

## SYNTHESIS

# EVIDENCE GAPS FOR DRUGS AND MEDICAL DEVICES AT MARKET ENTRY IN EUROPE AND POTENTIAL SOLUTIONS





## **SUMMARY**

# **EVIDENCE GAPS FOR DRUGS AND MEDICAL DEVICES AT MARKET ENTRY IN EUROPE AND POTENTIAL SOLUTIONS**

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## ■ SUMMARY

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## 1. INTRODUCTION, OBJECTIVE AND METHODOLOGY

Healthcare has an ethical dimension, given that its purpose is to prevent and alleviate human suffering. However, healthcare has also become one of the most important economic sectors. According to the figures of the European Federation of Pharmaceutical Industries and Associations (EFPIA), which were cited in a recent analysis by Garattini<sup>1</sup>, the pharmaceutical industry contributes more than 110 billion euro to the trade balance of the European Union and employs over 800 000 people in Europe. However, the author also emphasises the downside of this leading sector: "Certain medicinal products with relatively little utility and 'innovations' that are not really worthy of the name constitute a major cost for payers. This cost could be limited to the benefit of other activities that contribute more to public health." Here he cites a 2020 study by the independent French scientific journal *Prescrire*. It appears from this study that only 10% of the medicinal products that received marketing authorisation in 2019 had added therapeutic value.<sup>1</sup> These figures are also confirmed by Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), the German Institute for Quality and Efficiency in Health Care.<sup>1</sup> A recent report by the KCE on innovative cancer drugs also confirmed that the added therapeutic value in overall survival and quality of life is very limited for patients with advanced cancer, despite the impressive price tag.<sup>2</sup>

A special feature of the healthcare market is that most of the bills are paid by health insurance or public payers. The medicinal products and medical devices sector is subject to industrial policy and public health policy at the level of Europe and the member states. This results in a delicate balancing act. Moreover, the clinical development of medications and devices has a more and more global dimension. Within the European Commission, powers in the field of medical devices have been transferred from the Directorate-General for Health to the Directorate-General for Enterprise and back again, illustrating the tension between economic interests and public health.

In Europe, market regulation is a centralised competence of the EU, while the member states are authorised to organise and finance healthcare. Because it is important to assess the safety and effectiveness of interventions compared to existing alternatives, most member states have set up an agency for the evaluation of new health technologies (Health Technology Assessment, HTA). This has taken place either under the auspices of the healthcare payer, or as a separate agency that advises the healthcare payers. The aim of HTA is to ensure fair and commensurate reimbursement for sometimes very expensive innovations. The HTA bodies often work with the same clinical study data that have been submitted to the European regulatory bodies to obtain market access. The HTA agencies must however assess the added therapeutic value of the new product and its cost-benefit ratio compared to that of the standard of care in effect. This is always a comparative evaluation, and a different task from that of the regulatory bodies. **In this report we examine the lack of comparative evidence HTA agencies and payers face in evaluating new medicinal products and high-risk medical devices at market entry.**



## 1.1. Market access is regulated at the European level, while reimbursement is determined by the member states.

### 1.1.1. Medicinal products

In both Europe and the United States, the regulation of market access for **medicinal products is primarily centralised**.<sup>a</sup> In Europe the **European Medicines Agency (EMA)** is authorised to do this; in the US it is the Food and Drug Administration (FDA). Marketing authorisations are issued on the basis of the **quality, safety and efficacy of the medicinal product and a favourable benefit-risk ratio**. This does **not** mean, however, that an **added therapeutic value or equivalence compared to existing alternatives** must be demonstrated. Usually at least **two randomised controlled trials (RCTs)** are requested, the clinical data of which are summarised and made available in a public document, the **European Public Assessment Report (EPAR)**.

Changes in the laws and regulations in Europe and the US have led to a complex mix of programmes for accelerated access to new medicinal products.<sup>3</sup> Naci et al. (2020)<sup>3</sup> have shown that the proportion of EMA medicinal products approved annually on the basis of at least one RCT with an active comparator between 2015 and 2018 was only one quarter to one half. It can of course be that no active comparator is available for some new medicinal products, but then the new medicinal product can still be compared with the best supportive care.

We have not examined the scientific developments or pressures (policy, a presumed demand from patients, industry, competition between regulators, etc.) that have induced the regulators to lower the bar for clinical evidence. A general but unsubstantiated assertion is that patients would be prepared to accept greater uncertainty as to the possible utility just to get faster access to inadequately tested medications. On the other hand, it is the case that

patients and sometimes also caregivers have little knowledge of the clinical requirements necessary for market access of medicinal products or medical devices.<sup>4</sup>

Under existing reimbursement practices, it is in the interest of companies to only satisfy the requirements for market access. The time needed to come to market and obtain reimbursement is an important factor in calculating the return on investment. For a company, conducting a confirmatory comparative trial entails more risk, more costs and/or a longer lead time. The EMA initiatives to issue marketing authorisation more quickly on the basis of non-randomised studies or non-validated surrogate markers has the consequence that the efficacy remains unknown. The consequence is also that the population studied, comparators used, and endpoints that are sufficient for the EMA may not allow an HTA to be conducted, and also do not allow physicians to practise evidence-based medicine. Specialist physicians in various fields have in fact indicated that there is a need for more comparative clinical trials.<sup>5-8</sup>

The erosion of the clinical requirements for marketing authorisation by the EMA and the FDA<sup>9</sup> over the past decades can be seen as a reason for the increased 'evidence gap' at market entry that is seen by HTA bodies and healthcare payers.

**Reimbursement under health insurance is a national competence (i.e. under national jurisdiction)**, sometimes even with regional autonomy within a member state. Because **there is currently no requirement to conduct comparative trials for marketing authorisation**, the data in the dossiers are sometimes insufficient to support a decision on reimbursement.

If comparative evidence is not provided in the pre-marketing period it may be possible to obtain this evidence after the medication has been put on the market. The business community criticises the lack of coordination between regulators, HTA organisations and payers, claiming that it leads to a

<sup>a</sup> In addition to the centralised procedure, where the application is submitted directly to the EMA, each Member State has its own national authorisation procedure for medicinal products that are not subject to the mandatory centralised procedure.



multitude of post-market demands on the companies with regard to evidence, requests they cannot always fulfil.<sup>10</sup> Thus, the EMA talks about “post-authorisation measures”, and healthcare payers talk about “coverage with evidence development” (CED) or “managed entry agreements” (MEA). From reports on the collection of evidence in the **post-market** period, whether this is requested by regulatory bodies or payers/HTA bodies, it appears that **major uncertainties continue to exist regarding the provision of data on comparative effectiveness**.<sup>11</sup> For example, Davis et al. (2017) determined that most cancer drugs come on the market without clear evidence that they improve the survival or quality of life of patients, and that added value is only rarely demonstrated for these endpoints via a randomised study following market access of these cancer drugs.<sup>12</sup> The consequence is that for approximately half of the oncology drugs that have been on the market for a median period of 5 years, it is not yet known whether there is any benefit with regard to the overall survival.<sup>12</sup> Over half of the obligations placed on the company after a medication has been brought onto the market via a conditional authorisation by the EMA are postponed.<sup>13, 14</sup> In 6 of the 18 cases the FDA has even taken no action after the oncology drug showed no effect on overall survival in the post-market phase.<sup>15</sup> The lack of comparative evidence generated in the framework of CED or MEA initiatives by healthcare payers makes it virtually impossible to make evidence-based decisions on this basis.<sup>16, 17</sup> **For all these reasons, the emphasis in this report is on the pre-market trials.**

### 1.1.2. Medical devices

Medical devices constitute a wide range of products, from wound dressings to radiotherapy equipment and implants. This report deals only with high-risk medical devices (Class IIb and III). Regulation in Europe is centralised. Access to the market consists of a “**CE marking**” (Conformité Européenne) that the producer may affix to the medical device. Control of this marking falls within the competence of **conformity assessment bodies (notified bodies)**. These notified bodies are usually companies. They are accredited by the government of the member state where they are located. The clinical data that notified bodies request for approving a CE marking are rather limited, even for high-risk medical devices. Only the **safety** and **performance** of the medical device must be demonstrated to obtain a CE

marking, along with an acceptable benefit-risk ratio. Many medical devices also come onto the market in Europe on the basis of a literature review of similar devices rather than direct clinical data, thus without clinical studies of their own. In Europe, it is not necessary to demonstrate the efficacy of the medical device or conduct comparative studies. The CE marking system trusts that the necessary evidence of safety and effectiveness will be provided after the product is placed on the market. Studies of high quality are however seldom performed after the device is placed on the market<sup>18</sup>. Yet, physicians who implant cardiovascular or orthopaedic devices even consider reporting of adverse events with medical devices to be unnecessary, impossible or pointless for various reasons.<sup>19</sup> All of this leads to serious underreporting of possible problems.<sup>20, 21</sup>

In the United States, the **effectiveness** of innovative devices must be proven, for example, with a randomised study of the medical device used during a procedure in comparison with a sham procedure. Due to the differences in the European and American approaches, innovative medical devices are often available more quickly on the European market, but on the basis of minimal clinical data.

Prior to the introduction of the new European regulation on medical devices (MDR) in Europe, clinical data on medical devices did **not** have to be **made public upon market introduction** (in contrast to that on medications). This has been partially modified under the new regulation (see below).

### 1.1.3. Changes in the European regulations

The situation as described above may partially change with the **arrival of various new European regulations**:

- The old Directives with regard to CE marking of **medical devices** are being replaced as of 26 May 2021 (26 May 2022 for *in vitro* diagnostic medical devices) by a **new regulation (EU) 2017/745 (Medical Device Regulation, MDR)** that amends the rules applicable to medical devices, especially those with a high risk.
- The Commission has also planned a revision of **2001/83/EC and Regulation (EC) 726/2004 on medicinal products** by the end of 2022.



