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Author(s)	Tom Melvin (TCD)
Reviewers	Anneliene Jonker (UT), Marco Raaben (UT), Vincenzo Carbone (IST), Ali McDonnell (TCD), Ricardo Fernandes (c4c)
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Symbols, abbreviations and acronyms

c4c	connect4children Stichting
CE	Certification Européenne (European Conformity)
CF	Cystic Fibrosis
CLS	Compression Loading System
D	Deliverable
DCS	Delivery Catheter System
DeCODe	Develop Child and Orphan Device Evaluation support
DS	Delivery System
EC	European Commission
EXone	EXone Arm Supporter (Yumen Bionics)
IMDRF	International Medical Device Regulators Forum
ISO	International Organization for Standardization
IST	Istituto Superiore di Sanità (Italy)
M	Month
MDR	Medical Devices Regulation
MS	Milestone
NICE	National Institute for Health and Care Excellence
PPV	Percutaneous Pulmonary Valve
RVOT	Right Ventricular Outflow Tract
SMA	Spinal Muscular Atrophy
TAVI	Transcatheter Aortic Valve Implantation
TCD	Trinity College Dublin
TMT	Transcatheter Mitral Valve Therapy
UK	United Kingdom
UT	University of Twente
WP	Work Package

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Executive Summary

The DeCODe project aims to support the development and evaluation of orphan and paediatric medical devices. This deliverable outlines the process and rationale for selecting five hypothetical use cases. Case vignettes are then presented for each use case. Given the diverse and complex landscape of medical devices, a qualitative selection method was employed. Criteria for selection were derived from input from consortium members. A diversity of medical technologies were selected based upon CE-marking status, device class, target population, linkage to registries, and the need for clinical investigations. The five use cases — CFHealthHub, Yumen Bionics, Percutaneous Pulmonary Valve Replacement, Rehability, and Custom-made Medical Devices — were selected to represent a broad range of technologies and regulatory pathways. These use cases will serve as high level inputs for critical path mapping in subsequent project work.

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1. Introduction

The Develop Child and Orphan Device Evaluation support (DeCODe) consortium aims to catalyse innovation and address the unique healthcare needs of children and people living with a rare disease who rely on medical device technologies.[1] In this deliverable, we report on the hypothetical use cases which have been selected. These use cases will then be taken up by Work Package (WP) 3 , where a critical path will be created based upon these examples. The use cases will be subject to a modified Delphi process in order to identify the critical path, and to assess the tools, initiatives and supports identified by Task 2.1, that are needed (WP3, Task 3.1).

In this report we describe the methods that have been used to select the use cases. We then provide an overall summary of the use cases, followed by descriptions presented in case vignettes of each selected use case.

2. Methodology

Medical devices represent a great diversity of technologies, with estimates suggesting that 500,000 different medical device products are available in the European Union (EU) (1), and that 2 million are available worldwide (2). We do not know the number of medical devices that are available for orphan or paediatric use (3). Given the large number and diversity of medical devices, ranging from wheelchairs to implantable heart valves, and the small number of use cases that can be prepared (5), it is not possible to use a quantitative sampling method to select medical device technologies. As a result, a qualitative approach is needed to identify the 5 use cases which can best represent the particularities of orphan and paediatric medical devices and their development pathways.

To achieve this, WP2 and WP3 developed criteria to delineate example technologies. These criteria were presented to the full DeCODe consortium, in order to take feedback and iteratively refine the criteria. The criteria applied, and a rationale for their selection is presented in Table 1.

Table 1 - Criteria and rationale for use case selection

Criteria	Rationale for selection
Is the medical device CE-marked or not?	Medical devices may be disseminated on the basis of CE-marking, either by affixing the CE-mark by the manufacturer (for low risk, Class I devices), or by undergoing a third party notified body assessment (necessary for Class IIa, IIb and III devices and for Class I devices that are sterile, reusable or have a measuring function). Some of the devices discussed might be preparing for medical device CE-marking, but might not have achieved this point yet. Alternative pathways to dissemination are possible utilising other regulatory pathways, such as manufacturing within a healthcare institution, including the preparation of custom-made devices within a healthcare institution (4). This has major implications for the development planning for the introduction of a medical device in a clinical setting.
Class I, II, III	Medical devices are subject to risk classification rules, described in Annex VIII of the MDR. These risk class rules are based upon criteria such

