulatory
R&D	Research and development
R2B	Research to business
TMS	Transcranial magnetic stimulation
TRA	Threat risk assessment
TTO	Technology transfer offices
UDI	Unique device identification
UE	Usability engineering

USB	Universal series bus
U.S.	The United States (of America)
21 CFR	Code of Federal Regulations Title 21
510(k)	Premarket notification

1. INTRODUCTION

From the 26th of May 2021 all new medical devices (MDs) aimed to be placed on the European market must be developed in compliance with the new European Medical Device Regulation (MDR). Some major changes came up along with the new regulation, which, in some cases, drastically affected the manufacturers' declaration of conformity to receiving a CE (Conformité Européenne) mark. A CE mark is a mandatory conformity marking of the European Union (EU) for regulating the products and goods sold within the European Economic Area (EEA) since 1985[1]. It is estimated that certification times for CE marking will be prolonged from 3-6 months to 6-12 months depending on the device's risk class. [2] The MDR is aiming at having even more effective and safer devices to be placed onto the European market. However, there has been some discussion about the regulatory transformation's negative impacts on the market and, mostly, on the manufacturers. The MDR and its complexity might push small companies to launch their product outside the European market; market areas that are not in the middle of regulatory makeover, might become more compelling. Some publications [3], [4] also claim that the reclassification and manufacturers' focus on recertificating existing devices might cause some limitations on the availability of certain devices and a decrease in new medical device innovations on the market. However, this may in fact be an opportunity for academic groups involved in medical device development to use MDR as a tool for fast-tracking their technology transfer from the lab to the market. The more the researchers and scientists are educated and aware of the regulatory environments, the faster the innovations could reach their possible commercial potential, as the regulatory compliance would be implemented as far and as soon as possible.

Understanding and implementing the new MDR, indeed, requires resources and funding. The most common route to market is to rely on consultancy firms and/or agencies when it comes to quality and regulatory affairs (Q&RA). In general, universities do not offer their own Q&RA services or guidelines on the best practices in implementing compliance with the MDR, apart from technology transfer offices (TTO) for licensing and intellectual property (IP) services. In addition to learning centers, universities are innovation hubs consisting of collaborative experts from multiple fields who are constantly exploring science. A lot of basic, grass roots level research and development are done in universities.

However, typically MD and drug development is so expensive that only big companies with appropriate funding and resources can successfully complete all the steps. The academic research typically relies on external sources of funding, such as research grants and program financing, amounts of which are often very small for conducting the research and development (R&D) itself, let alone the costs of the innovation commercialization process. For these reasons, it is not uncommon that the academic commercialization projects are separate from the basic R&D projects with separate funding sources. Researchers most commonly lack the business development mindset as well as the Q&RA expertise, and consequently have reservations regarding the impacts of commercialization on the research and vice versa. What typically happens, is that only at the time of technology transfer from research results to early commercial stage (*e.g.*, pre-commercialization phase, or a start-up company) the awareness for MDR compliance arises [5].

This thesis will analyze/discuss the research project at Aalto University (Espoo, Finland) developing a novel technology and a MD for multi-locus transcranial magnetic brain stimulation (abbreviated as mTMS). This technology utilizes an innovative approach to transcranial magnetic stimulation (TMS) using multiple overlapping coils to form an energy efficient “transducer” [6], Number of coils in the transducer may vary from 2 up to 50. The first prototype mTMS device unit with a 5-coil transducer [6] has been placed to Helsinki University Hospital (HUS) for initial operational testing with human subjects. Thus, a joint effort has been established between technical and clinical researchers for seeking ways to improve the technology and to investigate its clinical applicability, aiming for the next, improved prototype. The work is performed under the framework of the research project called ConnectToBrain (C2B) that also involves partners from Italy (University of Chieti-Pescara) and Germany (University of Tübingen). The final goal is to develop a mTMS device capable of controlling up to 50 coils in various configurations. A separate project aiming at commercialization of this technology was also launched. This Research-to-Business (R2B) project is funded by Business Finland and supported by Aalto University’s innovation services. The project investigates ways of bringing the new mTMS technology onto the market [7], [8].

To be faster and more efficient in that process, current efforts are focused to learn and understand the Q&RA process and to find ways to comply with the new MDR already at early stages of device development. Efforts are also being put to identify and overcome possible barriers in commercialization process of this academic MD innovation. The technology and the project will be explained in more detail in section 2.1.1.

This master's thesis has been done for the Business Finland funded mTMS commercialization project and studies development of a risk management process and documentation of MDs, with a special focus to the mTMS device. The purpose of this thesis is to study thoroughly the international state-of-the-art standard ISO 14971 for medical device risk management and create a basis for mTMS prototype risk management system in compliance with the standard's requirements. The thesis proposes how to approach and complete the steps required by the ISO 14971 to ensure compliance already at the pre-commercialization stage (*i.e.*, prototypes). The focus will be in creating the first version (*i.e.*, preliminary version) of risk management system for the mTMS prototype, which could be used for the inside purposes of C2B project as well as a basis for the later commercialization process. In this thesis, also the following research questions will be studied from academic MD R&D point of view:

- What is the knowledge of Q&R requirements of MDs among academic researchers?
- What are the challenges in creating a risk management system for MD prototypes in R&D phase?
- How is risk management generally organized in academic MD commercialization projects?
- How could the risk management process and other Q&R related issues be improved in the early phases of academic R&D?

The risk assessment of the mTMS prototype will be built and completed by the following methods:

- Reviewing the requirements of the ISO 14971 standard and other relevant literature,
- Having discussions with the projects stakeholders who participate in design and manufacturing the prototype,
- Participating an online training concerning regulatory affairs provided by a consulting company, and
- Participating in training on the functional mTMS prototype in its operating environment.

The additional research questions will be considered and studied as well as through the case study of mTMS prototype risk management and by interviewing other academic research groups involved in MD R&D. In this thesis, also the theoretical background of TMS, regulations concerning MDs in Europe and in the United States (U.S.), and the

main standards that would apply for manufacturing a medical hardware device are introduced.

2. THEORETICAL BACKGROUND

The theoretical background essential for understanding the purpose and contents of this thesis are explained in this chapter. First, the technology and working principles of TMS together with its clinical usability and safety aspects are introduced. The theory continues with explanation of mTMS technology and the device prototype in more detail. The main contents and requirements of medical device regulation in the EU and U.S. as well as the main applicable standards for MD design and manufacture are introduced in the last two sections. Also, the global recognition of CE mark and placing a MD on the market are discussed briefly after introducing the regulations.

2.1 Transcranial magnetic stimulation

TMS is a non-invasive method to stimulate the functional neuronal tissue of the brain at a desired location [9]. The physical principle behind TMS relies on Faraday's Law on electromagnetic induction, where electrical energy is converted to magnetic energy and vice versa [10]. The brain stimulation in TMS is achieved by passing high currents through the coil placed adjacent to the subject's head. The current generates a magnetic field in the coil which penetrates through the skull and induces an electric field in the brain [11]. The equipment for TMS is essentially simple; in addition to the coil, typically made of copper wire, the device consists of a large capacitor, a charging unit, circuits for controlling pulse parameters and a user-control interface [10]. The history of the current use of electromagnetic induction and TMS technology goes back to 1980's in United Kingdom, where the first TMS device was constructed [10], [11].

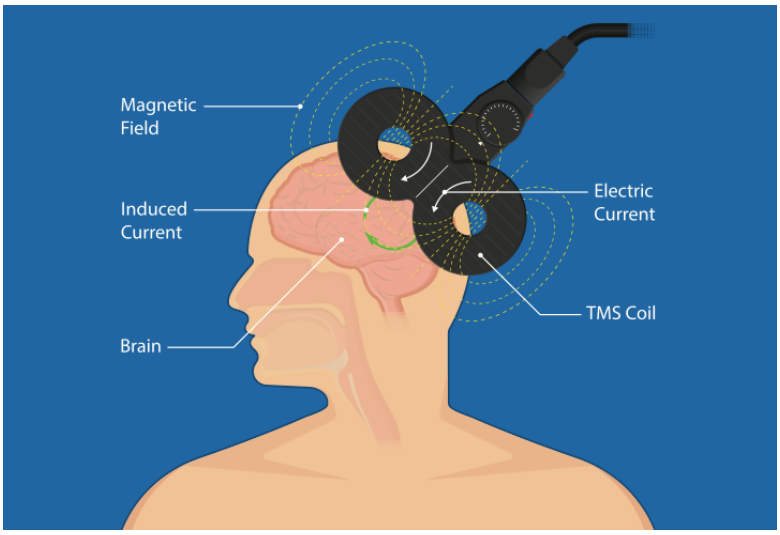

Figure 1. *A figure representing the working principle of TMS with a conventional figure-of-8 coil, where the coil is placed tangentially on the scalp. The electric current in the coil generates a magnetic field which penetrates the skull and induces an electric field in the brain tissue. (Figure directly from* [12])

The shape of the induced electric field in the brain depends on the structure of the coil as well as its location and orientation with respect to the underlying cortical anatomy [11]. The electrical properties of the brain tissue also affect the properties of the induced electric field [9]. The induced electric field is essentially tangential to the skull (Figure 1). The electric field locally in the brain changes the transmembrane potential of neuronal cells causing them to depolarize, fire an action potential and thus activate [9]. The effects of TMS in the brain depend on the features of the applied TMS pulses and can generally be either excitatory or inhibitory [9], [11].

The fundamental operational basis of TMS technology has mainly remained unchanged since it was first invented. The first experiments were done by using circular coils, which were later replaced by figure-of-8 coils (Figure 2). Figure-of-8 coil allows for better focality of the induced electric field compared to circular coil. For this reason, figure-of-8 has been the most widely used coil in clinical use. As mentioned before, the coil shape and positioning affect the pattern of the induced electric field in the brain tissue. Furthermore, depolarization of neurons depends on that electric field and its properties. Focality is one of the key factors in TMS. It is typically defined as an area where the electric field exceeds a certain value relative to the maximum at a given depth (*e.g.*, cortical surface) [13]. For example, half-value area is the area in the cortex where the electric field exceeds half of the electric field maximum strength. Being capable of modifying the induced electric field and by targeting it at a desired location by moving the coil, gives TMS technology its great clinical value. To reach different treatment outcomes, several kinds of coils have

been proposed. Some of the proposed coils include H-coil, halo-figure-8 assembly coil, halo circular assembly coil, double cone coil, H7-coil (Figure 2). All these coils are aiming to conquer the trade-off between the depth of the stimulation and the focality [11], [14]. A study compared the depth-focality trade-off between 50 different coil structures by simulating them in a spherical human head model by finite element method [13]. The electric field was characterized by the electric field penetration by half-value depth (a deepest radial distance from the cortical surface where the electric field strength is half of the maximum strength at the cortex) and focality by the tangential spread (the volume of the brain region that is exposed to an electric field as strong as or stronger than half of the maximum electric field). The results proposed that for any coil design the ability to directly stimulate deeper brain regions is achieved by the expense of inducing wider electrical field spread [13].

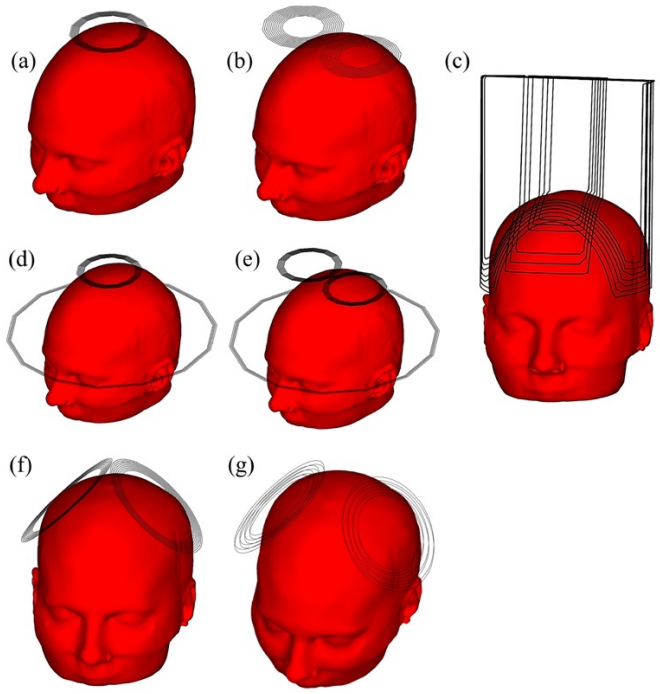

Figure 2. *A schematic representation of some different coil structures. a) Circular coil, b) Figure-of-8 coil, c) H-coil, d) Halo circular assembly coil, e) Halo-figure-of-8 assembly coil, f) Double cone coil and g) H7-coil. Figure directly from* [14].

TMS is used and investigated for various research and clinical applications. Several TMS devices have been cleared by the Food and Drug administration (FDA) and/or CE marked for treatment of different neurological and psychiatric disorders, such as depression, obsessive-compulsive disorder, Alzheimer's disease, stroke rehabilitation, chronic pain, schizophrenia, and epilepsy [9]. Importantly, TMS is also used for pre-surgical functional mapping of the brain, *i.e.,* identification of functionally important brain regions [9].

This allows for safer brain surgical procedures. Another important and emerging application of TMS is determining functional signatures for different neurological or psychiatric disorders, especially neurodegenerative disorders. These disease biomarkers could be defined by investigating cortical excitability, plasticity, and connectivity patterns [15], [16].

Depending on the purpose of the use, TMS can be applied in single pulses, pairs of pulses or as repetitive pulses ("pulse trains" or "pulse bursts") [11]. To measure and record brain activity caused by TMS, it has been combined with other brain imaging modalities like electroencephalography (EEG), functional magnetic resonance imaging (fMRI) and positron emission tomography [9]. Utilizing these methods allows for better understanding of the functional networks, brain connectivity and overall direct effect of the TMS in the brain. However, many of these paradigms involving TMS are still in experimental use.