- A **new regulation on clinical studies (Clinical Trials Regulation – CTR)** will also replace the current directive. This regulation formally took effect on 16 June 2014, but its implementation has been delayed and is now anticipated for 31/01/2022.
- Finally, there is the **European regulation on health technology evaluation (Health Technology Assessment, HTA)** that will amend Directive 2011/24/EU. This is in the final stages of preparation.

These new legislations are analysed in detail in the scientific report and a summary can be found in Chapter 4 here.

## 1.2. Initiatives that have increased the evidence gap and initiatives to reduce the evidence gap

As noted above, the various initiatives that the EMA developed to accelerate market access for medicinal products have also meant that the available clinical trial data upon marketing authorisation provide less certainty regarding the efficacy of the medicinal product, and even less regarding the relative effectiveness compared to existing alternatives (comparative effectiveness).<sup>22</sup>

In recent years various initiatives have been taken to close the growing gap – the evidence gap – between the decreasing requirements of EU regulators for marketing authorisation and the higher expectations for comparative effectiveness or comparative evidence by the HTA bodies and the payers. These HTA requirements are also of course related to the high prices being asked for new medications for which the companies claim added therapeutic value.

- Companies that develop **new medicinal products** can ask HTA agencies to give them advice in outlining the design of confirmatory clinical studies. This step, called '**early dialogue**', or more recently under the HTA regulation '**Joint Scientific Consultation**', is not mandatory, implies no prejudgement of the study results and is not legally binding. For medical devices, this initiative is still in its early stages.

- Since 2010 the EMA has also given pharmaceutical companies the opportunity to simultaneously ask for scientific feedback from the EMA and the HTA agencies on the planned clinical studies for new medicinal product. In this procedure of '**Parallel Scientific Advice**', the producer gives a description of the clinical development plans for a new medicinal product and submits a series of specific questions (and its own answers) to the EMA and the HTA agencies. In this case, the manufacturer chooses the HTA agencies to which these questions are directed. The HTA agencies voluntarily take part in the procedure.
- The competent authorities and the HTA agencies of the member states can also give scientific advice separately, but not all HTA agencies offer this service.

The HTA recommendations are not binding and the impact has been limited up to now. As a rule, companies follow the recommendations of regulators, but seldom follow the HTA recommendations (or not at all).<sup>23</sup>

## 1.3. Objective of this study and study questions

Healthcare payers, HTA bodies, and clinicians want a randomised comparison of the new intervention with the standard treatment. This is considered essential for being able to reliably assess any therapeutic benefits. This RCT is best conducted in a representative patient population and with outcomes that are relevant for patients (quality of life, symptoms, functional outcomes and, for life-threatening conditions, overall survival). The clinical study data that lead to market introduction also support the reimbursement procedure. Do these study data satisfy the requirements of HTA bodies and payers for the assessment of added therapeutic value? The aim of this study was to answer this question and to identify any gaps in the needed evidence.

The publication of this study comes at an opportune time, as it coincides with the introduction of the new European regulation on medical devices, the finalisation of the HTA regulation, and the revision of the regulations for medicinal products.



The study questions are:

- 1) What comparative evidence gaps exist at market entry of medicinal products and high-risk medical devices for which a comparison with the standard treatment is indicated, for example for research on added therapeutic value?
- 2) What are the possible solutions for preventing these evidence gaps during clinical development in the pre-marketing phase? Methodology

This project attempts to clarify the evidence requirements and the evidence gaps from various perspectives and with the aid of various information sources. For every source, a specific methodology was followed that is explained in its relevant chapter.

- An overview of the legal framework with regard to the evidence requirements for putting medicinal products and high-risk medical devices on the market in Europe. This is based on a combined analysis of legislation, court rulings and legal literature (Chapter 3 of the report). No systematic literature review on ethical or legal topics was conducted, however.
- A brief overview of the evidence gaps reported by INAMI/RIZIV in the evaluation dossiers of medical devices or medicinal products with a claim of added therapeutic value by the applicant for each for which a reimbursement dossier was submitted to INAMI/RIZIV in recent years, (Chapter 4)
- A literature study of the evidence gaps or general trends in levels of evidence for a group of new medicinal products or high-risk medical devices upon market access (Chapter 5)
- In the discussion chapter (Chapter 6) the findings are put into context and possible solutions are discussed, such as more efficient methods for randomised clinical trials or limitations of observational data. No additional systematic literature study was conducted for this, however.

In addition, external experts and stakeholders were consulted as follows:

A consultation with a group of experts in the field of medicinal products or high-risk medical devices from selected public HTA/payment institutes in Austria, Belgium, France, Germany, Ireland, Norway, the Netherlands and the UK, with the aid of a two-hour videoconference. A draft report was distributed in advance, and during the meeting, a summary of the most important findings were presented for discussion and for the collection of opinions from experts and additional references.

A similar consultation with a group of experts in the field of legislation, ethics and regulation and a group of physicians, expert in the field of medicinal products or high-risk medical devices, primarily authors of publications on the topic of this report.

Presentation of the most important findings of the report to, and feedback from, representatives who represent the Belgian and European medical device and pharmaceutical industry.

### Frequently used terms

- **Efficacy:** the extent to which an intervention does more good than harm under ideal circumstances.
- **Effectiveness:** the extent to which an intervention (medicine / medical device) does more good than harm when provided under the usual circumstances of healthcare practice; the meaning is similar to comparative effectiveness as the reference is the standard of care. The associated evidence is referred to as comparative evidence in this document.
- **Comparative efficacy:** the extent to which an intervention does more good than harm, under ideal circumstances, compared with one or more alternatives for achieving the desired results.
- **Comparative effectiveness:** the extent to which an intervention does more good than harm compared with one or more alternatives for



achieving the desired results when provided under the usual circumstances of healthcare practice.

- **Placebo:** inert substance provided to research participants to make it impossible for them, and usually the researchers themselves, to know who is receiving an active or inactive intervention. Clinical trials of medical devices that are part of a procedure may sometimes use a sham procedure for blinding.
- **Active control trial:** two-group experimental design in which one group receives the treatment under study and the second group receives a standard treatment.
- **Placebo-controlled trial:** a clinical research design that incorporates a placebo control group. There are two situations. The patients randomised to the placebo arm receive either the placebo in addition to the standard of care treatment (active treatment arm with placebo on top) or they only receive placebo (placebo only, without the standard of care active treatment). Of course, the latter will always be the case for indications for which no active treatment exists.
- **Standard of care** (definition by the National Cancer Institute, US, <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/standard-of-care>) is treatment that is accepted by medical experts as a proper treatment for a certain type of disease and that is widely used by healthcare professionals. Also called best practice, standard medical care, and standard therapy.
- Usual care<sup>24</sup> is a term used to describe the full spectrum of patient care practices in which clinicians have the opportunity (which is not necessarily seized) to individualize care. Usual care can refer to a (pragmatic) clinical trial control group receiving genuine (but documented) usual care as supplied in everyday practice. Pragmatic trials are performed to determine whether the intervention can improve current practice. In many papers and in this report however no distinction is made between the terms “usual care”, “standard of care” and “normal clinical practice”.

- **State of the art** (only for medical devices, definition by the Medical Devices Coordination Group, MDCG): Developed stage of current technical capability and/or accepted clinical practice in regard to products, processes and patient management, based on the relevant consolidated findings of science, technology and experience. Note: The state-of-the-art embodies what is currently and generally accepted as good practice in technology and medicine. The state-of-the-art does not necessarily imply the most technologically advanced solution. The state-of-the-art described here is sometimes referred to as the “generally acknowledged state-of the-art.”
- **Added therapeutic value:** the incremental therapeutic value brought by a new drug or medical device compared with the best available treatment options already on the market (also referred to as standard of care, usual care or state of the art).
- **Surrogate endpoint:** surrogate endpoints act as substitutes for clinical endpoints and are expected to predict the effect of therapy (benefit and/or harm). An improvement in a surrogate endpoint may or may not be perceived by the patient. In many cases, surrogate endpoints do not themselves directly measure a clinical benefit. The validation of a surrogate marker is complex and is valid only for a single mechanism of action in a single indication.
- **Clinical evaluation:** term used in the medical device regulation, a systematic and planned process to continuously generate, collect, analyse and assess the clinical data pertaining to a device in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer. Note that clinical data can come purely from the literature on a predicate device and does not necessarily require any clinical data on the actual device.
- **Clinical investigation:** term used in the EU medical device regulation, amongst others, for a clinical study investigating a medical device.



- **Pivotal/confirmatory study:** trial designed to demonstrate and confirm the safety and efficacy of a treatment, such as a drug candidate or a medical device, and to estimate the incidence of common adverse effects.
- **Adaptive platform trial:** trial studying multiple interventions in a disease or condition in a perpetual manner, with interventions entering and leaving the platform on the basis of a predefined decision algorithm.<sup>25, 26</sup>
- **Horizon scanning:** a process to identify important innovations before they reach the market.

## 2. ETHICAL AND LEGAL CONSIDERATIONS

The legal provisions concerning the marketing of medicinal products and medical devices and those concerning clinical studies determine the evidence that is needed to be able to put these products on the European market.

These legal rules primarily focus on the protection of public health, with respect for the principle of free movement of goods. They are closely linked to human rights, in particular the right to life, physical integrity, and health. They should also be analysed in the light of the ethical rules applicable to clinical research, on which they are expressly based.

The interested reader will find a thorough analysis of the ethical and legal considerations connected with marketing medicinal products and medical devices in Europe in Chapter 3 of the scientific report. In this summary, we limit ourselves to summarising the most important principles needed to understand the answers to the study questions.

### 2.1. Ethical standards on the provision of evidence and transparency

Ethical standards for clinical studies are a set of moral principles that aim to protect the rights, safety, and dignity of those who participate in research. The most widely recognised ethical text is the **Declaration of Helsinki (1964)**<sup>b</sup>. As the rules of this Declaration are not promulgated by legislative authorities but by an international association, these rules, despite their great moral authority, fall within a framework separate from the legal framework. The Declaration prescribes, among other things, that clinical studies must be registered and their results must be published.

