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PERSPECTIVE

Lifecycle evidence requirements for high-risk implantable medical devices: a European perspective

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ABSTRACT

Introduction: The new European Union (EU) Regulations on medical devices and on in vitro diagnostics provide manufacturers and Notified Bodies with new tools to improve pre-market and post-market clinical evidence generation especially for high-risk products but fail to indicate what type of clinical evidence is appropriate at each stage of the whole lifecycle of medical devices. In this paper we address: i) the appropriate level and timing of clinical evidence throughout the lifecycle of high-risk implantable medical devices; and ii) how the clinical evidence generation ecosystem could be adapted to optimize patient access.

Areas covered: The European regulatory and health technology assessment (HTA) contexts are reviewed, in relation to the lifecycle of high-risk medical devices and clinical evidence generation recommended by international network or endorsed by regulatory and HTA agencies in different jurisdictions.

Expert opinion: Four stages are relevant for clinical evidence generation: i) pre-clinical, pre-market; ii) clinical, pre-market; iii) diffusion, post-market; and iv) obsolescence & replacement, post-market. Each stage has its own evaluation needs and specific studies are recommended to generate the appropriate evidence. Effective lifecycle planning requires anticipation of what evidence will be needed at each stage.

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Clinical evidence; eu; technology lifecycle; high-risk implantable medical devices; observational study; mdr; hta; rct; real-world evidence; registry

1. Introduction

It is generally accepted that appropriate clinical evidence must be generated to inform licensing, coverage, and reimbursement decisions for medical devices (MDs) in publicly funded healthcare systems. However, what constitutes '*appropriate*' clinical evidence at each stage of the technology development process, in different jurisdictions and for different purposes, is still a matter of debate. Moreover, the application of the Medical Device Regulations 2017/745 [1] in 2021 and 2017/746 [2] and the proposal for a regulation of health technology assessment (HTA) [3] in the European Union, are further disrupting the regulatory and market access ecosystem for medical devices, especially for those for which clinical evidence is considered to be particularly important, such as the high-risk implantable medical devices.

This paper summarizes the deliberations of an expert panel named *'Evidence Council on Pathways to Clinical Evidence Generation for High-Risk Implantable Medical Devices.'* Our council, which included a selected group of experts from various jurisdictions and different backgrounds, including epidemiologists, health technology assessors, health economists, and policymakers, was created to debate the uncertainties and challenges concerning the generation of clinical evidence for devices across the product lifecycle. The final aim was to provide recommendations to all stakeholders engaged in generating and evaluating clinical evidence on high-risk medical devices.

The paper is structured as follows. First, the European regulatory and HTA contexts are presented in sections 1.1 and 1.2 respectively, together with the implications of the upcoming new EU regulations for clinical evidence generation for medical MDs. These developments in the policy arena are considered essential background for our review. Section 1.3 introduces the challenges of identifying the appropriate study designs throughout the product life cycle and section 2.0

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Article highlights

- High-quality clinical evidence is required to protect patients' health, to effectively inform regulatory, coverage, and reimbursement decisions.
- The new EU Regulation on medical devices aims at improving pre-market and post-market clinical evidence generation, but fails to indicate what type of clinical evidence is appropriate at each stage of the lifecycle of medical devices.
- HTA in EU Member States is not uniform with respect to clinical evidence requirements and is one of the reasons why the proposal of an EU HTA Regulation is still under discussion at the EU Council.
- Different approaches exist to inform clinical evidence generation across a technology's life cycle but encourage linearity in product development, in a particular order, each requiring a particular type of clinical evidence; this does not often apply to medical devices.
- Some jurisdictions have progressed in terms of recommendations for new types of studies to generate clinical evidence in the pre- and post-market stages, but no comprehensive and systematic picture exists so far.
- Recommendations are proposed for: i) the appropriate level and timing of clinical evidence throughout the lifecycle of high-risk implantable medical devices; and ii) how the clinical evidence generation ecosystem could be adapted to optimize patient access.
- Four stages are relevant: i) pre-clinical, pre-market; ii) clinical, pre-market; iii) diffusion, post-market; and iv) obsolescence & replacement, post-market and must be seen in a continuum: ideally, clinical evidence needs in the later lifecycle stages can be prepared for from the outset.

clarifies the methods used to address these challenges. Section 3.0 illustrates the council's recommendations by product lifecycle stages and section 4.0 summarizes the key elements to reduce uncertainties by different stakeholders (e.g. manufacturers, regulators, and HTA bodies), in identifying the 'best fit' study designs to generate the right clinical evidence to enable devices to progress smoothly through the whole product lifecycle.

1.1. EU regulation on medical devices

The Regulation (EU) 2017/745 on medical devices (MDR) and Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices (IVDR) were officially published in May 2017, replacing the EU's current Medical Device (MD) Directives (93/42/EEC, 90/385/EEC and 98/79/EC). A transition time of three and 5 years until May 26, 2020 and 2022 (for medical devices and *in vitro* diagnostics, respectively) was foreseen, to allow stakeholders to meet the requirements of the respective MDRs. Due to the global Covid-19 pandemic, which is consuming almost all efforts and resources of the health systems, the date of application of the MDR 2017/745 has been recently deferred by 1 year, from May 2020 to May 2021 by Regulation 2020/561 [4].

The new Regulations contain a series of extremely important measures to modernize the current regulatory ecosystem for MDs in the EU, among which the following that have a direct bearing on evidence requirements:

i.stricter *ex-ante* control for high-risk devices via a new pre-market scrutiny mechanism with the involvement of a pool of experts at EU level;

ii.the reinforcement of the rules on clinical evidence, including an EU-wide coordinated procedure for authorization of multi- centre clinical investigations;

iii.the strengthening of post-market surveillance requirements for manufacturers;

iv.improved coordination mechanisms between EU countries in the fields of vigilance and market surveillance.

From a legal perspective, the replacement of Directives with Regulations aims at strengthening the harmonization of the regulatory process for medical devices at the EU level. In this way, the process of obtaining a CE mark in order to launch the product in the EU market will follow common and more transparent rules [5].

After obtaining a CE mark, medical device manufacturers may face subsequent 'hurdles' before their products can reach patients. In some EU countries, a product-specific HTA is required to support the pricing and reimbursement decisions for MDs. These decisions are made separately in various jurisdictions of the Member States (MS), with inevitable heterogeneity in the timing of decisions and in reimbursement coverage for the same product [6].