TMS is generally recognized as a safe treatment and research method. However, some mild adverse effects, possibly occurring with all modalities of TMS applications have been reported. Most common are pain at the site of stimulation, headache, neck or jaw pain, muscle twisting and muscle pain, nausea, and toothache. Also, transient hearing changes and transient effects on mood, cognition, hormones, and immune system have been reported. The most dangerous side effect of TMS is the induction of epileptic seizures [17]–[19]. Seizures have been mostly reported with repetitive TMS and they hardly ever occur with single- or paired-pulse TMS, which are proved to be safe on healthy subjects [11], [17]. Several factors that increase the risk of a seizure have been reported. These factors include, *e.g.,* severe head trauma or increased intracranial pressure, family history of epileptic seizures, personal history of stroke, seizures, epilepsy or concussions, medications or neurologic diseases that lower/alter seizure threshold, excessive alcohol use, sleep deprivation and severe cardiac disease [20]. In addition to these risk-factors, the subjects should be screened for implanted metallic devices, such as cochlear implants, cardiac pacemakers, deep brain stimulators and other central or peripheral nervous system stimulators which might be a contraindication for TMS treatment. The need of treating pediatric or pregnant patients should also be considered case-by-case [19].

Other technical aspects that are related to TMS safety are those that should be assessed in the design and manufacturing phase. These aspects include, *e.g.,* electrical insulation of high voltages, heating, vibration, fractures, acoustic clicking, biocompatibility and weight of the coil, head/neck pain due the pressure or positioning of the coil, electromagnetic interference with other devices, reliability of generating the intended magnetic field,

and human factors, like incorrect or negligent use. In addition, aspects concerning operating software, network, data, and security should be considered carefully since TMS devices typically include information technology (IT) systems and might be connected to network. (Cyber)Security and technical and software safety are assessed with compliance of the design and manufacturing with relevant medical device safety standards and internationally recognized guidelines, regulatory requirements as well as the context the device is intended to be used. Formal, standard compliant, risk management of all these aspects during design, manufacture, delivery, maintenance, and use of MDs together with appropriate instructions for use guarantee the safety of devices [21].

2.1.1 mTMS technology and the project

mTMS stands for multi-locus transcranial magnetic stimulation. It is a novel TMS technology developed by researchers at Aalto University [22]. Compared to conventional TMS coils, where several coils might be combined to produce a single focal stimulation point, the mTMS consists of a set of differently shaped overlapping coils, capable of producing multiple focal stimulation points. Such coils are called transducers. Thus, the mTMS technology allows stimulation of multiple locations in a certain brain region with changed stimulation parameters such as location, intensity, and orientation of the induced electric field – all at a millisecond temporal scale. All these parameters (*i.e.,* induced electric field properties) are adjusted electronically, without physical movement of the mTMS transducer. mTMS overcomes the limitations of conventional TMS where the coil must be adjusted manually to change the desired stimulus location. Moving the relatively heavy coil is time consuming and requires an experienced operator [22].

Researchers in Aalto University have managed to build a device with two overlapping coils which is the simplest instance of an electronically controlled mTMS device [22]. That 2-coil mTMS transducer allows (only) linear shifting of the stimulation spot with maximum displacement distance being around 30 mm. The coil resembles traditional figure-of-8 coil topped with an oval coil (see Figure 3 below). The 2-coil mTMS device has been used for studies concerning short-interval intracortical inhibition and experimental pain [23], [24].

Figure 3. *The 2-coil mTMS transducer.*

In addition to 2-coil mTMS transducer, the researchers have successfully designed and manufactured a transducer that consists of a set of five overlapping coils [6]. This 5-coil mTMS transducer allows controlling the location and orientation of the induced electric field maximum electronically within a cortical region approximately 30 mm in diameter [6]. The 5-coil mTMS transducer consists of a round coil, two figure-of-8 coils, and two four-leaf-clover coils stacked on top of each other. The coil windings and a visualization of the transducer assembly is shown in Figure 4. The electronics in the present mTMS system can control up to six coils simultaneously (see Figure 6), which enables experimenting with different transducer designs without changing the electronics of the system. One may, *e.g.,* develop a transducer with more than five coils and enlarge the stimulation area beyond the 30-mm-diameter region, or use a 5-coil transducer with a separate figure-of-8 coil for different motor control studies [6].

The mTMS system is in clinical test use in HUS. The researchers are actively finding ways to improve the technology. For example, they are planning on combining the mTMS with EEG, to implement closed-loop paradigms [23], [25]. This would allow a real-time recording of the cortical responses to mTMS to be used in a feed-back loop that could control the change of stimulation parameters – location, orientation and stimulation intensity and timing [26]. The mTMS device is currently used in conjunction with commercially available neuronavigation and electromyography (EMG) systems for mapping the primary motor cortex, determining the motor threshold, and recording motor evoked potentials (MEPs) [22], [27]. The researchers have demonstrated that the 5-coil transducer allows automatic motor mapping without physical coil movement [6].

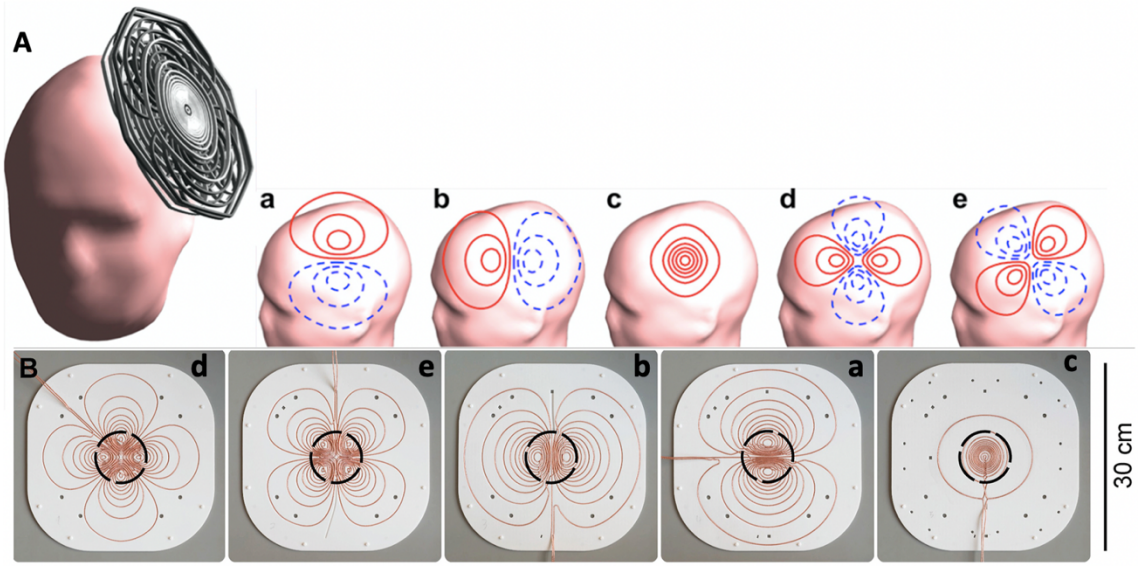

Figure 4. *The visualisation (A) at right top corner shows all overlapping coils forming a single 5-coil mTMS transducer. The photos on the bottom (B) show the coil windings in the 3D-printed coil formers and the shapes of the coils. In the transducer assembly, the leftmost coil (d) is in contact with the scalp whereas the rightmost (c) is the furthest from the scalp. The transducer consists of two figure-of-8 coils at 90º angle (a-b), a round coil (c), and two four-leaf-clover coils at 45º angle (d-e). The red and dashed blue line (visualization on the top) illustrate the direction of the current in the coils; clockwise and counterclockwise, respectively. With 5-coil mTMS transducer the location of the stimulation spot can be freely selected and moved electronically in 30-mm-diameter region. (Figure adapted from* [22] and [6]*)*

This thesis is made for mTMS commercialization project aiming to produce a preliminary risk management system for the 5-coil mTMS prototype. The block diagram in Figure 5 shows the components of the mTMS system. The central components are the mTMS cabinet that holds the power and control electronics of the device, the controlling computer and the mTMS transducer. Figure 6 shows the assembly of the mTMS prototype in the operating environment.

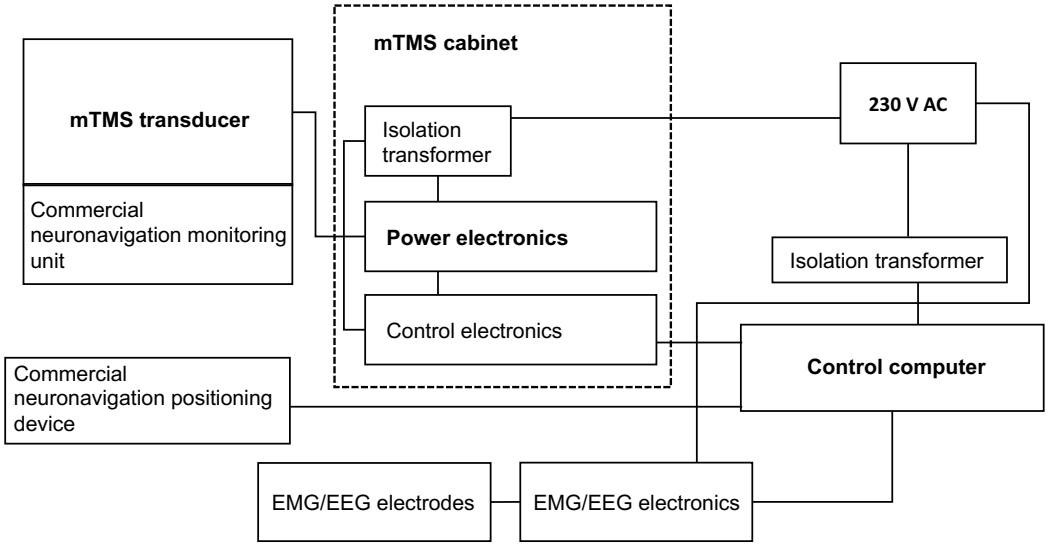

Figure 5. *A block diagram representing the components of the mTMS system.*

Figure 6. *The assembly of the first five-coil transducer prototype. In the background is the mTMS cabinet which allows attaching a transducer up to 6 channels (i.e., coils). The transducer is here held by a manually movable mechanical arm. (Picture courtesy of Dubravko Kicic)*

2.2 Medical device regulation

The MD industry is a highly regulated field in each country by national governments and international authorities. This is, simply, to ensure the patient safety and the best possible outcomes of the patient treatment. In this thesis, the focus will be in the MDR and obtaining CE mark.

2.2.1 European Union

The first directives concerning medical device industry and marketing of medical devices were published in the 1990s by the European Council. These directives were called the

medical device directive (MDD), the active implantable medical device directive and the in vitro diagnostic medical device directive. After publishing the directives, many guidance documents, recommendations, and amendments were added to the legislation through-out the years, which finally led to the need of whole new legislation. The constantly and rapidly growing medical technology industry and the scandals raised from harmful approved medical devices speeded up the process [28].

The new MDR 2017/745 and In Vitro Medical Device regulation (IVDR) 2017/746 entered in force in 26th of May 2017 replacing the old directives. 3-year transition time was given to manufacturers [3], which was then prolonged by 1 year due the global COVID-19 crisis. From 26th of May 2021 all the new medical devices will have to be developed according to the new MDR and the old MDD CE certificates will be valid until 2024. The product must have a CE mark to be sold as a product in European market. CE mark proves the safety and compliance of the device with MDR [29]. The change from directive to regulation means that every member of the EU must immediately comply with the regulation by law, whereas the directive set out goals to achieve and left it up to individual countries how to achieve them by their legislation [29]. The MDR will, then, greatly increase the harmonization in MD legislation among the member countries [29].

The main changes [3] in the new MDR are focusing on:

1. Clinical safety and benefit of the device and, ensuring the effective and safe treatment of the patient.
2. Increasing the transparency and traceability between the manufacturers and devices.
3. Enhancing the management and surveillance of the device throughout its whole life cycle.
4. Reducing the ambiguity in device classifications and definitions.

The MDR [30] defines a MD as: “any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment, or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,

- investigation, replacement, or modification of the anatomy or of a physiological or pathological process or state,
- providing information by mean of in vitro examination of specimens derived from the human body, including organ, blood, and tissue donations,

and which does not achieve its principal intended action by pharmacological, immunological, or metabolic means, in or on the human body, but which may be assisted in its function by such means."

MDR also defines conception control/support devices, and instruments for cleaning, disinfecting or sterilization of devices described above, as MDs [30].

The MDR classifies MDs into 4 different risk-based categories: I, IIa, IIb and III, with class III being the highest risk-class. Class I is divided into 3 subcategories implicating to a special function: s (placed sterile on the market), m (including a measuring function) and r (reusable surgical instrument). The MDR states classification rules that are based on the device's intended purpose and features, like invasiveness and activeness, duration of use and affected body area. The classification in the EU is well compatible with MD classifications internationally. [28] The change in legislation has resulted in reclassification of some devices into a higher risk class. This will strongly affect the conformity assessment and updating the old CE certificates since, for example, clinical investigation is now mandatory for all class III devices. [29] The right determination of intended purpose and classification of MDs at the early stage of development is very critical, since they define the procedures that the manufacturer must follow in order to achieve CE marking. The regulatory path to CE marking is presented in Figure 7.

