ANALYZING THE DEVELOPMENT PIPELINE OF MEDICAL DEVICES FOR RARE DISEASES

A mixed method study towards the development scope of medical devices for rare diseases and the perceptions of Key Opinion Leaders in the field of orphan devices

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Abstract

Background: Medical devices play a crucial role in the early diagnosis and treatment of diseases. While numerous medical devices are developed globally, the focus on developing and ensuring accessibility of medical devices for rare diseases is often lacking. In May 2021, the regulations towards medical devices changed in the European Union (EU) [1]. The Medical Device Regulation (MDR) had unforeseen effects and caused barriers in the development of medical devices for rare diseases in the EU [2]. To gain an understanding of the orphan device development landscape, this study aimed to identify the current landscape of orphan devices in the EU.

Methodology: A mixed method design of quantitative and qualitative data sources was used. First a dataset with clinical trials downloaded from clinicaltrials.gov was analyzed. Clinical trials were included in the analysis if it evaluated a medical device developed for one or more rare diseases. The dataset consisted of 2004 clinical trials. Several data visualization techniques (e.g. bar charts, histograms, box plots and network visualizations) and analytical techniques (e.g. descriptive statistics such as mean, median, standard deviation and mode) were used to provide an overview of the dataset. Second, interviews with Key Opinion Leaders (KOL) in the field of orphan devices were conducted. The interviews took place in April and May 2024, 12 interviews were conducted in this period. Participants with different specialties were interviewed; the analysis included 9 different specialties. The interviews were conducted via a semi-structured approach. Each KOL was interviewed with the same set of questions, except for the middle section. The middle section was tailored to the specialty of the participant. The interviews were recorded and transcribed afterwards. The transcriptions were coded using an inductive approach, the codes were grouped into themes.

Results: The dataset consisted of 2004 clinical trials that evaluated medical devices developed for at least one rare disease and some in combination with non-rare diseases with start dates between 1995 and 2025. The dataset consisted of 590 different rare diseases. Of the 2004 clinical trials, 736 clinical trials evaluated medical devices developed for only one or more rare diseases. The analysis showed an upward trend in the development of medical devices for rare diseases over the years in the EU till 2019, after this year the growth in the frequency of start dates stagnated. The interviews with KOL indicated that the MDR presents additional challenges in the development and accessibility of orphan devices. These challenges occur due to the different market dynamics of orphan devices, which makes them vulnerable to change and the requirement for clinical evidence, which is difficult to maintain due to the small patient populations.

Conclusion: The MDR poses additional challenges in the development and accessibility of orphan devices in the EU. Despite the increasing attention for rare diseases, increasing interest in orphan device development has stagnated since 2019. The regulatory hurdles have led to an increase in certification time and costs, making it more difficult for small and medium size enterprises to bring new orphan devices to the market. To enhance the development of orphan devices in the EU, it is necessary to address the challenges perceived by KOL towards the MDR. Streamlining the certification process of medical devices and drawing more attention to orphan device development could facilitate the development and increase the accessibility of orphan devices in the EU. By addressing these challenges, the EU can become a more attractive market for developers and manufacturers to bring their orphan devices to the market.

Inhoud

1. Introduction

Medical devices play a crucial role in the early diagnosis and treatment of diseases. Medical devices range from instruments, implants, assistive devices to diagnostic equipment. While numerous medical devices are developed globally, the focus on developing and ensuring accessibility of medical devices for rare diseases is often lacking. In May 2021, the regulations towards medical devices changed in the European Union (EU) [1]. The Medical Device Regulation (MDR) aimed to ensure the functioning of the internal market for medical devices and protect the health for patients and users. However, the MDR also had unforeseen effects, and caused barriers in the development of medical devices for rare diseases in the EU [2].

A rare disease is a condition or disease with a small population size. The small population size of a disease results in a high degree of variability between the symptoms that patients experience. This variability in symptoms can make it difficult to identify a rare disease, as the symptoms can resemble those of more common conditions. The definition of rare diseases differs per region. In the EU, a rare disease is defined as a condition that affects no more than 5 in 10.000 people [3]. Due to the rarity and the complications in developing a treatment, many rare diseases lack appropriate treatments [4]. In recent years, research into treatments for rare diseases has increased, but research into medical devices for rare diseases has lagged behind [5]. Medical devices developed for rare diseases are often called orphan devices [2]. Explained by Melvin et al., orphan devices are more vulnerable to change in market conditions, as they are characterized by low sales and reduced return on investment compared to more common medical devices [2]. The MDR aims to create a regulatory framework that prioritizes patient safety and device effectiveness, while also encouraging innovation within the medical device industry by introducing more transparency and traceability [6]. These regulatory changes hinder innovation in the orphan device development field. The stricter requirements discouraged manufacturers from investing in the development of orphan devices. This affects the development and availability of orphan devices in the EU [2]. The availability of orphan devices is often of significant value to patients with rare diseases, as patients with rare diseases have fewer available treatments than patients with more common diseases [7]. According to Peiris et al, who conducted a study in the US on the landscape of orphan development and unmet need, there is a great need for innovative medical devices for patients with rare diseases [5]. The current landscape of orphan device development in the EU is unknown [2]. This knowledge lacks in part as no centralized database for medical devices is available in the EU. To gain an understanding of the orphan device development landscape, this study aims to identify the current landscape of orphan devices in the EU by analyzing a dataset with clinical trials and conducting interviews with KOL in the field of orphan devices. The following research questions were established:

Research questions

RQ 1: What is the current landscape of orphan devices development in the EU and US?

- 1.1 How many medical devices developed for at least one rare disease, are being evaluated in clinical trials?
- 1.1.1 How many of these medical devices are developed only for one or more rare diseases?
- 1.2 What study types are employed in clinical trials to evaluate medical devices for rare diseases?
- 1.3 What study designs are employed in clinical trials to evaluate medical devices for rare diseases?
- 1.4 Which medical devices are developed for more than one rare disease?
- 1.5 What are the differences in the number of clinical trials evaluating rare disease medical devices developed for pediatrics compared to those assessing rare disease medical devices designed for adults?

RQ 2: How does the current orphan device landscape in the EU affect the development and accessibility of orphan devices according to KOL?

- 2.1 What does the current orphan device landscape in the EU looks like according to KOL?
- 2.2 What challenges are perceived by KOL in the current orphan device landscape in the EU?

2.3 What is the current mode of collaboration within the orphan device landscape in the EU according to KOL?
2.4 What effect does the current collaboration have on the accessibility and development of orphan devices?
2.5 What recommendations do KOL have regarding the current orphan device landscape in the EU?

First, the theoretical background of the key concepts is explained, then the methodology behind the research, followed by the results. The last chapter contains the conclusion and discussion, which interprets the results within the context of existing literature.

2. Theoretical framework

This chapter provides the basis for understanding the key concepts, relationships, and context that underlie this study.

2.1 Rare diseases

A rare disease affects a small percentage of the population, yet many individuals in the EU are affected by these rare diseases [3]. According to the definition of the EU, a rare disease is a condition or disease whose prevalence is not more than 5 per 10.000 people [8]. Many rare diseases affect much less than 5 per 10.000 people and are characterized by a wide variety of symptoms and signs. Some rare diseases have one identified case while other rare diseases affect ten to hundreds of people [9].

It is unclear how many unique rare diseases there are worldwide. The last few years, several studies were conducted to estimate the number of unique rare diseases, but no conclusive number has been decided upon. Many regulators, scientists, clinicians and patient advocacy groups cite the number of ~7000 rare diseases [10]. Nguengang Wakap et al. analyzed all data available on the Orphanet database and concluded that there are about 6172 unique rare diseases, which 3510 of them are of pediatric onset. According to them, around 263-446 million people worldwide and 17.8-30.3 million people in the EU are affected by rare diseases [11]. The RARE-X organization concluded that there are 10,867 rare diseases, genetic and non-genetic diseases were included [12].

There are a few reasons why these estimates differ so widely from each other. First, there is a difference in the definition of rare diseases between countries. The USA defines a rare disease as a condition that affects fewer than 200 000 people, which differs from the EU definition. Second, a disease may be rare in certain regions, but not necessarily in others [10]. Third, there are differences in terminology, some estimates include chromosomal disorders, others do not. There are also many subtypes, some estimates count them as a unique condition, others do not. The ambiguousness around the number of unique rare diseases affects the quality of care for people with rare diseases, as it limits the development of methods to lessen the impact of rare diseases [10]. Overall, the different estimates of the amount of rare diseases can create challenges in regulatory processes and patient access to treatments and therapies for rare diseases [12].

Significant challenges arise when conducting research into treatment or management strategies for rare diseases. Due to the limited group of eligible participants for a study, and the heterogeneity in the progression of the disease, it is often perceived as challenging to conduct research on rare diseases. A small population group may have variance in disease presentation, severity, progression, exposure to prior treatment and geographical differences [13]. This variability can complicate the diagnosis and treatment of those rare diseases. Furthermore, due to the limited number of cases, physicians and caregivers often lack appropriate expertise in rare diseases, which further hinders effective patient care [14]. According to Austin et al., who investigated the current state and future goals of rare disease research from 2017 to 2027, more than 90% of the rare diseases lack an appropriate medicinal treatment in the EU [4]. This indicates that treatments for a large number of rare diseases are either unavailable or inappropriate.

2.2 Regulatory processes of medical devices

Medical devices are products or equipment designed for medical purposes. It can be any instrument, machine, implement, implant, software or material. To ensure safety and efficacy of medical devices, various authorities have established legislation for medical devices, including the EU. The EU previously established two directives concerning medical devices. The directive for active implantable medical devices was established in 1990 and in 1993 the directive for general medical devices was established [15]. These medical device directives (MDDs) should facilitate trade and there was minimal focus on clinical evidence requirements. It resulted in establishing a single market for medical devices in Europe [16]. In April 2017 the EU adopted the MDR (Regulation (EU) 2017/745) as a replacement for the MDDs [1]. After a transition period, the MDR became applicable in May 2021 [1]. The in vitro diagnostic devices are assessed in a separate regulation, the In Vitro Diagnostic Devices Regulation

(Regulation (EU) 2017/746) [17]. The EU MDR differs from the US system for medical device regulation, called the Medical Device Amendments of 1976 [18]. First, the US regulatory system for medical devices is described, followed by an explanation of the EU regulatory process.

2.2.1 US

The aim of the US Medical Device Amendments is to protect the public's health. The US has a centralized regulatory structure for medical devices, the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA) regulates devices [6]. The market approval pathways of medical devices are based on device classification. A medical device is classified in one of the three classes. Class I are devices with the lowest risk, class II devices are medium-risk devices and class III devices are defined as high-risk [6]. Figure 1 provides an overview of the regulatory process, from the development phase to the market access phase.

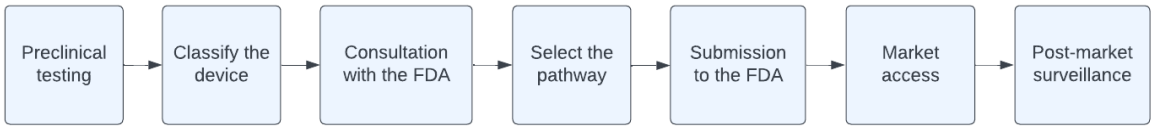

Figure 1: Overview of the regulatory process of medical devices in the US.

As displayed in the figure above, the developer should choose a pathway. The FDA established three market approval pathways for medical devices; Premarket Notification pathway (PMN), Premarket Approval pathway (PMA) and Humanitarian Device Exemption pathway (HDE) [19]. The pathway for market approval depends on the classification of the device and whether it has a marketed equivalent [6]. Figure 2 provides an overview of the different market approval pathways for medical devices.

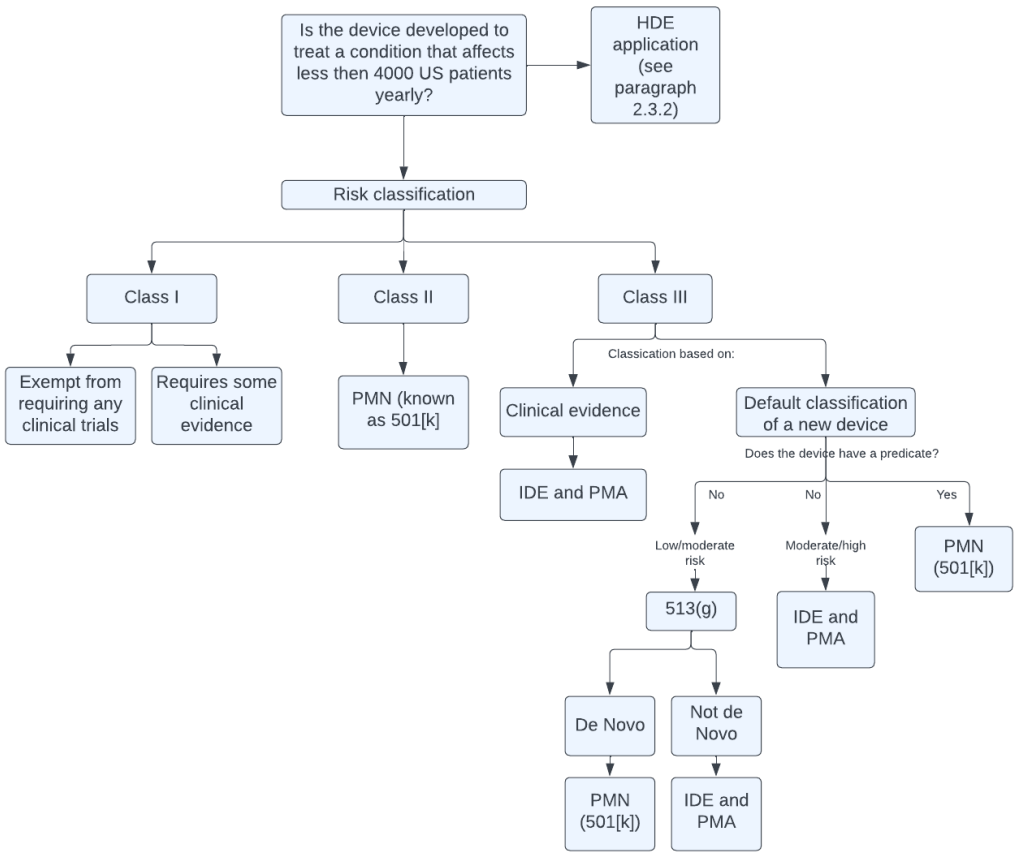

Figure 2: *Flowchart FDA medical device approval pathways. Adapted from: Van Norman. Drugs, Devices, and the FDA. 2016;1(4):277-287.*

Class I devices' approvals are focused on registration, manufacturing, and labeling. 75% of the Class I devices need no safety and efficacy data, they receive the status "exempt". However, some class I devices need some evidence on safety and efficacy, but they do not need to trough the standard PMN. Class II devices approvals are also focused on registration, manufacturing, and labeling. A small percentage of the class II devices receive the "exempt" status, but most must go through the PMN clearance process. The PMN clearance process is also known as the 501(k) application. Class III devices require a PMA process. The PMA involves a thorough evaluation of scientific evidence. However, not all class III devices are required to undergo the PMA process. If a class III device has a substantial equivalent, it may receive market approval through the PMN process [19].