1.2. EU regulation on HTA

HTA conducted and reported in different countries are not fully generalizable across MS [7–10]. This is due to potential differences in patient populations and in clinical pathways and disease management, which contribute to differences in the availability of alternative treatments, and in the general settings of the health care There are also differences among MS in how the clinical evidence is used in HTA. In some MS, the clinical evidence is used to give a judgment of the 'added clinical value' of the product, which may then be used in price negotiations [11]. In other MS, the available clinical evidence is synthesized with other forms of evidence in a decision-analytic model. Finally, the preferred form of clinical evidence for HTA in most situations is the comparative effectiveness between the new technology and the existing standard of care. This may or may not be the same as the clinical evidence used in the regulatory process [12–14].

However, product-specific HTA methodology and results available from other MS represent important benchmarks and guidance for national/local adaptations and conclusions, without unnecessary duplication of work – in line with the primary aims of transferability research [15].

Some form of collaboration between MS on HTA began about 30 years ago. However, it became systematic and organized with the creation in 2006 of EUnetHTA, the network of European HTA agencies, which today has over 80 organizations from 30 different countries. More than 10 years after the launch of EUnetHTA, at the beginning of 2018 the European Commission released to the European Parliament and the Council, a proposal for a new HTA regulation [3], in order to improve the functioning of the EU internal market and to promote the health of EU patients. Ultimately, the regulation aims at replacing the current voluntary-based network 'EUnetHTA' into a permanent consortium of nationally authorized institutions, that are expected to incorporate

centralized clinical assessments into their own national HTA systems. While the assessment on clinical dimensions is centralized, the final recommendation (appraisal) on the added value of the technologies, and on their reimbursement, remains with the MS.

Overall, by focusing on transparency, independence, efficiency, and quality of shared reports, the proposal aims to support evidence-based market access processes for innovative technologies in the EU. Although these principles are difficult to question, the proposal only received a lukewarm endorsement by various stakeholders and, in some cases, has been criticized, despite extensive public consultations conducted before the publication [16]. Major challenges remain concerning the role and acceptability of evidence from randomized and real-world data, the trade-off between internal and external validity requirements, and the obligation for MS to use the clinical assessment by the EU HTA coordination group for coverage and reimbursement decisions at local level. While avoiding duplication, a uniform clinical assessment also leads to debate. For example, some MS consider appropriate current care as the comparator relevant for a new technology; if this differs between MS, it makes it difficult, if not impossible, to produce a uniform assessment. Skepticism on the efficiency and effectiveness of the coordination EU HTA group by some stakeholders has hindered a smooth approval process of the regulation, which is still under discussion at the EU Council.

1.3. Lifecycle evidence generation for high-risk medical devices: overview of different approaches

A common way to consider the data needs for evaluating new technologies is to relate these to various states in the technology's life cycle. A basic product lifecycle for a technology includes research, development, production, clinical use and obsolescence. These stages can be expanded as needed to address a specific device design or manufacturing procedure, as well as device class, category, and classification. The main concern is to define the life-cycle in a way that best meets the objective of generating timely and appropriate clinical evidence, as it tracks various products and versions of products through development, the marketplace, and discontinuation (i.e. the company must still support those products in the marketplace even though their selling cycles have ended).

Different approaches have been proposed, and in some cases endorsed, by regulatory bodies. This is the case, for instance, of the Total-Product-Life-Cycle (TPLC) by the US Food and Drug Administration (FDA) [17] that combines data from various Center for Devices and Radiological Health (CDRH) databases to present an integrated record of premarket and post-market activity for MDs. The main disadvantage of the TPLC approach is that it encourages linearity on our thinking, in that it portrays a series of steps in product development, in a particular order, each requiring a particular type of clinical evidence. This approach works fairly well as a model for pharmaceutical product development, but the development of MDs is often more unpredictable. For example, it is possible for MDs to enter into regular clinical practice with relatively little clinical evidence, the evidence being predominantly gained through actual use of the device in clinical practice [18], as opposed to a research setting [19,20]. The adaptation of the IDEAL (Idea, Development, Exploration, Assessment, Long term study) framework to medical devices [21] is another attempt to inform a continuous evidence generation for devices although the proposal is awaiting empirical implementation and fuller consideration by regulatory and HTA bodies.

Another key aspect is to determine the appropriate study design required for the clinical evidence to be generated at each stage of the MD development cycle. The randomized-controlled study (RCT) is usually considered to be the study design giving the highest level of evidence for demonstrating the efficacy of a new health technology, compared with an alternative, typically current standard of care. However, intrinsic or organizational features of MD technologies may make it difficult to carry out a conventional RCT [22]. Moreover, the question of comparative efficacy is not always the one to be addressed at different stages of the lifecycle of an MD product. Alternatives to the standard RCT design have been proposed in order to minimize the impact of specific problems of MDs such as the timing of the assessment, small eligible patient population and recruitment, acceptability to patients or physicians, inability to blind clinicians and patients, choice of comparator group, and learning curve [23,24]. Real-world evidence – such as registries – have gained relevance to assess MDs over the last years [25–27]. Moreover, Bayesian methods are becoming increasingly applied to combine existing real-world data with information from the ongoing trial [28]. These methods are particularly useful in situations where the number of subjects is small, although a common disadvantage is the risk of including erroneous prior information derived from non-randomized data.

2. Methods

A multidisciplinary group, the '*Evidence Council on Pathways to Clinical Evidence Generation for High-Risk Implantable Medical Devices*,' was conceived, created, and led by the Center for Research on Health and Social Care Management (CERGAS) – SDA Bocconi School of Management (Full details of the composition of our council are given in Appendix 1). The council was assembled to address the following questions:

Q1: What is the appropriate level (in terms of type, quantity, quality) and timing of clinical evidence that is sufficient to satisfy value assessors and payers' needs throughout the lifecycle of high-risk implantable medical devices?

Q2: How could the evidence generation ecosystem be adapted to optimize patient access, considering the risks for patients, healthcare providers, payers and technology developers?

The workshops used a combination of modified Delphi and face-to-face expert panel methods to reach a consensus on the two questions. The Delphi method entails a group of experts who anonymously reply to questionnaires and subsequently receive feedback in the form of a statistical representation of the 'group response,' after which the process is repeated. However, it does not result in the same level of interaction as a live discussion. A live discussion can sometimes produce a better consensus, as ideas and perceptions are introduced, analyzed, and reassessed.

For these reasons expert panels can be more effective. They are used when specialized input and opinion is required for an

evaluation. Generally, a variety of experts are engaged, with various fields of expertise, to debate and discuss various courses of action and to make recommendations. They can be useful at different stages of an evaluation but have to take place to live, which can pose logistical challenges if experts are busy or geographically widespread.

