**Question-based development of high-risk medical devices: A proposal for a structured design and review process.**

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**Statement of significance**

**What is already known about this subject:**

* The recently introduced European Medical Device Regulation places stricter requirements regarding clinical evidence of high-risk medical devices before market approval.
* The requirements of clinical study design and developmental outcomes are only described in general terms, and little guidance and structure is provided.

**What this study adds:**

* A novel framework for clinical development of high-risk medical devices is proposed, translated from the field of medicinal drugs.
* This framework provides structure to medical device developers and facilitates communication with funding agencies, regulators and clinicians.

**Abstract**

The recent introduction of the European Medical Device Regulation poses stricter legislation for manufacturers developing medical devices in the EU. Many devices have been placed into a higher risk category, thus requiring more data before market approval, and a much larger focus has also been placed on safety. For implantable and Class III devices, the highest risk class, clinical evidence is a necessity. However, the requirements of clinical study design and developmental outcomes are only described in general terms due to the diversity of devices.

A structured approach to determining the requirements for the clinical development of high-risk medical devices is introduced, utilising the question-based development framework, which is already used for pharmaceutical drug development. An example of a novel implantable device for haemodialysis demonstrates how to set up a relevant target product profile defining the device requirements and criteria. This can then be used to define specific questions to be answered during clinical development, based upon 5 general questions as specified by the question-based framework. The result is a clear and evaluable overview of requirements and methodologies to verify and track these requirements in the clinical development phase. Development organisations will be guided to the optimal route, also to abandon projects destined for failure in an early stage to minimise development risks. Moreover, the framework facilitates communication with funding agencies, regulators and clinicians, while highlighting remaining “known unknowns” that are to be answered in the post-market phase after sufficient benefit has been established relative to the risks.

**Introduction**

Throughout history magical curative properties were advertised for some medicines that were found to be deleterious and this led to the first legislation that regulated the marketing of these products in 1938: the Federal Food Drug and Cosmetic act. This was followed by further US legislation in later years, specifically defining and regulating high risk medical devices. In the USA both medicines and devices have always been regulated by the FDA, that recognizes the strong overlap between medicinal products and devices (1). In Europe the development of these regulations went in separate directions and took place much later, with the EU Active Implantable Medical Device Directive (AIMDD) introduced in 1990 (2), and Medical Device Directive (MDD) in 1993 (3). The directives outline certain goals which the devices must meet and are subsequently selectively integrated in national laws. These goals are then controlled by national authorities and local notified bodies. This changed in 2017 with the adoption of the EU Regulation 2017/745 on medical devices, the Medical Device Regulation (MDR) (4) and the ending of the transition period in 2021, when all existing European directives on medical devices were replaced by this single binding law covering all medical devices in all member states. The conformity assessments in each EU country should now use similar standards as set out in the new legislation, which forces manufactures to change the development processes used in the past (5).

The development of new medical devices is in many aspects analogous to new medicines; the device has an assumed mechanism of action, and a designed profile with a potential positive value for health but may also generate risks. The MDR now requires that these properties are also formally determined for devices; a much larger focus has been placed on safety and mapping of side-effects, further increasing overlap and making the evaluation process more similar to drugs. The program of clinical investigations for new medicines has been well-established since 1998 (5) and is supported by an extensive set of guidelines issued by both the FDA and EMA. This is not the case for medical devices within the MDR. Here the requirements regarding clinical study design, necessary for devices considered high-risk, and outcomes during the development are described only in general terms in [Chapter VI of the EU MDR](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e5271-1-1) due to the enormous diversity of medical devices that fall under the under regulation (4).

A structured approach to the development of clinical trial programs would therefore be useful for industry, researchers and regulators. For pharmaceutical drugs, the ICH E8 guideline on clinical development (6) states succinctly *“The essence of clinical development is to ask important questions and answer them with appropriate studies. The primary objectives of any study should reflect the research questions and be clear and explicitly stated.”* The concept of Question-Based Drug Development originated from this statement (7–10) and utilises a set of 5 or 6 generic questions to be answered during the clinical development of drugs to properly design the clinical evaluation plan. In this paper we propose a structural approach to the development of high-risk medical devices based on the question-based development method for drugs as a means to dealing with the clinical MDR requirements. An example of a novel vascular access device will be utilised to demonstrate the application of this approach, but first more background information into the novel MDR will be provided. All references to specific sections of the MDR are shown as hyperlinks to get immediate access to the regulation.

**The Medical Device Regulation**

An overview of definitions of the terms in *italic* can be found in Supplemental File 1.

On the 26th of May 2021 the MDR has fully replaced MDD and AIMDD in the EU. An important change of the MDR is the stronger focus on clinical evidence required to the demonstrate the safety and performance of a medical device, which was a direct consequence of unsafe hip prostheses and breast implants that had been legally introduced on the European market (11,12). The safety of the device must be continuously monitored after market introduction, in the form of *post-market surveillance* and *periodic safety and update reports*.