The intended purpose is a part of manufacturer's technical documentation, which defines in detail for which purposes the device may and may not be used for. It also defines the use environments, users, and eligible patient populations. Any misuse, or off-label use against manufacturer's information is at user's own risk. [28]

MDR defines the manufacturer as "a natural or legal person who manufactures or fully refurbishes a device or has a device designed, manufactured or fully refurbished, and markets that device under its name or trademark" [30]. When demonstrating the conformity of the product, aiming to CE marking, the following procedures are solely on the manufacturer's responsibility and must be carried out [28]:

1. The product must fulfil the general safety and performance requirements stated in MDR Annex I. Appropriate technical documentation must exist to prove the compliance with MDR and other possible relevant legislation.
2. A quality management system (QMS) according to the latest ISO 13485 -standard, despite the device's classification, must exist.
3. The manufacturer must have established and maintained a risk management system for the product.
4. An adequate clinical evaluation and clinical investigation (if needed) must be performed and documented.
5. Appropriate labelling and instructions for use (IFU) must be provided with the product.
6. The product must have a unique device identification number (UDI).
7. A conformity assessment by the Notified Body (NB) must be performed and a certification granted. The device classes that require the latter procedure are Is/m/r, IIa/b and III.
8. The manufacturer must draw up a Declaration of Conformity (DoC) that bears the required contents.

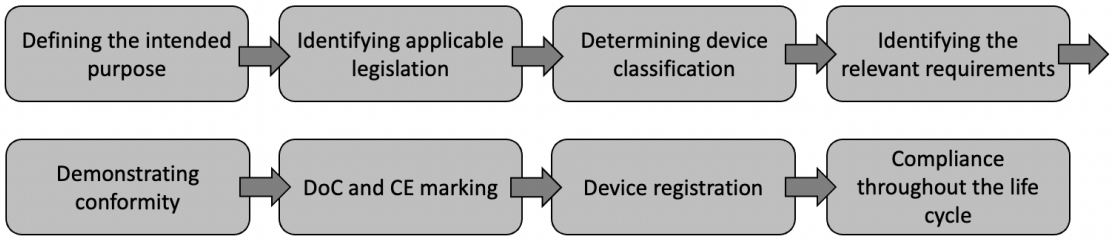

Figure 7. *The regulatory path to CE marking. The path to CE marking begins with proper formulation of intended purpose of the product. The intended purpose will indicate whether the product falls in the scope of MDR or IVDR and other possible applicable directives or regulation depending on the features of the product. The device classification also depends on the intended purpose and these factors together will dictate the relevant MDR/IVDR requirements and applicable standards. When demonstrating the conformity, the manufacturer must prove that all the requirements of MDR/IVDR are fulfilled and documented accordingly. This is conveniently demonstrated by applying international standards. After DoC a CE mark can be issued and placed on the device. The device is registered to European Medical Device Database and placed on market. Complying with MDR continues throughout the whole life cycle of the device.*

The effect of the MDR extends also to time after the manufacturer has declared the conformity of the MD, a CE mark has been issued and the MD has been put on the market. These responsibilities are stated in the MDR chapter VII. The manufacturer *"shall plan, establish, document, implement and maintain a post-market surveillance (PMS) system that is proportionate to the risk class and appropriate for the type of device"* [30]. The aim

of PMS is to ensure patient safety by vigilance activities, feedback-handling and post-market clinical follow up (PMCF). This is done by continuously updating the existing documents (*e.g.*, benefit–risk determination, clinical evaluation, IFU and labelling) and identifying needs and options for improving the usability, performance, and safety of the device. The results from collecting post-market experience data, clinical data and other PMS activities should be documented in an official PMS report for class I MDs and in periodic safety update report for higher risk-class MDs. [28]

Performing vigilance is a highlighted responsibility of the manufacturer that is even more important now due to the new MDR. [28] Vigilance significantly maintains product safety in problematic situations and improves the protection of health and safety of patients and device operators. Vigilance is performed by reporting any adverse incidents related to the use of the devices and by reducing the likelihood on reoccurrence by adopting appropriate field safety corrective actions. European database on medical devices (EUDAMED), was established to improve the transparency and vigilance of MDs on the European market among the public and healthcare professionals. All serious incidents concerning MDs and any field safety corrective actions must be reported to EUDAMED. [28] The publicly available information in EUDAMED covers [31]:

1. The manufacturer, importer and representer of devices.
2. The information and UDI database of all MDs on the market.
3. The NBs and certificates.
4. 4 The information about clinical investigations and clinical performance testing.
5. PMS.

However, the deployment of EUDAMED is still in progress and thus it is missing quite a lot of information regarding the commercially available MDs.

2.2.2 The United States

The regulatory authority for MDs, and many other products (*e.g.,* food, drugs, cosmetics), in the United States (U.S.) is the FDA. FDA is, also, the oldest comprehensive consumer protection agency in the U.S., having started its oversight on food and drugs in 1906. The first amendment concerning medical devices was published in 1976, which established regulatory pathways for new MDs to enter the market via premarket approval (PMA), via premarket notification (510(k)) or via De Novo procedure. It also created risk-based classification system for all MDs that has been in use ever since. [32]

The FDA defines [33] a MD as “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part or accessory which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and
- does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purpose.”

The definitions by FDA and MDR are very similar. The MDR limits the MD definition for humans use only, whereas the FDA includes products to be used also for any other animals. The FDA provides some regulatory oversight for veterinary devices; however, premarket approval or premarket notification are not required. There is no harmonized regulation for veterinary products at the EU level, apart from devices forming a part of medicinal product. In this case, the device is being evaluated by European Medicinal Agency (EMA). [34]

The FDA classifies MDs into three different classes based on their risks: I, II and III. As in the EU, the classification defines the regulatory and control requirements for the device. The regulation of MDs is defined in the Code of Federal Regulations Title 21 (21 CFR). 21 CFR has 1499 parts in total, but parts 800-1299 are perhaps the most important to a MD manufacturer [35]. The regulatory requirements are divided into 2 groups: general controls, which apply to all MDs, and device-specific special controls, which apply to class II MDs. Most MDs are placed onto market via 510(k) excluding some class I and II that are exempt. The FDA provides a list of exempt devices to assist with the RA. In 510(k) procedure the manufacturer demonstrates that the MD to be marketed is safe and effective as a comparison to some substantially equivalent [36] legally marketed MD. The manufacturer supports their claims by referring to the legal predictive device. There are three different types of 510(k) processes – traditional, special, abbreviated – that are applied based on the type and status of the MD. In turn, all class III MDs are subject to PMA approval. PMA is a strict, expensive, and completely separately regulated process and is required when general and special controls are insufficient to provide reasonable assurance of the safety and effectiveness of the MD. PMA always requires, *e.g.,* non-

laboratory studies and clinical investigations [37]. The so called De Novo procedure is a pathway for novel MDs for which general and special controls provide reasonable assurance of safety and effectiveness but for which there is no legally marketed predicative device. De Novo procedure applies to a small fraction of MDs and is in between of 510(k) and PMA by its demandingness. [32], [35]

Like the MDR, the FDA also requires Quality System Regulation (QSR) compliance from the manufacturers excluding some class I devices. ISO 13485 compatible QMS is not fully compatible with the QSR, which is also called the Good Manufacturing Practice. The requirements of QSR are more laborious and detailed than those of ISO13485 which is, thus, not enough to achieve FDA approval [35]. When all the applicable requirements of the CFR 21 are fulfilled and required documentation is in place, the manufacturer can demonstrate its conformity to the FDA. The manufacturer prepares its submission, pays the submission fee, and sends the submission to FDA. FDA reviewing times vary between 3–30 months depending on the submission type and device classification. FDA provides different programs for reviewing and giving feedback on the submissions before a final submission. Once the submission is successful, possible inspections executed and an 510(k) clearance or PMA approval letter received, the manufacturer must list the MD on FDA's Unified Registration and Listing System (FURLS) and register as a medical device establishment. Listing and registration fees must be paid. [37] As the MDR, FDA also requires post-market activities from MD manufacturers and other firms involved in distribution of MDs. These activities include tracking systems; reporting of device malfunctions, serious injuries, or deaths; registering the establishments where devices are produced and distributed; and post-market surveillance studies as well as post-approval studies at the time of PMA. [38]

2.2.3 CE marking's global recognition

CE marked device is free to be marketed in all the member states of the EU as well as EU member candidates and potential candidates. CE marking allows marketing the device also in countries that are not EU members, like EEA countries (Norway, Liechtenstein, Iceland) and European Free Trade Association countries (Switzerland). The United Kingdom has its own agency (Medicines & Healthcare products Regulatory Agency, MHRA) which defines how MDs are regulated during the transition period of Brexit. They will continue recognizing CE markings and certificates issued by European NBs until June 2023. However, the EU will no longer recognize NBs from the United Kingdom. [28]

Many countries allow free marketing of lawfully CE marked devices. However, the national authorities require proof of regulatory compliance in the country of origin, in this case, the lawfulness of CE mark by for example a Certificate of Free Sale issued by the local authority. This authority is Fimea in Finland [25]. CE marked devices must be registered or licensed appropriately in the country they are being imported to. For example, in the U.S., Australia, China and Brazil, all foreign manufacturers are required to appoint an approved local regulatory representative to take care of the legislation and registration processes (*e.g.,* U.S. agent, Australian sponsor). Some countries require technical documentation in their own language for registration processes. A certification of the international state-of-art standard, ISO 13485, for QMS of MDs is typically enough to prove regulatory compliance in many countries. However, the country might insist that the certificate is issued by their recognized registrars. Some countries, like the U.S, Canada and Brazil require some additional local regulatory requirements for a QMS, that are out of the scope of ISO13485. Some countries, like Brazil, also might do inspections on the manufacturer and manufacturing site and require re-registration of the device after a certain period of time. [35]

As the device classification dictates the regulatory path and registration process to market, the manufacturer must correctly classify the device according to the classification of the specific country. The device classification internationally is very often risk-based and similar to the classification specified in the MDR. However, the number of classes might differ, *e.g.,* Chinese National Medical Products Association (CNMPA, formerly China Food and Drug Administration [39]) has 3 device classes whereas Brazilian Agência Nacional de Vigilância Sanitária and Canadian Health Canada has 4 device classes. As stated before, the regulatory requirements, demonstrating the conformity and the amount of technical documentation needed depends on the device classification. Depending on the classification, also some additional clinical testing or other testing might be required. CNMPA, for example, requires testing in their approved testing laboratories by their own testing protocols for all class II and III devices. [35]

CE marking assists and opens possibilities but is rarely alone enough to demonstrate the conformity when entering global market regions. The manufacturers should always familiarize themselves thoroughly with the local legislation and regulatory requirements and be prepared to put resources, like time and money, into it.

2.2.4 Placing a device on the market

In addition to designing a safe and effective MD that complies with the regulation, the manufacturers must consider their business strategy. The regulatory requirements depend on the desired market areas for the product and can be, thus, considered as part of business strategy. Depending on the MD type, some regulatory paths might be easier, cheaper, and faster for placing the device on the market than others. European MD manufacturer might want to reach out to U.S. markets first, for example if their device could be easily approved via 510(k) submission by demonstrating the substantial equivalence to an existing approved MD. According to some sources, 510(k) submission is the cheapest and fastest route among all the regulatory processes [40].

According to a website [41], the U.S. is globally the biggest MD market region accounting for almost 40 % of all MD market in 2020. The next biggest market regions are Asia Pacific and the EU. The fastest growing regions will be South America and Africa where compound annual growth rates are at 11.1 % and 10.4 %, respectively. In total, the global medical devices market reached a value of nearly 456.8 billion U.S. dollars in 2020 having increased at compound annual growth rates of 3.5 % since 2015. The manufacturer should investigate the previous and predicted trends in the global medical device market as a part of planning the business strategy. Also, the intended use and patient population of the MD might determine the best regions for marketing the device.

2.3 Standards

Standards are jointly agreed documents that provide guidelines, requirements, and specifications for, for example, manufacturing, testing, building, or operating a product or a service. Standard is a definition of how something should be done to achieve the best possible outcome and to test if something is fit for its purpose. Standards can be international or national. Utilizing of standards is usually voluntary but might be, in some cases, also mandatory. The use of standards gives competence, reliability, and value for the organization. From the consumer's point of view, standards will secure that the product or service is safe, efficient and works how it's supposed to. [42], [43] In the following subsections the main applicable standards for developing a MD that contains hardware and software, such as mTMS device, will be introduced.

2.3.1 ISO 13485

According to the international organization for standardization, ISO 13485 “specifies requirements for a quality management system where an organization needs to demonstrate its ability to provide MDs and related services that consistently meet customer and applicable regulatory requirements” [44]. By applying QMS by ISO 13485, the manufacturer ensures that the safety and performance requirements, as well as clinical performance and risk management, are taken fully into account. Carefully implemented, the ISO 13485 will also enhance the organization’s ability to succeed in business. ISO 13485 is practically a mandatory standard for MDR compliance and will be audited and assessed by the NB for higher risk-class devices. It’s also recommended for manufacturers developing class I devices to get an ISO 13485 certification from a registrar to gain value in the eyes of clients and other stakeholders. ISO 13485 is a recognized standard in the EU, U.S. and Canada and is to be applied in many other countries that have specific regulations on MDs. It enables the harmonization of MD marketing. The standard is designed to be used throughout the whole life cycle of MD; from designing to production, and from distribution to installing and maintenance. [28]

The ISO 13485 sets requirements on general requirements of the QMS (*e.g*., quality manual, medical device file, control of documents); on management responsibility (*e.g.*, management commitment, customer focus, quality policy, management review); on resource management (*e.g.,* provision of resources, human resources, infrastructure, work environment); on product realization (*e.g.,* planning, design and development, customer relations, purchasing); and on measurement, analysis and improvement (*e.g.,* corrective and preventive actions, CAPA). [28], [44]

2.3.2 IEC 60601

IEC 60601 is a comprehensive family of standards concerning medical electrical equipment (MEE). It was first published in 1977 and has expanded since into many collateral and particular standards. The general standard, IEC 60601-1 is the core of the standard series. It defines the scope and basic contents for all the other parts of the series and is applicable to all MEE. The collateral standards, identified as IEC 60601-1-X, serve to define additional requirements for MEE, such electromagnetic disturbances (IEC 60601-1-2) and alarms (IEC 60601-1-8), which are not covered by the general standard. The particular standards, identified as IEC 60601-2-X or IEC 80601-2-X, are intended to define requirements to a specific equipment type, like non-invasive blood pressure monitors (IEC 80601-2-30) or magnetic resonance equipment for medical diagnosis (IEC 60601-

2-23). The particular standards can be considered as the most important part of the IEC 60601 family, since they can remove or modify the requirements of general/collateral standards and as well add additional requirements that would not apply to all MEE. [45]

The collateral standard, IEC 60601-1-11, sets general requirements for basic safety and essential performance for medical electrical equipment and medical electrical systems used in home healthcare environment. It is a very important standard, even mandatory when designing and building a medical hardware such as mTMS device.