Therefore, we used a combination of these techniques. Experts were selected to reflect different jurisdictions (European countries and Canada) and different backgrounds (health economics, public health, medicine, healthcare management) (see Appendix 1). Invitations were sent by e-mail and, once accepted, a briefing paper was sent to all participants, in preparation for the first round that consisted of a workshop held on June 14th, 2019 in Milan at SDA Bocconi School of Management. Those who could not physically attend the meeting were remotely interviewed in the following few days by OC and AT. Consent to record the interviews was obtained and the audio record was transcribed. A medical writer took notes of the meeting discussion and, along with interview transcripts, prepared a detailed overview of the discussion. This summary was emailed to experts in preparation for the second round, which was conducted as a second workshop at SDA Bocconi on October 25th, 2019, where the key points from the first round were discussed and recommendations agreed. A detailed report of the discussion was prepared by a second medical writer, summarized by RT, OC, AT, and MD in preparation of the manuscript that was finalized with the contribution of all experts.

The discussion and recommendations proposed by our Council are mainly intended to apply to a 'standard' high-risk implantable MD without any particular special circumstances. For instance, devices that are suitable for a 'breakthrough' designation [29] or 'fast-track' appraisal, such as those deemed 'life-saving' in addition to 'high-risk' or devices that are eligible for 'conditional approval' may have different requirements and are likely to deviate from the recommendations described here. According to Article 2 in the EU Regulation [1], an 'implantable device' is any device, including those that are partially or wholly absorbed, intended to be partially or totally introduced into the human body, or to replace an epithelial surface or the surface of the eye, by clinical intervention and which is intended to remain in place after the procedure for at least 30 days. In Annex VIII Rule 8 of the MDR, it is clarified that implantable devices and long-term surgically invasive devices will generally be classified as class IIb or higher. More specifically, medical devices intended to be used in direct contact with the heart, the central circulatory system or the central nervous system, active, wholly or mainly absorbed, with biological effect or undergoing a chemical change in the body, intended to administer medicinal products, are classified as class III. Ancillary components such as screws, wedges, plates, and instruments are considered as class IIb whilst implantable devices and long-term surgically invasive devices intended to be placed in the teeth are classified as class IIa.

3. Results

Q1: What is the appropriate level (in terms of type, quantity, quality) and timing of clinical evidence that is sufficient to satisfy value assessors and payers' needs throughout the lifecycle of high-risk implantable medical devices?

The recommendations given below outline the best standard of evidence attainable and the characteristics of the data collection process, in order to support the device's approval and access to the end-user. Considering a lifecycle approach to the identification of pathways to clinical evidence generation, four stages were envisaged as being relevant, including the i) pre-clinical, pre-market; in addition to the ii) clinical, pre-market; iii) diffusion, post-market; and iv) obsolescence & replacement, post-market.

As a general rule, effective lifecycle planning requires anticipation of what evidence will be needed at each stage; ideally, evidence needs in the later lifecycle stages can be prepared for from the outset.

3.1. Pre-clinical, pre-market evidence generation

In the early pre-market stage, pre-clinical research on high-risk implantable medical devices, tests on toxicology, and biocompatibility are normally required, as defined by European current standards for MDs [30]. This phase is intended for design optimization, prototype development, and manufacturing engineering. A recent trend gaining attention in this respect is the use of in silico trials. At their core, in silico trials make use of computer modeling and simulation to inform product design and predict how a novel medical product would perform in a particular patient or in a specific clinical setting. The possibility to gain a deeper understanding of the intrinsic properties of the device, as well as of the interactions with environmental or physiological characteristics of patients, early in the development phase may contribute to improve research efficiency. The potential of in silico trials has been recently recognized by regulatory bodies such as the US FDA, which has advocated the use of such systems as an additional innovative research tool [31]. FDA has advised that modeling and simulation could be used to, for example: 1) predict clinical outcomes, 2) inform clinical trial designs, 3) support evidence of efficacy and potential effectiveness, 4) identify the most relevant patients to study, and 5) predict product safety. However, they require more verification and validation [32].

At this stage it is also important for the MD manufacturer to explicitly start the definition of the appropriate 'business case,' or 'value proposition' for the technology; that is, the clinical need for the device, where the device sits in the diagnostic and therapeutic pathway, what advantages (if any) it may offer over existing alternatives (if any), what are the challenges that the new device may face when translating into regular clinical practice [33]. The challenges may relate to clinicians' attitudes toward the technology, or the organizational changes that may be needed to support its adoption. Based on the answers to these questions, it should be possible to make an early assessment of the likely evidence needs of regulators, payers, and product end-users. It may even be possible to undertake some 'early modeling' of potential clinical and cost-effectiveness [34,35]. These activities are often referred to as 'early HTA' and provide a conceptual framework to support industry and investors' decisions on investments, plus the design and management of the technology, regulatory, and reimbursement strategies [36]. Indeed, early HTA consists of a range of methods, typically based on evidence derived from

bench and animal tests, early clinical experience, and previous generations of the technology [37]. The objective is to inform industry and other stakeholders (such as hospitals, providers, and potential users of the technology) about the potential value of new medical products in development, including methods to quantify and manage uncertainty about their potential clinical and cost-effectiveness.

In a nutshell, the early pre-clinical, pre-market stage is relevant since it should aim at paving the way to future, more extensive and costly clinical evidence leading to the 'value proposition.' The following types of studies characterize this phase:

- toxicology and biocompatibility tests (e.g. materials testing, microbiological safety, animal studies);
- in silico trials;
- early HTA.

3.2. Clinical, pre-market clinical evidence generation

In the pre-market phase, clinical investigations may begin with an exploratory approach to answer specific questions that may condition the continuation or suspension of the product's development program. Exploratory trials include a small number of patients and expose them to the investigational medical device-based procedure. These trials are *de facto* first-in-man studies, but often lack a therapeutic or diagnostic goal and, by definition, cannot establish safety, tolerability, or efficacy.

At this stage, early feasibility clinical investigations may be a relevant tool. These are defined as clinical investigations of a device early in development, typically before the device design has been finalized for a specific indication [38]. They can be used to evaluate the device design concept with respect to initial clinical safety and device clinical performance or efficacy (if appropriate), as per its intended use in a small number of subjects. Such studies may be particularly important when this information cannot practically be provided through additional nonclinical assessments, or appropriate nonclinical tests are unavailable. Information obtained during early feasibility clinical investigation can guide device modifications. FDA has launched a specific Early Feasibility Study program to gain useful clinical experience to provide insights for sponsors and FDA review teams into device proof of concept, patient characteristics that may impact performance, operator technique refinements, device safety, necessary device modifications, and human factors [39]. However, it should be clarified that speed of approval should not be gained at the expenses of substantial evidence for safety and effectiveness for high-risk devices. A recent study demonstrated higher recall rates for devices approved with priority review vs. standard review at FDA highlighting concerns about the inherent risks of these first-in-class devices [40].

