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ORIGINAL ARTICLE

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

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[Correction added on 15 March 2023, after first online publication: The third affiliation has been corrected in this version.]

Introduction: 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 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.

Methods: A structured approach to determining the requirements for the clinical development of high-risk medical devices is introduced, utilizing 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. The framework can be used in the medical device design phase to define specific questions to be answered during the ensuing clinical development, based upon five general questions, specified by the question-based framework.

Results: The result is a clear and evaluable overview of requirements and methodologies to verify and track these requirements in the clinical development phase. Development organizations will be guided to the optimal route, also to abandon projects destined for failure early on to minimize development risks.

Conclusion: The framework could facilitate communication with funding agencies, regulators and clinicians, while highlighting remaining 'known unknowns' that require answering in the post-market phase after sufficient benefit is established relative to the risks.

KEYWORDS
clinical trials, framework, Medical Device Regulation, medical devices, question-based development

Joris I. Rotmans and Tim Horeman are both senior authors on this work.

1 | INTRODUCTION

Throughout history, magical curative properties of some medicines have been advertised that were later found deleterious. This led to the first legislation that regulated the marketing of these products in 1938: the Federal Food Drug and Cosmetic Act. In later years, this was followed by further US legislation, specifically defining and regulating high-risk medical devices. In the USA, both medicines and devices have always been regulated by the Food and Drug Administration (FDA), recognizing the strong overlap between medicinal products and devices.[1] However, it is suggested that 80 000 deaths and 1.7 million injuries were attributed to medical devices in the past decade, potentially linked to inadequate regulation of those products and their manufacturers.[2] 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,[3] and Medical Device Directive (MDD) in 1993.[4] The directives outline certain goals, which the devices must meet, and are subsequently selectively integrated into 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)[5] 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 manufacturers to change the development processes that had been used in the past.[6] 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 due to the enormous diversity of medical devices that fall under the regulation.[5] This regulation does place an increased focus on safety and performance, which should benefit patients.[7] Unfortunately, this often conflicts with the interests of manufacturers as it imposes substantial hurdles and financial burdens[8] and ultimately increases costs of devices, which hinders penetration of certain markets.[7] However, these interests should be synergistic as safe and well-performing devices should also encourage adaptation, thus creating more revenue, while recalls of poorly functioning devices have bankrupted companies.[9] Efforts exist to bridge this gap, although consistent structured approaches for such development programmes are scarce.[8]

The development of new medical devices is in many respects 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 that used for drugs. The programme 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 the European Medicines Agency (EMA). This is not the case for medical devices within the MDR.

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 are 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 can provide structure to medical device developers and facilitates communication with funding agencies, regulators and clinicians, although further validation in an actual development cycle is required to fully understand this potential.

A structured approach to the development of clinical trial programmes would therefore be useful for industry, researchers and regulators. Now more than ever, the knowledge and expertise from the field of clinical pharmacology could be valuable in the development of medical devices due to the aforementioned similarities in challenges. Conversely, clinical pharmacologists will be increasingly involved in the development of, for example, products that are combinations of medicinal molecules and devices. For pharmaceutical drugs, the ICH E8 guideline on clinical development[10] 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[11–14] and utilizes a set of five or six 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 of dealing with the clinical MDR requirements. An example of a novel vascular access device will be utilized to demonstrate the application of this approach. To support the development of this method for use in the MDR, a more in-depth section is provided to understand the background and implications of the new regulation. An overview of definitions of the terms in *italics* can be found in the supporting information.

1.1 | The Medical Device Regulation

Of patients receiving a specific breast implant in the early 2000s, over a third showed rupture of at least one of the silicone implants in a 10-year follow-up—far higher than most other breast implants.[15] In retrospect, the material used did not pass biocompatibility tests, posing significant risks to patients. In 2010, this resulted in a recall of this medical device legally marketed in the EU.[16] Additionally, in 2011, a faulty hip prosthetic was recalled from the European market after it became apparent metal particles resulting from wear of the device made their way into surrounding tissue. The revision rate for this implant was 49% at 6 years, where others were at 12%–15% after 5 years. In some patients, the implant caused permanent disability. Investigation revealed that clinical evidence that should have shown this before market approval was largely absent.[17]

Both these examples of unnecessary suffering demonstrated shortcomings of the European legislation on medical devices at the time and contributed to the introduction of a new EU-wide regulation: On 26 May 2021, the MDR fully replaced MDD and AIMDD in the EU. An important change introduced by the MDR is the stronger focus on clinical evidence required to demonstrate the safety and performance of a medical device. 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 (Classes 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). When compared with 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. As a result, an important change is that the amount and quality of clinical evidence necessary for market approval have increased. 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.

A *benefit–risk analysis* and clinical evaluation (MDR Annex XIV, 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,[10] clinical evidence from clinical investigations is always required for implantable and Class III, or high-risk devices (MDR, art. 61(4)). The exception is when it can be demonstrated that the drug or device is equivalent to other existing safe drugs[10] or devices (MDR, art. 61(4)). 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 are 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, for devices as with medicines, 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 programme to demonstrate safety and efficacy, while minimizing risks and costs, is currently still absent for devices, contrary to medicines. To facilitate development, a framework for a structured approach could be beneficial for developers, regulators and ultimately patients.