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<sup>b</sup> <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>



In the Declaration, it is also stipulated that, in principle, every new intervention that is tested in humans (for example, a new medicinal product or medical device) must be compared with existing, proven interventions. Comparison of a new intervention with a placebo/sham intervention or with a less effective intervention must be considered an exception only allowable on the basis of a sound scientific justification and if the patients are not exposed to extra risks of serious or irreversible harm due to this.

## 2.2. European legislation on medicinal products

### 2.2.1. Evidence requirements

The movement of medicinal products on the European market is primarily based on **European Directive 2001/83/EC on medicinal products for human use**. This directive is first of all based on **the benefit-risk analysis** of the product, but this analysis is primarily focused on the **safety** and **efficacy** in absolute terms and not the comparison with existing treatments. Manufacturers must therefore demonstrate the safety and effectiveness of their product by means of clinical studies, randomised if possible, but they are not required to compare the new product with existing alternatives.

In applying this legislation, the EMA uses a flexible approach in which it acknowledges the possible scientific value of **comparative effectiveness studies**, but strongly emphasises the utility of a placebo arm.

### 2.2.2. Procedure for the authorisation of clinical studies

The legislation on clinical drug research entrusts the ethical assessment of studies, including their design, to the medical ethics committees and national authorities competent to authorise such studies. This is a very important responsibility. As ethics committees are regulated at the national level, it is possible that they are not organised and funded/supported in the same way everywhere in Europe, with the risk of competition and differences in the quality of the ethical analysis.

A **new regulation on clinical studies (CTR)** will also soon replace the current directive on conducting clinical studies with medicinal products for human use (CTD).

This new regulation aims to simplify and rationalise the procedures, in particular for ethics committees. In this regard, the CTR allows the member states to limit the examination by ethics committees to certain aspects of the study (such as consent, financial compensation, etc.). This possibility deviates from the Declaration of Helsinki, in which it is specified that the protocols must be examined by ethics committees. This differs from the previous directive, which did not provide member states this possibility. This could weaken the protection of test subjects and reduce the quality of clinical evidence.

### 2.2.3. Transparency requirements

The new CTR regulation also provides for **more transparency** of the data and results of clinical studies and requires the establishment of a **centralised databank for the entire EU, called the CTIS** (Clinical Trials Information System). The **results** of clinical studies with investigational medicinal products must be published within a year after completion of the trial (6 months for paediatric trials), but this rule is not really observed (68.2% compliance). In Belgium, there are no penalties for noncompliance (in contrast to the provisions for medical devices).

The CTR provides certain exemptions however to protect personal data, commercially confidential information and confidential communications between member states in the preparation of their evaluation. In the traditional viewpoint of the EMA, commercially confidential information is defined as information the disclosure of which could unreasonably damage the commercial interests of persons or businesses. The EMA has however recently stated that clinical data cannot be routinely considered commercially confidential information.



## 2.3. European legislation on medical devices

### 2.3.1. Evidence requirements

The current regulation on medical devices is gradually being replaced by the new **EU Regulation 2017/745 on medical devices**, which took effect in May 2017 and became fully applicable on 26 May 2021 (for *in-vitro diagnostic* medical devices it is 26 May 2022). Various transitional provisions remain in force, however, and CE markings that were issued under the old directive remain valid until the expiry date of the certificate (or until 26 May 2024 at the latest).

As stated in the introduction, medical devices – in contrast to medicinal products – are currently subject to a certification procedure in Europe resulting in a **CE marking** that ensures that the devices "satisfy the essential requirements" with regard to safety and performance in normal use, and that their benefit/risk ratio is acceptable. For medical devices with medium-high and high risk. This compliance is assessed by **notified bodies**, usually for-profit organisations, with which the manufacturer has a contract.

Both the old directive and the new MDR require **clinical studies for all Class III medical devices**. These studies need not, however, necessarily be randomised clinical trials (RCTs), nor do they have to involve (comparative) clinical effectiveness. There are no specific requirements with regard to design, scope or duration of the study.

The **new MDR** has tightened the rules somewhat by requirements that "clinical performance" and "clinical benefit" be demonstrated. In addition, in the clinical evaluation (which differs from a clinical trial) other available treatment options must be taken into account. It is also new that the regulatory bodies and notified bodies of the EU for high-risk devices will have access to **independent Expert Panels** via a procedure called the **clinical evaluation consultation procedure**. These experts can also be consulted voluntarily by an individual manufacturer. This is an important innovation.

Finally, the term "**equivalence**" is now be defined - the absence of a definition of this term was considered a shortcoming of the previous directives.

### 2.3.2. Authorisation procedure for clinical research

The MDR provides for a rather similar procedure for approval of clinical research for the purpose of placing the device on the market (other clinical research does not fall within the regulation). These clinical studies may, in principle, only begin if the competent ethics committee has not issued a negative opinion of them and the competent national body has given authorisation for them.

This review is also organised at the national level in practice. The European regulation, in contrast to a directive, is however directly applicable, so that the member states have less room for interpretation. In Belgium, the Royal Decree on clinical studies with medical devices specifies a clear division of tasks between the competent authority (FAMHP) and the ethics committees (see Appendix 1.4 of the report). Both the competent body and the ethics committees are responsible for: assessment of the expected benefits for the participants in the clinical research; the assessment that the clinical research is being conducted according to a suitable research protocol that complies with the state-of-the-art science and technology; and the assessment that the clinical research includes a sufficient number of observations to ensure the scientific validity of the conclusions.

### 2.3.3. Transparency requirements

The new MDR increases the transparency requirements for high-risk devices and obliges the manufacturer to summarise the most important safety and performance aspects of its product and the results of the clinical evaluation in a document accessible to the public (**Summary of Safety and Clinical Performance - SSCP**). This document must, in particular, contain a description of the position of the device among the existing alternatives, taking account of the clinical evaluation of the device in relation to these alternatives. Misleading information can be cause for legal action. The SSCP will **be available to the public** via the long-awaited **EUDAMED databank** (see Box 2)



### The EUDAMED databank

The establishment of the EUDAMED databank for medical devices (<https://ec.europa.eu/tools/eudamed/#/screen/home>) is one of the most important aspects of the new regulation on medical devices.

EUDAMED aims to enhance overall transparency, including better access to information for the public and healthcare workers, and to improve coordination between the various member states of the EU. It will incorporate various electronic systems for collecting and processing information on medical devices and their manufacturers.

EUDAMED will consist of six modules that concern registration of stakeholders, unique device identification (UDI) and registration of devices, notified bodies and certificates, clinical research and performance research, post-marketing vigilance and market surveillance.

### 2.4. European evaluation of health technology

A **proposal for an EU regulation on the HTA** amending Directive 2011/24/EU is currently in the final stages of the EU legislative process. The proposal aims to introduce a **centralised HTA assessment procedure** at the EU level for certain medicinal products and medical devices. It should also ensure that the methodologies and procedures applied in the HTA become more predictable throughout the EU. The HTA and the marketing authorisation will remain two separate frameworks ("due to their different purposes"), but synergies will be created (mutual exchange of information, coordination of the timing of the procedures). Uncertainties continue to exist on the methodology, the obligation for developers to provide all available information, and the opportunity for member states to conduct additional HTAs.

## 3. ANALYSIS OF THE INAMI/RIZIV DOSSIERS

In Belgium, applications for reimbursement (reimbursement dossiers) for new technologies are submitted to, and assessed by, INAMI/RIZIV. In July 2019, the KCE submitted a request to be allowed to consult the most recent INAMI/RIZIV assessments of reimbursement applications for medicinal products and medical devices for which the applicant claimed added therapeutic value (regardless of the ultimate decision on reimbursement).

For medicinal products, 8 class-1 dossiers (innovation with claimed added therapeutic value) and 10 dossiers for orphan drugs were analysed. Most dated from the first half of 2019. The assessments of the INAMI/RIZIV (or, more precisely, of the Drug Reimbursement Committee, DRC) are usually made available on the INAMI/RIZIV website, although that does not always happen immediately. For this project, the KCE was able to view assessments that had not yet been published.

Assessments of medical devices are not routinely available to the general public. The KCE was able to view the assessment reports and the replies of the companies for 20 high-risk (class 2b/3) medical devices. The assessments dated from 2018 and the first half of 2019. Two dossiers were still incomplete at the time the report was drafted and were not included in the analysis.

In all, we thus examined the assessments of 36 INAMI/RIZIV reimbursement dossiers, 18 for medicinal products and 18 for high-risk medical devices, in which the applicant claimed an added value. The intention was not to discuss dossiers individually but to identify general trends.



**Table 1 – Evidence gaps reported by INAMI/RIZIV evaluators for reimbursement dossiers for 18 medicinal products and 18 high-risk medical devices**

**RIZIV-INAMI reimbursement dossiers,  
claiming added value (2018/19)**

PICO	Issue	Non orphan drugs (N=8)	Orphan drugs (N=10)	High-risk devices (N=18)
Patients	Subgroup not studied	2	4	2
Intervention	Different device studied			2
Comparator	No RCT		3	12
	No active control RCT; inappropriate comparator	5	3	
Outcome	Short term surrogate, no long term outcome	2	6	2
	No quality of life data; no functional outcomes	1	8	9

*Note that this only includes the problems explicitly reported by the INAMI/RIZIV assessor.*

**3.1.1. Results for the 18 assessment dossiers for medicinal products**

- 15 of the 18 dossiers included at least one RCT. For the other 3 there was no RCT; these involved orphan drugs.
- Of the 15 RCTs, there were 8 for which the comment was that the comparator was inappropriate (placebo in 7 of the 8 cases).
- In 6 of the 18 applications the exclusion from the trials of an important part of the target population was considered problematic.
- In 8 of the 18 applications the outcomes were considered problematic, primarily because short-term surrogate endpoints were used without evaluation of the long-term results (for example the quality of life and/or overall survival).