Ideally, consecutive patients treated with the investigational device, often in a single-arm, single-or multicentre study, should be tracked with an indication of the characteristics of the investigational product, organizational factors (such as training and the learning curve), and safety and performance outcomes.

Whilst evidence from single-arm studies may be enough to assess acceptability and preliminary safety in some jurisdictions, comparative data (ideally against current standard care) is often needed in others (e.g. UK and Germany, in the pharmaceutical sector) [41]. In any case, planning for comparative effectiveness evidence generation should be made at this stage [42] so as not to unduly delay the HTA and reimbursement process at a later stage [33]. Some HTA bodies, such as NICE [43] (in England and Wales), AQuAS [44] (in Spain) and EUnetHTA [45] (in the EU), already have programmes offering early scientific advice, or joint advice from the regulator and various payers. Discussion with stakeholders, including patients' associations, is fundamental in this and other stages of the clinical research and product development and may profoundly influence the study design [42].

When the technology is considered as a replacement for the current standard, an RCT should ideally be carried out. Randomized controlled trials are considered the gold standard for comparative effectiveness assessment. A well-conducted randomized clinical trial, with well-established and valid endpoints for efficacy and short-term safety, is the ideal pivotal investigation. As the evidence generated in an RCT will typically be used to inform regulatory bodies, payers, and clinical practice in multiple countries [42], a pragmatic approach is generally to be preferred, so as to make the results as generalizable as possible. In generalizing the results of a randomized trial, the assumption is not really that the patient population studied is representative of all patients but rather that the treatment effects should be transferable across healthcare systems [46]. Healthcare systems differ widely between countries, and each country's approval system moves at a different rate. Nevertheless, valid estimates of the absolute benefits and harms of a treatment can be obtained by applying reliable proportional effects, obtained from randomized evidence, to the baseline risks within a particular population.

Generally speaking, robust clinical data generated through high-quality studies are probably valuable across countries and would likely form the 'minimal dataset' of clinical evidence widely applicable for the regulatory and market access across different jurisdictions [47]. More complex and innovative variants of the simple two-group parallel RCT exist and include adaptive designs [48] which make use of data collected during the progress of a clinical study to allow modifications to the ongoing trial, such as dropping an ineffective arm or capturing incremental innovation throughout the evaluation process.

Whilst the cost of a standard RCT may be too high, and even prohibitive, for many small and medium device manufacturers, the explosion of electronic health records (EHRs) and the extraordinary penetration of mobile technology are currently fostering the digital innovation paradigm in the clinical trial sector [49]. Solutions are available to address various challenges from the study design to trial operations, data management, and report writing with a significant overall reduction in costs. In this regard, the Big Data for Better Outcomes (BD4BO) program by the Innovative Medicine Initiative as well as the European Database for Medical

Devices (EUDAMED), to be launched simultaneously for both medical devices and in-vitro diagnostics together in May 2022, may be potentially interesting [50,p.4] and, although acceptance of EHRs by regulatory bodies and HTA agencies is not common yet [51], the trend is for an increased use of this source of evidence.

There are several situations where an RCT is simply not possible or appropriate. These include 1) in small patient population where it is not possible to recruit sufficient numbers to demonstrate a statistically significant advantage over control, 2) when ethical issues discourage the use of a control or comparator arm (e.g. total artificial heart implantation), 3) when only considerably long-term outcomes are of interest (although an open-label period following an RCT may overcome this problem). In cases where an RCT is impossible, it would be necessary for the device manufacturer to justify why this is the case and to work collaboratively with the regulatory authorities, HTA agencies/units, clinicians' and patients' representatives to define a suitable alternative. Comparative evidence would still be needed in these cases [42,52,53], and this may be derived from conditional inclusion of the device in a pre-established disease registry, or comparison of single-arm study data on the investigational device with a proper defined control group taken from historical cohorts or from a well-designed patient registry [51].

Bias is, of course, a concern in observational studies, where it is likely that systematic differences in the distribution of patient characteristics between treatment groups will affect the treatment effect. Proper adjustment is therefore necessary, through the use of covariates in a statistical analysis. The bias would be aggravated if the time frames or context between the investigational study and registry do not reasonably coincide [54]. All these cause concerns regarding the validity of study design and the interpretability of study results, and consequently the ability of regulatory decision-making may be compromised. In this regard, the EU MDR 2017/745 establishes that manufacturers of Class III and certain Class IIb devices can access EU-level expert panels at a much earlier stage in the product development process, to obtain advice in relation to clinical development strategy and the proposal for clinical investigations. The independent panel experts will be selected on the basis of their clinical, scientific, or technical expertise in the field and shall perform their tasks with impartiality, independence, and objectivity, to provide an independent opinion on high-risk devices to Notified Bodies before such devices are certified for EU market access. The experts will also be involved in other tasks such as contributing to the development of common specifications for clinical evaluation of device categories, guidance documents, or standards. The ultimate aim is to improve manufacturers' product development plans, in order to facilitate better clinical data generation to satisfy Notified Bodies' conformity assessment process. A call for interest in serving on the panels was issued by the European Commission, addressed to a wide array of professionals (from all medical specialties but also from other backgrounds such as artificial intelligence, computer science, health outcomes research, statistics, etc. with at least 5-years experience in the area of medical devices or in vitro diagnostics) last September [55]. Following the call for interest, the EC clarified that eligible candidates who are not part of an expert panel yet may be included in a central list of available experts who may be used to appoint replacements, request advice, or find support for the expert panels as needed [56].

A separate consideration relates to devices claiming equivalence to a predicate device [1,57]. An RCT maybe not strictly necessary in this situation. However, with the EU MDR, criteria for equivalence are stricter and equivalence should be demonstrated based on proper scientific justification and through access to the data relating to the predicate device (e.g. access to patient data of the pivotal RCT of the predicate device). The Clinical Evaluation – Equivalence guide to notified bodies and manufacturers issued by the MDCG [58] further clarifies the necessary requirements to claim equivalence by different classes of devices as from the MDR (Annex XIV, Part A).

Finally, in some European countries (e.g. Belgium, France or the UK), HTA may be conducted [59]. This HTA does not control the entry of the MD into the market but may control its level of reimbursement. This could be direct, by determining the extent to which reimbursement to hospitals or other providers are given for the procedure in which the device is used, or indirectly, by providing information on clinical or cost-effectiveness evidence that may influence the price negotiations between device manufacturers and hospitals.