1.2 | Clinical development of devices—a proposal for structure

A structured programme 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 programme is also best suited for expert consultation. The MDR appears to give only general indications that a device should have proven efficacy and safety as could be determined in a confirmatory Phase III trial for a medicine. The reality is more complex in practice, because neither for a medicine nor for a device can such a trial be performed without preliminary studies that should logically lead to this confirmation in Phase III. The MDR provides little guidance about what to

TABLE 1 Overview of medical device classification of the Medical Device Regulation (MDR) and the conformity assessment route.

Classification and main characteristics	Examples of medical devices	Conformity assessment route (see art. 52)	Documentation requirements	Clinical trials required
Class I For example, 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[a]
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, assessment of technical documentation **By notified body**	*Base technical documentation* + *PSUR* every 2 years	No[a]
Class IIb Active and invasive devices or invasive devices that cause a direct hazard during malfunction (Annex VIII, 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, assessment of technical documentation (Chapter II, part (4), Annex IX) (alternatively, annex X coupled with annex XI for implantables) **By notified body**	*Base technical documentation* + *PSUR* every 2 years, or every year for implantables	Yes for implants (see exceptions art. 52(4)), otherwise no[a] Optional expert consultation prior for devices associated with medicinal products (Annex VIII, 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, assessment of technical documentation (alternatively, annex X coupled with Annex XI) **By notified body**	*Base technical documentation* + yearly *PSUR*	Yes with optional expert consultation prior through notified body (see exceptions art. 61(4))

Note: Further explanation of the terminology in *italics* can be found in the supporting information S1.
Abbreviations: PMCF, post-marketing clinical follow-up; PSUR, periodic safety update report.
[a]Unless necessary for the general safety and performance requirements (to be determined by the manufacturer).

do. In this section, we attempt to provide further structure to this programme of studies.

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.[18] During the clinical study, the researchers focused primarily 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 a 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, did it became apparent that this expensive treatment offered no clinical benefit. A more structured and properly defined clinical evaluation plan can lead manufacturers to abandonment of a project at a much earlier stage and save a lot on investments into a product destined for failure.

The system of question-based drug development proposed for drugs is based upon the classification of questions to be answered about the product under certain headings.[14] 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.[11] 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, similarly to how it is used in the development of medicines. The question-based approach is preceded by an analysis of the target product profile (TPP).

2 | METHODS

2.1 | Determination of a 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.'[19]

When used in drug development, the purpose of a TPP 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; it provides structure and clarifies the goals and expectations in the drug development process, as well as the type of clinical studies and endpoints necessary.[20] In general, a TPP specifies the medical need by including the current state of the art, includes a section on efficacy and safety and can be constructed analogous to the structure for medicines as suggested by Tansey.[21] 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 minimized. 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. It should be set up prior to the design stage as it defines how the device is to perform, while forming the basis of the technical documentation for the MDR at 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 to be considered safe and of clinical benefit (see Tansey[21] and MDR Annex I). The TPP can highlight not only which targets will require clinical data to be verified, but also those which can be verified non-clinically or pre-clinically. For example, certain targets may be studied and verified through in vitro studies, animal studies, in silico modelling and simulation or meta-analytical approaches (e.g. literature review), which could help avoid costly and slow clinical studies. At the start of clinical development of a high-risk device, the TTP should be updated with all non- and pre-clinical data, and only targets requiring clinical data should remain. The clinical programme has to be supported by, for example, adequate studies of mechanical properties of the device, toxicology or model studies in phantoms or animals. Clinical trial simulations should also be considered as a tool for the optimization of clinical trial design and evaluation of the potential effect of interindividual variability. In this paper, we concentrate on structuring the clinical development programme in terms of the development risks, and often, high costs of clinical trials make properly designing these trials to optimally verify the targets crucial.

TABLE 2 Suggested topics for a target product profile of a medical device (Tansey[21] and MDR Annex I).

Commercial	Intended markets Target price Development costs
Technical/engineering (MDR Annex I, Chapter 2)	Biological properties Robustness Technical safety Manufacturing Contamination If active: supply and transmission of energy
Medical (MDR Annex I, 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

2.2 | Design of a question-based clinical evaluation programme

The TPP includes verification methods of the targets. Thus, prior to the design stage, a development plan must also be determined for the 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[11–14] has been developed in which important questions

are asked and answered with appropriate studies to demonstrate safety and clinical benefit. Technical stability of the product is a prerequisite leading to a set of specific questions that is generated based on a predefined set of five or six generic questions, as shown in Cohen et al.[14] 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 at an early stage to provide insight into the information that needs to be collected.[22] When the appropriate questions have been defined, answering all of these should determine if the 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 guide endpoint selection.[23] 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.[13] 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 minimized, which limits the risk of development.[11] Developmental risks are made apparent and can be managed by determining the optimal sequence of studies that minimizes losses when results are not favourable. This will vary for each device and is dependent on the risks and costs of the studies necessary.[11,13] The highest risk questions should receive focus at an early stage to abandon drugs that will not be successful as quickly as possible to minimize losses. This optimal sequence can guide the development strategy in which risks and associated costs are minimized, 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.[13]

With the introduction of the MDR, necessitating more clinical evidence, the need for a well-defined and structured clinical evaluation programme has become more evident. Due to the increased parallels between devices and drugs, 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. Implementing this framework prior to the design stage and throughout development should maintain a focus on devices being safe and of clinical benefit in the relevant context. In the case of Class III and Class IIb devices intended to administer or remove medicinal products, this clinical development plan may be shared with an expert panel through the notified body for evaluation, prior to commencing the clinical development (art. 61(2)). In other cases, the notified body is not legally obliged to provide such feedback. Thus, success is dependent on the knowledge and expertise of the developers in which a structured approach is thought to be beneficial. Figure 1 shows a diagram of the question-based framework adapted for high-risk medical devices.