The classification of the device (class I, IIa, IIb and III) is an indication of the risk of the device to patients (class III being the highest risk), but more importantly, determines the assessment route for market introduction and thus the level of technical and clinical evidence required(table 1). The classification is determined by a set of classification rules as part of the MDR ([Annex VIII, MDR](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e32-140-1)). When compared to earlier directives, the MDR also increased the classification level of specific medical devices to the highest device class such as devices that are in direct contact with the central nervous system and the central circulatory system. For most devices the conformity assessment is required through a notified body. These are bodies appointed by the relevant national governments of EU member states for the purpose of assessing conformity of certain products to applicable legislation prior to receiving CE marking and market approval.

***Table 1***: An overview of medical device classification of the Medical Device Regulation (MDR) and the conformity assessment route. \*Unless necessary for the general safety and performance requirements (to be determined by the manufacturer) PMCF = post marketing clinical follow up. PSUR = periodic safety update report. Further explanation of the terminology in *italic* can be found in supplemental file 1.

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| --- | --- | --- | --- | --- |
| **Classification and main characteristics** | **Examples of Medical Devices** | **Conformity Assessment Route**  **(see** [**art. 52**](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e4837-1-1)**)** | **Documentation Requirements** | **Clinical trials required** |
| Class I  e.g., non-invasive or short-term invasive under direct control of the operator | Surgical gloves  Bandages  Wheelchair  Scalpel blades  Examination lamps  Surgical instruments | Conformity Assessment by Manufacturer  (by notified body in specific cases, sterility etc.) | *Base technical documentation* (includes *PMCF*) | No\* |
| Class IIa  Active and non-invasive or non-active but in contact with bodily fluids | Needles  Syringes  ECG  MRI scanner  Hearing aid  Contact lenses | Chapters I and III of [Annex IX](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e32-146-1), assessment of technical documentation  **By notified body** | *Base technical*  *Documentatio*n+ *PSUR* every 2 years | No\* |
| Class IIb  Active and invasive devices or invasive devices that cause a direct hazard during malfunction ([Annex VIII](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e32-140-1), rule 12) | Devices involving ionizing radiation  Vascular closure devices  Dialysis system  Ventilator  Infusion pump  IC monitoring software  Vascular grafts and stents | Chapters I and III of [Annex IX](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e32-146-1), assessment of technical documentation (Chapter II, part (4), [Annex IX](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e32-146-1))  **By notified body** | *Base technical*  *Documentatio*n+ *PSUR* every 2 years, or every year for implantables | Yes for implants (see exceptions [art. 52](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e4993-1-1)(4)), otherwise no\*  Optional prior expert consultation for devices associated with medicinal products ([Annex VIII](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e32-140-1), rule 12) |
| Class III  Implants and invasive devices in contact with vital anatomies | Neuroendoscopes  Cardiovascular catheters  Prosthetic heart valves  Intra-aortic balloon pump  Breast implants  Joint replacements  Drug-eluting stents | [Annex IX](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e32-146-1) (alternatively, [annex X](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e32-155-1) coupled with [annex XI](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e32-157-1))  **By notified body** | *Base technical*  *Documentatio*n+ yearly *PSUR* | Yes with optional expert consultation prior through notified body.  (see exceptions [art. 61](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e5279-1-1)(4)) |

A *benefit-risk analysis* and clinical evaluation (MDR [Annex XIV](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e32-164-1), part A) are integral parts of the *base technical documentation* of any medical device. The clinical evaluation must include all the relevant clinical information needed to demonstrate conformity with the *general safety and performance requirements* of the device that are determined by the developer, which should ensure suitability for intended use while remaining safe. In certain cases, *clinical evidence* is necessary to demonstrate conformity to these requirements prior to market approval, and the manufacturer must provide an overview and rationale of suitability of clinical evidence. *Equivalence* with prior data can be used as a means of providing clinical evidence, and may mitigate the necessity of *clinical investigations*.

As for medicinal drugs (6), clinical evidence from clinical investigations is always required for implantable and class III, or high-riskdevices (MDR [art. 61(4)](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e5279-1-1)). The exception is when it can be demonstrated that the drug or device is equivalent to other existing safe drugs (6) or devices (MDR [art. 61(4)](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e5279-1-1)). Prior to clinical evaluation or investigation, developers may consult an expert panel to review their clinical development strategy. The developer must document the findings in a clinical evaluation report, included in the technical documentation. Suitability of this data is evaluated by the notified body and appointed experts, which in turn prepare a clinical evaluation assessment report. For class III implantable devices and class IIb devices intended to administer or remove medicinal products, the conclusion is transmitted to the European Commission for additional assessment of the document by an expert panel. When conformity to the MDR is adequately achieved and the notified body provides a positive response, a declaration of conformity and the CE-marking are granted, and the device may be marketed in member states.