**3.1.2. Results for the 18 assessment dossiers for medical devices**

- Two applications were problematic because the population studied was different from the target population for which reimbursement was requested.
- In 12 of the 18 dossiers there was no RCT and data only on prospective (11/12) or retrospective (1/12) cohort studies.
- In 6 of the 18 dossiers there were results of at least one RCT, but in 2 of the 6 the RCT was conducted with a device other than the device for which reimbursement was requested.
- 9 of the 18 dossiers contained no data on the quality of life or other relevant outcomes for patients, such as overall survival.
- In 2 applications the lack of sufficiently long-term results was considered problematic.

In the discussion we consider these results further.



## 4. LITERATURE STUDY

The literature study focused on publications examining the lack of scientific evidence (evidence gaps) **for marketing** medicinal products or high-risk medical devices. Publications in which only one product was discussed were not considered. In addition, we also examined examples of evidence gaps in the grey literature, references cited in the selected publications or applied by external experts. The detailed results and the search strategy can be found in the scientific report. Here we discuss the most important aspects.

### 4.1. Medicinal products

The first general finding of this literature study was already noted in the introduction, namely that the scientific evidence provided for obtaining marketing authorisation **is frequently considered insufficient by the assessors of the HTA agencies**. This causes important uncertainties for the decision-making procedures on reimbursement.

For 42% of 68 oncology indications approved by the EMA in the period 2009-2013, no data were available on overall survival upon approval.<sup>12</sup> After at least 3 years of follow-up, this proportion was still 38%. Another important parameter, improvement in quality of life, was only seen in 10% of the dossiers upon approval. For approximately half of the cancer drugs that have been on the market for 5 years (median) there is still no evidence of improvement in overall survival or quality of life.<sup>12</sup> A similar lack of high-quality scientific evidence was also identified for orphan drugs, both at the time that they came onto the market and a number of years later.<sup>18</sup>

In general, the efficacy and safety of new medicinal products must be demonstrated by means of **at least 2 RCTs**, but this rule was only followed in somewhat more than 50% of the medicinal products approved by the EMA (2014-2019).<sup>27</sup> Moreover, HTA agencies and payers, in contrast to the regulatory bodies, request that these RCTs make use of **a direct comparison with the standard of care** and that they measure outcomes that are relevant for the patient, such as **overall survival, quality of life, symptoms or functional outcomes**, instead of non-validated surrogate endpoints. That is only rarely the case, however. Tafuri et al. (2016)<sup>28</sup> found

that for the parallel advice procedure the advice by the regulatory bodies and the HTA agencies differed in 23% of cases with regard to the population studied, in 56% of cases with regard to the comparator, and in 41% of cases with regard to the endpoints. The differences in the viewpoints of regulatory bodies and HTA agencies/payers are especially pronounced when conditional authorisations are involved.

Historically, companies have attached more importance to the requirements of the regulatory bodies than to those of the HTA agencies,<sup>23</sup> which moreover can also differ from country to country. Therefore, various authors recommend providing multiple opportunities for **collaboration and dialogue between producers, HTA agencies and payers** from the beginning of development of a new product. This should allow the strategies for generating scientific evidence (pre- and post-marketing) to be coordinated and the (common) requirements of the HTA agencies to be satisfied from the beginning.

The introduction of accelerated procedures has meant that more limited, shorter, and less expensive studies have been conducted and that surrogate markers (surrogate endpoints) are more often used. In approximately half of the accelerated procedures (in particular, conditional marketing authorisations by the EMA) the HTA agencies gave a negative opinion on reimbursement, not only due to the lack of scientific evidence but also due to the price and the consequences for the healthcare organisation.<sup>29</sup> Thus accelerated procedures for a conditional marketing authorisation do not always lead to reimbursement and faster access to these medicinal products for patients.

In addition, some authors request that the results of the RCTs be published more comprehensively in the EPARs, trial registers and peer-reviewed



articles for the sake of transparency. The German AMNOG documents<sup>c</sup> (*Arzneimittelmarkt-Neuordnungsgesetz* – Pharmaceuticals Market Reorganisation Act) are considered the most complete in this respect, and so could serve as an example, certainly with regard to results per population subgroup.<sup>30</sup>

## 4.2. Medical devices

Prior to the new MDR, no database of CE-marked medical devices existed. Even now, that the EUDAMED database is not yet accessible to the public. The previous European directives established no obligation to register clinical studies and publish their results. Interested researchers therefore had great difficulty determining what high-risk medical devices were on the market and what clinical studies supported market access. There are therefore relatively few studies devoted to the methodological deficiencies of the clinical studies and any evidence gaps. All the identified articles started with the same observation: **medical devices are still being marketed although there is no evidence of their clinical efficacy or the benefits for the patient in comparison with existing alternatives.**<sup>18, 31-34</sup> Often the CE marking is based purely on a literature study of “equivalent” medical devices. Moreover, several hazardous and/or ineffective medical devices have ultimately been taken off the market.<sup>34, 35</sup>

The primary reason that there is so little randomised research with medical devices is that no RCTs were/are needed to obtain a CE marking.<sup>36</sup> RCTs with medical devices are feasible<sup>37, 38</sup>, and there is a positive trend toward more RCTs,<sup>39</sup> which contradicts the argument of the sector that it would be impossible to conduct such studies. The RCTs conducted often still show methodological deficiencies, however (a lack of statistical power, poorly defined primary outcome assessments, missing data, etc.), so that the quality of the scientific evidence is therefore mediocre. In contrast to medicinal products, no platform yet exists for dialogue and joint advice by

expert panels, notified bodies and HTA agencies/payers for the clinical development of medical devices.

For implants, the observation period is often very short compared to its anticipated long, useful life, and registers can be highly useful for this.<sup>40-42</sup> Several articles point to the importance of device-specific factors such as a learning curve, or the connection between result and volume.<sup>31, 32, 43</sup>

The old European directives did not clearly specify what criteria had to be used to determine the equivalence of devices, and various authors indicate that it is therefore difficult to interpret the equivalence of the medical devices studied.<sup>31, 34</sup>

The assumption that clinical studies of high quality will be conducted in the post-marketing phase proves not to be correct for medical devices.<sup>18</sup>

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<sup>c</sup> The *Arzneimittelmarkt-Neuordnungsgesetz* is a German law from 2011 that requires that pharmaceutical companies demonstrate the added value of their new products compared to the standard of care.



## 5. DISCUSSION AND POSSIBLE SOLUTIONS

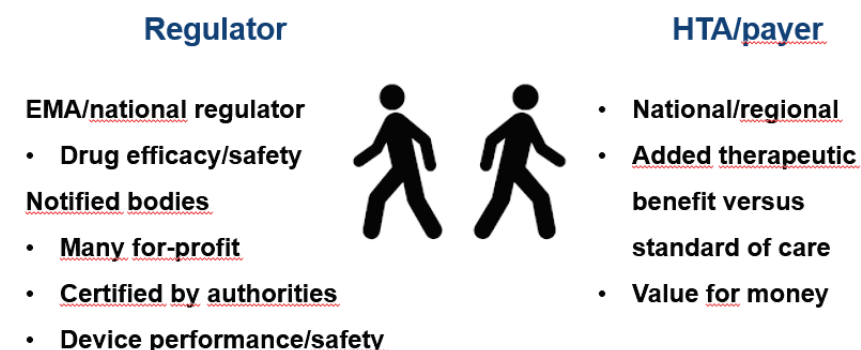
Only 10% of new medicinal products are a real therapeutic advance.<sup>1</sup> The rapid market introduction of new medicinal products and high-risk medical devices deserves a careful evaluation of the benefits and drawbacks for patients. The trend towards accelerated market access threatens to delay patient access to reimbursed, evidence-based innovations instead of accelerating it, which was after all the initial intention.

Many new medical devices come onto the market with evidence for their safety and performance provided via a literature review of equivalent devices, thus without any clinical studies of their own. The regulatory framework for medical devices relies on clinical studies taking place mainly after the CE marking, thus in the post-marketing period.

However, healthcare payers, HTA bodies that advise them, and also clinicians want to already have a randomised comparison of the new treatment with the existing standard treatment for a representative patient population and with patient-relevant outcomes (quality of life, symptoms and functional outcomes, and, for life-threatening conditions, overall survival) at market introduction. This is deemed to be essential to be able to reliably assess possible therapeutic benefits.

### 5.1. The separation between regulatory bodies and HTA bodies; more collaboration necessary

Figure 1 – Differences in perspective between regulators and HTA bodies/healthcare payers



The regulatory bodies (the EMA and the FDA)<sup>44</sup> and the notified bodies can only operate within their legal frameworks. Any changes in the system can therefore only be made with the full support of the Ministers of Public Health of the EU member states and the EU Commission. These system changes must not only mean that the regulatory bodies are required to include in their scientific advice to the companies those aspects considered essential by payers and HTA bodies, but also that the companies are required to conduct the studies required for the HTA before marketing authorisation is given.