New devices, that have no substantial equivalent, are in most cases automatically classified as class III. This means that the device needs to go through the PMA process to receive market approval. But there is an exemption, a sponsor can apply directly to the FDA to reclassify the device if it has low to moderate risk. Then the device gets the status "de novo" and can go through the PMN process. Devices with a high risk or the ones that do not receive the "de novo" status are required to undergo the PMA process [19].

The PMN/ 501(k) application is a fast-track process. If a device has a substantial equivalent, the FDA can decide that a PMA is not necessary, and the device can receive market approval via the PMN process. The submission of a PMN to the FDA must occur at least 90 days before the expected marketing date. Once the submission is accepted, the review process can begin. The submission will be assigned to a lead reviewer. In the PMN process, no criteria are defined for clinical evidence. A PMN must be submitted at least 90 days prior to the expected marketing date, which is the same as the PMA. In the PMA process, level I and II evidence are needed to obtain FDA approval. To conduct pre-market clinical trials, the investigators must obtain an investigational device exemption (IDE) first. The IDE means that the investigator can start with conducting clinical tests. Which clinical tests should be conducted depends on the characteristics of the device. The FDA can be asked for pre-investigational meetings to give advice on the needed clinical evidence of the medical device. Once the submission is accepted by the FDA, the review process can begin [19].

2.2.2 EU

While the entirety of the US Medical Device Amendments is designed to protect the public health, the EU's MDR primary aim is to facilitate trade between member states and to regulate a single market [1]. The regulatory structure of the MDR is decentralized; Notified Bodies regulate the market approval of medical devices [6]. Notified Bodies are organizations designated by EU member states, they assess the conformity of medical devices before providing market approval [20]. Notified Bodies establish contracts with device companies to oversee the certification process for medical devices. The Conformité Européenne (CE) mark allows devices to be marketed in all EU member states. The CE mark is granted by the Notified Bodies. Figure 3 gives an overview of the stages a medical device will go through.

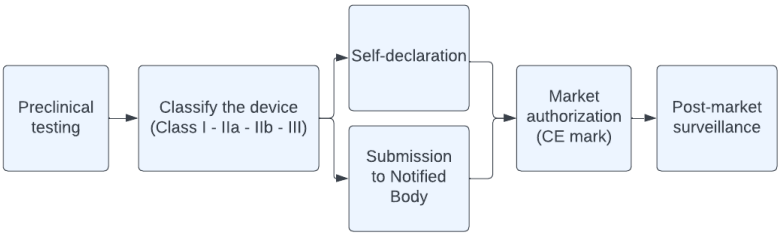

Figure 3: Overview of the regulatory process of medical devices in the EU.

In the MDR, devices are classified in one of the four classes: class I, class IIa, class IIb and class III. Class I devices have minimal risk of harm, class IIa devices have relatively low risk of harm, class IIb

devices have a relatively high risk of harm and class III has the highest risk of harm to humans [6]. Figure 4 provides a visual overview of the different market access pathways for medical devices.

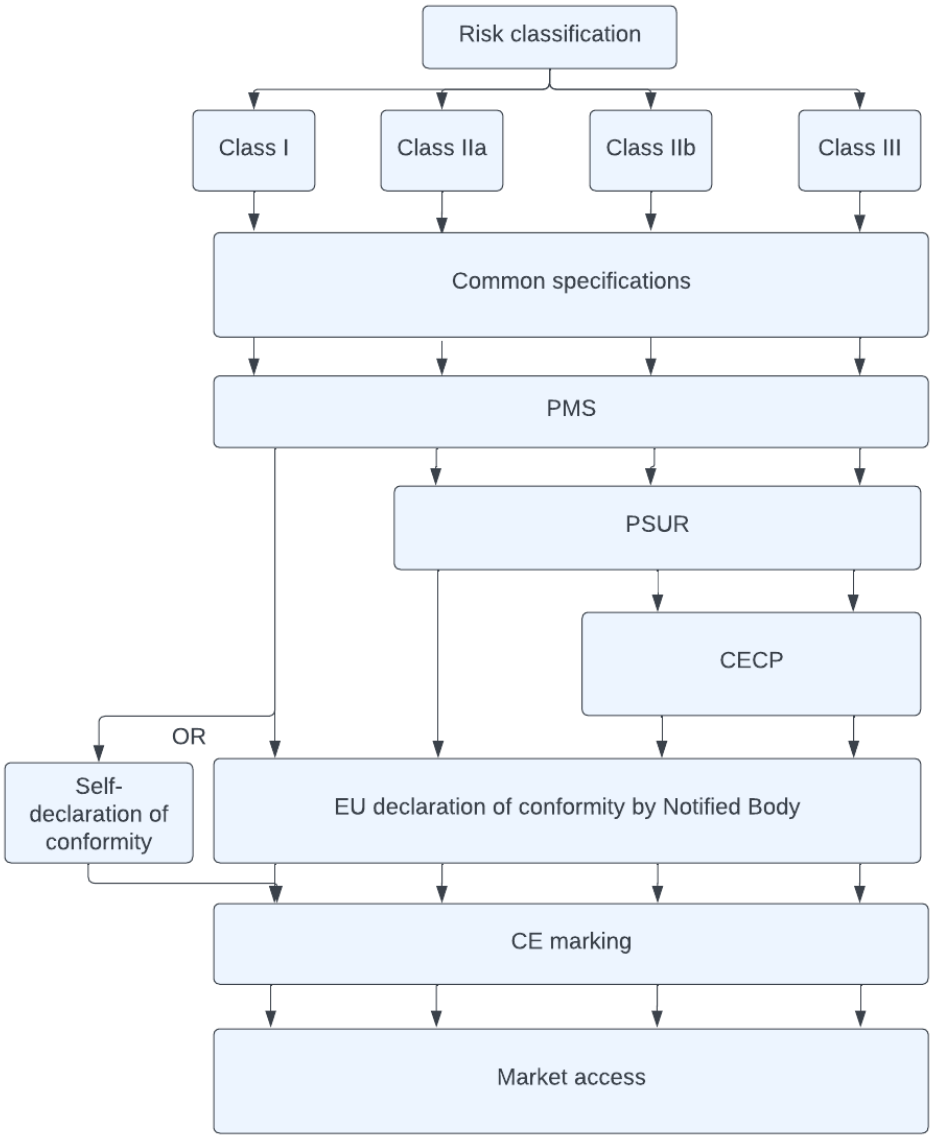

Figure 4: Market approval process of medical devices in the EU.

The risk of harm to humans must be identified to determine its classification. Based on the class, different regulatory requirements are established. All device classes must comply with common specifications. Common specifications are safety and performance requirements (set out in MDR Annex I), technical documentation requirements (Annex II and III), clinical evaluation and post-market clinical follow-up (Annex XIV) and clinical investigation requirements (Annex XV) [21]. Besides common specifications, all classes need to implement a post-market surveillance (PMS) system. It should gather, record and analyze data on the device's quality, performance and safety throughout its lifecycle. Class I devices can self-declare their declaration of conformity, this means that they do not need an assessment by a Notified Body. The EU declaration of conformity shows compliance with the requirements. After the EU declaration of conformity and approval by the national authorities, the device is CE marked and has access to the EU market. Class II and class III devices have some additional regulatory requirements that must be met before they can be marketed. Besides common specifications and a PMS system, Class IIa, IIb and III need to provide a Periodic Safety Update Report (PSUR). PSUR is a report that summarizes the results and conclusions of the analysis of post-market surveillance data [21]. Class IIa

devices manufacturers must update the PSUR every two years, class IIb and III must update the report annually. Class IIb and class III devices need, besides the PSUR, also a clinical evaluation consultation procedure (CECP). A CECP is an analysis of medical device's clinical data, including the benefit-risk profile and compatibility with the intended use. The CECP should be submitted to expert panels for review (Annex IX). Moreover, the competent authorities of the certificates must be notified [21]. Devices that have a marketed subsequent can be excepted from the clinical investigation requirement.

Having outlined the regulatory process for medical devices in the EU, it is essential to understand the new regulatory requirements of the MDR compared to its predecessors. The MDR aims to ensure safety for patients and increase the transparency and traceability of medical devices in the EU. Therefore, the MDR introduced stricter conformity assessment procedures and required clinical evaluation data, post-market surveillance and a comprehensive EU medical device database. The EU medical devices database is called EUDAMED [1]. EUDAMED should provide an overview of all medical devices marketed in the EU and should be accessible to the public. The EUDAMED database is currently not accessible to the public, consequently, there is no comprehensive overview of the marketed medical devices in the EU.

During the period of transition from the MDDs to the MDR, it became clear that there were some unforeseen factors that arose. First, more devices require clinical investigations due to the stricter and more detailed classification rules, leading to an increase in class III defined devices [22]. Second, the Notified Bodies needed to be redesignated by their national regulatory agency to continue evaluating medical devices under the MDR [2]. Therefore, the time to CE mark approval has expanded, which negatively impacts patient access to class IIb and III devices [22]. Third, the MDR does not specify the conditions of clinical investigations, i.e. it does not describe any specifics regarding the design, scope or duration of the study. Member states organize their own system for reviewing study proposals. This combination of no specifications in the conditions of clinical investigations with differences between member states in review systems results in disparity in the assessment procedure across the EU [16]. Additionally, seeking advice from a Notified Body before submission is impossible [2]. Therefore, it is unclear for manufacturers which clinical evidence is needed before submission for market approval.

2.3 Orphan devices

The incentivized markets for pharmaceuticals and biologicals for rare diseases have led to a significant increase in the development of those products [4]. These incentives include market exclusivity, reduced fees for regulatory activities and financial support, which makes developing medicines for rare diseases more attractive [8]. The development and research of orphan devices have received significantly less attention; they are less frequently mentioned in journal articles or stakeholder conversations than orphan drugs and biological products and challenge inequities in access [2,5]. Orphan devices are medical devices used to diagnose, prevent or treat rare diseases/conditions. Orphan devices have low sales and profitability due to the fact that only a small portion of the population uses the product. Orphan or pediatric medical devices are often adapted versions of a device marketed for adults/ other diseases, this is called “off-label use”. Off-label use is not always realized by manufacturers. A potential decline in investment in products with low-volume sales could have a significant impact on patients with rare diseases [2].

Several countries worldwide, including the US, have established pathways for orphan devices to support the development. However, the EU did not establish such a pathway.

2.3.1 EU

Longtime, there was no clear regulatory definition in the EU for orphan devices, and no definition of orphan devices is included in the MDR. The MDR does also not include incentives for the development of orphan devices in the EU [1]. However, in June 2024 the Medical Device Coordination Group (MDCG) created a definition for orphan devices in the EU. Orphan devices are defined by the MDCG as “medical devices that are intended to benefit patients in the treatment, diagnosis, or prevention of a

disease or condition that presents in not more than 12,000 individuals in the European Union per year, and there insufficiency of available alternative options for the treatment or management of this disease/condition or the device will offer an option that provide an expected or probable clinical benefit compared to available alternatives or state of the art for the treatment/management of this disease/condition" [23]. This definition was given in the Clinical evaluation of orphan medical devices guidance document which is endorsed by the MDCG [23]. The purpose of the guidance document is to provide guidance to manufacturers and Notified Bodies on the clinical evaluation required by the MDR for medical devices that qualify as orphan devices.

The MDR particularly affected orphan devices due to the nature of these products and market dynamics. Moreover, in the EU many orphan devices are often developed by Small and Medium-sized Enterprises (SMEs), who have only little expertise on regulatory affairs. Regulatory changes can be hard to manage for SMEs. This makes orphan devices extra vulnerable to being withdrawn from the market [2].

This research aims to provide an understanding of the landscape of orphan devices in the EU. Therefore, it is essential to have a clear definition of orphan devices. Since the MDCG definition of orphan devices was published after the conduction of this research and was unknown at the time, this study adopted the EU definition of rare diseases to define orphan devices. This implies that medical devices used for a disease with a prevalence of less than 5 per 10.000 people in the EU are included in this study as an orphan device.

2.3.2 US

The US has established a regulatory measure for orphan devices since 1990; the Humanitarian Use Device program [24]. In the US an orphan device is defined as a device that is designed to treat or diagnose a disease or condition that affects not more than 4000 individuals in the US per year [25].

The US established regulations to improve market access for orphan devices. They established the Humanitarian Device Exemption (HDE) pathway, intended for devices that treat or diagnose conditions or diseases that affect small or rare populations. The HDE is a part of the 21st Century Cures Act (Pub. L. No. 114-255) [26] and consists of two steps for marketing authorizations. The program established an alternative pathway to achieve market approval for orphan devices. The first step for a manufacturer of an orphan device is preparation and submission of a HUD request to the FDA's office of Orphan products development. To achieve the HUD designation, the manufacturer needs to demonstrate that the device meets the definition of orphan device, provide indications of the use of the device and provide reasons why such a device is needed for the patient population. Once the manufacturer has achieved approval of the HUD application for the orphan device, the manufacturer can submit Humanitarian Device Exemption (HDE) marketing application for marketing review [26].