2.3.3 IEC 62366

IEC 62366-1 is a standard for application of usability engineering (UE) to MDs. It is a very important part of medical product development, since use-related hazards are a serious and, unfortunately, common problem [46]. The standard specifies a UE process for manufacturers to analyze, specify, develop, and evaluate the usability of a MD. It addresses the user interactions with a MD from transportation and storage to installation, operation, maintenance, repair, and disposal of the MD, thus the whole lifecycle of a device. The MDR states that the manufacturer must reduce as far as possible the risks related to the ergonomic features of the device and the environment it is intended to be used, as well as consider the users' knowledge, training, and other personal conditions [28]. IEC 62366-1 helps to assess and mitigate the risks related to the normal use of the MD, which includes correct use and use error [46], [47]. The effort put into UE should be proportional to the characteristics of the device, to the complexity of the user specification and to the severity of the harm associated with the use [28].

UE strongly supports MD risk management. Some of the required steps of IEC 62366-1 work as an input to some steps of ISO 14971 and vice versa. Use specification described by IEC 62366 is a direct input to specifying the intended use by ISO 14971. Also, UE process provides a list of items that help to accomplish identifying known or foreseeable hazards by ISO 14971 for a user interface of a MD. IEC 62366-1 requires that a hazard-related use scenario is selected for summative evaluation and user interface specification. Identified sequences of events leading to a hazardous situation from ISO 14971 are inputs for determining the hazard-related use scenarios in IEC 62366. Like other standards, also IEC 62366 requires recording of the UE results in a specific file, such as usability engineering file. The parts of the file can form other documents also. [47]

2.3.4 IEC 62304

IEC 62304 is a standard that provides a framework of MD software lifecycle processes. These processes are software development and software maintenance which are further divided into different activities and tasks that are necessary for the safe design and maintenance of software. The standard also identifies two additional processes that are very essential for developing a safe MD software. These processes are software configuration management and software problem resolution. The activities for software development process are software development planning, software requirements analysis, software architectural design, software detailed design, software unit implementation and verification, software integration and integration testing, software system testing and software release. For the software maintenance process, the activities are the same, apart from first two activities which are establish software maintenance plan and problem and modification analysis. [48]

IEC 62304 also defines a three-scale software safety classification. The manufacturer must assign a safety class to each software system based on the severity of the possible hazards that the software can cause to the patient, operator, or other people. The classification is as follows: A. No injury, B. Non-serious injury possible and, C. Death or serious injury is possible. The standard addresses some additional risk management requirements for identification of contributing software factors related to hazards. These requirements should be integrated into ISO 14971 (discussed in 2.3.6 and 3.1) compatible risk management system. [48]

The first version of IEC 62304 was published in 2006 for which an amendment was made in 2015. Amendment's intention is to add requirements to deal with legacy software, where the software design is prior to the existence of current version. [49]

2.3.5 IEC 81001-5-1

IEC 81001-5-1 is a recently published standard concerning health software and health IT systems safety, effectiveness, and security. It applies to the development and maintenance of health software, including software as a part of MD, software as a part of specific health hardware, software as a MD and software-only product for other use. Its purpose is to increase the information security of health software by establishing certain activities and tasks in the health software life cycle processes. It concerns the security related issues in design and development, configuration and verification, and maintenance. [50]

The standard assists in, for example, software system testing for security requirements, threat mitigation and vulnerability as well as for identifying, estimating, and evaluating the risks related to information security. It describes the methods for threat risk assessment (TRA) that can be integrated as a part of ISO14971 compatible risk management system. [50]

2.3.6 ISO 14971

ISO 14971 specifies terminology, principles, and a process for risk management of medical devices. Its aim is to assist the manufacturers to identify the hazards associated with the medical device, to estimate and evaluate the associated risks, to control these risks and to monitor the effectiveness of the controls. The risks of MDs are typically related to biocompatibility, electricity, usability, radiation, data, and system security and moving parts/mechanics. The standard gives definitions to different terms used in the document. It defines a harm as a *"injury or damage to the health of people, or damage to the property or the environment"*, a hazard as a *"potential source of harm"*, hazardous situation as *"circumstance in which people, property or environment is/are exposed to one or more hazards"*, and a risk as a *"combination of the probability of occurrence of harm and the severity of that harm"*. Safety, in turn, means *"freedom of unacceptable risk"*. ISO 14971 is designed to be applied throughout the whole life cycle of the product. [51]

Risk management can be considered as one of the most crucial parts of MD development since the safety of the device is a top priority.

It is very important for the manufacturer to identify **all** possible risks and to weigh them against the benefits the product will bring to the patient. All risks must be reduced and/or eliminated as far as possible and the standard insists the manufacturer to establish objective criteria for risk acceptability. The ISO 14971 requires that the manufacturer comes up with a risk management plan that consists of risk analysis, risk evaluation, risk control, evaluation of overall residual risk, risk management review and production and post-production information [51]. The technical report ISO/TR 24971 provides practical guidance on producing a risk management that complies the ISO 14971. There are different tools for risk analysis, however, the authorities and NBs are most accustomed with Failure Mode and Effects Analysis (FMEA) model [28]. FMEA can be efficiently applied for different steps of MD development, like design, production, or use. Other tools are, for example, Failure Tree Analysis (FTA) and Hazards Analysis Critical Control Point (HACCP). [28], [52] FMEA will be utilized to some extend in the risk analysis of mTMS prototype.

2.3.7 Other applicable standards

The standards briefly introduced in previous sections are all very closely aligned to the ISO 14971 and implementation of those will aid implementing ISO 14971 and vice versa. All MD manufacturers aiming to CE mark should at least follow the ISO 13485, which is mandatory for MDR compliance. In addition to the described standards, there are several other standards that provide guidance on different steps of MD manufacturing. Some of these standards are, *e.g.,* ISO/TR 20416:2020 which provides guidance on performing post-market surveillance, ISO 14155:2020 which addresses the good clinical practice for clinical investigation of MDs for human subjects, ISO 15223-1:2020 which sets general requirements for labelling and information to be supplied with the device as well as for the symbols to be used in MD labels, and ISO 20417:2021 which sets the requirements for the information to be supplied by the manufacturer concerning for example the accessories and packaging.

Excluding ISO 13485, application of all the other standards is theoretically voluntary. However, they greatly increase the credibility and reliability of both the product and the manufacturer. Standards are designed to help with all the steps of a MD lifecycle, resulting in a safe and effective MD manufactured by efficient and recognized processes. MD manufacturers should carefully consider which standards are applicable to their device and to which extent.

3. MATERIALS AND METHODS

The materials and methods for conducting the objectives of this thesis are introduced in this chapter. The international state-of-art standard for MD risk management is explained thoroughly together with the guidance document assisting in its application in the first section. The second section explains how the risk management of mTMS prototype was organized and conducted and how the relevant data was collected. In the last section, the method for conducting the interviews is explained.

3.1 Overview of ISO14971:2019 and ISO/TR24971:2020

To start the risk management process of mTMS prototype both the standard ISO14971:2019 and the guidance document ISO/TR24971:2020 were studied thoroughly. Also, an online training series provided by a medical Q&R consulting company considering the main requirements of the MDR 2017/745 was watched [2]. The requirements of ISO14971:2019 and some of the proposals of the guidance document for completing the requirements are precisely introduced in this section.

3.1.1 General requirements for risk management system

Risk management process

Risk management process means the whole ongoing process that the manufacturer shall establish, implement, and document throughout the whole life cycle of a MD [51]. The steps and contents of the process are represented in Figure 8.

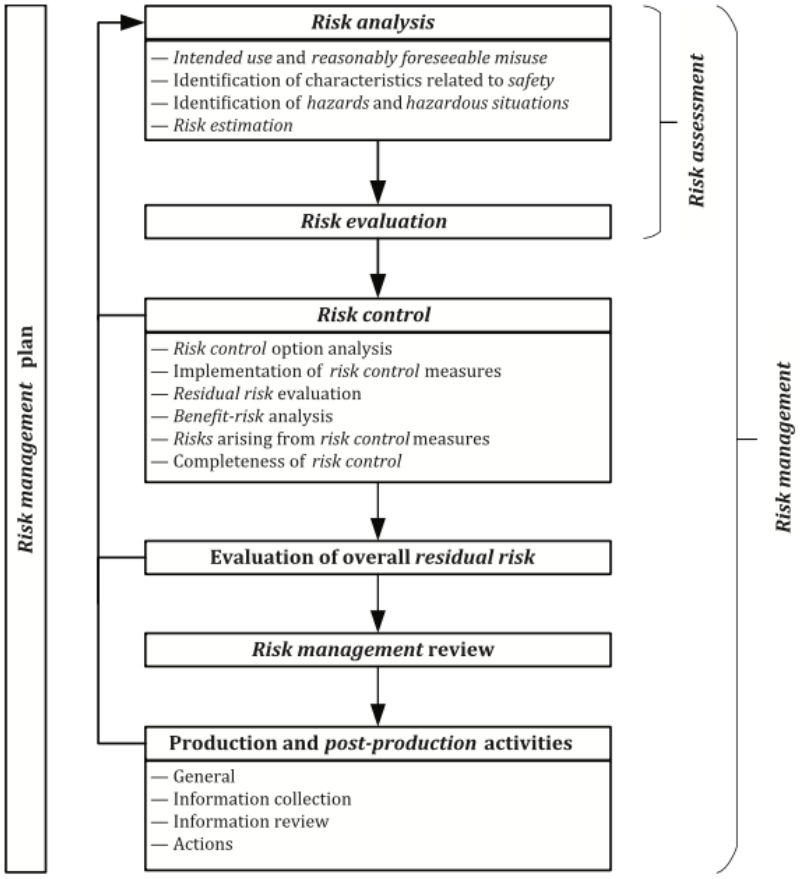

Figure 8. *A schematic illustration of the risk management process.* [51]

Management responsibilities and competence of personnel

The standard requires that person(s) who direct and control the manufacturer, *i.e.*, top management, shall provide evidence of their commitment to risk management process by providing adequate resources and assigning competent personnel for completing the risk management. Those personnel shall be competent based on education, training, skills, and experience appropriate to the tasks assigned to them. The personnel shall also have knowledge and experience of the particular/similar MDs and its use as well as the involved technologies and applied risk management methods. These personnel can be, for example, engineers, scientists, clinicians, and employers from different parts of the MD lifecycle. The management's responsibility is to define and document a policy that provides a framework for establishing the criteria for risk acceptability. The policy typically addresses the following elements [51]:

- *"purpose;*
- *scope;*
- *factors and considerations for determining the acceptable risk;*
- *approaches to risk control;*

- *requirements for approval and review."*

Some factors and considerations that ISO/TR 24971 states, are for example relevant standards and regulatory requirements, state-of-art information on research or best practices in technology related to similar MDs, or validated concerns from any stakeholders. [53]

Risk management file

The manufacturer shall establish and maintain a risk management file for each particular MD or MD family for documenting the risk management process. The file shall provide traceability for each identified hazard to the risk analysis, the risk evaluation, the implementation, and verification of the risk control measures and the results of the evaluation of the residual risks. There is no specific form or type assigned how the risk management file should be created and its contents can form parts of other documents, like the QMS. It does not need to physically contain all the records or documents, but they should be referred or pointed to be browsed in a timely manner. [51] The risk management file used for documenting the risk management activities of mTMS prototype is a Microsoft Excel template provided by a consulting company.

Risk management plan

The standard requires planning of all the risk management activities. The manufacturer shall establish and document a risk management plan that is consistent with the risk management process. The plan shall be a part of the risk management file and it shall include at least the following [51]:

- "the scope of the planned risk management activities, identifying and describing the medical device and the life cycle phases for which each element of the plan is applicable;
- assignment of responsibilities and authorities;
- requirements for review of risk management;
- criteria for risk acceptability, based on the manufacturer's policy for determining acceptable risk, including criteria for accepting risks when the probability of occurrence of harm cannot be estimated;
- a method to evaluate the overall residual risk, and criteria for acceptability of the overall residual risk based on the manufacturer's policy for determining acceptable risk;

- activities for verification of the implementation and effectiveness of risk control measures; and
- activities related to collection and review of relevant production and post-production information."

The plan is a living document and possible changes shall be recorded in the risk management file.