As mentioned earlier, some HTA bodies review the existing clinical data and make an assessment of 'added clinical value.' Other HTA bodies synthesize the existing clinical data with other available data for use in decision-analytic models to assess the comparative (clinical) effectiveness or cost-effectiveness of the new technology with the current standard of care. These models may use observational data to extrapolate from the clinical data gathered in clinical trials [60].

The early scientific advice, mentioned earlier, can be important in these situations, since the clinical data needs of the HTA bodies may be different from those of the regulators [61]. The extent of differences in data needs is likely to vary on a case-by-case basis. However, it is possible to identify three dimensions along which these differences in data needs are likely to be. First, HTA bodies almost always require clinical effectiveness data comparing the new technology and the existing standard of care. Hence, the preference of HTA bodies for head-to-head clinical studies where possible, or indirect or mixed treatment comparisons in the absence of head-to-head studies [62,63]. As to the regulatory phase, the Medical Device Coordination Group (MDCG) explains that when the device is compared against the 'state of art,' this must be supported by recognized guidelines by scientific societies or educational bodies [64]. Although comparative effectiveness vs. standard of care is not as binding as for HTA purposes, it is notable that the EU MDR acknowledges this case (recital 49) thus making evidential requirements between the regulatory and HTA processes more consistent. Secondly, HTA bodies require clinical data that relates, as far as possible, to 'real world practice' in their local setting. For example, the current standard of care should be one that reflects actual clinical practice in the setting concerned, and the clinical data should, as far as is possible, reflect the results obtained from using the device in the same, or similar, setting. This distinction, between the

efficacy of interventions in the controlled environment of clinical studies and their effectiveness in the real world, is particularly important in the case of MDs, given the potential impact of the user 'learning curve' and other organizational characteristics. Finally, HTA bodies tend to prefer data reflecting patient-relevant outcomes in the long term. Therefore, they tend not to favor surrogate outcomes or biomarkers, but prefer outcomes like survival and health-related quality of life [47,65].

These clinical data preferences imply that, even if some RCTs comparing the new technology with the current standard of care do exist, in the HTA they are likely to be supplemented with data from observational studies, since these often include elements of 'real world data.' Therefore, various HTA bodies have begun to specify their need for and their likely use of observational data [51,60,66] although it must be acknowledged that – compared to other initiatives such as the Cochrane Collaboration [67] – the use of real-world data in HTA was foreseen since its inception [68]. The other main implication of the expressed preference for clinical data by HTA bodies is that it is unlikely that all these data would be available at the time the new device enters the market. This suggests that, although an HTA may be possible pre-market, any assessment will need to be refined by data collected after the new device is being used in regular clinical practice. Indeed, it has often been argued that, while for pharmaceuticals the emphasis on clinical data collection is pre-launch, the emphasis for MDs might be post-launch. The EU MDR, together with the guiding documents issued by the MDCG [53], makes an effort to change this attitude by i) strengthening the clinical evidence requirements, and ii) advising manufacturers to develop a clinical development plan indicating progression since from exploratory investigations. The collection of data post-market is discussed in the following section.

In summary, the clinical, pre-market stage is central since it aims to generate the evidence that will determine the appropriate place for the device in the market. Clinical evidence generation may go through different, incremental steps as described in Figure 1.

3.3. Diffusion phase, post-market evidence generation

Once the medical device is on the market, the EU MDR (article 2, recital 60; Annex XIV, Part B) requires a 'systematic procedure to proactively collect and review experience gained from devices […] on the market […] for the purpose of identifying […] any necessary corrective or preventive actions' and considers the post-market clinical follow-up as a continuous

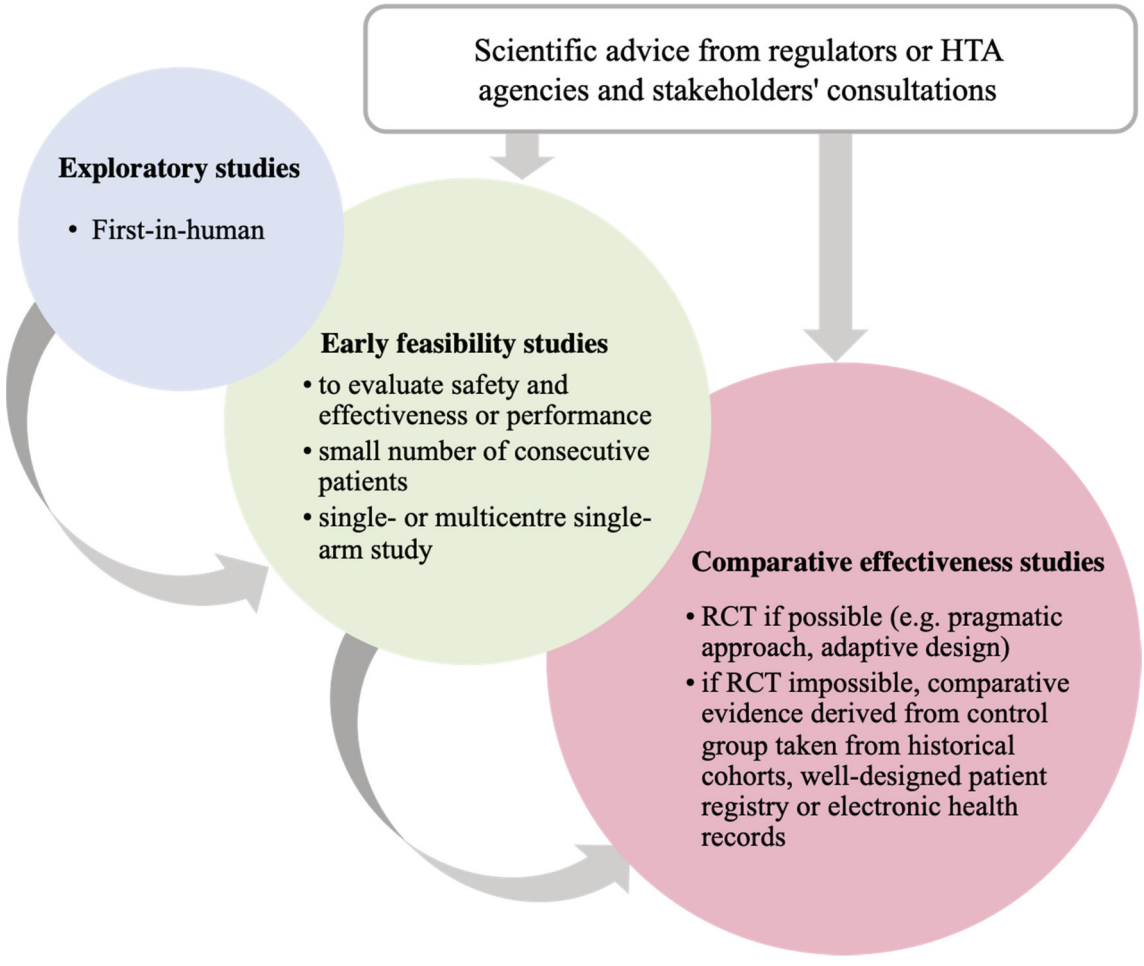

Figure 1. Clinical evidence generation in the clinical, pre-market stage.