2.3 | Post-market surveillance to answer remaining 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 such as unexpected complications, will be apparent to the manufacturer. These will most likely remain a 'known unknown'. More challenges arise when very small patient populations or rare diseases are involved, which pose similar challenges for devices as seen in the development of drugs: low statistical power, difficulty in patient recruitment and lack of randomized control trials. As such, it would make sense to utilize the same approaches as recommended in the EMA guidelines for such cases.[24] There has to be a transparent plan for monitoring any long-term complications, and the situation is analogous to the risk management plans as outlined in the EMA pharmacovigilance guidance.[25] However, this is outside the scope of this paper.

When sufficient clinical data have been collected to clearly demonstrate the potential benefit of the use of the device outweighing the risks, these risks may be considered acceptable. There is a likelihood that new and unexpected long-term complications occur, and these will generate an unknown risk that can only be monitored. The MDR requires manufacturers 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 unknown risks and update the risk–benefit analysis accordingly. For devices, such long-term effects may be more important than for medicines and require long-term monitoring through registries.[26,27]

Clearly, spontaneous reporting of adverse events that coincide with the use of a device requires evaluation of causality to interpret them as side effects. The associated problems are evident but not different for devices, medicines or food, and this discussion is beyond the scope of this paper.

3 | RESULTS

Figure 2 shows a generalized flowchart of the process from detection of a clinical need to application to a notified body and market approval as described in the previous sections.

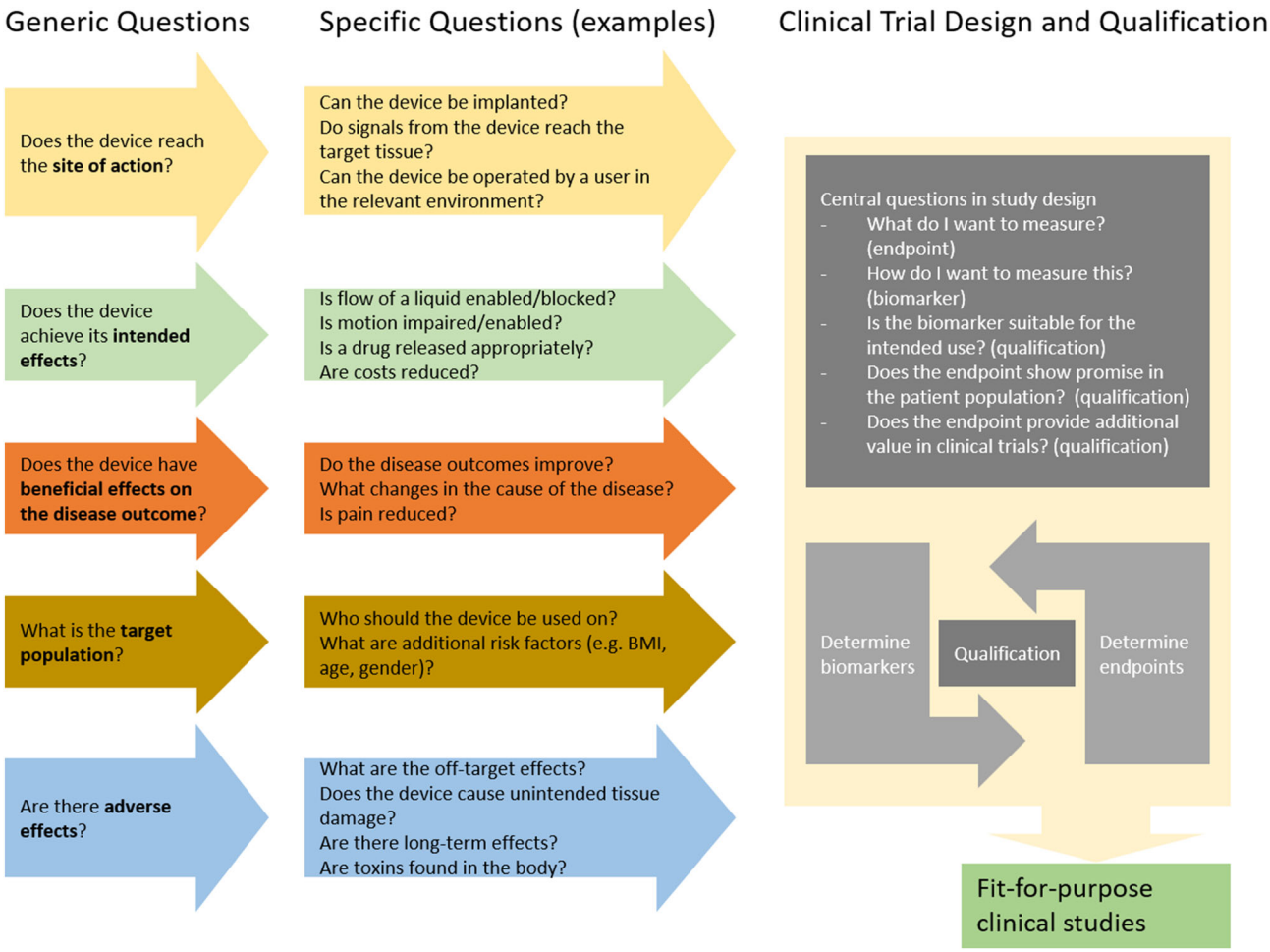

FIGURE 1 Structure of a question-based development plan of a high-risk medical device, showing how generic questions give rise to specific questions for a device in question. These specific questions are to be answered through clinical studies. The design of the clinical studies is determined based on 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 Cohen et al.[14] and Kruizinga et al.[23] with permission.