3.1.2 Risk analysis

Risk analysis is a systemic process where the available information is used to identify all the hazards related to the MD and to estimate the associated risks. The risk analysis process starts with identification and description of the analyzed MD together with the person(s) and organization performing the risk analysis. The scope and date of the risk analysis shall also be included in the risk analysis documentation. The manufacturer shall document the intended use and the reasonably foreseeable misuse of the MD. The identification of known and foreseeable hazards associated with the MD is based on the intended use, reasonably foreseeable misuse, and the safety characteristics of the MD. The intended use should consider the medical indication, patient population, body/tissue interaction, user profile, use environment and operating principle. [51] Annex A in the guidance document ISO/TR24971 provides a list of several questions that assist with the identification of the safety characteristics of the MD. The questions concern, *e.g.,* the manufacture, intended use and intended users, reasonably foreseeable misuse, and the ultimate disposal of the MD. It is advised to ask these questions from everyone involved in the entire life cycle of the proposed MD (*i.e.,* scientists, clinicians, engineers, hardware and software developers, patients, users, and other personnel related to the use or maintenance of the device) to gain a more complete picture of the risks that might exist. [53]

For each identified hazard leading to a hazardous situation the manufacturer should estimate the associated risk(s) using available information or data, like scientific or technical investigation, relevant field data, clinical evidence, usability tests employing typical users or expert opinion. A qualitative or quantitative categorization system of the probability of the occurrence of the harm, and severity of the harm shall be used and recorded. [51] It should be emphasized that the estimation considers specifically the probability of and severity of the harm. A hazardous situation does not necessarily lead to harm each time of its occurrence. ISO/TR24971 gives examples of both qualitative and quantitative categorization systems, which typically are N-by-M matrices. ISO/TR24971 states that

the probability estimation should be at least based on the following factors: the usage rate and lifetime of the MD; the patient exposure time; the number of users and patients as well as user and patient population. The severity, in turn, should be described appropriately related to the particular MD. [53] All the features and the results of the risk analysis shall be documented in the risk management file.

As stated in chapter 2.3.6, there are different tools that can support the risk analysis process. Annex B in ISO/TR24971 introduces 5 different tools which can be utilized in different steps of MD development. Preliminary hazard analysis (PHA) is a technique to identify hazards, hazardous situations and events that can cause harm when little is known about the details of the MD, thus it is good for the early development process. FTA and Event tree analysis (ETA) are useful in safety engineering in the early development process. FTA analyses how and why and undesirable top event occurs whereas ETA considers the impact of a failure in the system on the overall system and on operators and patients. They both are systematic and use the same logical and mathematical techniques. FMEA identifies and evaluates consequences of an individual failure mode in every component of the MD as well as failures in manufacturing and assembling of the components. FMEA can also address the failures in use or misuse of the product by the end user. FMEA is usually more useful when the design relatively mature and the failure modes are better understood. Hazard and operability study (HAZOP) assumes that hazardous situations and harms are caused by design deviations or operational variations. It is used to study these factors from the intended performance of the MD in the early development phases where only the design and development inputs are defined. HAZOP can be to the operation/function of the MD or to a process used in manufacture or maintenance of the device. HACCP is used to control and monitor the associated risks identified from hazards and hazardous situations by focusing on the established critical control points in the manufacturing process. It is typically used in later stages of product development to verify, record, and optimize design concepts or changes. [53]

3.1.3 Risk evaluation

In risk evaluation phase the manufacturer shall evaluate the estimated risks for each identified hazardous situation and determine whether the risk is acceptable or not using the acceptability criteria defined in the risk management plan. If the risk is acceptable it's treated as a residual risk according to the standard. If not, risk control activities shall be performed to each hazardous situation to reduce the risk to an acceptable level. The results of risk evaluation should be recorded in the risk management file. [51]

3.1.4 Risk control

To reduce the estimated risk to an acceptable level, the manufacturer should utilize one or more of the following risk control options listed in priority order [51]:

- “inherently safe design and manufacture;
- protective measures on the medical device itself or in the manufacturing process;
- information for safety and, where appropriate, training to users.”

Many internationally recognized standards address the risk control options listed above. Standards may cover some or all risks associated with a specific MD. Complying relevant standards will result in risks that are on acceptable level for specific hazardous situations addressed in the standard. In these cases, further risk management would not be necessary, and standards could be referred as a verification of acceptable residual risk and risk control in the risk management file. Risk control activities can either reduce the severity or the probability of the harm, or both. [53] IEC 60601, IEC 62366, IEC 62304 and IEC 81001-5-1 are standards that should be applied in order to design and manufacture a safe and secure mTMS system.

Annex D in ISO/TR 24971 provides guidance on how information for safety can be provided and what factors should be considered. Information for safety should only be used when the manufacturer has determined that further risk reduction by other measures is not practicable. Information for safety is supposed to give clear instructions for the user of the actions that should be taken or avoided in order to prevent a hazardous situation or a harm from occurring. The information can be in the form of warnings, (pre)cautions, contraindications, instructions for use or training. The factors that the manufacturer should consider include: the need of classifying the information for safety, the necessary detail level to convey the information for safety, the location for the information for safety, the wording, pictures or symbols to be used to ensure the clarity and understandability of the information for safety, the intended recipients, the appropriate media for providing the information and the local regulatory requirements. [53]

The residual risks after risk control measures shall be evaluated like described in 3.1.3. Acceptable residual risks can be disregarded but more risk control measures shall be applied to residual risks that are above the acceptability criteria. If the (further) risk reduction is not practicable for some reason, the manufacturer should perform a benefit-risk analysis by reviewing data and literature to determine whether the benefits of the intended use of the MD outweigh the risks. If not, the residual risk remains unacceptable,

and the manufacturer should consider modifying the MD or its intended use. [51] ISO/TR24971 gives further guidance on performing benefit-risk analysis. It states that the benefit can be estimated from the performance of the MD in clinical use and the clinical outcomes expected from the use, benefits resulting from other similar MDs on the market and factors relevant to the risks and benefits of other alternative treatments. [53] For example, the benefits of mTMS treatment for depression could be justified against traditional anti-depressant treatment by less side-effects (see reference [54] for side-effects of anti-depressants). The criterion for benefit-risk analysis is very product-specific. Those involved in establishing such criteria should understand and consider the technical, regulatory, economic, and sociological context in their benefit-risk related judgments. The direct comparison between the risk and benefit is typically complicated and case specific. It should consider the available production and post-production information of similar devices on the market as well as their information on benefits and residual risks. This should be compared to the same information on similar devices under development. The characterization of disease or condition of the intended patients also plays an important role in benefit-risk comparison. [53]

The manufacturer should note and review the possible new risks arising from risk control activities. New hazards or hazardous situations can be introduced, or previously identified risks can be increased. If new risks arise, the manufacturer should perform risk estimation and possible benefit-risk analysis as before. The manufacturer shall verify the implementation and effectiveness of risk control measures for example as a part of design and development verification or process qualification or validation within a QMS. Like described before, the state-of-art standards can work as risk control verification *e.g.,* by applying a usability engineering process by IEC 62366 to verify the effectiveness of implemented safety information. The manufacturer shall review and ensure that all identified hazardous situations have been considered and risk control activities have been completed. All completed actions and their results shall be recorded in the risk management file. [51]

3.1.5 Overall residual risk evaluation

The manufacturer shall evaluate the overall residual risks remaining from all the identified hazardous situations after completing, implementing, and verifying all the risk control measures. Overall residual risk evaluation is especially important for complex MDs and devices with many individual risks. There is no specifically defined method in ISO 14971 how to perform the overall residual risk evaluation and it’s left up to manufacturer to

decide. However, the overall residual risks associated with the MD should be considered and evaluated from a broader perspective and weighed against the benefits the MD will bring to the patient. The acceptability criteria for overall residual risk does not necessarily be the same as used before for the individual risks but can be based on it. [51] ISO/TR 24971 gives guidance, advice and examples on the input, considerations, and approaches of the evaluation the overall residual risk. ISO14971 requires the manufacturer to inform users about significant residual risks. Annex D in ISO/TR24971 provides guidance on how to inform the disclosure of residual risks along the MD. It emphasizes what is to be informed and to whom the information is directed. Thus, the manufacturer should consider the level of detail of the information provided, the intended recipients and the wording to be used as well as the means and media to be used. [53] Also, the results of residual risk estimation shall be recorded in the risk management file.

3.1.6 Risk management review

Prior to commercial release of the MD the manufacturer shall review the execution of the risk management plan. The manufacturer shall ensure that the plan has been appropriately implemented and the overall residual risk is acceptable. They also shall ensure that appropriate methods are set to collect and review information in production and post-production phases. The review should be documented as risk management report and included in risk management file. The personnel with appropriate authority for reviewing the risk management shall be assigned in the risk management plan with other personnel involved in the risk management process. [51]

3.1.7 Production and post-production information

The standard requires that the manufacturer actively collects information related to the safety of the MD in production and post-production phases. This information allows the manufacturers to close the feed-back loop and make the risk management process a continuous lifecycle process. The manufacturer shall establish, maintain, and document a system for the activities used and the information collected. The information relevant to the safety of the MD can originate from several different sources. The typical sources are feedback from users, distributors, service personnel and training personnel as well as publicly available information like adverse event databases, incident reports and clinical literature. The information does not necessarily need to be directly related exactly to the MD – other MDs with similar intended use, hazard, or operating principles yield useful information for the manufacturer. The activities recorded can be a part of the required post-market surveillance system by the MDR. [51]

The manufacturer shall review the collected information and determine whether the information related to the safety of the MD changes the earlier established and accepted features in the risk management process. These changes include e.g., unrecognized hazards/hazardous situations are present or estimated risks or overall residual risks are no longer acceptable. [51] ISO/TR24971 provides questions that can assist the manufacturer reviewing the production and post-production information from a right perspective. [53] If the collected information changes the safety related issues, the manufacturer must complete required CAPA and for example reassess some sections of the risk management process.

3.1.8 Security risk management

It is emphasized that the risk management process introduced in ISO14971:2019 can also be applied to risks related to security, such as cybersecurity and data and systems security. However, some different terminology and risk assessment methods are used when dealing with security related risks. Security is *"a condition that results from the establishment and maintenance of protective measures that ensure a state of inviolability from hostile acts or influences, where hostile acts or influences could be intentional or unintentional".* Addition to security, some of the used terms are threat, vulnerability, confidentiality, integrity, and availability. Threat is a potential violation of security which could breach security and lead to a harm. It is an event or sequence of events that can exploit vulnerability leading to a hazardous situation. Vulnerability, in turn, is "*flaw or weakness in a system's design, implementation, or operation and management that could be exploited to violate the system's security policy".* Confidentiality means that the information is made not available for unauthorized access whereas integrity is the accuracy and completeness of information and availability means being accessible and usable upon a request by authorized entity. [53]

Annex F in ISO/TR24971 provides guidance on security risk management and describes the differences between safety and security. Another important and useful guidance document regarding security risk management is "Guidance on Cybersecurity for medical devices" by Medical Device Coordination Group [55]. It describes the basic concepts related to cybersecurity and states the cybersecurity requirements of the MDR. Like annex F in ISO/TR24971, it also provides guidance on security risk management but also assists how to fulfill other regulatory requirements, such as documentation and PMS, regarding MD security.

Figure 9 shows the relation between security and safety risk management processes. Both previously introduced guidance documents give several examples of typical security hazards and incidents and their relation to safety hazards. They also give examples of security control measures. A secure data system maintains high confidentiality, availability, and integrity. The severity concerning security related risks is usually estimated by the consequences of loss or degradation of these three factors whereas the severity concerning other risks is estimated by the degree of degradation in person's health. The harm caused by security related risks is often damage to property and related to information on the MD itself or information available on connected devices. The probability of security related risks is typically not easily estimated, since the probability of occurrence is often a function of motivation, financial gain, or function of opportunity. When evaluating the security related risks, the manufacturer must ensure that the three factors (*i.e.,* confidentiality, availability, and integrity) are prioritized accordingly by the intended use of the MD. [53]

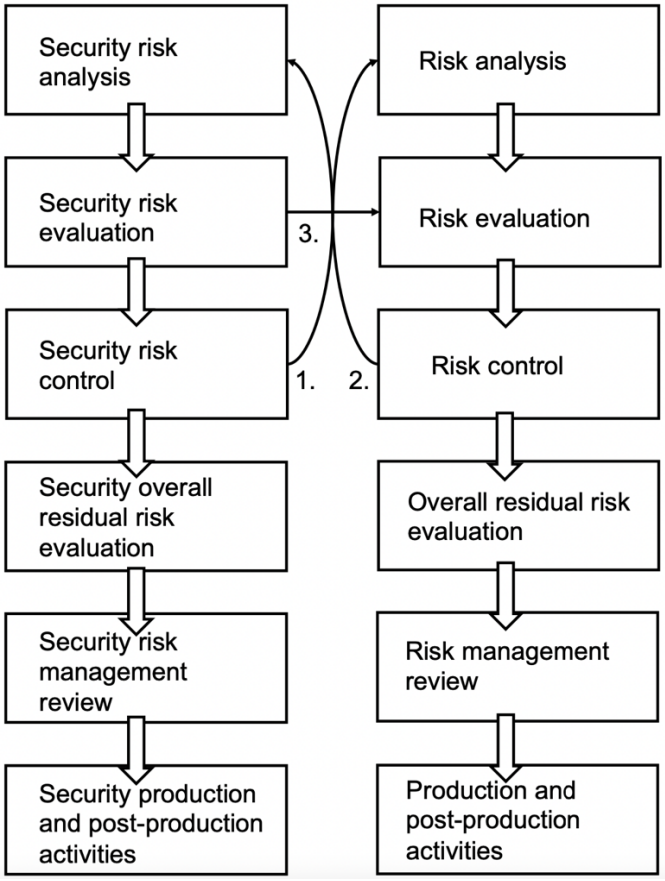

Figure 9. *The relation between security risk management process (on the left) and safety risk management process (on the right). Both processes consist of the same steps. The arrow number one presents the security control measures that impact the safety, whereas the arrow number two represents the safety risk control measures that impact security. In case of new risks arising from either of these control measures, re-analyzing the risks is needed. Arrow number 3, in turn, represents the security risks that may cause safety risks and thus require re-evaluation of the safety risks. (Figure adapted from* [53]*)*

3.2 Risk management system of mTMS prototype

The ways for collecting the data for creating the preliminary risk management system and the completion of its steps is explained in this chapter. It was decided to use a Microsoft Excel template provided by a consulting company for recording the risk management activities. The outlook of the template is represented in Figure 10. The file also serves as a risk management file. According to the consulting company [2] the NBs are familiar with such a model. The file can also be called a hazard traceability matrix (HTM).