HDE will be granted if the device meets these three criteria:

- The device should not pose an excessive or significant risk of illness or injury to patients and the health benefits should outweigh the potential risks.
- The device should be the only available option for treating or diagnosing a specific disease/ condition, individuals cannot access it without the HDE, no comparable device is available for treating or diagnosing the same disease/ condition.
- The device treats or diagnoses a disease/condition that affects not more than 8000 individuals in the USA on an annual basis. [25]

HDE applications have the following benefits from the normal submission pathway:

- Exemptions for the effectiveness requirements of section 514 and 515 of the Federal Food, Drug and Cosmetic Act.
- HDE will be reviewed in 75 days.
- It is not subject to user fees.

Besides the alternative pathway for orphan devices, the FDA established three grants to support medical product development for rare diseases. These grants are the Orphan Products Grants program, the pediatric device consortia grant program and the rare neurodegenerative disease grant program. The grants provide funding for research [25].

2.4 Clinical trials

The World Health Organization defines clinical trials as "a type of research that studies new tests and treatments and evaluates their effects on human health outcomes" [27]. In clinical trials, people volunteer to test medical interventions. Before starting, clinical trials are carefully designed, reviewed, executed and approved [27]. Clinical trials of medicines consist most often of four phases: Phase 1 studies test a product for the first time on a small group of people to evaluate a safe dosage range and identification of side effects. Phase 2 studies test products on a larger group of people to monitor adverse effects. Phase 3 studies are conducted on larger groups of people in different regions and countries. Phase 4 studies are conducted after market approval and are needed for further testing in a wide population over a longer time [28].

The phases of clinical trials on medical devices are somewhat different. It distinguishes between a pre-market phase and post-market phase (see Figure 5). The pre-market phase consists of two stages: pilot and pivotal stage. Pilot studies are used to provide preliminary information on the functionality of the device and clinical safety. These studies occur when nonclinical testing is unable and often occur before the device design is finalized. Pivotal studies are used to provide definitive evidence on safety and effectiveness of the medical device. It includes more participants and the results of the study are used to gain regulatory approval. After market approval, post-market surveillance study can be conducted to confirm safety, efficacy and long-term safety/performance of the medical device. The requirements of clinical studies for medical devices are determined by the national authorities [28]. Each clinical trial is designed and characterized by important attributes, including study design, study type, recruitment status etc. Because some of these characteristics are used in the results, a few key ones are explained in Appendix A.

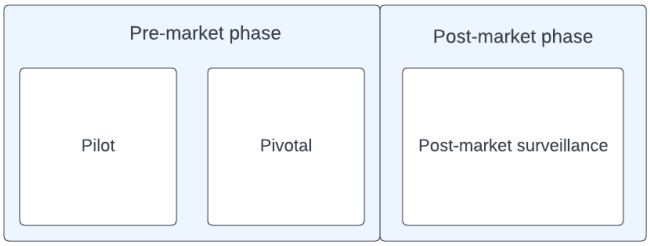

Figure 5: Phases of medical device clinical trials

3. Methodology

3.1 Research design

A mixed method research design of quantitative and qualitative data sources was used to gain better understanding of the landscape of orphan device development. Using two research methods to collect data minimizes the risk of missing important details and increases the likelihood of gaining a comprehensive understanding of the context [29]. Initially, quantitative research was conducted through a desk-top analysis of current clinical trials of medical devices developed for rare diseases. The clinical trial data was extracted from clinicaltrials.gov and analyzed using descriptive statistics to provide a comprehensive understanding of the development landscape of medical devices for rare diseases. Secondly, qualitative research was conducted through a series of interviews with key opinion leaders (KOL) in the field of orphan devices. The series of interviews were conducted to dive deeper into the perspectives of KOL towards the current landscape of orphan devices. This qualitative part of the study allowed for the exploration of diverse viewpoints and insights from KOL involved in the field. By combining quantitative analysis of clinical trial data with qualitative data from the interviews, this study aims to draw conclusions based on data from different perspectives.

3.2 Data collection

Desktop-analysis of clinical trials

The data collection process of the desktop-analysis involved collecting data that was needed to answer sub questions 1.1- 1.5. This data was collected from clinicaltrials.gov [30]. Clinicaltrials.gov is a clinical trial registry managed by the US National Institute of Health (NIH). The registry was launched in 2000 and is currently the largest clinical trial registry worldwide [31]. The metadata of clinical trials is publicly available on clinicaltrials.gov and can be downloaded from the site. The metadata available of clinical trials consists of various variables, including study title, study type, study design, locations etcetera. All variables available of the clinical trials were collected. The filters used on clinicaltrials.gov were “Medical devices” and Studies by Topic “Rare Diseases”. Specific inclusion and exclusion criteria were established for the analysis to ensure the relevance and reliability of the collected data. The in- and exclusion criteria are described in Table 1. All clinical trials available based on these filters were downloaded from clinicaltrials.gov on 27 February 2024. Resulting in 969 CSV files being obtained. Each CSV file could contain more than one row and each row contains information about one clinical trial.

Table 1: In- & exclusion criteria clinical trials

Inclusion criteria	**Exclusion criteria**
Medical devices that are developed for rare diseases, according to the filters of clinicaltrials.gov	Medical devices developed for rare diseases, but the rare disease does not occur in Europe or the US
Medical devices designed for adults, pediatrics or both	

Interviews with KOL

Interviews were conducted to answer research question 2 and its sub questions. The target population were KOLs in the field of orphan device development. Each KOL represents their own expertise and role within the field of orphan device development. Table 2 provides a list of which experts were the target population. To gain a comprehensive understanding of the perspectives of KOLs in the area of orphan devices, a sample size of 1 or 2 participants from each specialty was deemed necessary to provide sufficient variety.

Table 2: Target population interviews

Expertise
Board member of a patient advocacy organization
Policy maker related to policy development of rare diseases
Healthcare professional who has experiences with orphan medical devices
Manufacturer of orphan medical devices
Healthcare payer, such as a health insurance company, who reimburses orphan medical devices
Member of one of the Notified Bodies, and who certifies orphan devices

The interviews were conducted via a semi-structured approach, this allowed the necessary flexibility to capture the unique insights of each participant while maintaining consistency in gathering qualitative data [32]. The interview protocol was designed with the same set of questions for all stakeholders to ensure consistency needed for comparative analysis. However, the middle section of the interview protocol was tailored to the expertise of the KOL. This tailored middle section allowed to delve deeper into the participant's unique role and experiences in the field of orphan devices. By keeping consistent begin and end questions, a common ground was established, while the middle sections provided flexibility to explore specific topics within the field of orphan devices, which allows for a more nuanced analysis of the field. The interview protocol consisted of the following subjects: a) Background b) Organisations role c) *Tailored middle part* d) Collaboration e) Closing. The interview protocol is added in Appendix B. Prior to conducting the interviews, the protocol was tested on a test person to ensure the clarity and relevance of the questions. The aim was to conduct the interviews with the KOLs via in-person interactions. But exemptions were made when in-person interactions were not possible due to logistical constrains, these interviews were conducted via video conference using Microsoft Teams. Ten of the twelve interviews were held online. The interviews took place in April and May 2024 and lasted around 30 to 45 minutes. Before the interview, the participant was asked verbally to consent for the data's use. Participants indicated that they understood the purpose and the procedure of this study by providing informed consent. Two participants requested to review the results before the findings were used in the research, the review was sent to them. The online interviews were recorded via the Microsoft record function, the in-person interviews were recorded via a recording device.

3.3 Data analysis

Desktop-analysis of clinical trials

To analyze the collected clinical trials data, several steps were taken. The steps included importing, data exploration, data preparation, data cleaning and analyzing the cleaned data.

The first step was importing the data into R studio, which was used for analysis. All CSV files were merged into one dataset so the data could be explored. After merging, the dataset consisted of 24161 clinical trials. During the exploration phase, it was found that many clinical trials were developed for only non-rare diseases, those clinical trials needed to be excluded from the analysis.

The second step consisted of data preparation. In this step, the clinical trials in the dataset that were developed for non-rare diseases only were identified. To identify these clinical trials, the dataset was compared with the Orphanet nomenclature. Orphanet maintains a nomenclature of rare diseases, it uses the European definition of rare diseases [33]. The nomenclature includes two versions of the

International Classification of Diseases (ICD). The ICD is a categorization system for physical and mental illnesses established by the WHO [34]. In this research the ICD10 version is used. The nomenclature was downloaded on 22 March 2024 from Orphanet [33]. Diseases in the dataset were written in different ways, e.g. “Cystic Fibrosis” was also written as “Mucoviscidosis” and “CF”. Text analysis methods were used to find synonyms between the Orphanet nomenclature and the clinical trials dataset. First, text normalization and tokenization were applied to the “Conditions” column of the clinical trials dataset and to all columns of the Orphanet nomenclature dataset. The second step was reordering the words of conditions in alphabetical order, this was done on both datasets. A list with all unique conditions was extracted from the clinical trials dataset for easier comparison with the Orphanet nomenclature. At this stage, all diseases in the datasets were written without capitals, punctuation and the words were ordered in alphabetical order. To identify the corresponding diseases in Orphanet nomenclature and the unique conditions list, a text mining algorithm was applied. Two text mining algorithms were tested: Fuzzy matching Jaro Winkler and Levensthein distance [35]. Both algorithms were tested with different thresholds: 0.1, 0.2, 0.3, 0.4. Manually was checked which combination of algorithm and threshold had the best results. This was done manually as there was no clear benchmark which could measure the precision of each threshold. Finally, the Fuzzy matching algorithm with a threshold of 0.1 was used to find the corresponding diseases between the Orphanet nomenclature and the unique conditions list. A column was added to the clinical trials dataset, which displayed whether the clinical trial was designed for rare diseases only, both rare and non-rare diseases or only for non-rare diseases.

Once the data was prepared, the data cleaning began. Table 3 gives an overview of the filtering process. First, all duplicate rows and the columns Rank and Source were deleted from the dataset (17042 clinical trials remaining). Second, the clinical trials that were developed for only non-rare diseases were removed from the dataset (3297 clinical trials remaining). After that, the dataset was re-examined and a few non-rare diseases were seen as a rare disease. These errors were introduced due to the inherent uncertainty of using a text mining algorithm. This uncertainty arises because text mining algorithms can misinterpret context [35]. These diseases were COPD, pain, Parkinson disease, fever and Malaria. Malaria is a rare disease according to the Orphanet nomenclature [33]. However, since Malaria has a high prevalence in Afrika, much research is done on this disease [36]. Therefore, Malaria is not considered a rare disease. These rows were filtered out manually (3157 clinical trials remaining). The dataset contained also not device related clinical trials, like medicines and procedures. These not device related clinical trials were deleted from the dataset. The variables relevant to answering the research question and sub questions were selected, and the non-relevant columns were removed from the dataset. Columns were transformed when needed, e.g. data columns were transformed into standardized dates, so that the duration of trials could be calculated. During the filtering process, 22157 clinical trials were removed. The large number of exclusions is due to several factors, including the presence of 13745 clinical trials for non-rare diseases and 1153 not device related clinical trials. The final dataset contained clinical trials developed for rare diseases only and clinical trials developed for both rare and not rare diseases, which were 2004 clinical trials. Of this dataset, a sub-dataset was created containing clinical trials evaluating medical devices developed for only rare diseases, consisting of 736 clinical trials. This was later used to compare the clinical trials developed for both rare and non-rare diseases with the clinical trials developed for only rare diseases.

After the data cleaning, data visualization techniques (e.g. bar charts, histograms, box plots and network visualizations) and analytical techniques (e.g. descriptive statistics such as mean, median, standard deviation (SD) and mode) were used to provide an overview of the dataset. These techniques were used to further identify patterns, outliers, and highlight specific values.

To validate the relevance of the obtained data to the research question, several sampling methods were used. The first validation moment was checking the dataset with the Orphanet nomenclature, the process was described above. The second validation moment was checking which devices were approved via

the HDE pathway. Therefore, a list with all original HDE approved devices was downloaded from fda.gov on 11 June 2024, this list included 73 devices. To identify all matching devices, the HDE list was compared with the clinical trial dataset by using text analysis methods. First the text was preprocessed by removing punctuation, capitals, extra white spaces and special tokens. After cleaning the text mining algorithm Cosine similarity was used [35]. This algorithm was used as it provided the most matches; the chosen threshold was 0.2. Through this comparison, 25 matches were identified. All matches were manually checked, eventually 13 comparisons were identified. Appendix C gives an overview of these matches. The third moment of validation was to check if it was applicable to the EU market. This was done by comparing the dataset with the CCMO database. All studies that were conducted in the Netherlands were searched in the CCMO database. Six studies were conducted in the Netherlands, and all the studies were found in the CCMO database. A list of these studies is provided in Appendix D.

Table 3: Filtering process clinical trials

24161 clinical trials
Delete "Rank" and "Source" column + delete all duplicate rows
⬇
17042 clinical trials
Filtering out clinical trials not designed for rare diseases (based on Orphanet nomenclature)
⬇
3297 clinical trials
Manually filtering out clinical trials not designed for rare diseases (removed diseases: COPD, pain, Parkinson disease, fever, spinal cord injuries, Malaria)
⬇
3157 clinical trials
Removing columns that were not relevant to answer the research questions (URL, study documents) + Removing rows that are not device related
⬇
2004 clinical trials

Interviews with KOL

The first step in the data analysis of the interviews was to transcribe the interview recordings. The transcriptions were performed to ensure the maintenance of the original context. Following transcription, the text was examined to identify important text fragments. These text fragments were systematically coded using an inductive approach. An inductive approach has advantages in exploratory studies. Interviews with different stakeholders may introduce new perspectives that were not pre-determined at the beginning of the interviews, therefore an inductive approach can be helpful [37]. Atlas.ti, a qualitative data analysis software, facilitated the coding process. Codes were grouped into themes and relationships were explored. Direct quotations from participants were extracted and included into the analysis, during the coding process. The quotations provide direct descriptions of the perspectives of the participants. The quotations included in the analysis were translated to English when it was written in Dutch, and the translation was checked by a second person (see Appendix E).