3.1 | Practical example: a Class III novel vascular access device

Medical device manufacturers are developing a novel implantable device for haemodialysis patients that can open and close a tubular anastomosis between a vein and artery, shown in Figure 3, and consider this as Class III. This example does not cover Class IIb devices, but the regulations and requirements are similar, that is, technical documentation including the same elements and clinical evidence demonstrating performance and safety, as well as a post-market clinical follow-up plan. The practical execution of clinical evidence generation therefore follows the same general approach from definition of targets and questions, to the evaluation thereof. A major difference is that not all clinical development plans of Class IIb devices may receive an expert consultation through the notified body. This absence emphasizes even more the need for a well-structured approach. The case presented is based upon ongoing development work by our departments and serves for illustration only. Supporting information S2 includes more explanatory images showing part of the development process.

Haemodialysis is 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 h a week. The manufacturers aim to develop a device that can open and close this fistula to enable control of the high and

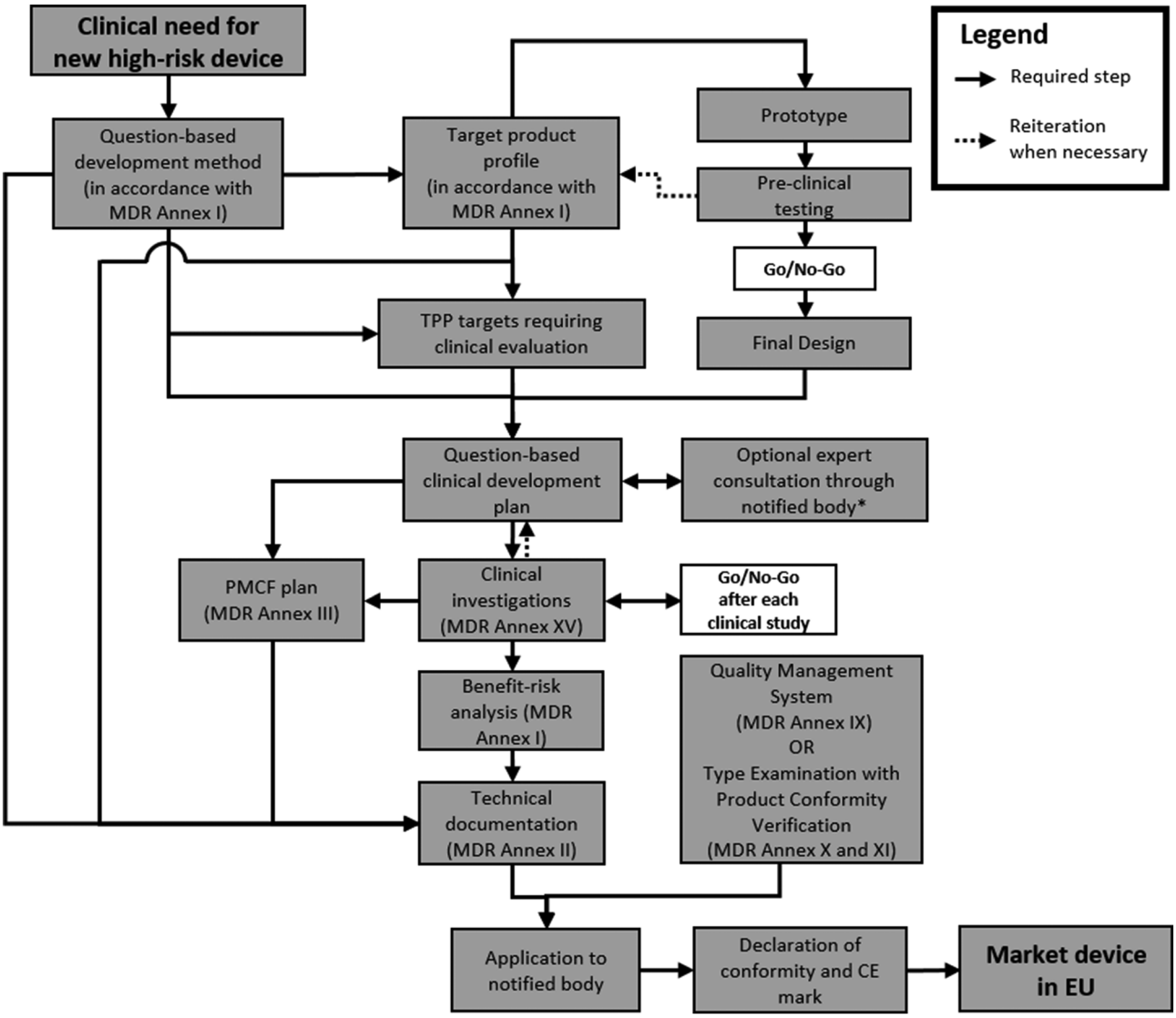

FIGURE 2 Flowchart illustrating the generalized process from the detection of a clinical need for a high-risk medical device to the application to a notified body utilizing the target product profile (TPP) and question-based development method as described in this paper for the Medical Device Regulation (MDR). PMCF, post-market clinical follow-up. *The MDR allows developers to request an expert consultation for their clinical development plan through the notified body in the development of Class IIb devices intended to administer and/or remove a medicinal product and Class III devices (MDR, art. 61(2)).