The potential necessity of clinical investigations is apparent from the MDR. However, the structure and goals of the clinical trials and the amount of clinical evidence required to demonstrate conformity with the general safety and performance requirements is not clearly defined and left to the developer. As the function of clinical trials is to show conformity with the general performance and safety requirements, these requirements to some extent dictate what is to be investigated. However, the design of the clinical trials also plays a part in the definition of the requirements, as they must be able to provide certain data (e.g., from biomarkers) with which the requirements can be objectively verified, are subjected to ethical assessments, and patients must consent to participation. This interplay can be complex, but guidance to structure a program to demonstrate safety and efficacy, while minimising risks and costs, is currently still absent. To facilitate development, a framework for a structured approach could be beneficial for developers, regulators, and ultimately patients.

**Clinical development of devices-a proposal for structure**

A structured program for clinical development serves several functions. Most importantly the strategic aspects of the development are made explicit in clear terms that can be approached experimentally. In listing the “known unknowns” and how these can be dealt with, the risk of development becomes transparent. Such a structured program is also best suited for expert consultation.

The importance of defining proper questions and studies can, for example, be highlighted by the recent introduction of an aspiration-thrombectomy catheter in the US market (13). During the clinical study, the researchers primarily focused on the difference in ventricular diameters in a broad target population and found positive results. However, if they had focused more on clinical outcomes, such as risk of death or better functional status, while enrolling participants from more accurate target population, the results may have differed significantly and changed the course of development. Unfortunately, only after numerous patients had already been treated with this device it became apparent that this expensive treatment offered no clinical benefit to the patient. A more structured and properly defined clinical evaluation plan can lead manufacturers to abandonment of a project in a much earlier stage and save a lot on investments into a product destined for failure.

The system of question-based drug development is based upon the classification of questions to be answered about the product under certain headings (10). This system provides a clear and evaluable overview of the “known unknowns” of the product and the methodology to resolve these. Unresolved questions obviously determine the development risk of the product and the system can be used for modelling the financial value of a product using real options decision techniques (7). Due to the increased focus on the demonstration of safety through clinical evidence in the MDR, this framework can now also pose a solution for the development of high-risk medical devices. The question-based approach is preceded by an analysis of the target product profile.

**Methods**

**Determination of a target product profile (TPP)**

According to the World Health Organization (WHO), TTPs “*aim to inform product developers, regulatory agencies, procurement agencies and funders on R&D and public health priorities. They describe (1) the preferred and (2) the minimally acceptable profiles for vaccines, therapeutics, diagnostics or medical devices criteria. They also provide information for funders and developers on the performance and operational characteristics expected of products if they are to meet WHO’s needs.*” (14)

The purpose of a target product profile is to clearly define what the product should accomplish in a fixed document that clearly defines a desired state and the minimally accepted profile. Preferably, the document is supported by literature, research, properties of competing products and above all by the requirements of the patient. At the same time, it facilitates communication between developers and regulators (15). In general, a TPP includes a section on efficacy and safety and can be constructed analogous to the structure as suggested by Tansey (16) for medicines. The MDR states that a set of general performance and safety requirements must be set for a device to ensure the clinical condition or safety of patients is not compromised. When such a guarantee is not possible, these risks must be minimised. Thus, these are the minimum requirements a device must meet in order to be safe and of benefit, analogous to a minimally accepted profile in a drug TPP. By defining a desired “target” state with a number of criteria, design choices can be made to most closely approximate this state. Determining these elements in this fashion forces the manufacturer to consider scientific reasoning for these measures alongside measures that can be objectively evaluated. Thus, the elements of the TPP can already summarize what is necessary to achieve a marketable product that is of benefit to patients, while forming the basis of the technical documentation for the MDR in an early stage. As such, defining such a profile should also be of benefit in the development of medical devices. However, it must be noted that the TPP is a living document that is to be updated as more information becomes available throughout the development cycle, for example after conducting pre-clinical studies or other treatments or devices enter the market.

The content of the TPP is dependent on the type of product and its intended use, but a medical device in the EU should usually at least cover the points shown in table 2 ((16) and [MDR Annex I](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e32-94-1)). Certain targets may be studied and verified without clinical data, e.g., through in vitro studies or literature, but many can only be answered through clinical studies. However, due to the development risks and often high costs of clinical trials, properly designing these trials to optimally verify the targets is crucial.

***Table 2***: Suggested topics for a TPP of a medical device ((16) and [MDR Annex I](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e32-94-1)).