[1] Ref. https://decode-rd.com/index.php/about-decode/

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	as the anatomical invasiveness, the duration of exposure to the technology etc. An implantable heart-valve is a Class III device, whereas a wheelchair is a Class I device. Selecting a diversity of risk classes, is important to understand the similarities and differences in their critical path. A range of classes of cases shows an increasing difficulty.
Children and adults or children only	Medical devices require an 'intended purpose', which is the use intended by the manufacturer. This is important for a manufacturer, as all of their technical documentation must be based upon this intended purpose. The intended purpose may be restricted to specific diseases, or populations, or it may simply refer to the functionality of the medical device. Delineating the intended population from an intended purpose can allow us to understand if the device is intended for use in the treatment of a rare disease, is intended for use in paediatric populations, or both. Ensuring that technologies are selected that relate to rare disease, paediatric patients or both is important in order to delineate similarities or differences in the critical path.
Connected to registry	Patient registries can provide a real-world view of clinical practice, patient outcomes, safety, and comparative effectiveness (5). There have been a number of initiatives in Europe to prepare a European Directory of Registries (6); for rare disease specifically, there is a central database of registries (7), and infrastructure to support interoperability of rare disease registries (8). The International Medical Device Regulatory Forum (IMDRF) group describe a medical device registry as an 'organized system with a primary aim to increase the knowledge on medical devices contributing to improve the quality of patient care that continuously collects relevant data, evaluates meaningful outcomes and comprehensively covers the population defined by exposure to particular device(s) at a reasonably generalizable scale…' (9) . Different technologies, for example those used as part of treatment pathways for rare diseases, or within certain specialisms (for example cardiology or orthopaedics) may have different opportunities to utilise registry platforms to gather clinical evidence.
Clinical trial or not	Understanding whether a pre-market clinical investigation is necessary for a novel medical device is challenging, and there is currently no methodological framework which can help developers to make this determination with confidence (10). For orphan and paediatric indications, the conduction of a clinical investigation may be challenging for a variety of factors such as small patient populations (making recruitment challenging), the need for prolonged follow-up (for permanent implants placed in children for example), and challenges with study design (such as endpoint selection and use of patient reported outcome or experience measures). As such, it

	is important to include devices which are likely to require a pre-market clinical investigation(s) versus those which do not, to examine differences in their critical path.

These criteria were then applied in order to find the hypothetical cases, and to describe the rationale for their selection. 'Hypothetical' is defined as *involving or being based on a suggested idea or theory (11)*. Some of the use cases are based upon real companies and products, with available evidence, and in some cases project contributors (in the Workshop on 8-9 April 2025) who had experience of product development and reimbursement.

EU regulators have prepared a definition of an orphan device in regulatory guidance (12). This definition includes an epidemiological criterion, which requires that the disease or condition that presents in not more than 12,000 individuals in the European Union per year. This definition is different to the criteria for an orphan medicinal product (13), or the definition of rare disease published by the World Health Organisation (14). For the purpose of this report, we did not conduct an epidemiological analysis to make a formal determination as to whether a medical device qualifies as an 'orphan device', however we engaged with consortium members to ensure that the devices selected were related to a paediatric or rare disease.

Suggestions for hypothetical use cases were generated as a result of brainstorming and consultation amongst consortium members. We sought to include as great a variety as possible by ensuring to include both high risk, permanently implantable technologies, as well as low risk externally contacting technologies. Examples including both hardware and software, including digital health technologies were identified as priorities, as these products have significantly different development pathways. Inclusion of a pathway for medical devices which are disseminated via pathways other than CE-marking (for example by means of in-house manufacturing) was also prioritised. This resulted in the 5 hypothetical use cases presented below. One further example was identified – hemofiltration sets for use in renal replacement therapy for children. This case was not included in the hypothetical use cases. The challenges associated with dissemination of renal replacement therapy have been well characterised (10,15,16) .