3.4 Ethical considerations

This study adheres to ethical guidelines for research that involves human subjects. Before the start of data collection, the research project was reviewed by a member of the BMS ethics committee of the University of Twente to ensure an ethically responsible research practice. The ethical approval for the study was granted on 12 February 2024. Prior to the interview, the participant was fully informed about the aim of the study, the intended use of data, storage of the data collected, and the risks/benefits of their involvement in the interview. The consent of the participant was asked orally before the start of the interview. The participants had the autonomy to withdraw from the study during, or for an agreed period afterwards. The participants were informed about the partial anonymization of their identities. Their functional roles and organizational affiliations were disclosed, but names were anonymized to protect confidentiality.

In studies involving patients with rare diseases, the personal information included may sometimes reveal the identity of the study participant due to the small study population. This study only includes analyzed metadata of the clinical trials. Patients cannot be traced through the results of this study.

4. Results

In this chapter the findings of both the desk-top analysis and interviews are described.

4.1 Desk-top analysis of clinical trials

The analysed dataset contained 2004 clinical trials that evaluated medical devices developed for at least one rare disease and some in combination with non-rare diseases. On average, a clinical trial evaluated a medical device that was developed for three diseases simultaneously (282 clinical trials). There were 590 different rare diseases found in the dataset. The first clinical trial started at 19 September 1995, and the last clinical trial is expected to start at 1 October 2025. Figure 6 demonstrates a histogram illustrating the start dates of clinical trials. The histogram demonstrates a right skew, indicating that in recent years more clinical trials were registered at clinicaltrials.gov. Some of the trials in 2024 have already started, but the rest of the dates in 2024 and 2025 are planned start dates.

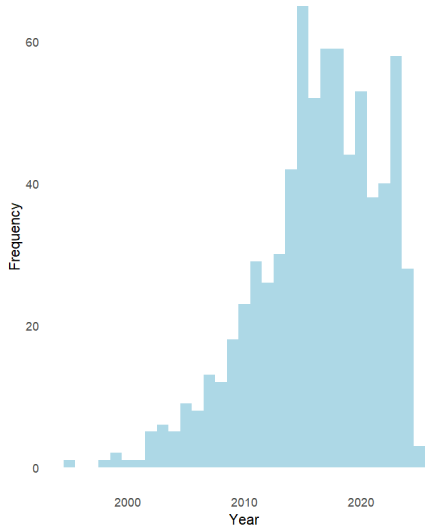

Figure 6: Start dates of clinical trials

Of the 2004 clinical trials, 736 clinical trials evaluated medical devices developed for only one or more rare diseases. The remaining findings relate to the analysis of the 736 clinical trials developed for only rare diseases.

EU located clinical trials

Of the 736 clinical trials, 192 clinical trials had as study location the EU. The start dates of these clinical trials show an increasing trend that stagnated in 2014 (see Figure 7). In 2019 a major decrease in start dates is visible. After 2019 the amount of start dates differs each year, no clear trend is visible. In 2024 the amount of start dates is higher than the years before (20 clinical trials started in 2024).

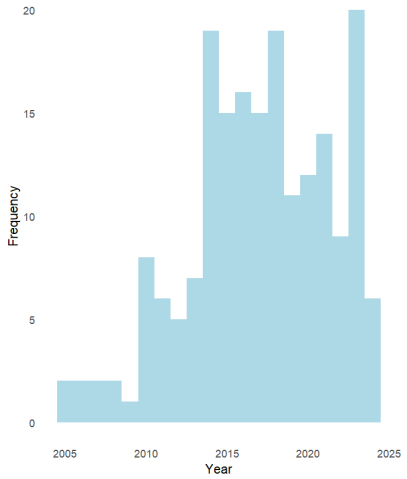

Figure 7: Start dates of EU located clinical trials

Rare disease types

The dataset of 736 clinical trials consisted of 299 different rare diseases. The clinical trial analysis revealed that some rare diseases appeared most frequently in the clinical trials (see Table 4, which shows the top 10 most occurring conditions). Cystic Fibrosis (20,1%, 61) and Abdominal Aortic Aneurysm (19.4%, 59) occurred the most in the dataset, followed by Amyotrophic Lateral Sclerosis (15.8%, 48). This could reflect current trends in research, potentially highlighting rare diseases that are deemed important or relevant by researchers. As shown in Table 4, most clinical trials target one rare disease at a time (95.5%, 703), 28 clinical trials are developed for two rare diseases (3.8%) and five clinical trials aimed three rare diseases (0.7%). An overview of all rare disease combinations is available in Figure 8. It illustrates a network of all connections between rare diseases. When a clinical trial is designed for two or more rare diseases, a node exists. The thickness of the line indicates the frequency of the combination, the ticker lines represent more frequent occurrences. From this network analysis we see that the clinical trials that are designed for two or three diseases are often combinations of subtypes of diseases, but also groups of familiar diseases occurred in the dataset.

Table 4: Rare disease characteristics

Characteristics	**Frequency**	**(%) Percentage**
Condition		
Cystic Fibrosis	61	7.9
Aortic Abdominal Aneurysm	59	7.6
Amyotrophic Lateral Sclerosis	48	6.2
Glioblastoma	31	4.0
Pigmentosa Renitis	27	3.5
Preeclampsia	18	2.3
Congenital Diaphragmatic Hernia	18	2.3
Multiple Myeloma	15	1.9
Glioblastoma Multiforme	14	1.8
Spinal Cord Injury	13	1.7
Number of diseases per clinical trial		
1	703	95.5
2	28	3.8
3	5	0.7

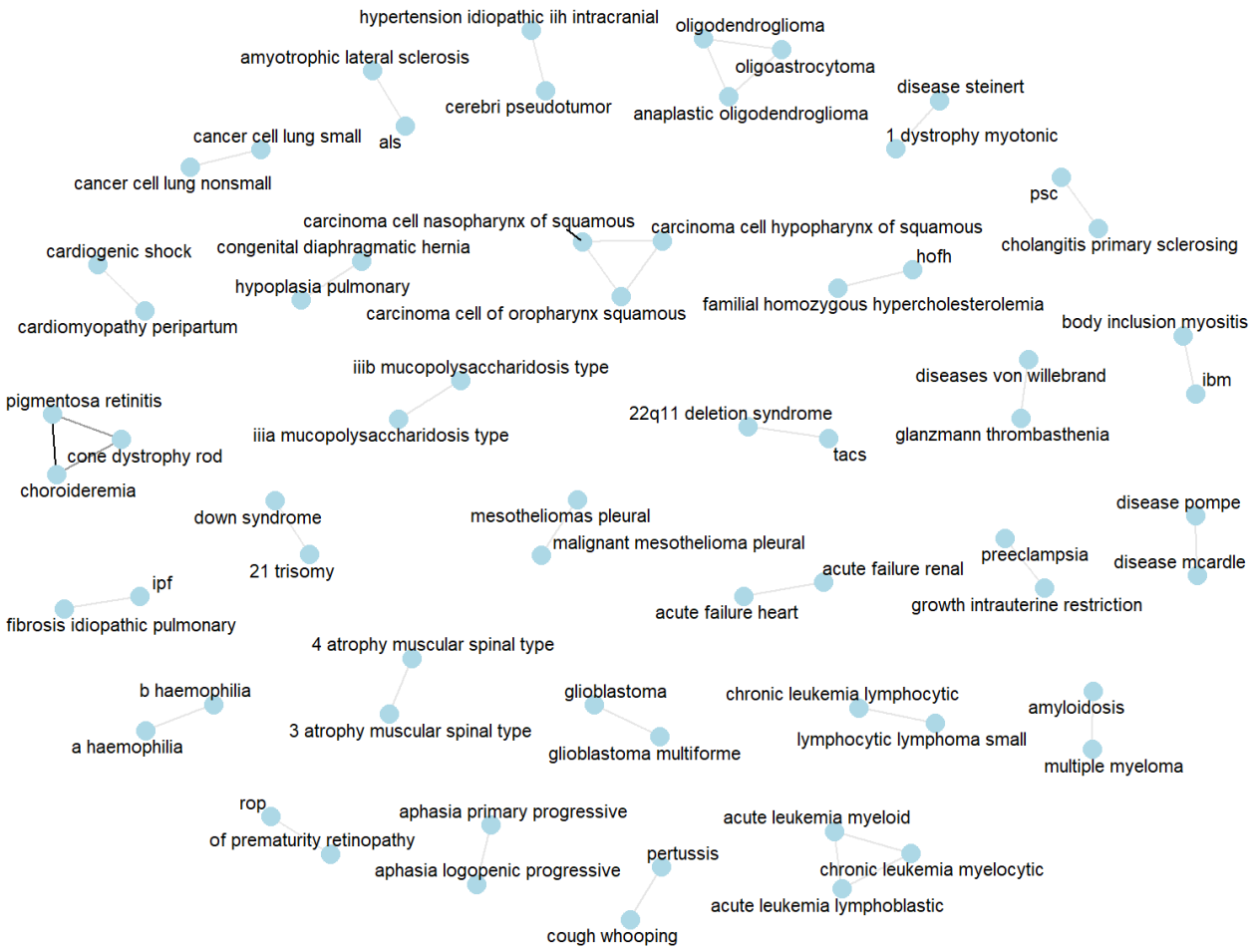

Figure 8: Rare disease combinations

Study population characteristics

The most clinical trials are tested on only adults or a combination of adults and older adults (70.9%, 552). 56 clinical trials are designed special for children (7.6%) and 113 clinical trials are designed for children in combination with adults or older adults (15.4%). This is shown in Table 5. Besides age characteristics, interesting insights in the gender distribution were found (see Table 5). Most clinical trials targeted both males and females (90.8%). When only one of the two genders is targeted, a slight majority targeted females (6.0%) compared to males (3.1%). For most clinical trials the recruitment status has been completed (46.5%, 342). Currently 137 clinical trials are still recruiting (18.6%) (see Table 5).

Table 5: Overview study population

Characteristic	Frequency	(%) Percentage
*Age category**		
Adult	48	6.5
Adult, Older Adult	474	64.4
Child	56	7.6
Child, Adult	53	7.2
Child, Adult, Older Adult	60	8.2
NA	45	6.1
Gender		
Males	23	3.1
Females	44	6.0
Both	688	90.8
Recruitment status		
Active, not recruiting	31	4.2
Completed	342	46.5
Enrolling by invitation	4	0.5
No longer available	2	0.3
Not yet recruiting	32	4.4
Recruiting	137	18.6
Suspended	4	0.5
Terminated	43	5.8
Unknown status	119	16.2
Withdrawn	22	3.0

**Child= 0 to 18 years, Adult= 18 to 60 years, Older Adult= 60 years of older*

Study population size

Most clinical trials (59.4%, 434) have a study population size between 1 and 50 participants. The population size ranged from a minimum of 0 to a maximum of 2721, resulting in a range of 2721. Figure 9, boxplot 1 provides a summary of the distribution. The median is represented by the horizontal line within the box, the median is 35 participants. The box itself represents the interquartile range, which contains 50% of the data. The lower and upper edges of the box correspond to the first quartile and the third quartile. The outliers, in total 84, are excluded from the boxplot to provide a clearer view of the central data distribution.

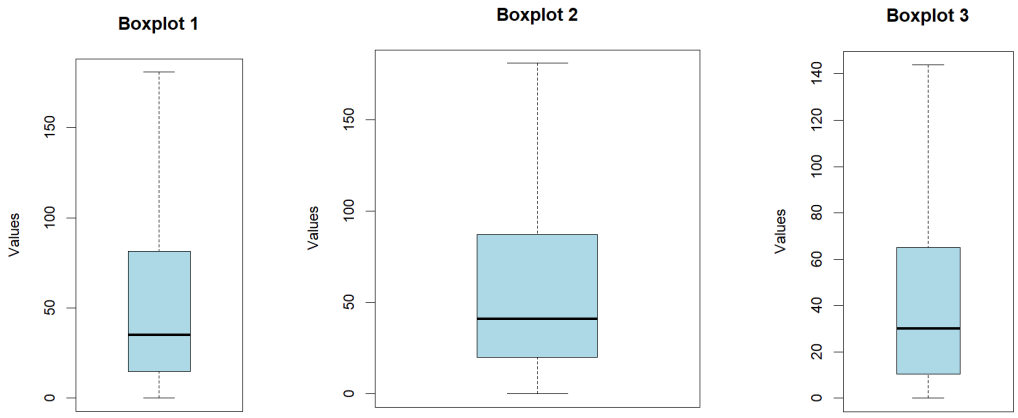

Figure 9: Enrolment participants

Boxplot 2 displays the population size distribution of clinical trials located in the EU. The median is 41 participants and there are 25 outliers. The population size ranged from a minimum of 0 and a maximum of 2159, resulting in a range of 2159. The distribution of population size in US located clinical trials have a median of 30 participants and 43 outliers (see boxplot 3). The range of study population size was 950 participants, with a minimum of 0 to a maximum of 950 participants.

The clinical trials located in the EU were split up in clinical trials that started before 2019 and after 2019 to see if there were differences in study population size. Before 2019 the median was 38 patients, after 2019 the median was 43 patients.

Duration

The clinical trials vary in duration (see Figure 10), with a mean of 3.1 and a standard deviation of 2.7. The median is 2.3 years and the mode is two years. The duration ranged from a minimum of 0 and a m aximum of 19.6 years, resulting in a range of 19.6. The clinical trial that studied Fetal Endoscopic Trac heal Occlusion for Congenital Diaphragmatic Hernia had a duration of 19.6 years.