3.2.1 Risk assessment

The risk assessment phase constitutes of risk analysis and risk evaluation (Figure 8). The template used for the risk management system is based on a generic FMEA template. However, since ISO14971:2019 requires identification of all possible risks, including risks in normal and fault condition as well as the foreseeable misuse, the risk analysis cannot fully follow the steps of a traditional FMEA. Another important difference between the requirements of ISO14971:2019 and FMEA is the rating of severities; the standard requires that severities are rated based by the harm caused to the patient whereas the FMEA solely rates severities based on effects on system performance. [56]

	Risk Analysis			Risk Estimation & Evaluation			SW class
Risk ID	Hazard (Known and foreseeable sources of harm)	Hazardous situation (How the patient is exposed to the hazard)	Harm (Physical injury or damage to health)	S Severity of the harm	P Probability of harm occurring	S x P Risk acceptability	

Risk Control / Mitigation			Risk Control Verification		Residual Risk Estimation & Evaluation				
Inherently safe design and manufacture	Protective measures in medical device or manufacturing process	Information for safety (warnings, precautions, contraindications) and training	Risk control implementation verified (Y/N)	Validation of the effectiveness of risk control (proof)	S Severity of the harm	P Probability of harm occurring	S x P Risk acceptability	Benefit-Risk analysis	New risks arising from risk control? Existing risks affected?

Figure 10. *A section of the utilized Excel template that consists of all the steps of the risk management process. The template provides traceability to each identified hazard and the executed risk management activities.*

The first step in risk assessment process was to identify the characteristics of the mTMS prototype that could affect the safety. This was completed by considering each guidance question in the ISO/TR 24971:2020 Annex A and their relevance to the prototype. An example of the created table is presented in Figure 11. The preliminary identification of the possible hazards was guided by the identified characteristics and discussion sessions with personnel involved in the project. These discussion sessions concerned the technology of the device and its operating principles, as well as the intended purpose and patient populations. The system was decided to divide into subsystems to enable more organized and easier hazard identification. The subsystems were mechanics (M), electronics (E), software (S), cybersecurity (C), usability (U), accessories and conjugated devices (A&CD) and other (O).

Question	Guidance	Relevance (Yes/No)	Response
What is the intended use and how is the MD to be used?	Factors that should be considered include: what is the MD role relative to;		
	diagnosis, prevention, monitoring, treatment, or alleviation of disease;	**Y**	The device is to be used in direct noninvasive stimulation of brain by inducing an electric field in the brain tissue. This is achieved by passing high currents in electromagnetic coils, which are placed adjacent to subject's head.
	diagnosis, monitoring, treatment, or alleviation of or compensation for an injury;	**Y**	The device can be used to treat e.g., stroke, spinal cord injury and patients with psychiatric and neurological disorders, such as depression, chronic pain, Alzheimer's and OBCD.
	investigation, replacement, modification or support of anatomy or a physiological process, or	**Y**	The device can be used to investigate basic functioning of brain. The device can be used to investigate the functioning of the central and peripheral nervous system.
	control of conception?	**N**	N/A
	What are the indications for use?	**Y**	The mTMS device is used for mapping brain structures, measuring brain function, treatment of psychiatric and neurological disorders as well as several research purposes. When combined with EMG, the device can be used to study the functioning of PNS.

Figure 11. *A section from the table made for identification of hazards and characteristics related to safety. In total there were 37 guidance questions, one including 9 subquestions, and each of them were considered individually in relevance to mTMS prototype.*

Other data gathered for identification of hazards, hazardous situations and harms were collected from training and test use sessions with the prototype, discussions with project members, watching videos and photos of operating the prototype, from literature and from FDA:s Manufacturer and User Facility Device Experience (MAUDE) database. Searching MAUDE resulted in 72 hits with a search phrase "transcranial magnetic stimulation". The first reports were recorded in 2011 and latest in 2021. All the reports were studied but only a few could actually contribute to the risk analysis of the mTMS.

In some cases, the hazards were identified from the harm by working the way back to the cause(s) of the harm, but mostly the hazards were identified first. The criteria for risk estimation and evaluation were scaled from 1 to 5. The scaling with the level of risk acceptability was established by the consulting company and was provided along the risk management system template. The scaling of qualitative severity and semi-quantitative probability with explanations are shown in Figure 12 and Figure 13. The initial risk estimation was considered for each harm before implementation of **any** risk control activities. The factors considered when estimating the initial probability were related *e.g.,*

to the operating principles and experiment protocols of the system and whether the identified hazard could be present in every single experiment. The estimation of the severity and probability was based on communication with project members and on author's own opinions. The probability could also be estimated with two separate probabilities: probability for the occurrence of hazardous situation and probability for hazardous situation leading to a harm. These two probabilities would be multiplied together to obtain the final probability for the occurrence of the harm. In this case, however, it was decided to use only one probability to clarify the estimation process. Also, since the development process of the mTMS system was in such an early phase, there was not enough data to favor estimation process with two different probabilities.

		S1	S2	S3	S4	S5
	INITIAL	**Negligible**	**Minor**	**Intermediate**	**Critical**	**Catastrophic**
P5	**Frequent**					
P4	**Probable**					
P3	**Occasional**					
P2	**Remote**					
P1	**Improbable**					
		S1	S2	S3	S4	S5
	MITIGATED	**Negligible**	**Minor**	**Intermediate**	**Critical**	**Catastrophic**
P5	**Frequent**					
P4	**Probable**					
P3	**Occasional**					
P2	**Remote**					
P1	**Improbable**					

Figure 12. *The scaling used for estimating the probability and severity of risks. The rating for risk acceptability.*

	Severity	
S5	Catastrophic	Can cause serious injury or death
S4	Critical	Results in injury or impairment requiring professional medical intervention
S3	Intermediate	Results in temporary injury or impairment not requiring professional medical intervention
S2	Minor	Temporary discomfort
S1	Negligible	Inconvenience
	Probability	
P5	Frequent	Likely to occur frequently during the lifetime of an individual system; will be continuously experienced among all installations of the device
P4	Probable	Likely to occur several times during the lifetime of an individual system; will occur frequently among all installations of the system
P3	Occasional	Likely to occur sometime during the lifetime of an individual system; likely to occur several time among all installations of the system
P2	Remote	Unlikely to occur but possible during the lifetime of a system; unlikely but reasonably expected to occur among all installations of the system
P1	Improbable	Extremely unlike to occur to a system; probable among all installation of the system

Figure 13. *The explanations for different severity and probability levels used in risk estimation and evaluation. The probability was semi-quantitative and severity was qualitative.*

3.2.2 Risk control and risk control verification

The risk control activities were divided into 3 groups according to the standard. These groups were

a) Inherently safe design and manufacture
b) Protective measures in medical device or manufacturing process
c) Information for safety (warnings, precautions, contraindications) and training.

Risk control activities were implemented for all risks regardless of their initially evaluated acceptability. Data for the risk control options was gathered from literature, from existing prototype design and from personal proposals for future design of the mTMS system. Risk control verification was implemented where it was applicable considering the current design of the prototype. Suggestions for verification methods were made regarding the proposed, not yet implemented, risk control measures. The risk mitigation could either lower the severity or the probability of the harm, or both.

3.2.3 Residual risk estimation and evaluation

The residual risks were estimated and evaluated by using the same scaling (see Figure 12 and Figure 13) as for estimation and evaluation of the initial risks.

3.3 Interviews

Interviews for other MD commercialization projects in Aalto University were organized to gather qualitative information and insights on risk management processes among other similar projects. The semi structured interviews consisted of 4 main questions that were asked in the same order. The questions were:

1. What was your knowledge about Q&R requirements for MDs before starting the project?
2. How was the risk management organized in your project? Describe the completion of steps.
3. What were the challenges in the risk management process/steps? What did you find the most challenging?
4. How do you think the risk management process could be improved at the early stages of academic MD commercialization projects?

Some sub questions were performed to guide the answering to questions 2 and 4. Otherwise the interviews were quite freeform. They were organized remotely (Zoom or Microsoft Teams teleconferencing platforms) and recorded for further analyzing and writing purposes. After all, 3 interviews were performed. The interviewees were managers of the commercialization projects similar to the mTMS R2B project. Like the mTMS commercialization project, all the other projects were also funded by Business Finland.

4. RESULTS

The aim of this thesis was to produce a preliminary risk management system for the mTMS prototype and to answer the research questions regarding organization of risk management and Q&R awareness among academic MD commercialization projects. The results of these objectives are presented in this chapter.

4.1 mTMS risk management process

In this chapter, the results of each step of the preliminary risk management process of mTMS prototype are described. Since the produced risk management file cannot be published because of confidentiality issues, some examples of risks are derived from each subsystem and described in more detail.

4.1.1 Risk assessment

In total, 35 hazards leading to 74 hazardous situations and 112 harms were identified in the preliminary risk analysis. 19 of the identified hazards led to more than one hazardous situation, whereas 16 lead to only one hazardous situation. Each hazardous situation could either lead to one or several separate harms. The division of hazards by subsystems was: 6 for mechanics, 12 for electronics, 3 for software, 23 for usability, 5 for accessories and conjugated devices, 9 for other and 2 for cybersecurity. It is notable that several hazards were related to more than one subsystem. The initial estimation of risks resulted in 59 harms at an unacceptable level, whereas 53 harms were on acceptable level. Most of the unacceptable risks were related to electronics, usability, and mechanics. The software-related risks were classified by the classification in IEC 62304 as well as by the 1 to 5 scale criteria.

Examples from each subsystem

A failure of the mechanical arm is a hazard that applies to mechanics and usability. In the current mTMS design, the transducer is held and adjusted manually by moving an articulated mechanical arm (see Figure 6). The transducer is held by the arm's screws around the wooden handle. If the mechanical arm failed to function as intended, it could lead to 5 different hazardous situations and 7 harms. The most critical hazardous situation caused by mechanical arm failure is transducer falling when operated. The 5-coil transducer is relatively heavy and could cause serious head or neck injury to the patient.

The initial risk of this harm was unacceptable with catastrophic (5) severity and probable (4) probability. Another hazardous situation caused by mechanical arm failure is the malfunction of the arm and thus being unable to adjust the transducer as desired. This would lead to delay or cancellation of the treatment and might cause deterioration of patient's health. The initial risk of this harm was unacceptable with critical (4) severity and occasional (3) possibility.

Overheating of transducer surface material due insulation failure is a hazard that applies to electronics. It could lead to a hazardous situation where the operator or the patient gets in contact with the hot surface material possibly resulting in skin burn. The initial risk of this harm was unacceptable with a critical (4) severity and occasional probability (3).

Unwanted magnetic induction is a hazard that applies to two different subsystems, usability and other. A hazardous situation where the user unintentionally stimulates sensitive objects/devices nearby the transducer could lead to damaged external electronic devices. This initial risk remained acceptable with intermediate (3) severity and remote (2) probability. Unwanted magnetic induction could occur also to the adjacent sites of the targeted brain areas. This might lead to increase of adverse effects. The initial risk of the harm was estimated acceptable, with intermediate (3) severity and occasional (3) probability.

Poorly attached EEG or EMG electrodes is a hazard that applies to accessories and conjugated devices. The lack of diagnostic/measurement data due poor electrode connection could lead to incorrect stimulation and risk of increased adverse effects. This hazard is especially relevant, when the device is operated with closed-loop paradigms, where the EMG/EEG responses are used to determine the stimulation parameters. The initial risk was unacceptable with critical (4) severity and occasional (3) probability.

Software failure is a hazard that applies to software and usability. One of the hazardous situations that software failure could lead to, is a program fault. This would lead to delay of treatment and loss of device functionality. The initial risk was acceptable with negligible (1) severity and occasional (3) probability. If the patient is in critical condition, a delayed treatment could cause deterioration of health. The initial risk for this harm was unacceptable with critical (4) severity and occasional (3) probability. The risk classes according to IEC 62304 for these risks are A and C, respectively.

Unauthorized access to the system is a hazard that applies to cybersecurity, software and other. It could lead to three different hazardous situations and six harms. One of the

hazardous situations is modifying, stealing, or abusing private patient data. Loss of data integrity could lead to wrong clinical decisions or performing of incorrect treatment and, thus, increase of adverse effects. In addition to physical harm, the patient might undergo some anxiety or psychical harm. The initial risk of this harm was estimated unacceptable with critical (4) severity and occasional (3) probability. Another hazardous situation caused by unauthorized access is installation of malware through USB ports leading to corrupted software or bugs in the system signaling. Problems in system signaling could lead to incorrect treatment and increase of adverse effects. The initial risk of this harm was unacceptable with critical (4) severity and occasional (3) probability.

4.1.2 Risk control and risk control verification

Risk control measures belonging to each group described in 3.2.2 were introduced and recorded in the risk management file. Some of the implemented risk control measures are existing features in the current mTMS prototype design, but many mitigation measures are suggestions and proposals for a safer design and manufacture for the future. Examples of the existing risk mitigation measures in the current design are manufacture according to the safety requirements stated in IEC 60601-1 and an embedded safety monitor that monitors *e.g.,* cabinet door status, coil connection status and emergency stop button status. Also, a training for operating the system and relevant safety information, precautions and warnings stated in the user manual are existing risk control measures.