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3. Summary of selected Use Cases

Table 2 - Summary of selected Use Cases

Technology	Short description	CE-marked?	Risk Class	Orphan / Paediatric / both	Registries available	Clinical investigation needed?
CFHealthHub	A digital self-care and behaviour change platform, for adults with cystic fibrosis (CF)	No	Class I in the UK Possibly a higher risk-class under Annex VII, Rule 11 of MDR	Orphan	Yes Disease registry – unknown if outcomes related to technology included	Unlikely
Yumen Bionics - EXone	A passive upper limb exoskeleton for use in patients with Duchenne muscular dystrophy	Yes	Class I	Both	Yes Disease registry – unknown if outcomes related to technology included	No Clinical trials will likely be needed to support reimbursement
Percutaneous Pulmonary Valve Replacement	A percutaneous heart valve used to treat right ventricular outflow tract obstruction	Yes	Class III	Paediatric (from 12 years) Possibly orphan device – depending on the intended purpose of the manufacturer	Yes	Yes Multiple pre-market clinical investigations needed
NeuroRehabilit y	A gamified tele-rehabilitation software with specific modules for stroke, MS, Parkinson's disease and spinal cord injuries	Yes	Class I	Paediatric Some modules are intended for adult populations (eg. the stroke app)	Unknown	No Clinical trials will likely be needed to support reimbursement

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Technology	Short description	CE-marked?	Risk Class	Orphan / Paediatric / both	Registries available	Clinical investigation needed?
Custom-made medical devices produced in a healthcare institution	There are a variety of medical devices that can be produced within a hospital, ranging from high-risk technologies such as 3-D printed external bioresorbable splints implanted for tracheomalacia to simple devices such as moulded cups to allow patients with neurodegenerative diseases to hold a cup	N/A – No CE-marking is needed	N/A – multiple technologies	Both	No	No Clinical trials are not required but are important to understand outcomes related to the use of the investigational-stage technology

4. Use Case 1: CFHealthHub

The first case was selected from the literature. CFHealthHub is a digital self-care and behaviour change platform, extensively codesignedwith patients and embedded in over 60% of adult cystic fibrosis (CF) units in the UK (17).

The technology comprises the following components (18):

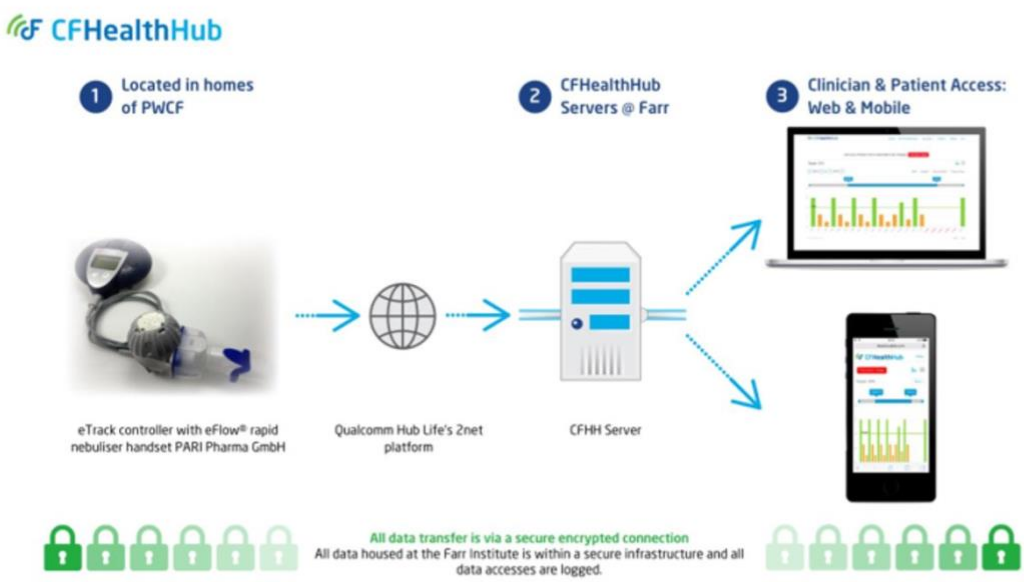
1. **eTrack rapid nebuliser** (manufactured by PARI Pharma GmBH). These are eFlow nebulisers that include a sensor that records the time, date and duration of each nebuliser use. These data are encrypted and sent by Bluetooth to the 2net Hub (Qualcomm Life). This transmits the data on to the CFHealthHub server using 2G (data transfer for mobile devices). Each CFHealthHub user has 1 eTrack nebuliser. This is used to give all of their nebulised CF treatments.