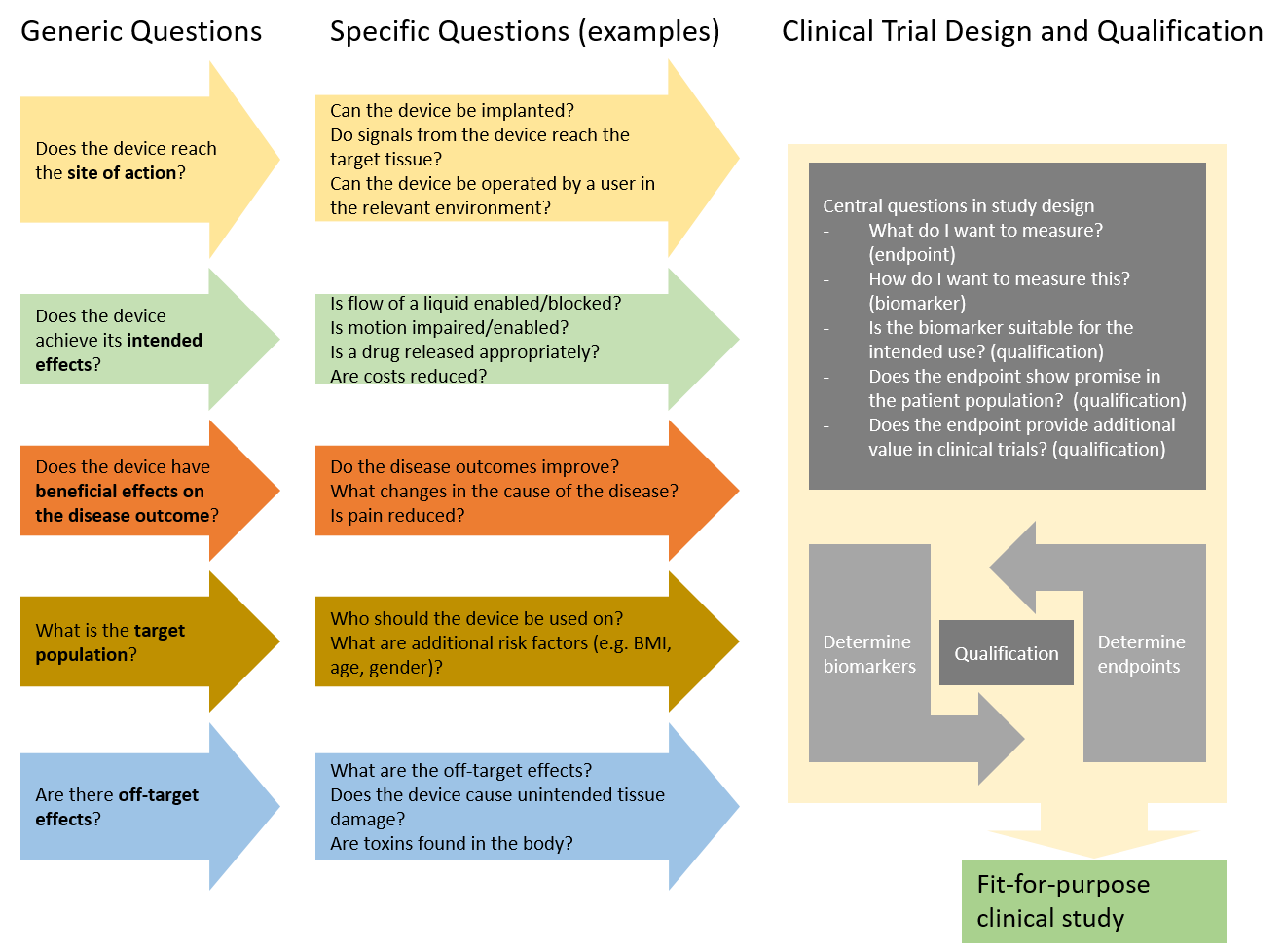
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| **Commercial** | * Intended markets * Target price * Development costs |
| **Technical/Engineering (**[[**MDR Annex I**](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e32-94-1)](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e32-94-1)**, Chapter 2)** | * Biological properties * Robustness * Technical Safety * Manufacturing * Contamination * If active: Supply and transmission of energy |
| **Medical (**[**MDR Annex I**](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e32-94-1)**, Chapter 2)** | * Patient indication * Target population: age, gender, etc. * Safety * Efficacy * Adverse events |
| **Intellectual Property** | * Patentability * Competitor interference |
| **Patient Perspective** | * Outcomes * Cost of treatment * Quality of Life |

**Design of a question-based clinical evaluation program**

Together with the TPP, a development plan must be set up for the design and evaluation of the device. In the case of high-risk devices, clinical investigations must form an integral part of this plan, and logically should provide objective data demonstrating safety and performance according to the MDR. For drugs, the question-based model of clinical development (7–10) has been developed in which important questions are asked and answered with appropriate studies to demonstrate performance and safety. Technical stability of the product is a prerequisite leading to a set of specific questions that is generated based on a predefined set of 5 or 6 generic questions, as shown in Cohen et al. (10). When combining this system with a TPP, answering the questions should also provide data on remaining, unanswered TPP targets that call for clinical data. Together with the TPP, the questions can be identified in an early stage to provide insight into the information that needs to be collected (17). When the appropriate questions have been defined, answering all of these should determine if benefits outweigh the risks. To enable objective assessment, effective and measurable clinical endpoints, and minimally accepted values must be determined prior to commencing the studies. The endpoints dictate which biomarkers need to be measured, while the availability and qualification of biomarkers guides endpoint selection (18). The endpoints translate to TPP targets, thus the TPP dictates the methodology and vice-versa.