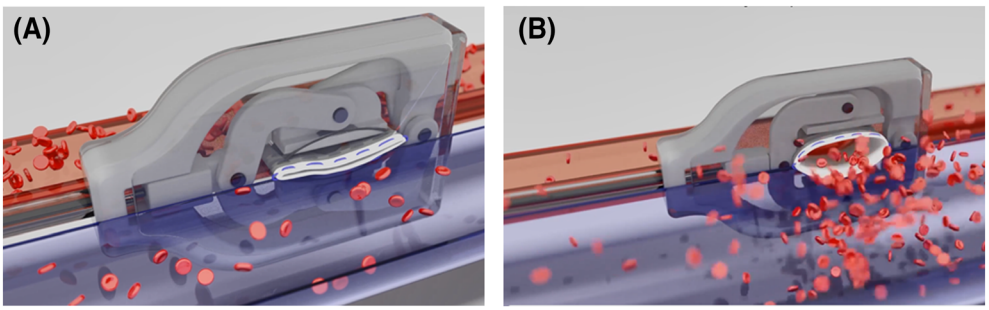

FIGURE 3 Conceptual depiction of a novel implantable device for haemodialysis that can open and close a tubular anastomosis placed between a vein and an artery to control the flow through these vessels. This device is considered a Class III device under the European Medical Device Regulation. (A) The anastomosis is closed and the circulation is normal; (B) the anastomosis is opened and the flow is increased to enable haemodialysis.

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.

3.2 | TPP and pre-clinical studies

First, relevant specific questions are raised, based on the main category question-based development questions. These questions are translated to TPP targets, and the TPP is amended with elements that have been identified from the relevant parts of Annex I of the MDR, cross-referenced with the TPP components as described by Tansey[21] (Table 2). A number of example targets are shown in Table 3. The developers consider these target 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 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.

Figure 4 shows the interaction between the question-based scheme, TPP and pre-clinical studies in the haemodialysis device example. By preceding the TPP with the question-based scheme, the questions form the basis of the non- and pre-clinical study design. However, targets are not always easy to properly define at an early stage and may change depending on the outcomes of studies. Clinical expertise is crucial in translating readouts to clinical use cases, indications and risks in this learning process, and they can be fed back into the question-based scheme and TPP. Hereafter, performance and safety of amended targets and questions will require confirming. If confirmation fails, discontinuation may be necessary. Defining questions and seeking preliminary answers in a non-clinical setting resulted in the revision of the TPP of the haemodialysis device throughout the development. This has been further elaborated in the supporting information S2.

3.3 | The question-based clinical development plan

The remaining targets that cannot be fully 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. The clinical development roadmap can be determined analogously to the method described in de Visser et al.[11] 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 parallels with clinical development of drugs allow valuation and determination of the optimal clinical study sequence similarly to the method described by de Visser et al.,[11] in which estimates of costs are determined through historical data and experts, for example from clinical pharmacologists. Similarly, a go/no-go decision point including a detailed benefit/risk analysis follows each clinical study.

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 likely that >50% will be functional after 3 years. 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. The final, critical step is a benefit–risk analysis showing that the benefits of using the device outweigh the risks and the device is safe for use. This can be an integration of all TPP values found during development.

3.4 | Key learnings

Applying this framework to the vascular access device at an early stage provided several learnings to the manufacturers:

- The question-based framework forced the developers to focus on the greater context with a stronger focus on clinical benefit and safety, and set up TPP targets focused on clinical endpoints rather than technical requirements. Technical requirements to achieve these outcomes could be drafted subsequently.
- As an example, utilizing the question-based framework, it became evident that there were uncertainties regarding the concept of intermittently adjusting a fistula and how vessels would respond. Asking this question early on resulted in the rapid development of a cheap device that was intended to assess a fundamental developmental question in a chronic animal model rather than an end product. Conducting such a study to collect this information earlier than planned prevented time-consuming and costly prototyping when it was unclear if the concept was feasible.

TABLE 3 Some examples of target product profile targets for a novel implantable vascular access device.

	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 to reach EU market approval	Development costs €14 mln to reach EU market approval	Similar vascular access devices	Reassess development programme
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 600 mL/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

(Continues)

TABLE 3 (Continued)

	Target profile	Motivation	Measure	Target value	Minimal viability requirement	Comparative data	Differentiation
Technical	Contamination	Introducing foreign materials into the body poses a risk of, for example, infection. It is thus necessary to sterilize implantable medical devices	Surface micro-organisms after sterilization	Theoretical probability of micro-organisms on surface <10e-6	Theoretical probability of micro-organisms on surface <10e-6	Conform to ISO standard 10 993	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

Abbreviation: AVF, arteriovenous fistula.