2. **The online CFHealthHub server**, a secure cloud-hosted server that is managed by Manchester University.

3. **CFHealthHub online portal and app**. This can be accessed by clinicians and patients using computers, tablets, or smartphones. It presents real-time data from the eTrack nebulisers. This allows daily and weekly adherence to nebulised CF medicine to be viewed by patients and their clinical team. Users can add their body weight and home-spirometry measurements to CFHealthHub, and these can also be viewed by their clinical teams. Spirometers with open application programming interfaces (APIs) are being added to the CFHealthHub system to allow remote lung function monitoring with automated data upload. The app also has educational content and evidence-based behaviour change tools to support people with CF to develop self-care habits.

A summary overview of the system is provided in Figure 1 (19) .

Figure 1 - Overview of the CFHealthHub platform



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The data generated by the CFHealthHub is reviewed at weekly meetings of clinical teams to improve the way that they deliver care. This enables a community of practices to support continual improvement of both care delivery and of the CFHealthHub platform itself.

As this is a system of different components working together, not all components are medical devices. The eTrack controller is a Class II medical device, which was granted in 2015. The server, online portal and app are not considered to be medical devices (18) .

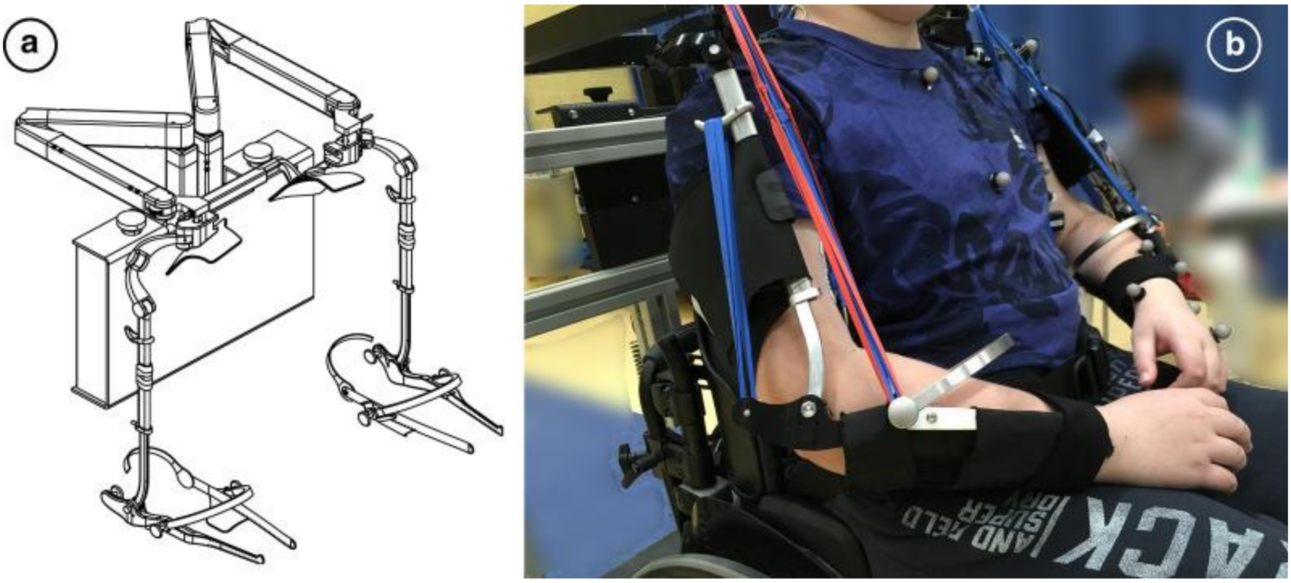
Currently, the CFHealthHub is utilised in the UK. As a result of Brexit, the UK (with the exception of Northern Ireland) is no longer part of the EU regulatory framework for Medical Devices, and the, somewhat confusingly titled Medical Devices Regulations 2002 in the UK apply. This law transposes the previous EU regulatory framework, the Medical Device Directives 93/42/EC into UK law. As a result of this, if the CFHealthHub were to be distributed outside of the UK as an overall system, each component in the system would have to be considered as to whether it would qualify as a medical device for the purpose of the EU Medical Device Regulation 745/2017.