process [69]. Post-market evidence generation can take several forms, but the most common approach is to establish a registry or another type of prospective observational study. Several factors specific to medical devices make registries appropriate as a research methodology for post-marketing surveillance, or for informing the payers' ultimate decision on pricing and reimbursement [25–27]. These factors include: uncertainty about long-term outcomes in what are often permanent implants, incremental design variation within a class of products, the potential for clinically significant heterogeneity in outcomes across populations due to patient-, operator- and organizational-factors, or extension of indications to other target populations [70]. Typically, a registry will accompany the device to bridge evidence gaps across the medical device total product life cycle.

The International Medical Device Regulators Forum (IMDRF) defines a registry 'as an organized system with a primary aim to increase the knowledge on medical devices, contributing to improve the quality of patient care that continuously collects relevant data, evaluates meaningful outcomes, and comprehensively covers the population defined by exposure to particular device(s) at a reasonably generalizable scale (e.g. international, national, regional, and health system)' [71]. Common characteristics that stand out in this and other definitions of registry are: observational, non-interventional, post-authorization, long-term objectives and follow-up, high patient coverage, naturalistic (or 'real world') data collection, in contrast to the carefully selected populations of clinical trials.

A properly designed and well-executed national or international registry has the potential to play an important role in the decision-making concerning medical devices. The key points here are: (1) how closely a registry approximates to standard clinical practice (procedures that do not pose more than minimal additional risk or burden to the safety of the subjects) and thus capture real-world data and (2) how simply a registry can be organized and conducted to maximize participation and to ensure sustainability over the long term (3).

The PRECIS-2 (Pragmatic-Explanatory Continuum Indicator Summary 2) has identified nine domains (i.e. Eligibility, Recruitment, Setting, Organization, Flexibility in delivery and adherence, Follow-up, Outcomes, Analysis) that should guide a common rigorous approach to the design of a clinical study, on a continuum of explanatory attitude (ideal situation) to more pragmatic attitude (usual care) [72]. Ideally, registry data would be reliable, complete, consistent, accurate, and contain all relevant patient-, device-, operator- and organizational information, including all key baseline covariates and clinical and patients' reported outcomes at baseline and follow-up points. Ensuring transparency in the design, collection, access, and reporting of the data in the registry is of fundamental importance. High-quality registries can also serve as a basis for registry-based RCT, an innovative and efficient study design that can be particularly useful to investigate when the evidence of clinical benefit vs. the standard of care is small [47].

Consent is an important and sensitive issue. The EU clinical trial regulation [73] allows for a simplified informed consent to be obtained in single-country, low-intervention cluster trials where groups rather than individuals are allocated to a treatment. In general, consent in registries, relies on the balance between respecting data privacy and their public policy role. Another ethical consideration is outside-instructions for use (IFU) deployment of devices, analogous to 'off-label' use for drugs. This aspect would in fact allow the study of the performance of an approved device for a new indication ('indication creep') and make the registry a useful source for the pre-market stage evaluation in other indications. However in the EU, according to the Art.5(1) of MDR, a medical device is placed on the market if used in accordance with its intended purpose, that is an off-label use of a medical device is to all effects a nonconform use and is therefore discouraged.

The breadth of variables to be included for a device evaluation may discourage systematic and extensive establishment of medical device registries. However, such limitations could be mitigated through interoperability solutions that strategically link complementary registries and data sources, to produce networks for which the data composite could support robust device evaluation, by adjusting for confounding factors and taking into account differences in key variables across countries, that can influence the results for a specific variable in each country. This is the approach proposed by the Medical Device Registries Task Force (MDRTF) in the US through the strategically coordinated registries network (CRN) [74]. The newly introduced unique device identification (UDI) implementation introduced by the EU MDR is certainly instrumental to the uptake of this new approach.

Registries' outcomes can be very relevant to payers who need to know how devices perform once diffused, in order to eventually decide whether coverage and reimbursement are to be confirmed. For example, to payers, information on secondary effects or impacts of devices would be very useful, as secondary effects, such as hospital re-admissions, affect the whole process of patient care, and impact directly on budgets.

In addition, when designing registries, it is important to anticipate the needs of payers in conducting HTAs. Registries are likely to be more useful to payers if they include several devices of the same type or group, so that comparative clinical data can be collected. The outcomes measured in registries should also include those of interest to patients and payers, such as use of key resources and, where possible, assessments of patients' quality of life. It is also important to include information on relevant covariates that can be used to adjust for known confounders in observational studies. Finally, it may be of interest to payers to enroll patients from different countries and settings, in order to explore the generalizability of clinical outcomes from one setting to another. Some payers have entered into various types of performance-based risk-sharing arrangements, such as 'coverage with evidence development' with device manufacturers. For example, several such arrangements were agreed between the Ontario Ministry of Health and manufacturers between 2000 and 2010 [75]. These arrangements take various forms but have the common feature that the device is approved for payment on the condition that more data on its clinical and cost-effectiveness are gathered. In principle, these arrangements appear to be particularly useful for MDs, given that the clinical data are often sparse when the device enters the market and there is an interest in assessing the effectiveness of

the device in regular clinical practice. However, there are several challenges in designing and conducting these arrangements [76].

In a nutshell, the clinical evidence needed in the diffusion, post-market stage, can be drawn from registries or other observational study designs. Registries must be reliable, accurate, and complete, i.e. they must contain all:

- patient-, device-, operator and organizational data;
- key covariates, clinical and patients' reported outcomes at baseline and follow-up;
- data of all other devices of the same type used in routine practice so to help support policymakers' evaluation;
- interoperability solutions that link complementary registries and data sources (e.g. electronic health records) can reduce their complexity and costs.

Therefore, stronger coordination at the EU level to leverage existing registries on same devices, currently scattered across different Member States, would be highly beneficial and would also help analyzing whether actual differences in routine practices in EU countries are truly preventing the EU from having a more centralized HTA process.