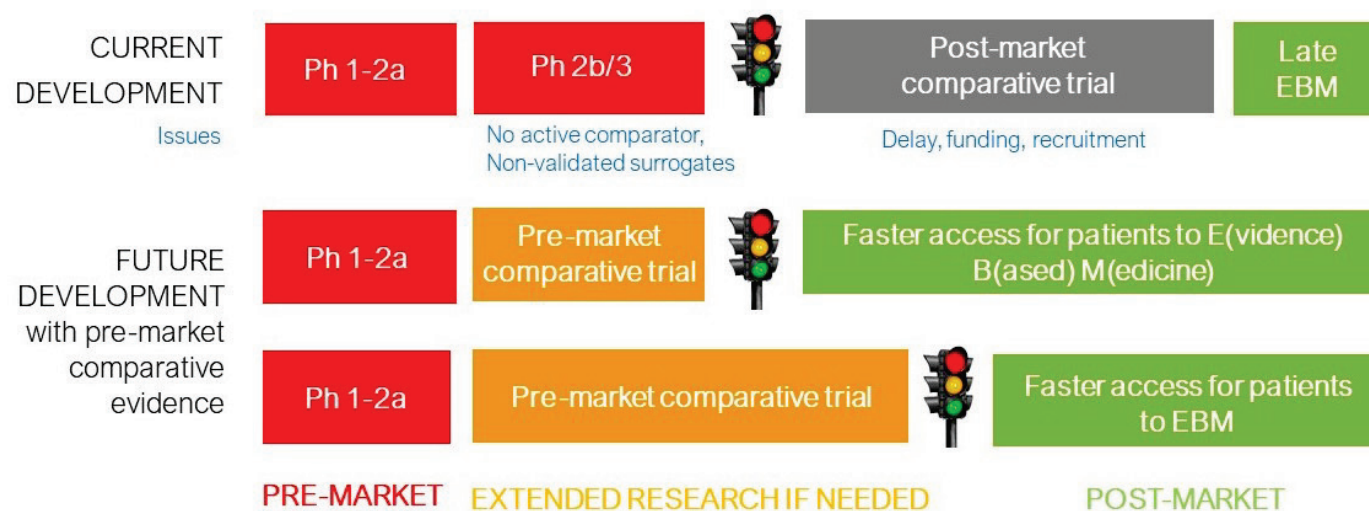
**Coordination** of the requirements with regard to scientific evidence for HTAs among the member states can be a great asset for Europe. This would certainly enhance the negotiating position of the EU in establishing and developing medicinal products at the global level.<sup>45</sup>



HTA agencies and payers argue for pre-marketing trials that **are comparative and more pragmatic**, and representative of the patients who later receive a reimbursed treatment. If possible, that study should also be compatible with the requirements of the regulators. If this is not possible, a separate pre-marketing clinical trial should be organised specifically for healthcare payers. This comparative trial can, for example, be a **registry-based RCT** (randomisation within a registry), or be part of an **adaptive**

**platform trial**. Such a trial with products from multiple companies is best conducted by an independent organisation. The public sector can help finance the needed infrastructure to guarantee the independence of the platform. In the case of relevant long-term endpoints it can also be desirable to continue these clinical trials, or at least the active treatment arms, during the post-marketing phase.

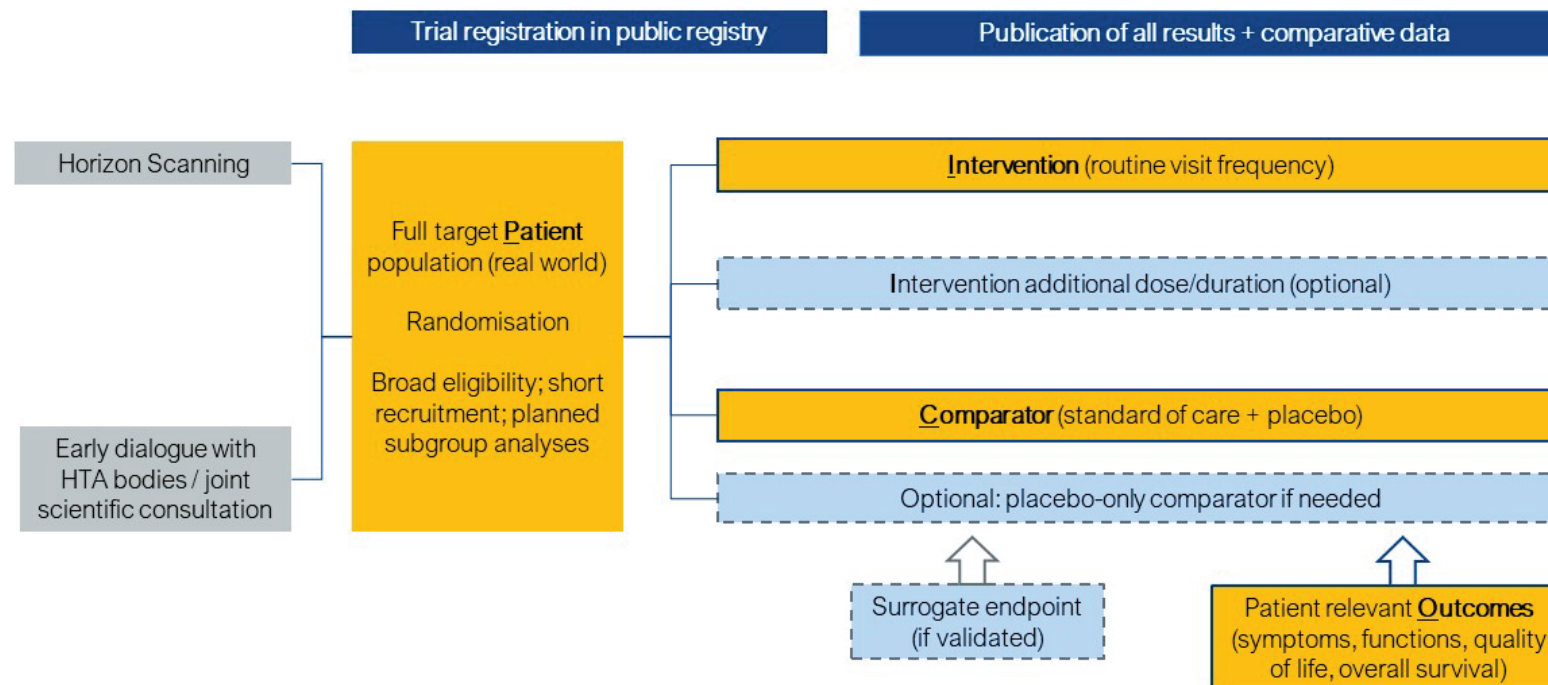
Figure 2 – Toward a practice-oriented, comparative phase 2b/3 trial



*The comparative RCT needed from a healthcare payer perspective should start at the same time as the current phase 2b/3. The trial may not take longer if patient-relevant endpoints are measured instead of (non-validated) surrogate markers. Even then patients would benefit more rapidly from evidence-based medicine (EBM). The comparative trial may be part of an adaptive platform trial or a registry-based randomised trial, with public co-funding of the infrastructure.*



Figure 3 – The ideal design of randomised phase 2b/3 trials from the viewpoint of the healthcare payer (and the clinician)





### 5.1.1. Study population requirements

Clinical studies are more informative for patients, treating physicians and healthcare payers if they are conducted on a **population comparable to the population for which the medicinal product or medical device will normally be used**.

Dossier assessors of RIZIV INAMI observed that the target population in the application for reimbursement did not correspond to the trial patient population for 6 out of 18 medicinal products and 2 of the 18 medical devices, and that for some subgroups no evidence of extra benefit was demonstrated. For medicinal products, the AMNOG reports in Germany have been shown to provide more complete information in this respect than the European Public Assessment Reports (EPARs).<sup>30</sup> For medical devices, it was observed that the patient population for which the medical device was indicated was often unclear, so that it was difficult for the HTA bodies to clearly describe the target group and it was also difficult for the payers to check for an undesirable extension to the indication(s) for use. Moreover the trial setting was not always a reflection of clinical practice. To be as informative as possible for healthcare payers, the trial setting should reflect the visit frequency of the normal care setting with regard to routine clinical follow-up.

### 5.1.2. Requirements regarding the intervention

With regard to the intervention itself, evidence is frequently missing on the optimal dose or treatment duration (e.g. duration of the cancer treatment with immunotherapy). When these variables are not tested in a phase 2b/3 study with multiple arms, extra uncertainty arises, which also affects budget impact and cost-effectiveness analyses.

While for medicinal products the product tested in the clinical studies is the same as the product marketed, this is not necessarily the case for high-risk medical devices. For 2 of the 18 reimbursement dossiers it was explicitly reported as a problem by the dossier assessor that the trials in the dossier were conducted with a different device.

The availability of clinical studies that reflect routine use is probably even more important for medical devices than for medicinal products given the

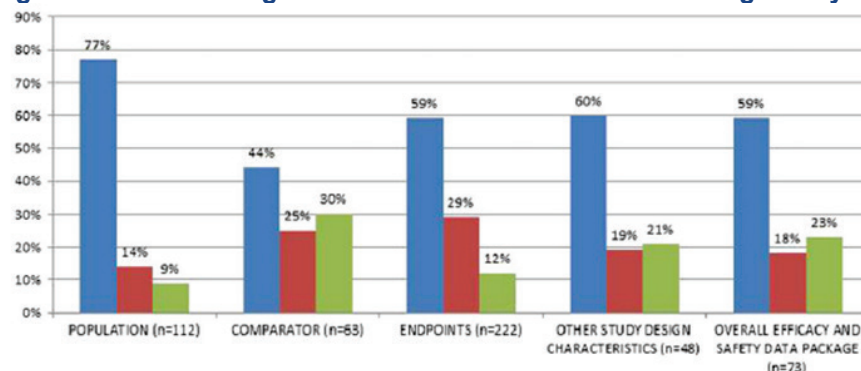
importance of, among other things, the learning curve of the surgeons in the use of invasive medical devices and implants.

### 5.1.3. Requirements regarding the comparator

For HTA agencies and payers, a randomised and **direct comparison with the standard of care** is essential to be able to assess the added therapeutic value of a product and calculate its cost-effectiveness. This applies to both medicinal products and medical devices. Comparative RCTs are also important for clinicians, so that they can make well-considered treatment choices and openly discuss them with the patient.