As the CFHealthHub server is incorporated into clinical workflows in hospitals, it is likely that compliance with ISO/IEC 27001, which is the international standard for information security management will need to be complied with (20), in addition to considering cybersecurity requirements (21).

5. Use Case 2: Yumen Bionics

Yumen Bionics manufacture a passive upper limb exoskeleton, called the EXone Arm Support, for use in patients with Duchenne muscular dystrophy. Duchenne muscular dystrophy has a prevalence of about 6 per 100.000. It was developed based upon a question from the community, on the wish to continue moving their arms once the disease progresses. The system utilises mechanical energy provided by elastic bands to provide dynamic arm support. The system is designed to be adapted to the length of arm of the patient, and the degree of muscle weakness. The device can be used with a variety of wheelchairs.

Figure 2 - Yumen Bionics, EXone Arm Supporter. (a) Design sketch without elastic bands, (b) Prototype fitted on one of the participants (22)



The EXone Arm Supporter is a Class I medical device, and as such it is unlikely that a clinical investigation will be needed. The manufacturer has conducted clinical investigations to examine the feasibility and effectiveness of the device (22). This study enrolled 6 subjects, 3 boys with DMD and 3 persons with SMA (2 female, 1 male). This investigation examined the performance of the upper limb, in addition to activities of daily living.

Although this device achieved CE-marking, and is supported by clinical evidence, there may be different evidence requirements expected for local, regional or national reimbursement assessments, which may challenge further dissemination.

6. Use Case 3: Percutaneous Pulmonary Valve Replacement

Percutaneous valve replacement interventions allow an interventionist to gain access to the vascular system via a site distal to the heart (for example the femoral or subclavian artery) and to place a heart valve without the need for open-heart surgery. This type of intervention was first undertaken in 2002 for replacement of the aortic valve for patients with severe aortic stenosis and these technologies are known as transcutaneous heart valve implants (TAVI).

This case concerns the use of a similar technology to place a percutaneous valve in the pulmonary position. The case which we have selected is based upon a medical device which was subject to a clinical evaluation consultation procedure (CECP) opinion by the medical device expert panels. These CECP opinions do not identify the name of the medical device or the manufacturer. As a result of web-searching, we can identify that the technology subject to the CECP was the Venus P-Valve, manufactured by Venus MedTech.

The intended purpose of the device is to replace the pulmonary heart valve with an artificial valve using a minimally invasive percutaneous approach, to treat right ventricular outflow tract (RVOT) dysfunction and specifically for the dilated outflow tracts to restore pulmonary valve function. The device consists of a Percutaneous Pulmonary Valve (PPV) which is for the first time mounted on a self-expanding nitinol frame, a Delivery System (DS), including a Delivery Catheter System (DCS) and a Compression Loading System (CLS) (23).

Other PPV systems have been marketed, such as the Medtronic Melody valve, which was CE-marked in 2009. The Medtronic system is a balloon expandable valve, whereas the Venus P-Valve is a self-expanding valve with a different frame design. The device is manufactured from nitinol and porcine material.

These valves are typically used for patients with congenital heart disease, such as tetralogy of Fallot, which results in pulmonary atresia. For some of these patients, the stenotic right ventricular outflow tract may be widened by surgical interventions and the use of grafts to improve patency.

There are specific international standards for heart valves, for example ISO 5840-1 outlines an approach for verifying/validating the design and manufacture of a heart valve substitute through risk management. This allows developers to have a clear specification of pre-clinical testing that should be undertaken as part of early-stage development of the valve.

As this device has been subject to a CECP opinion, it opens the possibility of EU-level joint clinical assessments for health technology assessments, as only medical devices subject to a CECP are eligible (24), when the medical device assessments begin in 2026 (25).

7. Use Case 4: NeuroRehability

Rehability market a variety of videogames which are used for gamified tele-rehabilitation. There are a variety of versions which have been investigated in a variety of conditions such as stroke, MS, Parkinson's disease and spinal cord injuries. A version specifically intended for use with children 'Rehability Kids' is available.