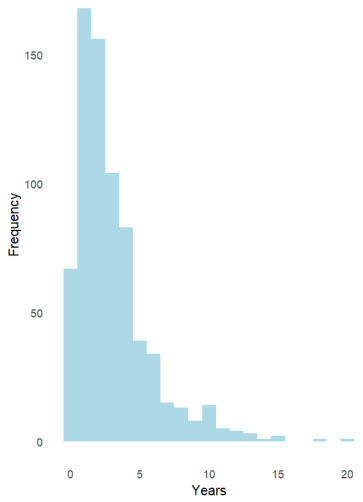

Figure 10: Duration of clinical trials in years

Interventions

The clinical trials included many different types of device interventions (see Table 6 where an overview is given of the five most occurring interventions). TTfields is the intervention that occurs the most in the dataset (5). The most clinical trials evaluate one intervention at a time (62.4%, 459). 277 clinical trials evaluate a combination of interventions, e.g. TMS combined with MRI and VASO Imaging (37.6%). A few of these clinical trials evaluate a combination of device with drug intervention, e.g. NovoTTF-100A combined with Temozolomide (16.2%, 45).

Table 6: Top 5 most occurring interventions

Interventions*	Frequency	(%) Percentage
Device: TTfields	5	0,7
Device: MRI	3	0,4
Device: Transcranial Magnetic Stimulation	3	0,4
Device: Actimyo	2	0,3
Device: Deep Brain Stimulation	2	0,3

Study types and designs

This analysis revealed four distinct study types, see Table 7. Most clinical trials are interventional studies (79.5%, 585), followed by observational studies (20.2%, 149). Two clinical trials have the study type "Expanded Access" this means that it the clinical trial is designed for individual patients (in emergency) or under a treatment IND/ protocol.

In the dataset, six types of study designs were identified (Table 7 gives an overview of all study designs and its frequencies). The most employed study design is Masking (22.2%, 582), followed by Intervention Model (22.2%, 580) and Allocation (22.2%, 580). A clinical trial could employ one or more study designs (see Table 8 for the five most occurring study design combinations). Each study design has its own characteristics, e.g; Time Perspective can be cross-sectional, prospective, retrospective or other. Appendix F provides an overview of the study designs with the frequencies of all characteristics.

Table 7: Study types and designs

Characteristics	Frequency	(%) Percentage
Study type		
Expanded Access	1	0.1
Expanded Access: Treatment IND/Protocol	1	0.1
Interventional	585	79.5
Observational	149	20.2
Study design		
Allocation	580	22.2
Intervention Model	580	22.2
Masking:	582	22.2
Observational Model	149	5.7
Primary Purpose	577	22.1
Time Perspective	148	5.7

Table 8: Top 5 most occurring combinations of study designs

Combinations	Frequency	(%) Percentage
Allocation: N/A|Intervention Model: Single Group Assignment| Masking: None (Open Label)|Primary Purpose: Treatment	143	19.4
Observational Model: Cohort|Time Perspective: Prospective	75	10.2
Allocation: Randomized|Intervention Model: Parallel Assignment| Masking: None (Open Label)|Primary Purpose: Treatment	49	6.7
Allocation: N/A|Intervention Model: Single Group Assignment| Masking: None (Open Label)|Primary Purpose: Diagnostic	39	5.3
Allocation: N/A|Intervention Model: Single Group Assignment| Masking: None (Open Label)|Primary Purpose: Device Feasibility	25	3.4

Setting

Table 9 gives an overview of the funding resources. 25.0% of the clinical trials are funded by the industry (214). A small number of clinical trials are funded by the NIH (4.2%, 36) and US federal reserve system (0.6%, 5). Notably, 600 clinical trials (70.2%) had the funding resource "Other", indicating that the funding type was not identifiable within the dataset.

The clinical trials have many different sponsors (1202). Table 9 gives an overview of the top 15 most occurring sponsor types. Endologix, a US based medical equipment company occurs the most in the dataset (1.2%, 14), followed by Assistance Publique- hôpitaux de Paris, which is a hospital trust operating in Paris (1.1%, 13).

Table 9: Setting characteristics

Characteristics	Frequency	(%) Percentage
Funding resources		
Industry	214	25.0
NIH	36	4.2
US Fed	5	0.6
Other	600	70.2
Sponsors*		
Endologix	14	1.2
Assistance Publique - Hôpitaux de Paris	13	1.1
NovoCure Ltd.	12	1.0
Johns Hopkins University	11	0.9
National de la Santé Et de la Recherche Médicinale, France	9	0.7
University Hospital, Bordeaux	9	0.7
St. Jude Children's Research Hospital	8	0.7
University of California, San Francisco	8	0.7
University of Michigan	8	0.7
Assiut University	7	0.6
Gynuity Health Projects	7	0.6
Massachusetts General Hospital	7	0.6
National Cancer Institute (NCI)	7	0.6
National Taiwan University Hospital	7	0.6
University of Pennsylvania	7	0.6

**Top 10 most occurring sponsors*

4.2 Interviews with KOL

Twelve interviews were conducted with KOL (see Table 10 for a description of their function) of which ten interviews were held online and two interviews took place at the University of Twente. All interviews were conducted individually, except for one session where two participants were interviewed together. These participants were interviewed together because they specifically requested it, they felt they could complement each other well. Both participants were active for the same patient advocacy organisation, but had a different background and function within the organisation.

Table 10: List of participants, including a short description of their function

Participant:	Short description:
Developer 1	Employee of a company that develops class I medical devices for upper extremities.
Developer 2	Founder of a company that developed a medical device specifically for one rare disease.
Developer 3	Owner of a serious gaming company, they developed by change two interventions for rare diseases.
Patient	Patient who is actively involved in a patient advocacy organisation for a rare disease and runs its own foundation.
Patient advocacy organisation	Two employees of a patient advocacy organisation for a rare disease. One of them is a patient who has the disease, the other was a nurse who worked many years with patients who had the disease.
Distributor	Employee of a company which is supplier of several medical devices for the upper extremities.
Regulatory expert	Member of a working group on orphan devices and former regulator.
Physician 1	Rehabilitation physician with specialisation in amputation prosthetics.
Physician 2	Physician in paediatrics and geneticist in metabolic diseases, employed at an UMC.
Governmental affairs	A company that develops high-risk medical devices. The employee is focused on the governmental affairs in Europe and other parts of the world.
Independent governmental institute	Employee of a company that is an independent governmental institute. The institute works as a support for the ministry and inspection. The employee works within the medical device department.
Notified Body	Head of clinical compliance at one of the Notified Bodies.

In the coding process, codes were given to text fragments of the interviews. The result was a set of 21 codes for the categorisation of the interview data. Those codes were then grouped into four key themes that capture the core insights and perspectives of the participants. Those four key themes were: 1) Current landscape, 2) Challenges, 3) Collaboration, 4) Recommendations. From the analysis, a total of 195 quotations were derived. The length of the quotations differs from one sentence to several sentences per quotation. The findings of the analysis are presented in order of the four key themes. For each theme, the key findings associated with the four most cited codes are summarized in a concise manner.

4.2.1 Current landscape

Seven codes fit under the Current landscape theme. This theme describes the perspectives and experiences of KOL on how the landscape in the EU looks like for orphan devices. First is described what the effects of the MDR are, as it contained the most remarks.

Effects of the MDR on orphan devices

26 quotations were categorised under effects of the MDR on orphan devices.

Seven participants report that the MDR poses additional challenges for orphan devices. The regulation causes an expansion of the development time and costs. One of the developers mentioned that the new regulation stimulates developers to make good and safe products, which holds a positive effect, but it is therefore also hardly applicable for orphan devices. The MDR requires manufacturers to deliver statistical evidence of the medical device before marketing the product, which was no requirement under the MDDs. Delivering the statistical evidence for orphan devices is very hard in practice because of the small population and causes a higher burden of documentation on the manufacturer. Besides the requirement of statistical evidence, increase in development costs were also frequently mentioned by the participants. Increase in costs are due to higher certification costs. Higher certification costs have the biggest impact on the manufacturers of orphan devices, as they have lower economies of scale compared to large MedTech manufacturers.

"If you're an orphan device manufacturer and you only make a small number of products, you know in a proportionate sense you have a much higher cost in terms of cost as a function of your revenue and you also tend to generate far less profits."

A few participants indicated that these changes put many orphan devices at risk of being withdrawn from the EU market. One of the physicians explained that he/she saw the last two years certain devices could no longer be used which could be used under the MDDs. This has major impacts on the health of patients, especially when that device is the only product available for that patient. The patient and patient advocacy organisations did not experience that medical devices disappeared from the EU market. There are not only challenges perceived in keeping existing products on the market, but also in the development of new products.

Definition of orphan devices

10 quotations were categorized under this code.

Within the EU no definition is given on orphan devices and there is no pathway specifically for orphan devices. It varied a bit what the respondents saw as an orphan device. A few participants discussed what the meaning of an orphan device is. One participant explained that orphan devices are devices for which manufacturers have stopped production. Another participant explained it as that there are three types of orphan devices: custom made devices which are devices that are specifically designed for a patient, common devices that are used in a subset of orphan divide or orphan population and devices specifically designed for a rare (sub) population. As in the current situation, the definition of orphan devices in the EU can be discussed, three participants mentioned that they expect a definition when the MCDG guidance on orphan devices is published.

Differences between orphan and more commonly used devices

As described above, the MDR yields certain effects on orphan devices. But there are also some other key differences between orphan and common medical devices that influence the development and accessibility of orphan devices. 15 quotations were categorized under this code.

Respondents explain that the market dynamics of orphan devices are different from common medical devices. Orphan products are more expensive because of the expensive development process and the low market demand.

Several participants described factors contributing to the existence of orphan devices. One participant explained that due to research, causality of diseases shift from bigger to smaller groups, which causes more orphan diseases and lead to more orphan devices. In constrast to this statement, one of the

physicians mentioned that in her/his experiences, medical devices are often used for more than one disease as devices are often focused on symptoms. This statement was supported by the patient advocacy organisation and the patient, they both explained that they often see medical devices being used by a group of (rare) diseases. For example, often neuromuscular diseases can use the same medical devices. It is important to mention that the patient and patient advocacy organisation discussed supportive class I devices and not diagnostic/therapeutic devices.

Current mode of action

Under this code, 7 quotations were categorized that elaborated on the actions currently being taken in the orphan device field in the EU.

One of the physicians explained what they currently do in practice for patients with need for orphan devices. They collaborate between the metabolic disease centra on national and European level to quicker solve questions and to quicker identify unmet needs.

"The expertise center is responsible for the care pathway, the optimization of it and the use of medical devices. If a patient comes to you with a certain question, you should not think, I am going to solve this question on my own, but you must go to the expertise center. The expertise center can then pass it on to the European Reference Networks (ERN), they can identify needs and put them on the agenda to learn what is happening in other countries."

One developer mentioned that since funding for rare diseases entered the EU, there are more possibilities for getting funding for orphan devices. On regulatory level in the EU is a guidance on orphan devices is being developed. Both the member of the Notified Body and the regulatory expert explained that the MDCG guidance document will not describe a specific pathway for orphan devices, but how to consider orphan devices under the regulation. The guidance document will give a definition of orphan devices, which might help to identify those products. But it will not offer protection.

"MDCG guidance that's currently in its final draught in phase that will support, not necessarily a pathway for orphan devices, but how to consider orphan devices under the regulation"

EUDAMED

As explained in chapter 2, EUDAMED, a EU database with medical devices, will become available in the coming years. This code contained 4 quotations with explainations from the participants what they expect from EUDAMED.

The regulatory expert explained that EUDAMED can be nice in a policy sence but that we have to wait for years on its advantages and that the advantages have to be seen.

"It would be nice in a policy sense because in a few years time when the database has been populated, you might be able to find out some of this data from a database rather than hearing from doctors about what's disappeared off the shelf. So you might be able to gather some useful data from it. But in the meantime, I do not think it is going to make any particular difference"

The member of the Notified Bodies confirmed it. He/she mentioned that EUDAMED will probably be a basic database, which shows certificates and a summary of the safety and performance of devices. But it will not offer functionalities to identify orphan devices.

Unity between member states

In this code are quotations categorized that describe differences between member states in how orphan devices are being treated. The code contained 6 quotations.

The distributor of medical devices explained that he/she experienced differences in the cerfication processes of orphan devices between member states. The member of the Notified Bodies confirmed that

there are differences between Notified Bodies in certifying orphan devices, but that there is no evidence supporting this claim as Notified Bodies are commercial entities that can not speak openly about the devices that they certify. The member of the Notified Body explained the difference can be due the way Notified Bodies are managed by their competent authority.

"So we are managed, [organization name], by the [country] competent authority, who I have to say are very pragmatic and if I was to write a justification on my form today and said, well, this is an orphan device, this condition is, you know, five patients over the next five years are going to be impacted. This will limit the clinical evidence that's appropriate for this device. Therefore, we are accepting access of we're allowing this product to get CE certification. Some other Notified Body might be held by another country's competent authority, and they might come back and say, well, we won't accept that."

Another point that was mentioned is financial structures, two developers mentioned it. Reimbursement systems are nationally arranged, meaning that there are many different finiancial structures in the EU. Some member states have reimbursement systems for medical devices while other member states have little to no reimbursement system.

4.2.2 Challenges

This theme contains three codes that clarify the challenges experienced by the KOL in the field of orphan devices.

Challenges in the development of orphan devices

28 quotations were categorized under this code.

Several participants mentioned the small market potential as a challenge in development. The small market potential makes products expensive and causes barriers in collaboration with other organizations to improve the development process of medical devices. One of the developers explained that it is almost impossible to develop a medical device for a specific rare disease, he/she explained that the years of development to expensive for such a small population. The other developer explained that he/she has developed and marketed a medical device specifically for one rare disease, but that they are trying to deploy it for other diseases so that it will have bigger market potential.

Small sales also have an influence in gathering clinical evidence. When developing a product for a small population, it is hard to find enough clinical evidence. Reasons for challenges in gathering clinical evidence are called by three respondents; it's hard to find patients and the developing costs are less quickly earned back with a small population.

"You always need sufficient and good clinical evidence to know that you can use the devices for your population. If your population is a small group, then it is a challenge to derive sufficient clinical evidence."