Various non-profit organisations in Belgium have recommended that RCTs with an active comparator should be the norm in developing medicinal products.<sup>46</sup> It is not only necessary that these RCTs be conducted in the phase that precedes marketing of the medicinal product, but moreover it can be argued that an independent body should conduct such commercially sensitive "head-to-head" trials. Physicians struggle with the lack of suitable comparative RCTs and trials to optimise treatment. The clinical need for suitable comparative RCTs is reported in the fields of oncology,<sup>5</sup> severe asthma,<sup>7</sup> multiple sclerosis,<sup>6</sup> and other examples documented by Garattini et al. (2021).<sup>8</sup>

Use of a **placebo arm** can be justified, for example, if the standard treatment is not based on conclusive scientific evidence. This placebo arm could, for example, be embedded in an RCT with three arms, and could be dropped as soon as there is enough evidence for the superiority of one or both active treatment arms. If needed, the trial could then be continued with the active treatment arms for an evaluation of long-term endpoints. The EMA and the medical ethics committees however allow comparisons only with respect to a placebo-only arm, even when a cost-effective and accepted standard treatment exists. However, randomised comparison with a cost-effective standard treatment, with patient-relevant outcomes, is essential to be able to assess the therapeutic benefit and calculate the incremental cost-effectiveness. During parallel advice provided by regulatory and HTA bodies, the choice of the comparator that is recommended to industry is often the subject of disagreement between regulatory bodies and HTA bodies (see Figure 4).<sup>28</sup>

**Figure 4 – Extent of agreement between HTA bodies and regulatory bodies by topic<sup>28</sup>**

Level of agreement for each domain: Health Technology Assessment bodies (HTABs) vs. regulators (based on 31 procedures). *n* represents the total number of HTABs expressing an opinion for each domain. ■ full agreement ■ partial agreement ■ disagreement

Industry, however, primarily follows the advice given by the regulators and not the HTA bodies. The reason that HTA advice is requested is therefore unclear, but it is suggested that this helps determine the commercial strategy.<sup>23</sup> Why would companies conduct a comparative RCT if that is not needed to clear the EMA hurdle? Especially when the commercial advantages probably do not outweigh the fact that a comparative RCT is riskier and more expensive and may take more time.

In 8 of the 18 INAMI/RIZIV medicinal product dossiers studied, the RCT contained no active comparator or the comparator was deemed unsuitable. The lack of a comparative trial with a suitable comparator is also a frequently occurring problem in reimbursement decisions in Germany.<sup>47</sup> Only one quarter to half of the medicinal products that were approved annually from 2015 to 2018 by the EMA had at least one RCT with an active comparator.<sup>3</sup> The uncertainty for the payer is even greater in cases for which the marketing authorisation is based solely on non-randomised studies – an undesired side effect of the programmes for accelerated market access. Regulators run the risk of focusing on the wrong issue when discussing (and

disagreeing on) the topic of added therapeutic value.<sup>48</sup> Products that are equivalent can also have a place, for example, on the basis of a different side effects profile. There is thus no need to demonstrate that the new medication is superior to the standard treatment for it to be able to come onto the market. The real problem for clinicians and HTA bodies is, however, the lack of comparative trials.

For high-risk medical devices too, the lack of sound comparative clinical data hinders the national reimbursement procedures.<sup>49-51</sup> The MDR is not explicit regarding the comparator in clinical studies. For 12 of the 18 medical devices studied, the INAMI/RIZIV dossiers contained no RCT.



#### 5.1.4. Requirements regarding outcomes

In 8 of the 18 INAMI/RIZIV dossiers for new medicinal products, non-validated surrogate endpoints were used, and in 9 of the 18 dossiers for devices, endpoints relevant for the patient were missing. Missing long-term results were reported as a problem by the INAMI/RIZIV experts for 2 of the 18 device dossiers (implants). For oncology drugs the use of a response rate or progression-free survival without proof of benefit in terms of quality of life or overall survival is often a problem.<sup>2</sup> Quality of life is sometimes not measured or not reported, although this is a very important outcome for patients and the measurement of the impact on this has been recommended by the HTA bodies.<sup>2, 23, 52-54</sup>

For example, for approximately half of the available cancer drugs it is still not known after a period of 5 years (median) whether they actually have added value for the overall survival or quality of life.<sup>12</sup>

The data collected on quality of life are often not adequate, when they are collected. Ideally this is done using a **generic instrument** (e.g. EQ-5D-5L) that supplements the disease-specific instrument, measured at several times and over a longer period. Thus the QALYs (quality-adjusted life years, QoL), can be calculated over a long period. In the applications for approval for cancer drugs an improvement in the quality of life is demonstrated in only 10% of the cases.<sup>12</sup> Inexplicably, results for QoL are sometimes considered confidential.<sup>2</sup> It is therefore also necessary that the regulatory bodies and the payers/HTA agencies coordinate their recommendations on measuring – and reporting – data on the quality of life.

#### 5.1.5. Toward more efficient clinical studies; limitations of observational 'real-world data'

Planning and conducting randomised clinical trials takes time and is expensive. There are, however, a number of opportunities to increase the efficiency of randomised trials as well as their relevance for healthcare payers. Thus, it is usually estimated that only a small fraction of the target population satisfies the sometimes (over) strict criteria for RCT study participants, which does not enhance the external validity of the RCT. A solution for this consists of RCTs that are based on an existing registry

(registry-based RCTs),<sup>55</sup> in which the threshold for participation in the trial for patients and physicians is significantly lower. As an example, we take the experience in Upsala with registry-based RCTs in the field of cardiology.<sup>56</sup> No less than 70% of the patients in the registry gave consent for randomisation (instead of the typical 10-20%); the recruitment period for the RCT was therefore very short. The total RCT cost in this case was thirty times less than that of a standard RCT that took place simultaneously in the US. Moreover, the registry-based RCT benefitted from a longer follow-up. Registry-based RCTs should also be included in the discussions on the European Health Data Space, and more specifically the DARWIN project, which now appears to be limited to observational studies.

Another example is adaptive platform trials, with data collection based primarily on using routinely collected data that are linked. This model of "large simple trials" from Oxford, UK, was successfully used in the RECOVERY Covid-19 trial. ([www.recoverytrial.net](http://www.recoverytrial.net)) The information that the researcher himself had to fill in could be limited to a single page. Given that such more pragmatic trials include a broad patient population, they should be sufficiently large to allow subgroup analyses with sufficient statistical power.

The standard RCT situation in which a medicinal product with one company as sponsor is tested is probably too simplistic to satisfy public health needs.<sup>57</sup> Some opinion makers have argued, therefore, for having comparative RCTs conducted not by the company but by an independent third party. They have also emphasised the importance of harmonisation of study design to make later meta-analyses or network analyses possible.<sup>57</sup> International adaptive platform RCTs lead by definition to a harmonised study design for different medicinal products within a therapeutic field, including their companion diagnostics. These latter constitute an issue in themselves regarding harmonisation.<sup>58</sup>

Collins et al (2020)<sup>59</sup> also see **a greater future in the reduction of unnecessary costs and complexity of RCTs, rather than in dropping the randomisation.** This view is also shared by the KCE Trials programme, a publicly funded programme of primarily large-scale randomised trials for comparative effectiveness and drug repurposing purposes.<sup>60</sup> In the longer term it would be even more efficient to directly extract the needed data from



coded clinical data (e.g. SNOMED CT) in standardised electronic medical records that cover both hospital and non-hospital care.<sup>61</sup>

Polak et al. (2020)<sup>62</sup> reported that observational data collected during so-called “expanded access” programmes of the FDA or the EMA (until 2018) were the most important clinical data for 13 dossiers in all (FDA and EMA combined). Multiple initiatives are currently underway to be able to derive conclusions on efficacy based on observational real-world data.<sup>11</sup> **It is however important to realise that a large proportion of the conclusions with regard to efficacy that are drawn on the basis of observational data are contradicted by results based on an RCT.**<sup>63</sup> The degree of completeness of real-world datasets is also a problem that makes selection of well-defined patients impossible.<sup>64</sup> This means that for the vast majority of new treatments randomisation remains essential to balance the treatment groups not only for the “known unknown variables” but also for the “unknown unknowns”, to limit bias to a minimum and to justify the conclusions made. Replacement of RCTs by studies based on observational data thus seems premature.<sup>59, 63, 65-67</sup>

Large and complete observational datasets can however give a systematic overview of the patient population that has used the intervention, as well as the routinely collected outcomes. This could be a revolution for pharmacovigilance and materiovigilance, but it remains to be seen whether there is added value for comparative effectiveness analysis if this is not linked to randomisation.

Governments can facilitate these gains in efficiency on the basis of standardised electronic medical records by providing a suitable international legal framework, standardised clinical coding (e.g. SNOMED CT) and the accompanying infrastructure for information technology.

#### *5.1.6. Should the threshold of evidence for medical devices be lower?*

Do patients have the right to the same degree of protection from harmful effects when they are treated with a medical device as for a medicinal product? The obvious answer is yes, but the reality is different. New medical devices can come onto the European market without proper clinical studies or even without any clinical study if equivalent to existing devices.<sup>18, 31-34</sup> The MDR gives a more specific definition of equivalence for medical devices. Medical devices display other specific characteristics that should be taken into account in their clinical assessment, such as a learning curve for surgical procedures associated with the device, a possible volume/result relationship, and specific precautions required for blinding to measure the outcomes.<sup>68-70</sup>

The CE marking system for medical devices relies strongly on the collection of clinical data after the CE marking is obtained (thus post-marketing). For medical devices it has been shown, however, that high-quality studies are rarely conducted after the device is marketed, and clinical evidence for the effectiveness therefore often remains lacking.<sup>18</sup> The spontaneous reporting of safety incidents is also substandard. Physicians who implant cardiovascular or orthopaedic devices can for various reasons regard reporting of adverse events with medical devices as unnecessary, impossible or pointless, which leads to serious underreporting.<sup>19</sup> Therefore, it is difficult to weigh the benefits against the risks.<sup>20, 21</sup> For implantable medical devices, some countries have set up registries that could even be used for registry-based RCTs, provided the quality and completeness can be guaranteed.<sup>71</sup>

Various groups, including the KCE, have recommended a stepwise approach for the introduction of innovative medical devices based on the IDEAL model (Idea, Development, Exploration, Assessment, Long-term study), developed by a group of surgeons to improve research and reporting of the results.<sup>32, 50, 72, 73</sup> Stepwise introduction requires support from the regulator<sup>74</sup> as this would help limit the risk of harm.<sup>75</sup> For IDEAL it is important that all the necessary steps be followed, including the RCT step.<sup>32</sup>



RCTs with medical devices are feasible<sup>37, 38</sup>, and there is a positive trend towards more RCTs.<sup>39</sup> HTA institutions in Austria and France have published examples of possible clinical trials with medical devices.<sup>76, 77</sup>

There is an urgent need for more transparency on marketed medical devices and the clinical data on those devices. More communication is needed between the HTA bodies, the notified bodies and the authorities that control them. In addition, there is a need for early dialogues with the medical device industry.<sup>43, 78, 79</sup> Multi-stakeholder initiatives, such as the EU-funded CORE-MD initiative ([www.core-md.eu](http://www.core-md.eu)), can help with this.<sup>80</sup>

## 5.2. Transparency requirements

### 5.2.1. For medicinal products

The overall level of transparency on the results of clinical studies with medicinal products has significantly improved in recent years, and is clearly higher than that for medical devices. The clinical development of, and the results of, clinical studies with new medicinal products are summarised in European Public Assessment Reports (EPARs) that are available on the EMA website. The completeness of these EPARs (and that of peer-reviewed publications and the summaries from the registries of clinical studies) can still be better, however, especially when we compare them to the AMNOG documents in Germany. These latter are much more detailed, for example, with analyses on subgroups of the study population.