Examples from each subsystem

The falling of the transducer caused by mechanical arm failure could be controlled by *e.g.,* implementing a safety lock feature between the holder of the arm and the transducer. The safety lock would secure the transducer if other components of the arm happened to fail. Using materials and components only from certified manufacturers or using commercially available suitable mechanical arm ensures the safety and adequacy of the arm. Implementing safety and functionality tests during test use and providing safety information regarding the usage of the mechanical arm can be considered as risk control measures. These measures can be verified by referring to approved safety lock testing and to appropriate standard compliance. The standards include *e.g.,* IEC 62366-1, ISO 153223-1 and ISO 20417.

Insulation material failure and possible overheating of transducer surface can be controlled by designing and manufacturing the transducer in compliance with the safety requirements stated in IEC 60601-1. Temperature sensors monitoring the transducer temperature are embedded inside and on the surface of the transducer. The information monitored by these sensors is shown in the user interface to notify the user about the temperatures in the transducer during stimulation. The system prevents the output (and also the user from forcing applying the stimuli) when the temperature is beyond safety limits (41 degrees of Celsius at the contact to patient). In addition, the user should be informed for testing the condition of the transducer in a regular basis. These risk control measures can be verified by referring to IEC60601-1 compliance and appropriate testing of temperature sensors.

Unwanted magnetic induction can be controlled by allowing only trained users operate the system in a suitable operating environment. Sensitive external electronic devices and other personal belongings should not be taken in proximity of the device. Correct advising of patients about these issues is important. The patients could also be screened before the experiment for external and internal electronic devices left unnoticed. Eligible users should have a training certificate, which also serves as a risk control verification. Also, appropriate electromagnetic compatibility tests could serve as risk control verification. Unwanted magnetic induction in adjacent brain areas could, in addition, be controlled by designing, manufacturing, and testing the device in accordance with relevant standards to ensure that the *e.g.,* the stimulation parameters are passed correctly.

The risk caused by poorly attached EMG/EEG electrodes could be controlled by using only tested, strong adhesive pastes for electrodes and by operating the system only by trained personnel. Impedances of all EEG electrodes should be kept below the limit or equal to 5 kOhms. Eligible personnel should have a training certificate, which also serves as a risk control verification. The conjugated devices as well as accessories needed with the device are commercially available and should have their own safety instructions.

Software failure leading to system or user interface foul could be controlled by designing the software according to appropriate standards, such as IEC 62366 and IEC 62304 and regularly updating the software. Only necessary applications for the intended use should be installed on the PC to avoid excessive burdening of the system. Also, correct administration rights should be assigned to each user account and accessing the system should require appropriate identification. The system should notify the user for available updates and any detected software disfunctions. Patients with critical conditions should

be informed and assigned to receive treatment elsewhere if software failure precludes the intended treatment.

Unauthorized access to the system could be prevented by implementing physical security measures, such as access to operating room only by eligible badges or keys. The stored patient data could be encrypted and accessed only by strong identification procedure. The PC of the system should have up-to-date firewall and installation of any applications should enquire strong identification. In addition, the software should be designed and tested according to appropriate standards, such as IEC 62304 and IEC 81001-5-1.

4.1.3 Residual risk estimation and evaluation

After implementing the existing and suggested risk control measures, all risks were on acceptable level. In most cases, it was possible to only lower the probability of the hazardous situation from leading to a harm. In some cases, also the severity of the harm was lowered by risk control activities. There was no need for performing a benefit-risk analysis at this stage of the prototype design. A benefit-risk analysis should be considered for overall residual risk estimation later, when there is enough clinical evidence on the benefits of the device, and the design is finalized for commercialization.

Examples from each subsystem

The residual risk for mechanical arm failure causing the transducer to fall during operation was estimated acceptable. The probability was lowered from probable (4) to improbable (1). It is very unlikely that the transducer would fall if the mechanical arm has been manufactured and tested appropriately and a safety lock feature has been added. However, the risk control measures had no effect on the severity of the harm since they only prevent the harm from occurring. The residual risk for deterioration of patient's health due cancelled or delayed treatment was acceptable with intermediate (3) severity and improbable (1) probability. In this case, it was possible to also lower the severity since patients with critical conditions would be assigned to receive treatment immediately elsewhere. Like described earlier, it is very unlikely that the mechanical arm would fail to function if it has been manufactured and tested appropriately.

The residual risk for overheating of the transducer surface due insulation failure was estimated acceptable with probability lowering from occasional (3) to remote (1) after risk mitigation. IEC60601-1 compatible materials and manufacturing methods will ensure the safety and applicability of the transducer assembly. In addition, the temperature sensor

will continuously monitor the temperature inside and on the surface of the transducer. The user will be prevented from applying stimulus if the temperature is beyond safety limits.

The residual risk for unwanted magnetic induction of sensitive objects or devices in proximity of the system was estimated acceptable. Testing the system for electromagnetic compatibility, training the users, advising, and screening the subjects adequately would lower the probability from remote (2) to improbable (1). The risk for unwanted magnetic induction in adjacent brain areas was lowered from occasional (3) to remote (2).

The residual risk for poorly attached EEG/EMG electrodes was estimated acceptable. The probability was lowered from occasional (3) to remote (2) since it is possible that the electrodes might detach during lengthy stimulation sessions even though the described risk control measures would have been implemented. The device operator should be aware of this possibility and occasionally check the status of connected electrodes. In these situations, it is important that the operator is specialized enough to understand the validity of the responses obtained from conjugated devices.

The residual risk for program fault due software failure was estimated acceptable. The probability for loss of system functionality and delay of treatment was lowered from occasional (3) to remote (2). In contrast, in case of deterioration of health of patients with critical conditions due loss of device functionality, both the probability and severity were lowered. The severity lowered from critical (4) to intermediate (3) since the patients would immediately be assigned to receive the intended treatment somewhere else. The probability, in turn, lowered as well from occasional (3) to remote (2). The probability could not be lowered more since software related issues might emerge with the current prototype design.

The residual risk for unauthorized access causing exploiting of private patient data was estimated acceptable. The probability was lowered from occasional (3) to improbable (1) due strong risk control measures. The severity was also estimated one level lower (from critical (4) to intermediate (3)) due proposed data encryption. Encryption of the patient data would significantly complicate its further utilization. The residual risk for unauthorized installation of malware through USB ports causing usage of corrupted software and thus incorrect treatment and increase of adverse effects was estimated acceptable. The probability was lowered from occasional (3) to improbable (1) because it would be almost impossible to access the system through physical security measures and multiple identification steps on the PC.

4.1.4 Emergence of new risks

A possible failure of risk control measures would affect three of the previously introduced example cases from different subsystems. If the safety lock ensuring the transducer would fail to function, it could be possible the transducer would fall and injure the patient, the operator, or cause system damage. This obviously requires breakage of other components in the mechanical arm. The failure of the temperature sensor would increase the probability of overheating the transducer due insulation material failure or excessive stimulation. The user would not be aware of the temperature in the transducer and would not be prevented from applying stimuli if the temperature is beyond safety limits. Risks related to software failure could occur more frequently if the system failed to inform the user about available updates or any detected software disfunctions. If automatic software updates are in use, they might be left unfinished due some dysfunction and, thus, expose the system for external attacks.

To conclude, completely new hazards or hazardous situations were not identified in the risk management process after risk mitigation. However, some risks might become unacceptable if specific risk control measures failed to function as described with example cases above. These situations should be considered in later benefit-risk analysis. After all, their influence in the whole process should remain minor as the probability for the described risks to occur in the first place is exceptional.

4.2 Interviews

In this chapter the results of the interviews will be presented. The data will be reflected with the experiences gained during the preliminary mTMS risk management process The research questions set in the beginning of this thesis will be answered here.

4.2.1 Researchers' knowledge of Q&RA

Based on the interviews and communication within mTMS project the researchers generally know very little about the quality and regulatory requirements that are needed for developing a commercial MD. Two interviewees described that they "*basically had no knowledge at all*" or "*the knowledge was basically close to zero*" before they started working in the commercialization projects. However, it was described that some abstract level knowledge existed and that they were aware of some standards, such as ISO 13485 and ISO 14971, which needed to be considered during the R&D process. One

interviewee had some study background and one had been dealing with regulatory approvals but within another industry. No one of the interviewed researchers had any practical work experience on new MDs aiming for CE marking or FDA approval. All groups, including mTMS group, had utilized, or were going to utilize, training or coaching services from consulting companies. Generally, the help of consultants was found truly important and useful.

It seems like the awareness of Q&R requirements for MD commercialization purposes is increasing among academia. An interviewee had noticed a shift towards better in the amount of discussion concerning Q&RA in Aalto during the last few years. He described that as he started in the project there was hardly any discussion going on of what is needed to take into account when designing and manufacturing a new MD. The increase might be a result from the emergence of Business Finland funded commercialization projects in the department of neuroscience and biomedical engineering (NBE) in Aalto University. Also, *e.g.,* Tampere University has added study modules in their selection for solely focusing on the MD Q&R requirements, product development and commercialization to educate the future professionals to understand the importance of these aspects.

4.2.2 Organization of risk management activities

The results of risk management organization in the projects cannot easily be compared to each other due the variance of implemented risk management activities, thus the maturity of the whole system, and the variance of features in the MDs. However, I was able gather some similarities between all the projects including mTMS project. All projects utilized consulting at some stage and started recording the risk management activities in an Excel template provided by the consultants. The risk estimation and evaluation, if implemented, was scaled from 1 to 5 and the guidance for risk acceptance levels were required from the standard or from the provided risk management template. One project had started the whole risk management process with a consultant, who advised them how to proceed systematically with each step. In one project some risk analysis had been performed by clinicians and technicians who were working in R&D at the time. The analysis had been updated along the way with the developed safety measures in the manufacture and will be reviewed again in more structured way. However, the persons performing the risk analysis in R2B projects aren't always necessarily experts on the developed technology, but the expertise for risk analysis inputs are gathered from the communication with the stakeholders.

Generally, the risk management started with defining the intended use of the device. Defining the intended use is very important since it specifies all the needed regulatory requirements and guides, *e.g.,* identification of the hazards and device classification. This was found to be relatively easy but might have changed several times during the project. According to one interviewee the changes didn't affect the risk analysis since the main risks related to the MD remained the same. One interviewee stated that defining the intended use was also one aim of the project and the risk analysis was focusing on defining and identifying the risks on a very general level feature by feature. Going into too much detail or estimating and evaluating the risks was not found to be necessary at that stage in that specific project. Two interviewees described that their own tests and trials had been very useful for identifying and tackling the risks related to the technology, as well as proving that the risks don't exist. All interviewees emphasized that they don't have a full risk management process yet in place, which is also the case in mTMS project. Many described that they are acquiring knowledge, information, and evidence for the practical needs of later commercialization. Due the restrictions from the project funder, the researchers were not allowed to do product development. This means that almost without exception one must establish a commercial framework (*e.g.,* a start-up, licensing agreement etc.) to bring the device onto the market.

4.2.3 Challenges in the risk management process

The first impression of all interviewees' to this question was emphasizing again the non-existence of a complete risk management process. However, during the conversation challenges started to come up. One interviewee stated that at this stage the most challenging thing for him was to get a right mind set and think less complex and more about the bigger picture. He also found that communication within the project was challenging, and better communication might have helped to understand better the risks related to the device. All interviewees, including author, think that the lack of information about the final device, *i.e.,* the low maturity of the projects, accounts for the main challenges in creating a risk management system for a prototype still in developmental phase where all the details are not yet known. Also, one interviewee stated that especially scoring the exact statistical values for probabilities is difficult without repeating something several times during the process. Scoring becomes easier when one gets closer to the finalized device and possible incidents emerge. However, the standard does not require exact scaling and the estimation is very much dependent on the particular MD.

Even though one interviewee found working with the risk analysis by themself a bit challenging also challenges working within a large group of people appeared. One interviewee described that it is difficult to "*set everyone onto the same path*" since people with different expertise might have different visions about the end product, which directly affects identifying the risks related to the MD. Since most of the people working in these kinds of projects are very technology driven, it is challenging to motivate team members to also consider the details of quality and regulatory requirements. Different people are motivated by different things. The technology driven mindset of engineers might lead to situations where redesign is needed because a solution to a problem is presented in a way or another regardless of Q&R requirements.

4.2.4 Improving the risk management process and other Q&R related issues in the early stage of R&D

Generally, it was found that Q&R related issues, including risk management, could be improved by simply increasing the awareness, knowledge and understanding of the whole Q&R framework among the project members. However, one interviewee saw that there are two sides to this topic. He described that "on the other hand you want everyone to know the standards and apply them but then on the other hand you do not want to take away from the innovative thinking and progression of development". He thinks that in the early stage it is important to have different people taking care of different steps of the R&D process. It is important to keep the resources where they are needed the most in the early design and development. According to one interviewee, knowing the procedures needed to perform in the lab to fulfill the quality requirements for each specific task would highly improve all Q&R related issues. He sees that the current situation is that groups are performing experiments and hoping that the results would serve for their needs. Knowing exactly what is being done and why, in addition to appropriate documenting, is the key for more effective development processes. By just adding any documentation to the experiments could already significantly improve the identification of risks. For example, if some technical solution is envisioned better, it should be documented in the design input file and the results of testing it should be documented in the design output file. The potential risks would perhaps be more easily and specifically identified during this process. For example, well defined and documented intended purpose serves as a good starting point for a researcher to tackle risk analysis.