3.4. Obsolescence & replacement phase, post-market clinical evidence generation

The lifecycle of medical devices is normally shorter than drugs as products are replaced by newer, improved ones [77], often marketed by the same manufacturer. However, it is frequently the case that end-users and healthcare organizations are slow to adapt, which means that older devices tend to coexist with newer and more effective ones. In the very late stages of the product life cycle (i.e. obsolescence and replacement) guidelines need to incorporate new clinical evidence as soon as more effective devices enter the market, in order to inform end-users about stopping the use of old devices. Real-world data collection is important for old devices, until they are replaced by more innovative ones, since it frequently happens that a full picture of devices' performance, effectiveness, and adverse events is not clear except in the very long-run. If newer, more innovative devices' effectiveness and cost-effectiveness have to be compared with routine practice, it becomes important to gather sufficient clinical evidence for the standard of care, so to minimize uncertainty on its effectiveness, given that a certain degree of uncertainty would inevitably remain around the newer devices' performance till they progress through the learning curve.

Registries and electronic health records (EHR) can be appropriate at this stage to generate clinical evidence for old devices. Additional recommendations for EHR-based research on top of principled application of existing research and reporting guidelines have been proposed to improve the quality of EHR-based observational studies [78]. The digital transformation would also help in this regard as well as the development of a unique device identifier (UDI) for each medical device as prescribed by the EU MDR [1] and the US FDA [79] and its integration into EHR.

Recommendations for clinical evidence generation across the lifecycle of high-risk implantable medical devices are shown in Figure 2.

Q2: How could the evidence generation ecosystem be adapted to optimize patient access, considering the risks for patients, healthcare providers, payers and technology developers?

Clinical evidence generation for medical devices has traditionally been weaker than for drugs. This has led, in some cases, to scandals and loss of confidence among end-users and patients. The new EU regulations (MDR 2017/745 and 746) will improve the entire regulatory process for medical devices [1] and *in vitro* diagnostics [2], including clinical evidence generation. The stricter coordination at EU level will reduce, and hopefully eliminate, uneven assessments from Notified Bodies and competent authorities [5]. The EU MDRs are a great opportunity to improve the quality of clinical evidence across the entire life cycle of medical devices and to adopt a more participative approach that includes all stakeholders' perspectives.

Regulators, payers, HTA agencies, end-users and patients' perspectives would need to be taken into consideration, along the entire life cycle, from prototype development until abandonment and replacement of medical devices in order to minimize the risk to fail to deliver the potential benefits they could otherwise offer [33]. In this regard, the establishment of EU-level expert panels, who would advise both manufacturers and Notified Bodies on, respectively, the best study design to initially test devices' performance and efficacy and safety, and to assess manufacturers' clinical file, is an important innovation brought about by the MDR thus introducing a systematic 'early dialogue' approach. But this is not sufficient. Patients, payers, providers, and HTA agencies also need to be included in all phases, to streamline the whole process of clinical data generation so as to guarantee that promising medical devices, (i.e. those with an added value for the patients, end-users or the healthcare system), can progress from one step to another.

Thus, the new EU regulations offer a great opportunity to introduce a more integrated approach to decision-making and evidence generation for MDs, along the lines of the MARS Excite programme [80] in Canada. This programme is voluntary, and manufacturers can opt-in or not, depending on their perception of the value of early dialogue. However, in Europe, given the diversity among MS in the sophistication of HTA, a more coordinated programme would be beneficial. Given the plethora of MDs, even within Classes IIb and III, a key feature of such an integrated approach would be to determine the level of assessment required in each case. For example, minor modifications to existing devices, or new devices that are very similar to devices already on the market, may not need the same level of clinical assessment as devices that incorporate a completely new technology as also recommended by the MDR 2017/745 that has also introduced stricter requirements on when equivalence can be used as the basis for approval of a new high-risk medical device [58]. In addition, HTA could be quite 'light touch' if the new device is also not likely to have a premium price over existing ones. Therefore, priority setting to determine the level of assessments required will direct our efforts toward expedited

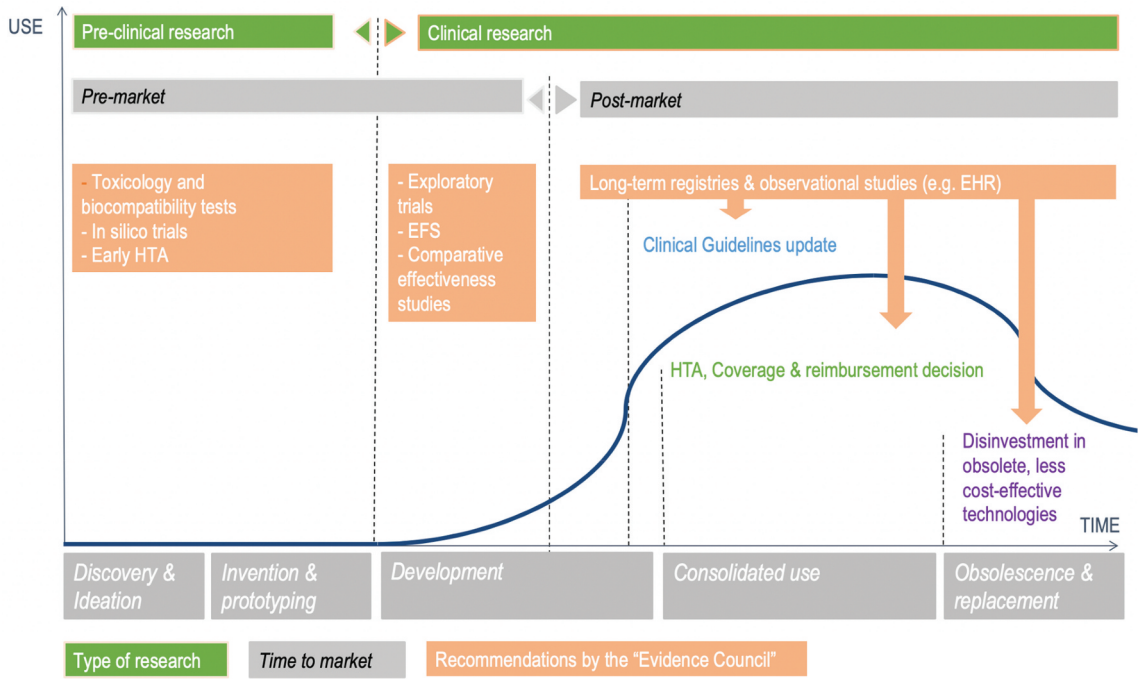

Figure 2. Recommendations on lifecycle evidence generation for high-risk implantable medical devices.

assessment for those new devices that have the potential to be clinically and cost-effective, to the benefit of patients and the health-care system more generally.