***

"It is often a less good business case for manufacturers, to make devices for that specific target group when it is intended use for a relatively small group. The development costs are less quickly earned back."

Challenges to get access in the EU market

This code describes the challenges KOL experienced in the marketing of legacy and orphan devices in the EU, 23 quotations were categorized under this code.

Developers and physicians both explained that they experience more challenges in the certification process of orphan devices since the MDR entered into force. One developer mentioned that they are

seeking for months to find a notified body to certify their innovation. The governmental affairs participant explained that in his/her experience, the queue for notified bodies decreases. His/her biggest concern is keeping MDDs' orphan devices on the market. Several participants mentioned the same challenge in marketing devices in the EU: It is difficult to gather enough clinical evidence for orphan devices, what makes it difficult to comply with the entire documentation requirement. One of the physicians explained that it is hard to make the step from, what is needed, to what should we develop and how should we market it. He/she thinks that there are unmet medical needs, and that there are potential devices developed, but that developers/physicians get stuck in the process.

"I think it is difficult to make the step to what is needed? What should we develop? How do we get that converted into a project plan, priorities? Who do we need, how should we request subsidies? I think that people are interested, but they are a bit lost. While in the field of new medicines or repurposing of medicines it a lot more clearly, even though that is also very complicated."

Challenges of patients in accessibility of orphan devices

This code shows the challenges patients face in the accessibility of orphan devices, 17 quotations were categorized under this code.

Since the MDR entered into force, according to the KOL challenges raised in the certification process of orphan devices. This caused that certain medical devices disappeared from the market, this mostly affects people with rare diseases and paediatrics. One of the physicians explained that he/she thinks that there are unmet medical needs, while there are potential devices developed, but those are not developed at a correct way.

"I think there are unmet needs while there are potential solutions and there are people who have developed solutions, but not in a good way. Those people do not get on."

In addition to the MDR, which is perceived as a barrier to accessibility, reimbursement systems in the EU are also perceived as a challenge. Especially the division between member states was appointed by the KOL. Once a developer has granted a CE mark for its device, it need to go through the reimbursement system before it gets accessible for patients. Reimbursement is not neccesarily, but as medical devices can be very expensive for patients, it is sometimes needed. A developer explained that you should know the infrastructure very well to get a medical device reimbursed. The same medical device, can be reimbursed by one member state, while other member states do not reimburse it. The challenges describe above are perceived in reimbursement of medical devices in general. For orphan devices some extra challenges appear. It can take months to get a orphan device reimbursed by a health care insurance.

"The application process is very long. The health insurance company must approve a pilot phase. Then, you must fill in many protocols and send it to them. Most times, the application gets rejected. That's almost always the experience. If it is rejected your appeal, that process can take sometimes a year."

The patient explained that in his/her experience, the most of the times orphan device gets reimbursed eventually, but that it takes extra time.

4.2.3 Collaboration

Current mode of collaboration in the field of orphan devices

This code explains the current collaboration in the field of orphan devices, it contained 13 quotations. This paragraph starts with explaining the collaborative initiatives on regulatory level, and ends with explaining the collaborative initiatives on patient level.

The regulatory expert mentioned the EMA pilot on health advice and MedTech Europe as a collaborative tool on regulatory level. MedTech Europe is a representative group of manufacturers. The

MDCG guidance document on orphan devices is being developed on EU level, and Notified Bodies collaborate in this development process. The Notified Bodies participant explained that the Notified Bodies also collaborate with each other to learn from each other. They have team NB, which is a collaborative of Notified Bodies.

"So we do try to share where we can certain things that our experience is. So we meet once every three months on the clinical topics and we say what are people's thoughts on a post market clinical follow up study for this type of device and again without giving specifics, we might share that."

Besides team NB, Notified Bodies try to educate developers by offering webinars. They try to educate developers by explaining what they are going to expect, what level of evidence we would expect for class III devices etc.

The developers explained that they sometimes collaborate with universities and patient advocacy organizations. But collaboration with competitors is impossible because of competition legislation. The physician mentioned collaboration between expertise centers to optimise the use of medical devices for patients with rare diseases.

"In the Netherlands for rare diseases and metabolic diseases, we try to collaborate with other centra. We divide the disease into different expertise centers."

The distributor also mentioned that if a patient has more medical devices, they collaborate with the other suppliers during the assembly if needed. The patient advocacy organization tries to guide patients when they need an orphan device.

Negative aspects towards the current collaboration

Some negative remarks were given towards the current collaboration in the field of orphan devices. This paragraph also starts at regulatory level and ends with patient level aspects.

The Notified Body participant mentioned that they can not share information about the orphan devices that they have certified because of the commercial contracts that they have with their manufacturers. Therefore there are no insights for manufacturers what level of evidence an other manufacturer delivered to gain certification of their device.

One of the developers explained that it is hard to find other companies, patient advocacy organizations, pharmaceutical companies to work together on orphan devices. The physician elaborated the difficulties in collaborating with other companies. The more companies involved, the more the price goes up. Therefore, not too many companies are involved in the development of one orphan device.

Three participants mentioned that medical devices often get in each other's way. One developer explained that this is mainly due to minor communication between developers of medical devices. The patient and patient advocacy organization confirmed this.

"There are many pitfalls because there is no good and well-known partnership. The collaboration differs per municipality and per company."

The collaboration between specialisms and UMCs in identifying needs can be improved, the physician explained that he/she thinks that physicians and other medical professionals want to optimise the use of medical devices, but that there is currently little collaboration between hospitals and medical professionals in that field.

4.2.4 Recommendations

Recommendations towards the regulation for orphan devices in the EU

There were 14 recommendations towards the regulation in the EU highlighted.

The regulatory expert mentioned if we want to protect orphan devices, we need targeted policy approaches. He/she said three things need to be done: define, identify and protect.

"When you can't have a perfect definition was my recommendation at that time, then you need to apply that to identify products at risk by engaging with industry. We would really need to hear from companies as to what their intentions are. And then you would have to give some protection that was almost amnesty to those devices at risk. To essentially say, keep that on the market because we've defined and identified that's important for public health purposes. So define, identify and protect would be my very simple approach."

According to the regulatory expert a sustainable way is to create a discrete market access pathway for orphan products to tackle the current challenges. A discrete market access pathway was also mentioned by one of the developers. He/she doubted if they would use it if there was an orphan device pathway created. A different pathway means also learning all the ins and outs of that pathway, besides the normal medical device pathway that they use for the other medical devices they develop. That is too cumbersome for their company. Another developer sees possibilities in a discrete pathway, he/she mentions the situation in the US as an example.

The participant that works for the independent governmental institute called that a sort of incentive should be needed for manufacturers. An incentive that encourages manufacturers to develop orphan devices, something that makes it more attractive. The member of the Notified Bodies mentioned a European system of registries that captures rare diseases as a recommendation to make the certification process of orphan devices clearer.

"So I think what we need to build is a framework in Europe, a registry framework specific for medical devices and rare disease. And I think that would give Notified Bodies the confidence to move forward with certifying orphan devices, knowing that they've got sufficient data. It gives transparency to patients, physicians and the competent authorities and the EU Commission on the types of devices being used and being put on the market to support on from devices."

Recommendations towards collaboration in the field of orphan devices

16 quotations were highlighted as recommendations to improve the collaboration in orphan devices.

The most mentioned is that the collaboration between developers, suppliers and the reimbursors of medical devices should be improved. Four participants elaborated that there should be sort of tool/ organization that could match interested parties with each other.

"There should be a tool or organization that can say: "Hey, you two should have a talk with each other". Then we do not have to arrange 15 congresses to meet that one person or organization to collaborate with."

The patient explained that it would be an improvement if there were less parties involved in the process of getting a new orphan device. He/she said that there are so many parties involved in the application procedure. The patient advocacy organsiation mentioned that collaboration between patient advocacy organisations could maybe optimise the application procedure of orphan devices.

"[names of several patient advocacy organisations] they should arrange a delegation of their boards together with other stakeholders in the field of orphan devices, they should sit down together to streamline the whole process. I think that then, you gained support to investigate, how can we support patients in this area as quickly as possible."

One of the physicians mentioned that a positive approach can be stimulating. By looking at what is already developed for rare diseases and what is already available for patient.

5. Conclusion and discussion

5.1 Conclusion

This study investigated the current landscape of orphan devices development and accessibility in the EU. The two research questions for this research are: "*What is the current landscape of orphan devices development in the EU and US?"* and *"How does the current orphan device landscape in the EU affect the development and accessibility of orphan devices according to KOL?".* The research questions were investigated through a combination of the desktop analysis of clinical trials and interviews with KOL. Based on the research question, the analysis revealed several key findings regarding the current landscape of orphan devices in the EU. Between 19 September 1995 and 1 October 2025, 2027 clinical trials evaluating medical devices were developed for at least one rare disease. Of those 2027 clinical trials, 736 medical device clinical trials are developed only for rare diseases. The analysis showed an upward trend in the development of orphan devices over the years in the EU till 2019, after this year the growth in the frequency of start dates stagnated. The interviews with KOL indicated that the MDR presents additional challenges in the development and accessibility of orphan devices. These challenges occur due to the different market dynamics of orphan devices, which makes them vulnerable to change and the requirement for clinical evidence, which is difficult to maintain due to the small patient populations.

The MDR poses additional challenges in the development and accessibility of orphan devices in the EU. Despite the increasing attention for rare diseases, increasing interest in orphan device development has stagnated since 2019. The regulatory hurdles have led to an increase in certification time and costs, making it more difficult for small and medium size enterprises to bring new orphan devices to the market. To enhance the development of orphan devices in the EU, it is necessary to address the challenges perceived by KOL towards the MDR. Streamlining the certification process of medical devices and drawing more attention to orphan device development could facilitate the development and increase the accessibility of orphan devices in the EU. By addressing these challenges, the EU can become a more attractive market for developers and manufacturers to bring their orphan devices to the market.

5.2 Discussion

This discussion starts with explaining the significance of the results, followed by explaining how the results align or differ from existing literature. Afterward, the implications of the results for both research and practice are examined, followed by recommendations for future research and practical applications. Finally, the limitations and strengths of this research are outlined.

5.2.1 The gap in orphan device development

The results of the clinical trial analysis showed that for many rare diseases no medical device is being developed. There are 590 different rare diseases for which medical devices are in development, while there are around 6000 different rare diseases in the EU based on the Orphanet nomenclature [11]. Less than the half of the analysed clinical trials target rare diseases only. Although the analysis exposed the gap in medical device development for rare diseases, it also showed that some rare diseases are frequently studied e.g. Cystic Fibrosis, Abdominal Aortic Aneurysm and Amyotrophic Lateral Sclerosis. These diseases have a higher prevalence than some other rare diseases, which may explain that more research is done on diseases with higher prevalence. However, there are two other potential explanations, which are media attention and active patient advocacy organisation. According to Miller et al. the last 15 years more social media is used to facilitate health research on patients with rare diseases [38]. In their research is described that Cystic Fibrosis and Amyotrophic Lateral Sclerosis are most frequently studied, which may explain the positive effect of social media. According to Gentilini and Miraldo, the activeness of patient advocacy organisation is of positive influence on the research activity [39]. Active patient advocacy organisation could also be an explanation for the higher research frequency.

The existing literature provided insights in the unmet medical needs of patients with rare disease for medical devices in the USA perceived by health care professionals [5]. Concrete data on the medical device development landscape for rare diseases lacks. This result is significant because it highlights the underdevelopment of medical devices for rare diseases. This finding has practical implications as it provides insights for regulators into the gap of orphan device development. It also gives concrete insights into what the characteristics of the clinical trials for orphan devices looks like. Knowledge of this gap and these characteristics could help regulators in shaping the regulations. But it provides also implications for health care professionals, which could improve the quality of care for patients with rare diseases. It can drive health care professionals to seek alternative treatment options. It has also practical implications for developers, as it provides insights into what competitors provide as clinical evidence for orphan devices.

Based on this, it can be concluded that to protect the health of patients with rare diseases, we need to prevent a possible lack of available orphan devices in the future in the EU. While this research provides an overview of the gap in the medical device development for rare diseases, it is important to note that it is based on the US database. Further research is needed to confirm these findings within the EU context.

Recommendation

It is recommended to conduct research by gathering and analysing certification data of medical devices from Notified Bodies. Although Notified Bodies are commercial entities, which may make them reluctant to share their data, it is crucial to obtain insights into the EU landscape of orphan devices. This research could not only provide valuable information for regulators, but also for the Notified Bodies themselves. It can gain insight into how other Notified Bodies certify orphan devices, which is normally not insightful [2]. To encourage Notified Bodies to share their data, anonymized data collection methods should be used.

5.2.2 The effect of the MDR on the orphan device development landscape

The analysis showed an increase in start dates of medical device clinical trials for rare diseases in the last decade. The clinical trials with a study location in the EU, showed an increasing trend of start dates of clinical trials till 2019. Since 2019 the increase in start dates of clinical trials for rare diseases stagnated. This trend may be related to the introduction of the MDR in 2019. Developers may wait with starting new studies because they did not know what was expected of orphan devices when the MDR entered in. The results of the interviews supported this finding. Participants indicated that it is difficult to meet the clinical evidence requirement for orphan devices, especially since it is not clear what level of evidence a Notified Body finds necessary. In 2023 more clinical trials started than the years before, this could indicate that developers better understand what is expected from them under the new regulation. This finding was not supported by the findings of the interviews.

The literature indicated an increasing interest in rare disease research the past decades and major public research initiatives for rare diseases are established in many countries [4]. EU funding and initiatives for research on rare diseases are mostly focused on medicines. Policy and incentives are established for orphan medicinal products in the EU, leading to an increase in the number of orphan medicine approvals the last decade [4]. The attention on orphan medicines could implicate the increase in start dates of medical devices for rare diseases. But still, the development of medical devices for rare diseases is far behind the development rate of orphan medicines [5]. Compared to orphan medicines, no policy and incentives are established for orphan device research in the EU [1]. Another possible explanation for the increasing development rate of medical devices for rare diseases could be the increasing rates of medical devices development in the EU, which was described in the booklet of MedTech Europe 2024 [40]. According to them, the European medical device market has been growing on average by 5.4% the last 10 years.