Applying the relevant standards already in academic design and manufacture of the MD and keeping records of the evidence gathered during the R&D process will highly contribute to DoC:s and approval submissions at later stage when a start-up company is

established. By doing as much as possible Q&R wise from the very start will decrease the possibility of redoing the whole MD when it would be ready for commercializing. One interviewee stated that with the help of consultants they managed think about the broad picture around their MD commercialization project. He thinks that the Q&R related issues could be improved if one would for example estimate how much money and time goes into these issues. Also, utilizing the existing evidence and information in available databases helps a lot.

Among the interviewees, it was generally agreed that if one aims to enter the market fast, they need to include someone with previous experience of commercializing a MD into their project. The help of consultants was found to be very vital. However, finding the right timing for bringing a Q&R expert into the project was described to be challenging in these kinds of R2B projects. One interviewee described how the consultants say that is never too early to bring an expert into the project. However, he thinks that it is difficult since the academic settings differ a lot from companies with similar kinds of MD development projects. In a company the aim is to make a profitable product whereas in academic projects there might be an existing challenge of which the researchers want to accomplish without any thought of it possible being market worthy.

Two interviewees supported the idea of having a department wide expert, person in responsible or a shared resource for all Q&R related issues. One interviewee praised the innovation services in Aalto University for being very supportive for R2B ideas. However, since the MDR is so specific it is most likely out of the scope of typical innovation services or TTOs of universities, which typically assist in, *e.g.,* patenting and IP rights. Having someone with Q&R expertise in the departments which could possibly produce new MDs might truly be a good idea for the universities to consider in the future.

5. DISCUSSION

The results of this thesis are discussed and reflected thoroughly in this chapter.

5.1 Risk management of mTMS prototype

Risk management as a concept sounds quite simple. The core of it truly is quite straightforward: identifying all possible and foreseeable hazards associated with the specific MD. There is just so much more depth to MD risk management than simply writing down the hazards and the harms they lead to. Risk management process is time consuming and demands deep understanding of the standards' requirements and other regulatory aspects, understanding and knowledge of the specific device technology as well as its clinical prospects.

The preliminary risk management system for mTMS prototype was produced successfully in this thesis. The required understanding and knowledge of the device technology and regulatory requirements were managed to acquire on adequate level in order to obtain a comprehensive risk analysis that covers all the possible risks in normal and fault condition as well as the risks caused by foreseeable misuse. The division of the system into subsystems assisted the consideration of all the aspects of different risks related to the prototype. The risk management system was produced to be mainly compatible with the prototype at its current state at the time of completing this thesis. However, some suggestions for future risk control measures and risk control verification methods were included in the risk management system together with possible hazards related to a different prototype design. These suggestions were based on internal communication within the project and author's own visions. The risk management system is a living document which evolves as the device design develops and changes. In the future, this will require constant rethinking of different aspects related to risk management.

The biggest challenges in the risk management process of mTMS prototype were related to the low maturity of the project and the lack of clinical data. The prototype considered in this thesis was the very first version of the five-coil mTMS transducer which is why the design and manufacture was expected to differentiate as the project matures. The unknown features and lacking information of all the details in the final product design caused complexity to the risk management process. The experiments conducted with the prototype so far, were mostly experimental proof-of-concept and feasibility studies

with volunteers. Thus, there was not much evidence to which, for example, the probability estimation could be based on. To obtain a more reliable probability estimation, the specific procedures should have been iterated several times in an established manner. This would have not been possible with the available resources and timeline. Another challenging issue related to the probability estimation was the initial estimation of probability for each harm occurrence, which was supposed to be estimated before any risk mitigation. At first, this was found to be slightly odd, since logically then all the harms should have had the highest probability because the risk control measures prevent them from happening. Yet, this wasn't the case, because a hazardous situation would not lead to a harm every time. Because of these challenges the probabilities were re-estimated a few times to reach the most accurate and truthful level. Also, if the prototype had been tested more clinically with possible future patient populations, there would have been more concrete data for identifying hazards and hazardous situations. As the device reaches its final design and the clinical evaluation of the device starts, some of the identified hazards and hazardous situations might become irrelevant and some new hazards might be identified. Thus, it should be emphasized again that the risk management system produced in this thesis is a preliminary version and it should be updated accordingly when new information is available.

One other issue was found to be challenging in the risk management process which was the separation between hazards and hazardous situations. ISO 14971 defines hazard as a potential source of harm whereas hazardous situation is defined as a circumstance in which people, property or environment is/are exposed to one or more hazards. There were situations where it was easier to identify the possible hazardous situation and the harm caused by it. Specifying the exact cause, *i.e.,* hazard, was more complicated in these situations. Like described in beginning of the section 4.1.1, one hazard could lead to several separate hazardous situations and one hazardous situation could lead to several different harms. Expressing the hazards, hazardous situations and harms in this manner was found to be practical and providing clarity to the process.

Overall, 35 hazards leading to 74 hazardous situations were identified in the risk management process. The initial number of hazards was not very high, from which it can be judged that the design and development of the prototype is well on track. The division of hazards between subsystems, however, reveals which areas in the system design might need more attention in the future. The majority of the hazards were related to usability (23 hazards) and electronics (12 hazards). The electronic parts of the prototype have been designed and manufactured according to the requirements of IEC 60601 because

it is the very first way of ensuring the safety of MEE. However, it does not remove the existence of the electrical risks and thus, they had to be carefully considered in the risk assessment. The amount of usability related hazards shows that those issues have not been assessed as thoroughly in the design and manufacture. However, these aspects will become more into consideration when the prototype is operated also by other people than the people who have designed and manufactured it, as the subjectivity and professional bias will be absent. Usability engineering activities should be applied to help with the usability related risk assessment. At later phases, the external feedback and communication from users and patients becomes even more important and will greatly contribute to the whole risk management process.

5.2 Interviews

The purpose of the interviews conducted in this thesis was to gather more insight on Q&R related issues, especially, on organization of risk management activities in other similar academic MD commercialization projects. The data gained from these quite freeform semi-structured interviews, reflected together with experiences from mTMS project, was sufficient to form a general idea of the organization and the challenges of MD risk management in Aalto University. The data supported well the assumptions regarding the level of awareness of Q&RA among academic researchers in NBE. Generally, the researchers are not that familiar with the Q&R requirements nor are too interested in starting to implement these requirements into their processes. The low level of existing documentation and the interest towards completing it creates challenges and might delay these projects. Typically, there were one or two persons who were responsible of implementing the risk management activities. These persons might have also been responsible for other Q&R related issues in the project. The risk management activities were typically recorded in a similar Excel template which was also used for mTMS risk management system. The communication within the stakeholders and utilizing the help of consultants was found crucial. Typically, the researchers were battling with similar kind of challenges in the risk management processes. These challenges were related to maturity of the device design, lack of clinical data and other information as well as motivational issues and information passage within the project members.

Because only researchers from Aalto university were interviewed, the results cannot be generalized to represent all academic MD R&D projects. However, the results might give some starting points and directions to a possible later and larger interview study. To achieve more comprehensive results, more similar research projects from Finland and

even from the major universities from Europe should be included. The research questions should be set carefully, and the interviews designed to cover the topic thoroughly. However, this would have been completely out of the scope of this thesis, since the focus was in creating the risk management system for the mTMS prototype.

5.3 Prospects for MDs originating from academic R&D

Researchers in NBE at Aalto University are doing precious work around new MD technologies with several ongoing commercialization projects. The R2B projects funded by Business Finland, however, have some restrictions. The funding allows commercial preparation, *e.g.,* proof-of-concept studies, analysis of competitors solutions, market, and customer research, searching for investors and business model mapping, but it does not allow product development, branding or business plan creating. Because of these restrictions, commercializing a MD device originating from such projects undoubtedly requires establishing a private organization, *i.e.,* a company, or selling the idea to someone already operating in the field. The biggest obstacles in these situations are, then, related to funding and resources and to business-minded decision making.

Even though a company would be successfully created, there are some other issues related to academically developed MDs. The main issue is related to the ISO 13485 compatible QMS, which academic R&D projects are typically lacking. Like described in the previous chapter the required documentation might not exist and the completed activities and processes might not be compatible with the standard's requirements. There is a lot of information being collected but no organized system for documenting them with the required level of traceability. The information passes mainly orally inside the projects and there might be someone left unaware.

The worst-case scenario in these situations, is that the whole device design and manufacture must be redone in order to achieve ISO13485 compliance which is mandatory for obtaining a CE label. This drastically delays the planned market release of the device and might take up all the resources designed to spent elsewhere leading to possible termination of the whole project due financial difficulties. For these reasons researchers with new MD technologies containing commercial potential should be aware of the Q&R requirements and start implementing those as early as possible. Even a little amount of QMS documentation would be beneficial and speed up the processes, even if the device would have to be redesigned to some extent.

It is good that the researchers in NBE have noticed more discussion existing around these topics nowadays. Perhaps it is resulting from the legal change regarding the regulation or from the constantly advancing and arising new technologies and possibilities in the MD science. The universities should start offering degrees to specifically educate MD Q&R professionals, since there is currently a high demand for these professionals. Universities could also hire consults or experts to assist the researchers with their regulatory strategy and offer, *e.g.,* templates covering the main requirements to get the processes appropriately documented from the very start. Perhaps this kind of support would motivate the researchers to pursue with their ideas and in the future even more technologies and devices on the global market could be originated from academic MD R&D.

5.3.1 Prospects for mTMS device

By the time of completing this thesis, the researchers in Aalto University had successfully built several mTMS transducers with different number of coils. They had earlier received an ethical approval from HUS to use the system for research and therapeutic purposes together with the clinicians in their premises. They are also planning to install a system soon in University of Tübingen and later to University of Chieti-Pescara. This is possible by fulfilling the local requirements and getting an approval of the Universities' Ethics Committee. A preliminary risk assessment is typically one of the requirements of Ethics Committee. The clinical evaluation is intended to be conducted with different patient populations in University of Tübingen, whereas the measured data are used to analyze and understand brain communication and develop advanced closed-loop algorithms in Chieti-Pescara.

In addition to the produced preliminary risk management system, implementing and documenting the requirements of ISO 13485 compatible QMS was started in mTMS commercialization project. The appropriate documenting has been built in tandem with the manufacture of the second five-coil prototype with the help of external consulting company and a hired junior Q&R expert. This approach was found to be practical and probably the fastest way to proceed in this project. By the time commercialization becomes topical, the project should have appropriate quality management and risk management systems in place. However, this requires good communication and understanding of both systems since they very strongly intertwine and support each other. The systems should be constantly updated as the project proceeds and more data become available. Information passage and effective feedback loops between different sections are vital for risk management to succeed. Especially the feedback from the end users back to design

engineers in manufacturing is very important, as the mTMS device is still in experimental use. Risks in the risk management process, such as subjective risks, vision/thinking of personnel performing the risk management and their possible unintentional negligence/ignorance should be also considered. Subjectivity is easily reduced by receiving checkups from external experts or consultants.

The intended use and the device classification should be determined and defined soon in order to specify the regulatory requirements for entering different markets. Typically, these are the very first things that are done in MD product development, but since the academic nature of the project the intended use and device classification might be modulated as the device and its clinical usability has been finalized.

The mTMS technology has been patented in several countries to ensure the exclusive rights for the inventors. As C2B project proceeds, the options for commercializing the device are most likely via a spin-off company or via existing company. The search for suitable investors has already been started. At later stages, it is very important that there are also business minded members in the team. These members should be competent in business and administration as well as financing and marketing. The company must establish their business and marketing strategy and start identifying business related risks. These risks should be then further analyzed and managed in business risk management. In order to facilitate the process for obtaining a CE label and/or receiving FDA clearance, all the standards introduced in this thesis should be implemented in relation to each other.

6. CONCLUSIONS

The purpose of this thesis was to produce a preliminary ISO 14971 compatible risk management system for mTMS prototype developed in NBE at Aalto University. In addition, the aim was to research the level of Q&R awareness and organization of risk management in similar kind of academic MD commercialization projects by interviewing researchers from such projects. The produced risk management system serves well the internal needs of the project and works as a great base for future needs regarding commercialization of the device. The risk management system helps to understand how different subsystems are related to each other and what kind of hazards each of them they include. Each hazard, hazardous situation, and harm together with specific risk control measures are analyzed and introduced clearly in the system. Hazards caused by foreseeable misuse of the system are also thoroughly considered and might have pointed out some issues that had not been considered earlier.

The interviews showed that risk management is organized very similarly in different MD commercialization projects in NBE. The researchers were typically facing similar issues and challenges in the risk management process. The level of Q&R awareness is generally not very high amongst researchers, but it seems to be increasing. It was generally agreed that by increasing the Q&R related knowledge and receiving consulting (from commercial companies or from department wide Q&R specialist) the risk management and other Q&R related processes could be improved in academic MD R&D. However, it seems like the best way is to have only a small group of people responsible for the Q&RA instead of burdening everyone in the project with all the detailed, likely new, information. This way the stakeholders can intensely concentrate in what they do the best, which creates the cornerstone for good and innovative R&D.

To conclude, the objectives of this thesis were successfully accomplished. The obtained results together with the theoretical background introduced in this thesis highlight the importance of understanding, correct implementing and documenting of the standards and other regulatory requirements concerning MD product development. The MD industry is highly regulated and controlled for crucial reasons. This is to ensure the safety and effectiveness as well as the clinical beneficence of the devices on the market. MD R&D requires a lot of different physical resources such as time, money, expertise from several fields and appropriate facilities but also many mental resources such as patience, innovative thinking, can-do mindset, and cooperation. Perhaps inspired by this thesis, even

more biomedical innovations originating from academia could be commercialized. If only the funding can be organized, the universities have a lot of the listed resources and, thus, all the potential to operate in the MD science.

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