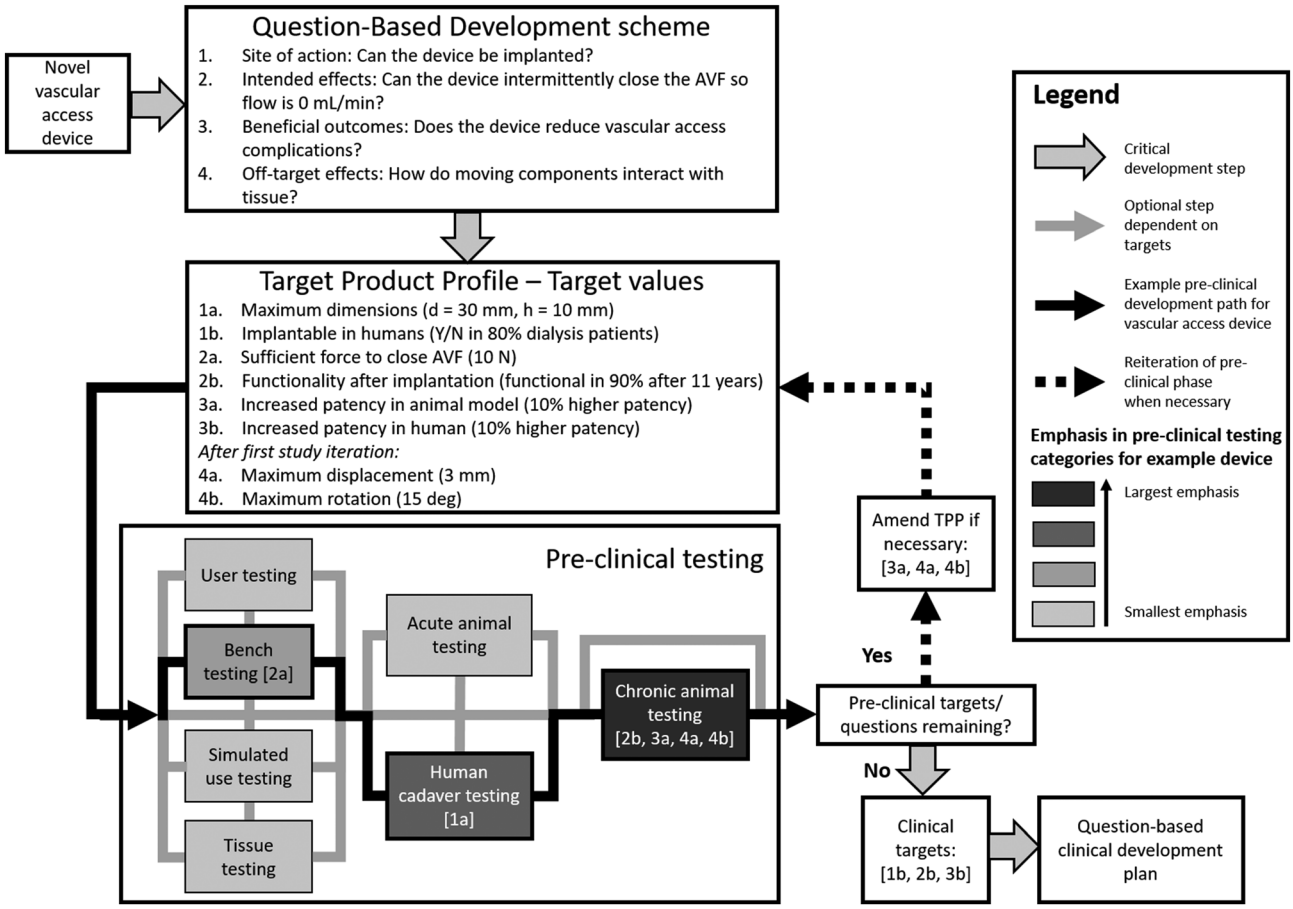

FIGURE 4 Clinical development framework for the novel vascular access device synthesized from the results of the question-based development scheme. The pre-clinical testing scheme has been adapted from Yock et al.[28] The black line indicates where the main emphasis lies in the pre-clinical testing used to demonstrate the safety and performance of the vascular access device. The numbers in brackets refer to the targets assessed at each study category. The shade of the category box indicates how resource intensive each category is for this example. AVF, arteriovenous fistula.

- Additionally, the question-based framework revealed uncertainties relating to the interaction of moving components with surrounding tissue, which could also be assessed in this initial chronic animal study. Findings could be incorporated into the TPP (Figure 4). It was also a starting point of a broader research area of moving implantable devices to be studied in the future.
- Amending the TPP with targets relating to management of fibrosis around moving components in this stage changed the design of the device to accommodate these essential requirements early on rather than after a larger and later study. Paired with the initial confirmation of functionality potentially reduces total development time and costs.
- It clarifies the current achievements and necessary milestones to reach the market, for example clinical trials and endpoints (Figure 4). This provided a clear and evaluable step-by-step overview that supports greater planning, both useful for the developers and appreciated by investors. In our case, the clear development plan has led to financial support for the manufacturer to develop the device further.

4 | DISCUSSION

In this paper, we have presented a structured generic approach for the design and subsequent performance of a clinical development programme for medical devices. The vascular access device case was used to gain practical insights into the relation between the question-based framework and the TPP. The definition of questions at an early stage showed that many unknowns were present, and a proper TPP could not be created without in vivo data. These data were consequently collected at an earlier stage than initially planned with a prototype that was not intended to function perfectly. Not only did it show that the concept was feasible, but also much more insight into the biological responses and interaction between moving components and tissue was gained which helped guide further development. Each study aimed to provide initial answers, and estimate uncertainties and potential risks, which could amend the question-based scheme and TPP. This process should always precede continuation of studies, as amendments could require assessment in subsequent (clinical) studies, changing the development plan. As development progresses, results

TABLE 4 Simplified example of the question-based framework for a novel implantable vascular access device illustrating how generic questions are used for the generation of specific questions relating to the TPP targets and how the methodology could originate from here.