Depending on the situation, one question may be answered with multiple studies, but one study can also answer multiple questions. In many cases it can be wise to maximize the amount of data generated to answer as many questions as possible, bearing in mind the possible biomarkers and potential interactions between them. The system of question-based development then assumes that estimates of costs and probability of success can be made from either expert opinions or historical data (9). These studies are implemented in a real options decision tree, and after each study a decision between abandonment and continuation is taken. When a study is successful, value will have been added to the project. When not successful, losses will have been minimised, which limits the risk of development (7).Developmental risks are made apparent and can be managed by determining the optimal sequence of studies that minimises losses when results are not favourable. This will vary for each device and is dependent on the risks and costs of the studies necessary. (7,9) The highest risk questions should receive focus in an early stage to abandon drugs that will not be successful as quickly as possible to minimise losses. This optimal sequence can guide the development strategy in which risks and associated costs are be minimised, while making the central issue in drug development explicit rather than implicit; whether all relevant questions have been asked and answered adequately to demonstrate safety and performance can then be objectively assessed (9).

With the introduction of the MDR, necessitating more clinical evidence, the need for a well-defined and structured clinical evaluation program has become more evident. Due to the increased parallels between devices and drugs mentioned, as well as the lack of guidance, the question-based approach can now also pose as a framework for the clinical evaluation plan for high-risk devices imposed by the MDR. Figure 1 shows a diagram of the question-based framework adapted for the field of high-risk medical devices.



***Figure 1:*** A diagram of the structure of a question-based development plan of a high-risk medical device. It shows how generic questions raise questions specific to a device in question. These specific questions are to be answered through clinical studies. The design of the clinical studies is determined based on the endpoints to be measured and the available biomarkers. The biomarkers need to be suitable and qualified for the intended purpose. All questions are answered in a certain population with regard to, for example, age, genetics, and genomics, and the methods to stratify the population (especially genomic or biochemical methods) also require validation and fit-to-purpose qualification. Adapted from References (10) and (18) with permission.

**Results**

**Case: A novel vascular access device**

Medical device manufacturers are developing a novel implantable device for haemodialysis patients. Haemodialysis performed by taking blood from the body, filtering it in an external dialysis machine, and then returning the clean blood to the body. For this, a vascular access site is necessary in which the circulation can easily be accessed, and a high flow of blood is present. These patients usually receive an arteriovenous fistula in the arm, in which a vein is ligated on one side and connected to an adjacent artery. The pressure drop between the vein and artery stimulates a large increase in flow through these vessels, enabling dialysis. This high flow is usually also very turbulent and is present all the time. Patients very frequently suffer from complications related to the fistula, most of which can be attributed to this constantly present high and turbulent flow. However, patients rarely require dialysis more than 12 hours a week. The manufactures aim to develop a device that can open and close this fistula to enable control of the high and turbulent flow between the artery and vein being connected. The researchers argue that by removing the high anastomotic flow outside of dialysis sessions, complications related to the presence of the fistula, such as stenosis and thrombosis, should decrease greatly, while dialysis remains possible when opening the fistula. However, as such an implant will likely have moving components that interact with their surroundings, complex energy transmissions can be expected between tissues and implant components.

**Target Product Profile**

The developers set up an initial TPP with elements that have been identified from the relevant parts of [Annex I of the MDR](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e32-94-1), cross-referenced with the TPP components as described by Tansey (16). A number of example targets are shown in Table 3. The developers consider these targets requirements for this device to be safe and of added value. The minimal viability requirements form the design requirements of the device, and the categories “technical”, “medical” and “patient perspective” translate to the general performance and safety requirements as specified by the MDR. The target measures translate to design criteria aimed at guiding the manufacturers in design choices. Moreover, these targets may also result in more design-specific requirements, for example relating to maximum dimensions and force transmissions, and often need to be verified prior to commencing clinical studies. These must also be included in the technical documentation in the application to the notified body.

However, the targets are not always easy to properly define in an early stage. A few examples of how the targets of the haemodialysis device can be updated throughout the development are:

* cadaver studies could provide new data on maximum dimensions of a device;
* a maximum vessel traction could be added after adverse events during animal studies;
* biological property targets could be modified as biological responses are better understood during animal survival studies; or
* the target efficacy values could be shifted up or down when pilot clinical data becomes available.

**The question-based development plan**

The remaining targets that could not yet be verified during pre-clinical studies require clinical evaluation. Table 4 shows an example of a question-based plan for the development of the vascular access device from Table 3. First, relevant specific questions are raised, based on the main category question-based development questions, for which a methodology is developed. The data collected by answering these questions should then further supplement the example TPP from Table 3 to the point of either (near) completion or abandonment. As demonstrated, a main category question is associated with one or a number of TPP targets described previously, and conducting these studies will thus amend the TPP further.