Data on the quality of life should be systematically recorded and reported as an outcome measure in clinical trials. However, this is sometimes not the case. The assertion by industry that such data are "commercially sensitive" and should remain confidential is difficult to justify in the framework of transparent reporting of all the results of clinical studies. Medical ethics committees could play an important role by routinely following up on the registration of studies as well as the timely publication of all results.

### 5.2.2. For medical devices

The introduction of the new medical device regulation should improve transparency, an area in which Europe lags behind the United States. To ensure transparency of clinical studies on medical devices there is the promised European database, EUDAMED, that will be accessible to the general public. However, the degree of detail with which data will be reported in this databank is not yet completely clear. The implementation of this databank has, unfortunately, also been delayed.

## 5.3. Published policy recommendations

A number of documents have been published with relevant recommendations on the issues addressed in this report.

Several **non-profit organisations in Belgium** (2018)<sup>46</sup> have developed a number of policy recommendations for medicinal products, some of which are also important for this report.

- **"International collaboration** on price negotiations, horizon scanning and HTA are to be encouraged.
- In order to assess added therapeutic benefit, pre-marketing RCTs with a **relevant active comparator should be the norm** for the development of medicinal products."

Policy brief 29 of the **European Observatory on Health Systems and Policies** was drafted in support of the Austrian Council Presidency in 2018 and is entitled "How to stimulate innovation to meet patients' needs?". Panteli et al. (2018)<sup>81</sup> make a number of recommendations of relevance for this report:

- "Improving the **efficiency of evidence generation in clinical research** is not only good for driving down the costs of clinical trials, it can also help to remediate some of the related technical and ethical challenges, such as the fragmentation and duplication that unnecessarily expose patients to risk; the lack of comparative effectiveness data; the evidence gaps regarding specific patient groups and therapeutic areas; or the perceived conflicts of interest and related publication bias.



- Raising the bar for market entry by **requiring that a new product demonstrate its superiority or equivalence to existing alternatives** could encourage manufacturers to focus more on areas with limited treatment options and facilitate increased alignment with specifications applied in post-marketing evaluations for pricing and/or reimbursement (for example HTA). Increased collaboration and **alignment on evidentiary requirements** between and within EU Member States are likely to simplify evidence generation for manufacturers as well as increase efficiency on the evaluators' side.
- Only a comprehensive approach that combines initiatives to guarantee funding, optimize evidence generation and align regulatory requirements can effectively tackle innovation deficits. An overall vision with greater policy coherence and **backed by strong political commitment and transparency** is needed."

The **European Public Health Alliance** (EPHA) (2017)<sup>82</sup> has recommended a new model for scientific advice (SA):

- "To avoid detrimental effects of confidential SA and simultaneously ensure clarification of scientific and procedural requirements, SA should be conducted in a transparent way. As such, SA should include:
  - General guidelines on scientific principles for conducting RCTs, including comparative RCTs against standard treatments using patient-relevant endpoints, assessing efficacy as well as harms. Indeed, current EU regulation does not rule out marketing applications containing such comparative RCTs that are essential to help patients and professionals choose the best options.
  - Disease-specific guidelines to clarify disease-specific requirements (e.g. on patient populations, interventions and comparators, outcomes and study duration). These guidelines are partly already available.
  - Public general or disease-specific workshops to clarify upcoming questions at shorter notice. Guidance developed by means of these workshops could then be used to update existing guidelines or develop new guidelines. To avoid any inappropriate influence on

the workshop outcomes, clear guidance about how to conduct these workshops should be developed.

- Written questions of individual companies to the EMA (and/or HTA bodies or payers), which are also answered in writing (without confidential meetings), with both questions and answers made publicly available at the time the answers are issued. EMA services should prepare publicly available frequently asked question and answer documents. New requests for SA should be limited to questions which are not yet covered in the available question and answer documents. This procedure would substantially reduce the number of questions to be answered. In this context, the EMA should refrain from collecting fees for SA.
- SA processes should be public to avoid confidential waiver negotiations to existing guidelines.
- SA should be given by independent advisors, not part of the marketing approval process nor the pharmacovigilance process as well as independent from industry."

The **European Public Health Alliance (EPHA)** (2020)<sup>57</sup> has provided recommendations to generate better evidence on new drugs.<sup>57</sup>

- "Regulators should **routinely inform patients and clinicians** about what is and what is not known about the benefits and harms of new drugs at the time of approval.
- Regulators should proactively encourage companies to **harmonise the designs of clinical trials** within each therapeutic area.
- The European Medicines Agency should routinely require **individual participant level data on clinical trials** supporting its approval decisions, and allow re-analysis of this data by a pre-defined set of third-party organisations.
- **Adaptive platform trials** should be used to generate timely comparative evidence on multiple drugs for suitable indications.



- **Regulators should be more selective** in approving drugs on the basis of incomplete benefit and harm data.
- When drugs are conditionally approved on the basis of limited data, **post-approval RCTs** should be routinely required to address those limitations.
- In the post-marketing period, manufacturers should design their studies hierarchically: priority should be given to studies aimed at evaluating a product's net clinical benefit in RCTs compared with current known effective therapy.
- Post-marketing study requirements should be **more actively reinforced by regulators**.
- **Payers should use their policy levers and negotiating power** to incentivise the generation of better evidence on new and existing drugs, for example by explicitly considering proven added benefit in pricing and payment decisions."

Similar recommendations are made in two 2020 articles in The Lancet.<sup>3, 11</sup> Naci et al. (2020)<sup>3</sup> focussed on pre-marketing comparative effectiveness data and formulated five policy recommendations:

- "First, **labelling** should routinely inform patients and clinicians **whether comparative data exist** on new products.
- Second, **regulators** should be **more selective** in their use of programmes that facilitate drug and device approvals on the basis of incomplete benefit and harm data.
- Third, **regulators** should encourage the conduct of **randomised trials with active comparators**.
- Fourth, **regulators** should use **prospectively designed network meta-analyses** based on existing and future randomised trials.
- Last, **payers should use their policy levers and negotiating power to incentivise the generation of comparative evidence** on new and existing drugs and devices, for example by explicitly considering proven added benefit in pricing and payment decisions."

Cipriani et al. (2020)<sup>11</sup> focussed on post-marketing data and gave seven key guiding principles:

- "First, regulators (for drugs and devices), notified bodies (for devices in Europe), HTA organisations and payers should develop **customised evidence generation plans**, ensuring that future post-approval studies address any limitations of the data available at the time of market entry impacting the benefit-risk profiles of drugs and devices.
- Second, post-marketing studies should be designed hierarchically: **priority should be given to efforts aimed at evaluating a product's net clinical benefit in RCTs compared with current known effective therapy**, whenever possible, to address common decisional dilemmas.
- Third, post-marketing studies **should incorporate active comparators** as appropriate.
- Fourth, use of **non-randomised studies for the evaluation of clinical benefit in the post-marketing period should be limited** to instances when the magnitude of effect is deemed to be large or when it is possible to reasonably infer the comparative benefits or risks in settings, in which doing an RCT is not feasible.
- Fifth, **the efficiency of RCTs** should be improved by streamlining patient recruitment and data collection through **innovative design elements**.
- Sixth, **governments should directly support and facilitate** the production of comparative post-marketing data by investing in the development of **collaborative research networks and data systems** that reduce the complexity, cost, and waste of rigorous post-marketing research efforts.
- Last, **financial incentives and penalties should be developed or more actively reinforced**. The authors state: 'First, the level of payment for drugs and devices should correspond to their added benefit according to robust comparative effectiveness studies. Second, longer marketing protections should be considered for products that convincingly demonstrate their superiority to established standards of



care. Third, public reporting of best research practices in the post-marketing period might incentivise companies to invest in comparative studies. **Last, regulatory approval might be more formally linked to payer policies such as coverage with evidence development whereby the treatment is only available within the context of an ongoing post-marketing clinical trial.** 'In terms of penalty mechanisms, regulatory agencies should actively consider license suspensions, indication restrictions, monetary fines, or even market withdrawal on a case-by-case basis'<sup>11</sup>."