The entering of the MDR has some scientific implications. Developers may switch their research focus on medical devices that are less affected by the regulation, less focus will stay on orphan devices. This will cause a decrease in availability of medical devices for patients with rare diseases. Less clinical trials on orphan devices, causes a slowdown in new scientific knowledge on rare diseases. It has also practical implications. Less research on orphan devices, causes a decrease in new innovative medical devices on the EU market. Innovative medical devices are needed to improve the diagnosis and treatment of rare diseases [5]. Therefore, this finding provides valuable insights for regulators.

Based on this can be concluded that the entering of the MDR caused a decrease in orphan device development in the EU. Both the literature as the interview findings described the barriers developers perceive the marketing of orphan devices in the EU since the MDR came into force.

Recommendation

To prevent a public health problem for happening, the causes of the decrease in development in the EU should be tackled. In paragraph 5.2.3 and 5.2.4 are the barriers perceived by KOL further clarified, and recommendations regarding them will be provided. In this paragraph is recommended that collaborative initiatives who represents people with rare diseases, shift their focus as well to research for orphan devices. What can be learned from the last decade is that cooperation and collaboration in rare disease research has contributed to a significant increase in the development of new medicinal treatments for rare diseases [4]. It is important that collaborative initiatives, such as IRDiRC, include orphan device research in their goals [41]. Action is particularly needed now, as the number of medical devices developed for rare diseases in the EU has decreased in recent years. This will make the gap with the orphan medicinal development scope in the coming years even larger than before.

5.2.3 Clinical evidence

The results of the interviews revealed that developers perceive the requirement for clinical evidence in the MDR as a barrier in the development of orphan devices. The participants described that rare diseases often have small patient populations with high heterogeneity, which makes it difficult to find a big research population. The clinical trial analysis showed that orphan devices have a median study population of 35 enrolled patients.

The literature supports the finding of the interviews. In the article of Melvin et al. is described that developers find it difficult to include a study population that is big enough to adhere to the requirement of clinical evidence in the MDR, as rare diseases have small disease populations [2]. Bell and Smith [42] state that clinical trials for rare diseases have a median of 29 enrolled participants, compared to non-rare disease clinical trials, they have a median of 62 enrolled participants. This indicates that orphan device research indeed has smaller study populations than non-rare disease research, which makes the requirement for clinical evidence of the MDR as a barrier in development. The MDR requires sufficient clinical evidence for medical devices. However, it does not explicitly describe what level of evidence is needed for orphan devices [1]. This allows Notified Bodies to specify the level of evidence required for certification of orphan devices, but this also leads to disparity between Notified Bodies. To overcome these differences the Notified Bodies established the representative group Team-NB and the MDCG group has developed a guidance document on orphan devices.

In the literature was found one article that describes that an orphan device regulation needs to be established in the EU [24]. The US established such orphan device regulation, called the HUD. The HUD was explained in chapter 2. The HUD provided an alternative pathway for orphan devices. Since the introduction of the HUD, 74 HDEs are approved by the FDA [43]. The HUD regulation is a successful initiative for improving the accessibility of medical devices for patients with rare diseases. However, it also yields some negative aspects. The HUD has less stringent requirement for evidence, which can bring the safety of the patient in danger [25]. The analysis of the interviews showed different opinions about a discrete pathway for orphan devices. As many medical device developers in the EU are

Small Medium Enterprises (SME's), SME's often lack the resources to maintain specialised departments. A new pathway means learning all the ins and outs of that pathway, which costs time and resources [2].

In other fields is established a structured dialog to improve the innovation and development processes of new treatments. The EU established in the field of orphan medicines the structured dialog, this was introduced in 2021 [44]. It aims to provide scientific advice and regulatory support. Currently the EMA has launched a pilot on scientific advice for developers of high-risk medical devices, 10 applicants were selected for this pilot [45]. The US has established the Q-submission program, this enables manufacturers to request for feedback and meetings for medical device submissions [46].

This finding has practical implications. The ambiguity for developers in the level of evidence needed for orphan devices implicates a decrease in development rate. It is important to clarify the requirement of clinical evidence needed for orphan devices in the regulation. Clarifying yields scientific implications as it will make the certification process of orphan devices clearer.

Based on this can be concluded that the requirement for clinical evidence in the MDR is perceived as a barrier in the development of orphan devices. It should be clearer for developers what level of evidence is appropriate for orphan devices.

Recommendations

Considering the small sample size per area of expertise in this study, and the different opinions of the KOL, it is recommended to further investigate the opinions of more KOL on the introduction of a discrete pathway for orphan devices in the EU.

The second recommendation towards the requirement of clinical evidence for orphan devices is introducing the structured dialog between Notified Bodies and developers of orphan devices in the EU. Structured dialog can have a positive impact on orphan devices. It gives manufacturers the opportunity to discuss the level of evidence that the Notified Body considers necessarily for certification. This makes the certification process of orphan devices more predictable for manufacturers.

5.2.4 Certification costs

The interview analysis showed a second challenge that was perceived by the KOL. The higher certification costs are a barrier in the development of orphan devices. Orphan devices tend to make far less profits than common medical devices, higher certification costs can make an orphan device no longer profitable anymore.

This finding aligns with the challenge mentioned in the article of Melvin et al [2]. The costs for certification are much higher than in the US. According to Peiris et al. are orphan devices vulnerable to additional costs and regulatory changes [5]. In an open letter that representatives of the European medical association send to the EU commissioner for Health and Food safety EU commission, was described that single device costs over 80,000 euro and gives 5 years market access. In the US, the 510k lifetime market clearance costs around 5,000 euro [47]. This is a major difference. This causes that many manufacturers prefer the US market entry above the EU [2].

In the US are several programs established to financially support the development of orphan devices. The Orphan Products Grants program funds clinical studies on safety and effectiveness of medical products for rare diseases, this includes medical devices [48]. The Paediatric Device Consortia Grants Program provides advice, networking and prototyping services to medical device innovators for paediatric devices [49]. These grants give opportunities for developers that develop orphan (paediatric) devices.

This finding has several implications. First, the higher certification costs can be a reason that SMEs do not enter new medical devices on the EU market, or even withdraw MDD devices. Therefore, the

medical device innovation in the EU can decrease. Higher certification costs can increase the price of orphan devices, resulting in higher expenses for patients or health care payers and making orphan devices less accessible for patients.

Recommendation

As mentioned in the previous paragraph, it is too early to demand for a discrete pathway considering the small sample size of this research and the different opinions of KOL. However, action is needed towards the high certification costs as many innovations are leaving the EU for the US. Establishing such a program as the Orphan Products Grants program for orphan devices can be of positive influence on the development rate of medical devices for rare diseases in the EU.

5.2.5 Reimbursement systems

The analysis of the interviews highlighted disparity between member states in reimbursement systems as a challenge in the development and accessibility of orphan devices. Developers need to know the infrastructure very well to get their device reimbursed.

This challenge was not emphasized in the literature on orphan devices [Melvin et al]. This finding is noteworthy given the importance of reimbursement systems in the availability of health products in the EU. Addressing this challenge is important as it impacts the quality of care for patients with rare diseases in certain EU member states.

Currently, the reimbursement of medical devices in the EU is primarily arranged per member state. Every country has its own Health Technology Assessment body which evaluates the clinical-, cost-effectiveness and added therapeutic benefit of medical devices. There are no standardized requirements in the EU for the design, scope or duration of clinical trials for medical devices, and variability exists in the ethical review process [16]. The EU tries to harmonize the HTA processes by introducing the Health Technology Assessment Regulation, the regulation entered into force in 2022. The HTAR aims to facilitate a more consistent and efficient assessments of medical devices [50]. The European Network for Health Technology Assessment (EUnetHTA) is a network that aims to improve the collaboration between HTA-organisations.

In conclusion, disparity between member states in reimbursement is perceived as a barrier in development, currently the EU is implementing the new HTAR, which aims to foster a more consistent and efficient reimbursement process.

Recommendation

It is recommended to make the clinical evaluation data of medical devices, that are used for CE marking, publicly available. This will make the reimbursement process clearer and enhances transparency for both developers and HTA bodies. Publicly available clinical evaluation data yield also positive effects in the certification process of orphan devices, which was explained in paragraph 5.2.3.

5.2.6 Collaboration

The collaboration between stakeholders in the field of orphan devices can be optimized according to the interview respondents. The patient, the developers and the physicians all mentioned that there is no good collaboration network for medical devices in the EU. One important perceived challenge was that stakeholders with the same goals cannot find each other well. This finding has implications as good collaboration and engagement of stakeholders can improve the development and accessibility of orphan devices.

In the EU several collaboration initiatives for rare diseases are established. The European Reference Networks (ERNs), European Joint Programme (EJP) and IRDiRC. These networks aim to facilitate stakeholder engagement, sharing knowledge and research on rare diseases, but do not explicitly match stakeholders with each other that have the same goals. The FDA's Pediatric Device Consortia program

aids in identifying potential manufacturers for pediatric devices. They try to connect developers of pediatric devices with manufacturers who can produce the pediatric devices. The consortia make use of its own network to match manufacturers with developers.

Recommendation

Based on this, it is recommended that research consortia such as the IRDirC shift their focus to include orphan device research, and a body should be established that brings researchers, developers, patients and manufacturers in the field of orphan devices together. It could have a major impact on the availability of orphan devices for patients. It can be an advantage in the collaboration between developers and manufacturers, as well for developers finding patients to participate in clinical trials.

5.3 Limitations and strengths

Limitations

The first limitation of this research is that the clinical trials that were used for the analysis were distracted from the US clinical trials database. The reason to use the US database instead of the EU database of clinical trials was well considered. The EU database is perceived as incomplete compared to the US database [51]. However, by using clinicaltrials.gov some clinical trials were included that might not be developed for the EU market. Another limitation in using clinical trials as tool so identify which medical devices for rare diseases are developed, is that not all devices assessed in clinical trials will eventually become available at the EU market. Low risk medical devices (class I and IIa) do not necessarily need to do a clinical trial to get market access in the EU [1]. Due to these limitations, the analysis does not represent the total number of medical devices for rare diseases available on the EU market. Since there is currently no database in the EU that displays the number of medical devices for rare diseases available in the EU, this research could still be of significant value.

Another limitation in the clinical trials analysis is that the filters of clinicaltrials.gov not filtered all not rare diseases out. Therefore, the rare diseases had to be filtered out with the use of the Orphanet nomenclature. However, due to differences in how diseases are spelled a text mining algorithm was needed to match the rare diseases of the dataset with the Orphanet nomenclature. The Orphanet nomenclature included synonyms for disease names, but a disease may still have a different name than described in the Orphanet nomenclature. Therefore, it is possible that rare diseases with different names are excluded from the analysis. However, it is also possible that diseases that are not rare may have been matched to a rare disease and therefore included in the analysis. To limit this uncertainty, was chosen to have a low as possible threshold. Before deleting all mismatched disease names from the analysis, the most appropriate threshold was manually checked. Most rare diseases were included and not rare diseases excluded.

A limitation of the interviews is that the analysis and coding was conducted by a single reviewer. Preferably the analysis and coding are performed by two or more reviewers. The involvement of one reviewer makes the risk of subjectivity and personal bias higher. This may lead to the selective interpretation of the data.

Another limitation of the interviews is that per area of expertise, only one or two participants were interviewed. Small sample size restricts the ability to generalize the results, as the perspectives and experiences of the participant may not be representative of the broader population within each expertise.

The interviews highlighted national reimbursement systems as a perceived barrier, therefore it would be valuable for the research to include the perspectives and experiences of a health insurance/HTA expert. However, this research did not include participants with a reimbursement background. Three participants with HTA background were approached, none of the participants agreed to participate in an interview.

Some of the interviews were conducted in Dutch, therefore some quotations had to be translated to English. Translating may introduce variations in interpretation of tone and expression. To minimize the risk of various in the translations, there was chosen to check the quotations by a second person.

Strengths

Despite these limitations, this research possesses several key strengths that enhance its validity and contribute valuable insights to the field of orphan devices. The first strength is that the interview population size was bigger than previous was thought as achievable. The goal was to include 5 to 10 participants in the interviews, eventually 12 KOL participated. A larger number of participants allows for a more comprehensive and diverse range of perspectives, which leads to more reliable and generalizable results [52]. So including more participants than planned enhances the robustness and credibility of the research findings.

A second strength is the use of a mixed-method approach. It combines the strengths of both qualitative and quantitative methods, leading to a more comprehensive understanding of research problems [53]. Some insights derived from the interviews could be checked through the results of the clinical trial analysis and vice versa. But is also balanced the weaknesses out of each other. Where the clinical trial analysis might lack some depth, the interviews provided an in-depth knowledge of perspectives. The interviews might lack some objectivity, whereas the clinical trial analysis provided objective results.

To validate the results of the clinical trial analysis, the data was compared with the CCMO database and HDE database. This data triangulation approach strengthens the clinical trial analysis by confirming the reliability and validity of the findings.

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Appendix A: Explanation characteristics of clinical trials

Study type

There are three study types; interventional, observational and expanded access.

- Interventional studies evaluate the effect of intervention on health-related outcomes of patients. This study type involves active interventions.
- Observational studies evaluate interventions without altering routine medical care.
- Expanded access studies investigate a product that is available through expanded access for patients who do not qualify for enrollment in a clinical trial.

Study design

The study design refers to the structure of the clinical trial. There are many different subtypes of designs.

- Primary Purpose: Main objective of the intervention being evaluated in the clinical trial. (Example objectives are treatment, prevention, diagnostic etc.)
- Interventional Study Model: Strategy for assigning interventions to participants. (Example strategies are single group, parallel etc.)
- Masking: Describes the parties involved that are prevented from having knowledge of which participant the intervention is assigned to. (Example: triple, single etc.)
- Allocation: Describes which participants are assigned to arms. (Example: N/A, randomized etc.)
- Observational Model: Primary strategy for participant identification and follow-up. (Example: cohort, case-control, case-only etc.)
- Time perspective: The period to time of participant enrollment. (Example: retrospective, prospective etc.)