The targets that remain after completing the clinical development plan are the “known-unknowns”. Additionally, some questions and targets may not be fully answered and merely have an initial estimate. For example, if 90% of devices remain functional after 2 years it is probably likely that >50% will be functional after 3. However, the clinical data can already be adequate to show sufficient benefit over the risks to be considered a viable option to patients to allow market approval.

Upon completion of the clinical investigations, the TPP and question-based development process can form the basis of the technical documentation required by the MDR for application for approval at a notified body. The TPP clarifies the general performance and safety requirements set, and the values found, while the question-based plan clarifies the clinical development steps taken to facilitate objective assessment of the data and decisions made. It should finish with a benefit-risk analysis that shows the benefits of using the device outweigh the risks and the device is safe for use. This can be an integration of the TPP values found during development.

**Post-market surveillance to answer remaining known unknowns (as phase IV studies)**

At the end of the clinical investigations for MDR conformity, a number of unknowns, or risks that have not yet been fully quantified, will be apparent to the manufacturer. These will most likely remain a “known unknown”. When sufficient clinical data has been collected to clearly demonstrate the potential benefit of the use of the device outweighing the risks, these risks may be considered acceptable. However, the MDR requires manufactures to conduct *post-market clinical follow-up* and provide a plan to proactively monitor safety and efficacy prior to market approval from the notified body. For Class IIa, IIb and III devices *periodic safety and update reports* must be shared in order to continuously monitor these known-unknowns and update the risk-benefit analysis accordingly.

**Table 3:** Some examples of Target Product Profile targets for a novel implantable vascular access device.

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| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Target profile** | **Motivation** | **Measure** | **Target value** | **Minimal viability requirement** | **Comparative data** | **Differentiation** |
| Commercial | Market share | To be commercially viable, a sufficient market share is necessary | Number of implantations | 5% of market share 5 years after introduction | 2% of vascular access market years 5 years post-introduction | Haemodialysis patients | If worse abandon |
| Commercial | Development cost | To be able to receive sufficient funding and develop a marketable product, the costs for development cannot be excessive | Developmental costs | Development costs 7 mln euros to reach EU market approval | Development costs 14 mln euros to reach EU market approval | Similar vascular access devices | Reassess development program |
| Technical | Operation | The device can be operated non-invasively with a correct user input to prevent excessive discomfort to the patient. | Pain scale | 0 on the Numeric Pain Rating Scale | 3 on the Numeric Pain Rating Scale | n/a | Redesign if not compliant |
| Technical | Fully close anastomosis | The core of the issues with fistulae lies in the elevated and turbulent flow. The aim of the device is to improve outcomes by removing this flow outside of dialysis sessions and returning circulation to normal. | Shunt flow, measured by duplex | Shunt flow in closed position is 0 mL/min | Shunt flow in closed position is 0 mL/min | n/a | Redesign if not compliant |
| Technical | Open anastomosis | To enable dialysis a shunt flow of at least 600mL/min is necessary, with higher flows being linked to complications. Ideally, the shunt flow can approximate this value as closely as possible | Shunt flow, measured by duplex | Shunt flow in open position is 600 mL/min | Shunt flow in open position is greater than 600 mL/min | AVF data | Redesign if not compliant |
| Technical | Robustness - remains functional | To prevent the necessity of frequent intervention, the device must remain functional for a suitable time. | Percentage of patients with functional device | Device outlives 90% of HD patients, functional after 11 years | Device outlives 50% of HD patients, functional after 3 years | Traditional AVF/AVG patients | Redesign if not compliant |
| Technical | Contamination | Introducing foreign materials into the body poses a risk of, e.g., infection. It is thus necessary to sterilize implantable medical devices. | Surface micro-organisms after sterilisation | Theoretical probability of micro-organisms on surface <10e-6 | Theoretical probability of micro-organisms on surface <10e-6 | Conform to ISO standard 10993 | Redesign device or alternative sterilization method if not compliant |
| Medical | Target population | To be of added value to dialysis patients and to justify the integration into health systems, a significant percentage of patients must be eligible to receive the device. | Percentage of eligible dialysis patients | 80% of haemodialysis patients eligible | 50% of haemodialysis patients eligible | Dialysis patient indications etc. | If worse negative for continuation |
| Medical | Adverse events | Adverse events occur very frequently in VA patients. This device aims to target the main cause of these adverse events, thus decreasing them is a major criterion. | Rehospitalisation rate | Rehospitalisation decreased by 50% | Rehospitalisation decreased by 20% | Traditional AVF/AVG patients | If worse negative for continuation |
| Medical | Clinical outcomes | Patency rate of vascular access is generally too low and results in the necessity of surgical intervention. The device should improve this significantly to be a viable solution | Shunt patency rates | 1 year patency rate increases by 10% | 1 year patency rate remains the same | Traditional AVF/AVG patients | If similar or worse negative for continuation |
| Patient perspective | Quality of Life | As end-users of the device, the quality of life of the patients should improve in order to be desirable and adopted by patients | Relevant quality of life index | Quality of life improved by 5% | Quality of life remains the same | Traditional AVF/AVG patients | If worse negative for continuation |