Generic questions	Considerations	Specific questions	TPP targets	Methodology
Does the device reach the site of action?	The specific questions generated here can to some extent be assessed prior to clinical studies. However, clinical verification remains necessary due to differences between (e.g. animal or cadaver) models and the actual working environment.	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 - Open non-blinded study with descriptive statistics only	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?	These questions usually relate to the main working principle of the device. Again pre- and non-clinical evaluation can provide a lot of preliminary data that can be used for optimization, but models can never completely mimic the real working environment so verification is required. Moreover, clinical trial design and evaluation of the potential effect of interindividual variability may be optimized through, e.g., in silico methods.	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?	In most cases these questions should primarily focus on the clinical outcomes in general terms. Selection of correct biomarker(s) and endpoint(s) is crucial and rarely straightforward, and multiple studies may be necessary.	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?	The aim of target population studies is to gain insight into the patient populations in which benefits can outweigh the risks. This includes analysis of eligibility (e.g. anatomical), but also of contraindications in which risk is increased. These studies may be combined with off-target effect studies. Studies of small populations or rare diseases are very challenging and	Age, gender, BMI, indications and contraindications? 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, rehospitalization, quality of life, etc. Correlations between characteristics and outcomes are analysed.

TABLE 4 (Continued)

Generic questions	Considerations	Specific questions	TPP targets	Methodology
	methodology must often be adapted.			
Are there off-target effects?	These studies should generally focus on quantifying expected adverse events but also on monitoring unexpected adverse events. However, unexpected adverse events, such as mechanical deterioration of the device, can take several years in certain cases. It can, however, be difficult to assess all these (potentially infrequent) events, in the pre-market phase for such long periods if benefits are shown to outweigh risks. 'Unknown unknowns' are likely to remain and must be monitored in the post-market phase, for which good systems and methodologies must be set up.	What are the off-target effects? Are there long-term effects? How are moving components in the device influenced by fibrosis formation?	- Device outlives at least 50% of HD patients, functional after 3 years - Rehospitalization 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 rehospitalization are recorded and compared to traditional fistula patients.

Note: Generally applicable considerations for each generic question are provided.

and uncertainties from detailed benefit–risk analyses or safety and performance monitoring may similarly be incorporated into the development plan and addressed in following studies or post-market surveillance where necessary.

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 programme. Such programmes must be assessed by companies, researchers, ethics committees, regulators and even investors, and all would benefit from a generally accepted structure to facilitate communication and quantification. When the clinical programme is completed, the results can also be evaluated against this programme, improving the review process by standardizing 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.

Analogies between clinical pharmacology and clinical development of high-risk medical devices have been made clear. However, some differences remain, the biggest 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 optimizing the clinical development path, one result of which is early abandonment of unsuccessful drugs. However, this is more easily 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.

Finally, the general performance and safety requirements from Annex I of the MDR focus primarily on the demonstration that the device functions as expected and is safe. The benefit–risk analysis must show that the risks have been minimized 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 currently proposed is focused on the clinical assessment according to the MDR. The exact assessment route and clinical requirements may vary per regulator (e.g. FDA, Medicines and Healthcare products Regulatory Agency [MHRA], Pharmaceuticals and Medical Devices Agency [PMDA]) which can be reflected in differences in the TTP. However, safety and clinical benefit are essential in the widespread adaptation of medical devices. 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, potentially reaching further than just the EU.

4.1 | Limitations and future work

The development of all medical interventions is usually iterative, highly complex and dynamic.[11] A structured question-based programme 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 harmonized manner. Similar to the MDR, this is left 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 described here aims to guide medical device developers in the development process. It has been tested extensively in the field of drug development, but it has not yet been utilized sufficiently for devices, so it awaits application in a wider practice. The developmental results obtained depend largely on assumptions made,[11] 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[1] without centralized controlling agencies, so we believe that this calls even more for a structured approach. A review of the limitations and gaps in current clinical protocol designs for high-risk medical devices should be conducted that should be carefully considered or modified given the new regulation. This should offer clear insight into the issues medical device evaluation faces. It will become evident if the proposed implementation offers a more efficient approach and whether the generic questions suffice to ensure effective compliance with the MDR.

Currently, it cannot be claimed that our approach is effective as this would require some sort of control situation for comparison. To do this would require at least a fully completed development programme, but that could only be evaluated in hindsight. The approach described could improve the development process of medical devices by both focusing on performance and safety and reducing development time and costs. It was valuable in the non-clinical development of the example device provided and helped focus attention on important safety and performance endpoints in the clinical stages. However, at the time of writing, non-clinical investigations are still ongoing. The approach has not been formally evaluated, and a formal evaluation of the clinical development stage will likewise not be straightforward due to the long development timelines and the large differences between innovation projects. It remains a proposal and should be interpreted as such.

5 | CONCLUSION

The question-based framework for medical device development proposed in this paper can support developers starting from the initial device design stage in overcoming the obstacles and ambiguity of clinical development presented by the newly introduced MDR. The framework could guide manufacturers in setting up the clinical development plan, but it also potentially has the added benefits of showing clear relations between design and validation steps and thus may contribute to the 'learn and confirm' cycle that forms the basis of any intervention development.[29] This can assist further research into the adequacy of the development process and help to responsibly dismiss risky technology at an early stage and introducing effective innovations more quickly with lower costs. Our proposal has not been formally evaluated, and this can only be done when put into practice.

CONTRIBUTORS

All authors contributed to the synthesis of the framework. The manuscript was written by N.A.W., T.J.C.O.V. and A.F.C. T.H., J.I.R., N.A.W. and K.E.A.v.d.B. designed the experimental methods described, which were conducted by K.E.A.v.d.B. and N.A.W. All authors commented on previous versions and have approved the final version of the manuscript.