Recruitment status

This describes the status of each participant in the clinical trial.

- Not yet recruiting: participants are not yet being recruited
- Recruiting: participants are being recruited
- Enrolling by invitation: participants are being selected from a predetermined population
- Active, not recruiting: participants are receiving an intervention or being examined, no new participants are being recruited.
- Completed: participants are no longer receiving an intervention or being examined.
- Suspended: Study halted prematurely but potentially will resume
- Terminated: Study halted prematurely and will not resume
- Withdrawn: Study halted prematurely, prior to enrollment of first participant

[54]

Appendix B: Interview protocol

Thank you for participating in this interview. It will be part of a series of five/six interviews with key opinion leaders in the field of orphan devices. The goal of this interview is to dive deeper into the insights, experiences and perspectives of key stakeholders.

Before we start, I would ask for your permission. I want to record this interview for the purpose of transcription. The data obtained will be analyzed and used for research purposes only. Data will be treated with confidentiality and respect. Furthermore, I will partially anonymize the analyzed data by removing your name to ensure privacy. The company/ organization will only be anonymized if possible. You are free to withdraw from the interview at any point, whether during or after its completion. Do you agree with these conditions? Then I would like to start with the interview.

Concept	Interview questions and follow-up questions
Background	- Can you begin with briefly introducing yourself?
	If not already mentioned, continue with these questions: - For what organization do you work? - What are your experiences in the field of orphan devices?
Organizations role	- What role does your organization play in the field of orphan devices?
	Extra note: in terms of accessibility, development, regulation, reimbursing, advocacy? - Could you provide insights into the specific initiatives/ programs your organization is involved in concerning orphan devices?

The next questions will differ per expertise of the stakeholder:

Regulatory expert	
Importance	- Could you define what constitutes an orphan device in the European regulatory context? - Why are orphan devices important in the care for people with rare diseases? - Could you provide an example illustrating the importance of orphan devices for a specific case in the care for people with rare diseases?
Challenges	- Wat are the most significant regulatory challenges when dealing with orphan devices? - How do you address these challenges? Or should be addressed? - Does the market approval process of orphan devices differ from more common devices? If so, how does it differ from each other?
(Developer of orphan devices)	
Developing process	- How does your organization identify needs of patients with rare diseases for orphan devices? How do you prioritize these needs for orphan devices? - How does the developing process of orphan devices look like? - Does the developing process differ from devices developed for common diseases?
Challenges	- What challenges do you encounter during the development process of orphan devices? Additional: challenges in stage: development, funding, market approval, reimbursing? - How do you address these challenges?
(Health care professional)	
Importance	- Why are orphan devices important in the care for people with rare diseases? - Could you provide an example illustrating the importance of orphan devices for a specific case in the care for people with rare diseases? - How do you stay informed about the latest developments in the field of orphan devices, related to your clinical practice?
Challenges	- What are some of the main challenges patients face in the accessibility of orphan devices for patients with rare diseases? - How do you support patients when they face these challenges?

(Patient advocacy organization)	
Importance	- Why are orphan devices important in the care for people with rare diseases? - Could you provide an example illustrating the importance of orphan devices for a specific case in the care for people with rare diseases?
Challenges	- What are some of the main challenges patients face in the accessibility of orphan devices for patients with rare diseases? - What challenges do you face when advocating for orphan devices?
(Health care payer)	
Reimbursement process	- Does the reimbursement process of orphan devices differ from more common devices? - If so, can you walk us through the steps of the reimbursement process of orphan devices? - What criteria does your organization use to determine whether an orphan device qualifies for reimbursement?
Challenges	- What are some of the main challenges you have faced in the reimbursement process of orphan devices?
(Notified body employee)	
Market approval	- Does the market approval process of orphan devices differ from common medical devices? - How does the market approval process of orphan devices differ from other medical devices? Additional: in terms of assessment criteria - Can you walk us through the steps of the market approval process of orphan devices? Most important steps
Challenges	- What challenges do you face in the market approval process of orphan devices?

Questions for all KOLs:

Collaboration	- How does your organization collaborate with other organizations to address the needs for orphan devices of patients? - How can organizations involved in orphan device development collaborate more to improve the development/accessibility of orphan devices?
Improve care	- What is your biggest hurdle in the field of orphan devices, and how should it be addressed? Addition: needed on regulatory level, patient level, national level, in reimbursement process etc.

Appendix C: Validity check - HDE database

HDE Dataset	Clinical Trials dataset
medtronic activa deep brain stimulation dbssystem	deep brain stimulation
fetoscopy instrument set	fetoscopy
medtronic activadeep brain stimulation for ocd therapy	medtronic implantable deep brain stimulation dbs system
neurx ra4 device	neurx dps
neurx diaphragm pacing system dps	neurx dps
argus ii retinal prosthesis system	argus ii retinal prosthesis system
liposorber la15 system	apheresis using liposorber la15 system
kaneka lixelle beta 2microglobulin apheresis column	lixelle treatment
impella rp system	impella cp
liposorber la15 system	apheresis using liposorber la15 system
optune lua	optune
plasma delipidation system pds2 system	hdl therapeutics pds2 system
mds nordion therasphere yttrium90 glass microspheres	therasphere yttrium90 y90 microspheres

Appendix D: Validity check – CCMO database

NCT.Number	Title	Other.IDs	Locations	Available on CCMO database:
NCT05871515	3D Ultrasound of Abdominal Aortic Aneurysm Characteristics	2021-1929|NL81910.091.22	Rijnstate Hospital, Arnhem, Non US/Canada, Netherlands	yes
NCT05064202	Unloading in Heart Failure Cardiogenic Shock	NL84199.018.23	Academical Medical Center (AMC), Amsterdam, Netherlands|VU University Medical Center (VUMC), Amsterdam, Netherlands|Univerity Medical Center Groningen (UMCG), Groningen, Netherlands|Leids Universitair Medisch Centrum (LUMC), Leiden, Netherlands|University Medical Center Utrecht (UMCU), Utrecht, Netherlands	yes
NCT05546372	Endobiliary Radiofrequency Ablation for Malignant Biliary Obstruction Due to Perihilar Cholangiocarcinoma	NL76591.029.22	Amsterdam UMC location VUmc, Amsterdam, Netherlands	yes
NCT05874934	Endoscopic Drainage of Presumed Resectable pCCA Using an Intrahepatic Plastic Stent With Retrieval String	2021.0249|NL83570.018.22	Amsterdam UMC, Amsterdam, Netherlands	yes
NCT02325921	MRI in Renal Tumors	NL49616.091.14	Radboud University Medical Center, Nijmegen, Netherlands	yes
NCT06258096	LI-TASTE Study: Light for Taste	NL84772.018.23		yes

Appendix E: Translations of the interview quotations

Original quotations	Translation
Het expertisecentrum is echt verantwoordelijk voor het zorgpad en het optimaliseren van, het gebruik van de medical devices daarin. Dus als er een patiënt bij komt met een bepaalde vraag, dat je dat niet bij je zelf houdt en denkt, dat ga ik wel even oplossen, maar dat je dan vrij snel naar het expertisecentrum toe gaat en dat die het ook weer door kan zetten naar de ERNs, de European Reference Networks om bepaalde behoeftes op de agenda te krijgen om te leren van wat er in andere landen gebeurt.	The expertise center is responsible for the care pathway, the optimization of it and the use of medical devices. If a patient comes to you with a certain question, you should not think, I am going to solve this question on my own, but you have to go to the expertise center. The expertise center can then pass it on to the European Reference Networks (ERN), they can identify needs and put them on the agenda to learn what is happening in other countries.
Je moet altijd voldoende en goede klinische data hebben om te weten dat dat je die devices kunt toepassen in je doelgroep. Als je doelgroep een kleine groep is, ja dan is het een uitdaging om voldoende klinische data te verkrijgen.	You always need sufficient and good clinical evidence to know that you can use the devices for your population. If your population is a small group, then it is a challenge to derive sufficient clinical evidence.
Het is voor fabrikanten vaak een minder goede business case, om devices voor die specifieke doelgroep te maken als het intended use voor een relatief kleine groep. Ja dan heb je de ontwikkelingskosten minder snel terug	It is often a less good business case for manufacturers, to make devices for that specific target group when it is intended use for a relatively small group. The development costs are less quickly earned back.
Ik denk dat is lastig om de stap te maken naar wat is er nodig? Wat moeten we ontwikkelen? hoe krijgen we dat omgezet in een projectplan, prioriteiten, wie moet er ingevlogen worden, hoe gaan we subsidie aanvragen? Ik denk dat mensen daar best geïnteresseerd in zouden zijn. Maar ze zijn een beetje verloren, terwijl dat misschien op het gebied van een nieuw medicijn of het repurposen van een medicijn al een stuk duidelijker is, ondanks dat dat ook een heel ingewikkeld traject is	I think it is difficult to make the step to what is needed? What should we develop? How do we get that converted into a project plan, priorities? Who do we need, how should we request subsidy? I think that people are interested, but they are a bit lost. While in the field of new medicines or repurposing of medicines it a lot more clearly, even though that is also very complicated.
Ik denk dat er unmet medical needs zijn en de potentiële oplossingen die er wel degelijk zijn en die mensen misschien wel hebben ontwikkeld, maar misschien niet op de goede manier. Die dus niet verder komen.	I think there are unmet needs while there are potential solutions and there are people who have developed solutions, but not in a good way. Those people do not get on.

Ja, dan gaat het aanvraagproces gaat gewoon heel lang duren. De verzekeraar dus, dan begin je eigenlijk eerst een proefperiode. Dat moet de verzekeraar al goedkeuren en dan moet je, ik weet niet hoeveel protocollen invullen en dan wordt het opgestuurd. Meestal wordt het standaard afgewezen. Het is ongeveer onze ervaring en dan ga je in beroep. Nou en dan ja dus dat dat proces kan soms wel een jaar duren.	The application process is very long. The health insurance company has to approve a pilot phase. Then, you have to fill in many protocols and send it to them. Most times, the application gets rejected. That's almost always the experience. If it is rejected you appeal, that process can take sometimes a year.
We proberen wel via, denk ik in Nederland voor de zeldzame ziekte, de Metabole ziekte wel in die zin goed met elkaar met de centra optrekken. We verdelen de ziekte in de verschillende expertisecentra.	In the Netherlands for rare diseases and metabolic diseases, we try to collaborate with other centra. We divide the disease into different expertise centers.
Er zitten heel veel haken en ogen aan die nog niet goed lopen omdat er geen bekende samenwerkingslijn is. De samenwerking verschilt per gemeente en per bedrijf.	There are many pitfalls because there is no good and well-known partnership. The collaboration differs per municipality and per company.
Er zal een soort van tool of organisatie moeten zijn die kan zeggen, Hé, babbelen jullie eens met mekaar. Dan hoeven wij niet eerst 15 concressen te doen voordat we eventueel die persoon of die organisatie tegenkomen.	There should be a tool or organization that can say: "Hey, you two should have a talk with each other". Then we do not have arrange 15 congresses to meet that one person or organization to collaborate with.
[names of several patient advocacy organisations] wat daar in dat gebied zit, Dat daar de besturen een afvaardiging hebben samen met alle stakeholders die er zijn, om daarmee aan tafel te gaan zitten om die heleboel te stroomlijnen. Ik denk dat je dan draagvlak hebt om te kijken van, hoe kunnen we dit bundelen en hoe kunnen we alle patiënten op dit gebied zo snel mogelijk helpen?	[names of several patient advocacy organisations] they should arrange a delegation of their boards together with other stakeholders in the field of orphan devices, they should sit down together to streamline the whole process. I think that then, you gained support to investigate, how can we support patients in this area as quickly as possible.

Appendix F: Study designs

Study design	Count	(%) Percentage
Allocation: N/A	267	0,102
Allocation: Non-Randomized	84	0,032
Allocation: Randomized	229	0,088
Intervention Model: Crossover Assignment	58	0,022
Intervention Model: Factorial Assignment	2	0,001
Intervention Model: Parallel Assignment	222	0,085
Intervention Model: Sequential Assignment	6	0,002
Intervention Model: Single Group Assignment	292	0,112
Masking: Double	1	0,000
Masking: Double (Care Provider, Investigator)	1	0,000
Masking: Double (Investigator, Outcomes Assessor)	5	0,002
Masking: Double (Participant, Care Provider)	1	0,000
Masking: Double (Participant, Investigator)	9	0,003
Masking: Double (Participant, Outcomes Assessor)	16	0,006
Masking: None (Open Label)	443	0,169
Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	22	0,008
Masking: Single	3	0,001
Masking: Single (Care Provider)	3	0,001
Masking: Single (Investigator)	7	0,003
Masking: Single (Outcomes Assessor)	28	0,011
Masking: Single (Participant)	19	0,007
Masking: Triple (Care Provider, Investigator, Outcomes Assessor)	2	0,001
Masking: Triple (Participant, Care Provider, Investigator)	6	0,002
Masking: Triple (Participant, Care Provider, Outcomes Assessor)	7	0,003
Masking: Triple (Participant, Investigator, Outcomes Assessor)	9	0,003
Observational Model: Case-Control	24	0,009
Observational Model: Case-Crossover	2	0,001
Observational Model: Case-Only	17	0,006
Observational Model: Cohort	90	0,034
Observational Model: Other	16	0,006
Primary Purpose: Basic Science	13	0,005
Primary Purpose: Device Feasibility	27	0,010
Primary Purpose: Diagnostic	59	0,023
Primary Purpose: Health Services Research	8	0,003
Primary Purpose: Other	43	0,016
Primary Purpose: Prevention	21	0,008
Primary Purpose: Screening	10	0,004
Primary Purpose: Supportive Care	45	0,017
Primary Purpose: Treatment	351	0,134
Time Perspective: Cross-Sectional	18	0,007
Time Perspective: Other	2	0,001

Time Perspective: Prospective	119	0,045
Time Perspective: Retrospective	9	0,003