***Table 4:*** Question-based framework for a novel implantable vascular access device.

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| **Questions main category** | **Specific Questions** | **TPP Targets** | **Methodology** |
| Does the device reach the site of action? | Can the device be implanted as a fistula in the arm as intended?  Does the device stay in the correct location?  Can the vascular access be adequately controlled non-invasively the operator? | * Pain score does not exceed 3 on the Numeric Pain Rating Score | Clinical pilot in which the device is implanted into a small number of patients requiring haemodialysis. Follow-up of several months to verify the device remains operable with the correct user input during this period and pain is acceptable. |
| Does the device achieve its intended effects? | Can the device control the flow of blood to 0 mL/min and at least 600 mL/min with the correct user input? | * Anastomotic flow >600 mL/min when open * Anastomotic flow 0 mL/min when closed | Single-centre study in which the device is implanted into a larger number of patients. On a regular interval, these patients will receive echography with duplex measurement to determine the anastomotic flow in different positions. |
| Does the device have beneficial effects on the disease outcome? | Does the device improve vascular access outcomes in haemodialysis patients? | * 1-year vascular access patency rate remains at least the same * Quality of life of haemodialysis patients remains at least the same | A large cohort multi-centre study in which the device is implanted into various patients with different indications. Follow-up of 12 months in which Quality of life and vascular access patency is recorded and compared to traditional fistula patients. |
| What is the target population? | Age, gender, BMI, indications and contra-indications?  How to determine for which patients this is acceptable?  For which patients are the on-target effects (not) likely? | * At least 50% of dialysis patients eligible | A multi-centre study in which is recorded whether clinicians consider haemodialysis patients eligible to receive the device. When patients agree and have the device implanted, patient characteristics are recorded together with patency, rehospitalisation, quality of life etc. Correlations between characteristics and outcomes are analysed. |
| Are there off-target effects? | What are the off-target effects?  How are moving components in the device influenced by fibrosis formation? | * Device outlives at least 50% of HD patients, functional after 3 years * Rehospitalisation rate decreased by at least 20% | A large cohort multi-centre study in which the device is implanted into various patients. Follow-up of several years in which device functionality, adverse events and rehospitalisation are recorded and compared to traditional fistula patients. |

**Discussion**

In this paper we have presented a structured generic approach for the design and subsequent performance of a clinical development program for medical devices. The vascular access device validation case was used to gain practical insights into the relation between the question-based framework and the TPP. The definition of questions in an early stage showed that many unknowns were present, and a proper TPP could not be created without in vivo data. This data was consequently collected in an earlier stage than initially planned with a prototype which was not intended to function perfectly. Not only did it show that the concept was feasible, much more insight into the biological responses and interaction between moving components and tissue was gained which helped guide further development. This question-based approach is analogous to the development of medicinal substances. Both medicines and devices are heterogeneous, cover a wide range of indications and have varied concerns regarding efficacy and safety. This would suggest that a generic approach is impossible, and all plans will be on a case-by-case basis. Although the clinical development will have widely varying aims and methodology, our case study showed that it can still be represented in a structured manner that transparently displays the considerations that form the basis of a clinical research program. Such programs must be assessed by companies, researchers, ethics committee’s regulators and even investors and all would benefit from a generally accepted structure to facilitate communication and quantification. When the clinical program is completed, the results can also be evaluated against this program, improving the review process by standardising it. Additionally, the structured approach highlights validation deficits in measures used to answer the questions. Finally unanswered questions define the development and commercial risks of a device.

Although the analogies have been made clear, some differences between devices and drugs remain present, the biggest of which being the ability to modify a device more easily than a molecule. Therefore, the possibility of redesign as a method to circumvent problems that occur in the course of the development has to be a more prominent part of the planning and the evaluation. The question-based framework is aimed at optimising the clinical development path, of which a result is early abandonment of unsuccessful drugs. However, this can more easily be avoided in devices; devices are often more easily redesigned than drugs because of their modularity, and “modification”, of one of its components may be an option. In drugs, often a project may need to be abandoned because a small failure requires modification of the complete molecule which can be a very costly process. When significant changes to the device are necessary, it may be required to change the TPP and/or redo the studies previously conducted, but when these are minor the failed study can be repeated while preserving the validity of results previously obtained through equivalency. Not only does this diminish some of the associated development risk, it also reduces the need for abandonment and the time-to-market of the device. In the case of modification at a decision point, an estimate of redesign costs should be made, along with re-evaluation of risks and costs in the following studies to verify the development plan is still optimal.