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## ■ RECOMMENDATIONS<sup>d</sup>

### *For the European Commission and Member States Governments*

After licensing and coverage of medicinal products, the regulatory and payer processes frequently fail to generate the comparative evidence required for informed decision making.<sup>13, 14, 16, 17, 83</sup> For high-risk medical devices, the assumptions that device safety can be relied upon based on spontaneous incident reporting<sup>19-21</sup> and that high-quality studies will be conducted in the post-market phase are simply not true.<sup>18</sup> Postponing essential comparative trials until the post-market phase causes a non-justifiable delay to patient access to evidence-based innovation. Therefore, the pre-market clinical trials generated for medicinal products and high-risk (Class IIb/III) medical devices should meet not only the regulatory requirements but also clearly answer the comparative effectiveness questions of relevance for patients, clinicians, and healthcare payers.<sup>81</sup> This aim can be achieved by adapting the EU legal framework, with the support of the Member States' governments and the EU Commission, to realise the following points:

1. The regulators will actively support the generation of the necessary comparative data that patients, clinicians, HTA bodies and payers need in order to choose the best treatment. More generally, the pre-market clinical trials for new medicinal products and Class IIb/III medical devices should meet the requirements of the regulators as well as the needs of the HTA bodies and the clinicians.<sup>5-8</sup> The regulators need to assure the following:
  - a. A timely start and completion of a pre-market comparative RCT in representative patients, so that HTA bodies can assess the comparative evidence in a timely manner to fulfill their role as foreseen in the EU HTA regulation. The comparative evidence that is needed is a pre-market, randomised trial of the innovation compared with the standard of care in patients who are representative of the population to be treated with the innovation and using patient-relevant outcomes as trial endpoints. A placebo-only arm, or sometimes a sham-only arm, can be added if scientifically and ethically justified. When no active treatment is available it is recommended that best supportive care be used in the comparator arm. The most relevant outcomes for the patient should be studied. The outcomes should include quality of life, and the use of non-validated surrogate endpoints should be avoided.

<sup>d</sup> The KCE has sole responsibility for the recommendations.



- b. If the clinical questions and evidence requirements of both the regulatory and the HTA processes cannot be answered using the same trial, a separate pre-market randomised trial is needed that meets the comparative evidence requirements of HTA bodies and clinicians. When the information for the regulator is already available, but the comparative evidence is not yet available, the EMA can provide a temporary marketing authorisation (using a new concept, still to be created), whereby the EMA assures the further follow-up, and the execution of the comparative trials by the manufacturer.
    - c. It should be a prerequisite that a clinical study comparing the new drug with the standard of care is available for HTA at the time of the final regulatory decision. In the absence of an active treatment, the comparator should consist of best supportive care.
  2. Expedited marketing approval of medicinal products should be used only by the EMA, and only in cases where the EMA can guarantee the timely delivery of the missing (comparative) evidence, followed by the necessary actions (e.g. expedited withdrawal).
  3. Today, a joint scientific consultation (JSC) with HTA bodies is only possible if it is requested by the company. This should also be possible at the request of HTA bodies, with the support of clinicians. The same applies for parallel scientific advice by HTA bodies together with the EMA, and could for example be based on information from horizon scanning. Prior to joint scientific consultations, HTA bodies and clinicians need to agree on the key trial design elements. If the advice of the HTA bodies is not followed by the company, a full justification needs to be provided and this should be made public in the HTA joint clinical assessment report. For medical devices, an efficient process is still to be defined, and a mandated communication platform between HTA bodies, Expert Panels, Notified Bodies, national competent authorities, the European Commission, and the device industry should be set-up.<sup>79, 84</sup> Regulatory capture is to be avoided, specifically, the expert providing advice should be different to the one who later evaluates the trial evidence. In order to harmonise trial designs for new interventions with a novel mechanism of action or with a new indication for use, the advice given on study design elements should be made public so that other companies can also make use of this information.
  4. It is recommended that a common discussion on the clinical evidence take place between the regulators and the HTA evaluators in order to avoid any misunderstandings arising due to their different objectives and the separate decision-making processes that regulators and HTA bodies must follow.



5. Given the continued need for RCTs, governments should aim for efficiency gains in RCTs:
  - a. The pre-market comparative randomised trial (RCT) could be registry-based<sup>55, 56</sup> or it could be part of an adaptive platform trial.<sup>25, 26, 57</sup> It would be best if registry-based trials or adaptive platform trials were to be run by an independent third party with public co-funding of the infrastructure. In some cases, when long-term outcomes are particularly relevant to patients, clinicians and payers, it may be justifiable to extend the RCT into the post-market period in order to study these outcomes in the longer-term.
  - b. In addition to the facilitation of registry-based RCTs and adaptive platform RCTs, governments can achieve efficiency gains for RCTs by the use of coded data (e.g. SNOMED CT) that are routinely collected or based on electronic health records.<sup>81</sup> The aim should be to recruit a large and more representative patient population in a shorter period and to lower the cost of RCTs while assuring data quality. The EU DARWIN project should be harnessed to develop a European infrastructure for less costly and easy to conduct RCTs. Restricting this project purely to observational research would be a missed opportunity. Observational studies are not a valid substitute for RCTs.<sup>59, 63, 65-67, 85</sup>
6. Full transparency of comparative evidence on drugs and devices should be assured for clinicians and patients through the European Public Assessment Report (EPAR, for drugs) or the Summary of Safety and Clinical Performance (SSCP, for devices), as well as the relevant HTA joint clinical assessment reports.<sup>3, 57</sup> These reports should be as complete as possible and regularly updated, including comparative evidence, quality of life results, and subgroup analyses as seen in the German AMNOG reports. Similar to the FDA, the EMA should also require the submission of individual patient data for re-analysis during the regulatory and HTA procedures, and to support public pharmaceutical research and comparative effectiveness research (e.g. indirect comparisons). The product insert should contain a link to the EPAR/SSCP and to the HTA joint clinical assessment reports.
7. For medical devices, public access to EUDAMED is urgently needed, not only for access to the registry of clinical investigations in the context of CE marking but also to the SSCPs entered immediately after CE marking. Medical device clinical investigations not performed for CE marking (and therefore not covered by EUDAMED), should also be prospectively registered in a publicly accessible registry, preferably EUDAMED.
8. With regard to orphan drugs, we refer to KCE report 112.<sup>86</sup> More specifically, the criteria for orphan drugs should be limited to truly rare indications that also have a concrete demonstrated problem of return on investment for the company.

***For medical and surgical scientific societies***

Medical speciality associations and clinical societies should become more involved and more vocal about their need for comparative data and the studies required to identify the optimal treatment for their patients.

***For (high-risk) medical device industry***

For high-risk medical devices, in case of doubt about the equivalence of a modified or similar device to an existing device, it is recommended that a pre-market clinical trial be performed in order to avoid harm to patients when it is used in routine care.

***For all ethics committees in Belgium and abroad***

All ethics committees giving advice should check if the study design aspects (comparator, endpoints) are in agreement with the Declaration of Helsinki.

More transparency is recommended about the opinions provided by the ethics committees.<sup>87</sup>

All ethics committees should ask the sponsor to provide:

- the link to the trial registered in a publicly accessible database - within one month of study start
- the link to the updated trial registry containing the results for all endpoints - within one year after study end (including early study end)

The most efficient way to apply this in practice must be identified.

***For all consumer organisations and patient organisations***

Patients and the public should be educated that comparative effectiveness is a key information requirement for clinicians to optimise patient care and management. They should also be informed that this information can be obtained in a timely manner by performing randomised trials comparing the new treatment with the existing treatment in a representative patient population and assessing patient-relevant outcomes. Without these comparative trials clinicians cannot know which are the best treatments, doses, durations of therapy, or combinations of treatments for their patients.

Patients should be aware that given the shortcomings of the current regulatory process such comparative data are frequently not available when a medicinal product or medical device is allowed to enter the market today, limiting the informed choice of patients and their doctors.



The aim is also to subsequently involve these informed patient representatives in the regulatory/HTA processes.

***To RIZIV-INAMI, HTA agencies and payers***

HTA bodies and payers should not accept evidence that is too weak to come to meaningful conclusions on added therapeutic benefit.

***To RIZIV-INAMI, international HTA agencies, and journal editors***

All HTA assessment reports for drugs or medical devices with all clinical information should be actively made public, including the declarations of (potential) conflicts of interest.<sup>88-90</sup> Specifically for the RIZIV-INAMI, we recommend complying with the legal obligation to publish the complete assessment files of all reimbursement requests.

Results of quality of life measures and all other clinical trial endpoints should never be considered as company-in-confidence, nor academic-in-confidence, information. Journal editors should clarify this point to authors.<sup>91</sup>

***Research agenda***

We recommend entering into a dialogue with the Belgian authorities to find out how the recommendations can be realised and applied to the Belgian situation.



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Reported interests:

All experts and stakeholders consulted within this report were selected because of their involvement in the topic of clinical development of medicinal products or high-risk medical devices. Therefore, by definition, each of them might have a certain degree of conflict of interest to the main topic of this report'.

Membership of a stakeholder group on which the results of this report could have an impact: Allan Fraser (Chairman, Regulatory Affairs Committee, Biomedical Alliance in Europe), Rob Nelissen (Secretary General EFORT (European Federation of National Associations of Orthopaedics & Traumatology)

Holder of intellectual property (patent, product developer, copyrights, trademarks, etc.): Rob Nelissen (Co-patent holder of class 2 medical device, heating device with induction for prosthetic infections. patent owner is LUMC. I am an employee of LUMC, so I have no personal financial interest in the product)

Participation in scientific or experimental research as an initiator, principal investigator or researcher: Rita Banzi (My research unit is involved in the conduct of investigator-driven clinical trials in oncology surgery supported by a commercial entity. The recipient of the grant is the Mario Negri institute), Alan Fraser (Scientific Coordinator of the CORE-MD consortium (coordinating Research and Evidence for Medical Devices, EU Horizon 2020 project no. 965246)), Kathleen Harkin (doing a PhD on medical device safety through the SPHeRE Programme with Trinity College Dublin, funded by the Health Research Board). Rob Nelissen (PI of Stryker Inc knee implant safety research; grant to the Department of Orthopedics LUMC. No personal financial interests), Stefan Sauerland (Participation as a researcher in the EUnetHTA21 project, EU funded)

Payments to speak, training remuneration, subsidised travel or payment for participation at a conference: Valérie Paris (In my previous functions at OECD, I participated in conferences which were sometimes funded by pharmaceutical companies. I was not paid but the travel and accommodation costs were taken into account.)

Presidency or accountable function within an institution, association, department or other entity on which the results of this report could have an impact: Valérie Paris (Yes, we can consider that the study could have an impact on the activity of the HAS)

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