The issue of how best to deal with the assessment with 'fast follower' devices (i.e. those very similar to a device or devices already on the market) needs particular consideration. Drummond *et al* [81] suggest that, if a registry has been set up in order to gather more evidence on the original device of that type, similar new devices could be added to the registry. This approach would have the dual benefits of (a) sharing the burden and cost of evidence generation among all the manufacturers, rather than it being borne by the first to market and (b) enabling us to assess whether the devices are truly equivalent clinically.

This process will not come at zero costs. Manufacturers need to improve their knowledge of how the healthcare systems work and what the needs of different stakeholders are. Resources allocated to clinical evidence generation need to be prioritized and this can represent a challenge for small and medium-size companies. In such cases, a co-funding model may be applicable. In some jurisdictions, such as France, clinical development funding can be obtained from the State for MDs considered as 'innovative' (e.g. 50:50 funding for clinical trials) [82]. Similarly, conditional adoptions (e.g. coverage with evidence development schemes) are becoming common in many jurisdictions and do help the industry to introduce innovative devices even when effectiveness has not been fully assessed [76].

Payers are keen to be involved even in the pre-market stage and see benefits in horizon scanning at a central (e.g. EU) level to help plan for future costs. Questions from industry to payers should be framed in terms of collaboration/co-developers/partners rather than regarding them as 'assessors'. For payers, the main value drivers for a new device are the cost offset, the overall survival (OS) gain, and the quality of life gain (e.g. QALY) as well as other effectiveness measures. The payer wants to see data relevant to these variables that can be used to estimate the value. Although this estimation usually comes after regulatory approval, early data collection should anticipate payer's needs [47].

Patients' needs and expectations are to be considered at all stages of the evidence generation, since they are increasingly taking charge of their own health thus co-creating value. A disruptive wave of patient engagement is shifting health systems from a traditionally paternalistic, provider-focused stance to a new healthcare model that integrates patient experiences and preferences at all stages of the healthcare chain from basic and preclinical research to regulatory, market access, post-marketing surveillance, and disease management.

Finally, as mentioned earlier, it would be desirable if HTA agencies could contribute to clinical evidence generation since the early phases, i.e. pre-market, pre-clinical; by advising manufacturers and regulators on what the 'business case' should address in order to plan in advance a successful value proposition (e.g. target population, place in the care pathway) [33]. This is already the case in some jurisdictions and would be more widespread if there was a more integrated approach as discussed above.

4. Conclusions

Empirical evidence suggests that there is significant difference in the criteria used to evaluate high-risk implantable medical devices compared with high-risk pharmaceutical treatments [83]. Many authors argue that the evaluation of complex

medical devices is more challenging owing to a less well-developed regulatory evidence base and potential incremental improvements in efficacy over time. These arguments underline the importance of adequate evidence generation throughout the lifecycle of medical devices.

This overview seeks to address the issue of evidence generation for high-risk medical devices in European context. The issue is particularly relevant for the current policy agenda in the EU with the new MDR to come into force and HTA regulation under discussion. Our discussion also contributes to the scientific literature on the issue by uncovering the main challenges of evidence generation in different stages of lifecycle of medical devices and provides suggestions on how best to overcome these challenges.

5. Expert opinion

Recent safety scandals and the COVID-19 pandemic have emphasized the issue of evidence generation for access to market of medical devices (MDs). While healthcare professionals were calling for new *in vitro* diagnostics that could more rapidly detect positive cases and hospitals were desperately searching for more life-saving devices to equip their intensive care units, governments and regulatory bodies struggled to keep the right balance between patients' and professionals' needs to access the technologies as quickly as possible and the necessity to assess whether they were safe and effective.

Evidential requirements for MDs have been the subject of debate for many years and in several jurisdictions. The regulatory systems for MDs have traditionally been less demanding in terms of clinical evidence generation compared with those for drugs and this is one of the reasons why MDs often gain market access with insufficient evidence to safely protect patients and to inform health policy decisions, such as coverage and reimbursement [84]. Moreover, MDs' performance can often only be fully assessed after their use has become routine clinical practice. Regulatory and HTA agencies, as well as scientific organizations and societies, are trying to improve the current state of art, either by explaining why medical devices must be treated differently from drugs or by providing recommendations on the types of evidence needed to access the market. One interesting stream of research is the one that considers clinical evidence generation across the entire lifecycle of MDs. This is what the new EU Regulations on MDs and vitro diagnostics embrace. Also, if the proposal for an EU HTA Regulation were to pass, the whole lifecycle of medical technologies would be covered by the European Commission and a complete and comprehensive vision of clinical evidence generation would be needed.

Although several advances have been made in some jurisdictions for the type of evidence required to evaluate medical devices along their development phases, these are scattered across the countries of the EU and no uniform vision exists. Lack of consistency across countries, especially between Members States in EU, could prevent the new Regulations from achieving their objectives and the MedTech industry from allocating R&D investments at the right time and in the right clinical studies.

The lifecycle of medical devices can be characterized in pre-clinical pre-market; clinical pre-market; diffusion, post-market; and obsolescence & replacement, post-market. However, each stage must be prodromic to the next, so that a long-term, strategic vision would govern the development of clinical studies across the entire lifecycle. In other words, manufacturers must have a clear idea of the 'business case' for their product from the very beginning and must clarify the value proposition, knowing that indications, target populations and the expected added value may change as long as the product's evidence is developed. However, these efforts must not be on manufacturers' shoulders alone. Regulatory bodies, HTA agencies, patients' organizations, payers, end-users and providers, all can contribute to improving clinical evidence generation for MDs, through participating in the development of designs for clinical studies at all stages. Early dialogue and engagement with all stakeholders are essential, especially if their involvement makes them feel co-creators rather than stakeholders.

Declaration of interest

Zenith Healthcare contributed to the 'Evidence Council' work by helping with the organization of the two meetings held in Milan (Sarah Bradbury, Event Manager) and with the preparation of the minutes of the first (John Bull, Medical Writer) and second round meetings (Colin Griffin, Medical Writer). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Appendix 1. Members of the Evidence Council

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Ulf Persson	Professor, IHE, Swedish Institute for Health Economics, Lund University, Sweden
Reiner Leidl	Professor of Health Economics and Healthcare Management, Ludwig-Maximilians University, Munich and Institute of Health Economics and Healthcare Management, Helmholtz Zentrum München – German Research Center for Environmental Health (Gmbh) Neuherberg, Germany
Leslie Levin, MD	Chief Executive Officer & Scientific Officer at EXCITE International, Toronto, Canada
Laura Sampietro-Colom	Deputy Director of Innovation, Head of Health Technology Assessment Unit at Hospital Clinic Barcelona, Spain
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