Figure 3 - Rehability gamified tele-rehabilitation

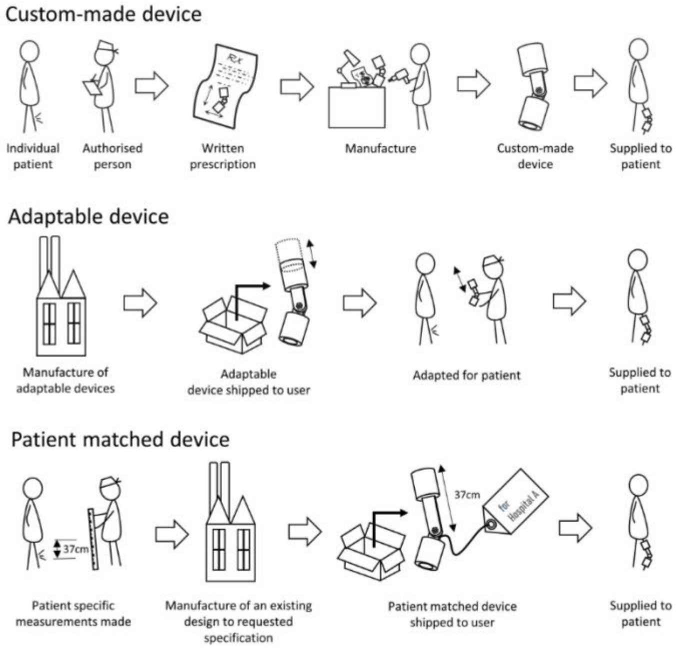
The software works by using a non-contacting sensor to monitor the movement of the patient. Different types of games are then used to prompt movement of the limbs or trunk. The parameters for duration and intensity of exercise can be set by the healthcare team. The system can also be linked with home monitoring and televisits (26). Home-based patients receive a hardware kit that connects their TV screen directly to the clinic for automatic data exchange. Once therapy is completed, the same kit can be used with other patients. Rehability Neuro is listed as a Class I medical device, however there is no CE-mark indicated for other versions of the software (26).

This range of software may present ambiguities concerning the qualification of the software as a medical device or not. This determination is made based upon whether the software meets the definition of a 'medical device' for the purpose of Article 2(1) of the MDR. A central aspect of this definition is determining whether the intended purpose of the software is a 'medical purpose'. For some of the versions of this app, it may not be considered to have a 'medical purpose', whereas for other versions it may. In any event, this is likely a very low risk software. Having clarity of understanding whether the software is a medical device or not is important as this will influence the regulatory strategy significantly. Similarly to Use Case 1, if the server used for patient data is incorporated into clinical workflows in hospitals, it is possible that compliance with ISO/IEC 27001, which is the international standard for information security management will need to be complied with, in addition to considering cybersecurity requirements. This is less clear in this case, as dissemination will be to different EU Member State hospitals, and there may be different rules applied locally for the integration of software in hospital systems.

8. Use Case 5: Custom-made medical devices produced at the point of care

Advances in science and engineering are supporting increased therapeutic options for personalized medicine. For some paediatric patients or patients with rare disease, it may be necessary to create a medical device which is unique to that patient, is matched to specific patient measurements, or is adapted prior to being given to the patient. These pathways are summarized in Figure 4.

Figure 4 - Devices intended to meet the needs of individual patients may be custom-made, patient matched or adaptable.



Medical devices which are custom-made may be produced by commercial manufacturers, or developed and used within a healthcare institution. For healthcare institutions who undertake 'in-house' manufacturing, there are a number of exemptions from regulatory requirements, or less onerous requirements are applied; for example, a quality management system should be 'appropriate' when compared to the activity (MDR, Article 5(5)).

The technology example selected is the use of 3D-printed bioresorbable splint. This technology was selected as one of the project contributors had knowledge of the application of this technology in their academic hospital (27).

This case may help to delineate specific challenges which may occur when technologies are developed and implemented in a hospital setting. The procurement of raw materials, preparation of specifications, sterilization processes etc. will need to be determined, and documented appropriately. Specific considerations for the informed consent with the patient and their families may be important, given the investigational nature of the technology.

9. Conclusion

This report has presented five hypothetical use cases that reflect the diversity and complexity of paediatric and orphan medical device development. The use cases were chosen based on collaboratively defined criteria to capture different regulatory pathways, device classifications, and clinical evidence needs. These use cases will inform further analysis within WP 3, supporting the identification of critical development paths and tool applicability. The findings will ultimately contribute to a clearer understanding of how best to support the development and dissemination of innovative devices for rare diseases and paediatric populations.

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