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COMPETING INTERESTS

All authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supporting information of this article.

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REFERENCES

1. Darrow JJ, Avorn J, Kesselheim AS. FDA regulation and approval of medical devices: 1976–2020. *JAMA*. 2021;326(5):420-432. doi:10.1001/jama.2021.11171

2. International Consortium of Investigative Journalists. *Implant Files [Internet]*. Accessed November 22, 2022. https://www.icij.org/investigations/implant-files/
3. 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*. The European Comission; 1990.
4. European Comission. *Council Directive 93/42/EEC of 14 June 1993 Concerning Medical Devices*. The European Comission; 1993.
5. European Comission. *Regulation (EU) 2017/745 of the European Parliament and of the Council on Medical Devices*. The European Comission; 2017.
6. 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):021004. doi:10.1115/1.3148836
7. De Maria C, Di Pietro L, Díaz Lantada A, et al. Safe innovation: on medical device legislation in Europe and Africa. *Heal Policy Technol*. 2018;7(2):156-165. doi:10.1016/j.hlpt.2018.01.012
8. Krucoff MW, Brindis RG, Hodgson PK, MacK MJ, Holmes DR. Medical device innovation: prospective solutions for an ecosystem in crisis: adding a professional society perspective. *JACC Cardiovasc Interv*. 2012;5(7):790-796. doi:10.1016/j.jcin.2012.03.023
9. Blot WJ, Ibrahim MA, Ivey TD, et al. Twenty-five-year experience with the Björk-Shiley convexoconcave heart valve: a continuing clinical concern. *Circulation*. 2005;111(21):2850-2857. doi:10.1161/circulationaha.104.511659
10. European Medicines Agency and Committee for Human Medicinal Products. *ICH Guideline E8 (R1) on General Considerations for Clinical Studies*; 2019.
11. de Visser SJ, Cohen AF, Kenter MJH. Integrating scientific considerations into R&D project valuation. *Nat Biotechnol*. 2020;38(1):14-18. doi:10.1038/s41587-019-0358-x
12. 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;260:371-397. doi:10.1007/164_2019_302
13. de Visser SJ. *A question based approach to drug development*. PhD Thesis,. Leiden University; 2003.
14. Cohen AF, Burggraaf J, van Gerven JMA, Moerland M, Groeneveld GJ. The use of biomarkers in human pharmacology (phase I) studies. *Annu Rev Pharmacol Toxicol*. 2015;55:55-74. doi:10.1146/annurev-pharmtox-011613-135918
15. Heneghan C. The saga of Poly Implant Prosthèse breast implants. *BMJ*. 2012;344(7839):e306. doi:10.1136/bmj.e306
16. Greco C. The Poly Implant Prothèse breast prostheses scandal: embodied risk and social suffering. *Soc Sci Med*. 2015;147:150-157. doi:10.1016/j.socscimed.2015.10.068
17. Cohen D. Out of joint: the story of the ASR. *BMJ*. 2011;342:d2905. doi:10.1136/bmj.d2905
18. Dhruva SS, Redberg RF. Coverage of transvenous pulmonary embolectomy—Medicare's missed opportunity for evidence generation. *N Engl J Med*. 2022;386(10):901-904. doi:10.1056/NEJMp2114960
19. World Health Organization. *Target Product profiles [Internet]*. Accessed July 25, 2022. https://www.who.int/observatories/global-observatory-on-health-research-and-development/analyses-and-syntheses/target-product-profile/who-target-product-profiles
20. 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. doi:10.1038/nrd.2016.264
21. Tansey M. The target product profile and its uses. In: *Intelligent Drug Development: Trials and Errors in Clinical Research*. Oxford, UK: Oxford University Press; 2014:31-46.
22. Cohen AF. Developing drug prototypes: pharmacology replaces safety and tolerability? *Nat Rev Drug Discov*. 2010;9(11):856-865. doi:10.1038/nrd3227
23. Kruizinga MD, Stuurman FE, Exadaktylos V, et al. Development of novel, value-based, digital endpoints for clinical trials: a structured approach toward fit-for-purpose validation. *Pharmacol Rev*. 2020;7(4):899-909.
24. European Medicines Agency and Committee for Human Medicinal Products. *Guideline on Clinical Trial in Small Populations*; 2007.
25. European Medicines Agency. *Guidance on Format of the Risk Management Plan (RMP) in the EU—In Intedrated Format Module V Rev.2*. Vol. 44; 2018.
26. Nelissen RGHH, Pijls BG, Kärrholm J, Malchau H, Nieuwenhuijse MJ, Valstar ER. RSA and registries: the quest for phased introduction of new implants. *J Bone Joint Surg Am*. 2011;93(Suppl 3):62-65.
27. Griffiths S, Behar JM, Kramer DB, et al. The long-term outcomes of cardiac implantable electronic devices implanted via the femoral route. *Pacing Clin Electrophysiol*. 2022;45(4):481-490. doi:10.1111/pace.14449
28. Yock PG, Zenios S, Makower J, et al. *Biodesign: The Process of Innovating Medical Technologies*. 2nded. Cambridge, UK: Cambridge University Press; 2015.
29. Sheiner B. Learning versus confirming in clinical drug development. *Clin Pharmacol Ther*. 1997;61(3):275-291. doi:10.1016/S0009-9236(97)90160-0

SUPPORTING INFORMATION

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