Development of all medical interventions is usually iterative, highly complex and dynamic. (7) A structured question-based program has been used in drug development in many forms and shown to be useful although no consensus has been reached on how this should be applied in a harmonised manner. Similarly to in the MDR, this is left up to the manufacturer. Moreover, as the MDR has only recently come into effect, experience with the clinical evaluation with respect to the new regulations is limited. The framework proposed here aims to guide developers in this process and has been tested extensively in the field of drug development, but it has not yet been verified sufficiently for devices so it awaits application in a wider practice. The developmental results obtained depend largely on assumptions made (7), which will be less accurate for devices than drugs because of this lack of experience. Thus, even more caution is required when interpreting and defining the optimal development path. The field of devices is ever diversifying without centralised (1) controlling agencies, so we believe that this calls even more for a structured approach.

Finally, the general performance and safety requirements from [Annex I of the MDR](https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN#d1e32-94-1) primarily focus on the demonstration that the device functions as expected and is safe. The benefit-risk analysis must show that the risks have been minimised and are acceptable with regard to the intended use, taking into account the relevant state of the art. However, the MDR has no hard requirements relating to beneficial clinical outcomes – as long as the risks are low – while the adaptation of novel medical devices in the clinic does for a large part depend on efficacy relative to the current standard of care; clinicians and healthcare payers will be reluctant to adapt novel devices without proven benefit to patients. The framework proposed here forces the developer to place a greater focus on the patient and clinical outcomes in the development plan. As a result, more appropriate care should reach patients, and adapting this approach should then logically also be of greater value to the manufacturer.

**Conclusion**

The question-based framework for medical device development proposed in this article can support developers in overcoming the obstacles and ambiguity of clinical development presented by the newly introduced MDR. Not only does it guide manufacturers in setting up the clinical development plan, it has the added benefits of showing clear relations between design and validation steps that helps to responsibly dismiss risk full technology in an early stage and introducing effective innovations more quickly with lower costs.

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**Competing interest**

All authors declare no conflict of interest.

**References**

1. Jonathan J. Darrow, SJD, LLM, JD, MBA; Jerry Avorn, MD; Aaron S. Kesselheim, MD, JD M. FDA Regulation and Approval of Medical Devices: 1976-2020. JAMA - J Am Med Assoc. 2021;326(5):420–32.

2. The European Comission. Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices. 1990.

3. The European Comission. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices. The European Comission; 1993.

4. The European Comission. Regulation (EU) 2017/745 of The European Parliament and of the Council on medical devices. The European Comission; 2017.

5. Pietzsch JB, Shluzas LA, Paté-Cornell ME, Yock PG, Linehan JH. Stage-gate process for the development of medical devices. J Med Devices, Trans ASME. 2009;3(2).

6. European Medicines Agency & Committee for Human Medicinal Products. ICH guideline E8 (R1) on general considerations for clinical studies. 2019.

7. de Visser SJ, Cohen AF, Kenter MJH. Integrating scientific considerations into R&D project valuation. Nat Biotechnol. 2020;38(1):14–8.

8. Kruizinga MD, Stuurman FE, Groeneveld GJ, Cohen AF. The future of clinical trial design: The transition from hard endpoints to value-based endpoints. Handb Exp Pharmacol. 2019;260:371–97.

9. de Visser SJ. a question based approach to drug development. PhD Thesis. Leiden University; 2003.

10. Cohen AF, Burggraaf J, Gerven JMA van, Moerland M, Groeneveld GJ. The Use of Biomarkers in Human Pharmacology (Phase I) Studies. http://dx.doi.org/101146/annurev-pharmtox-011613-135918. 2015 Jan 6;55:55–74.

11. Cohen D. Faulty hip implant shows up failings of EU regulation. BMJ. 2012 Oct 23;345.

12. Maijers MC, Niessen FB. Prevalence of rupture in poly implant prothèse silicone breast implants, recalled from the European market in 2010. Plast Reconstr Surg. 2012 Jun;129(6):1372–8.

13. Sanket S. Dhruva, Redberg RF. Coverage of Transvenous Pulmonary Embolectomy — Medicare’s Missed Opportunity for Evidence Generation. N Engl J Med. 2022;386(10):901–4.

14. World Health Organization. Target Product profiles [Internet]. [cited 2022 Jul 25]. Available from: https://www.who.int/observatories/global-observatory-on-health-research-and-development/analyses-and-syntheses/target-product-profile/who-target-product-profiles

15. Tyndall A, Du W, Breder CD. Regulatory watch: The target product profile as a tool for regulatory communication: Advantageous but underused. Nat Rev Drug Discov. 2017;16(3):156.

16. Tansey M. The Target Product Profile and Its Uses. Intell Drug Dev. 2014;

17. Cohen AF. Developing drug prototypes: Pharmacology replaces safety and tolerability? Nat Rev Drug Discov. 2010;9(11):856–65.

18. Kruizinga MD, Stuurman FE, Exadaktylos V, Doll RJ, Stephenson DT, Groeneveld GJ, et al. Development of Novel , Value-Based , Digital Endpoints for Clinical Trials : A Structured Approach Toward Fit-for-Purpose Validation. 2020;(October):899–909.