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Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

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

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ACE	Angiotensin-converting enzyme
ACL	Anterior cruciate ligament
AFMPS – FAGG – FAMHP	Agence Fédérale des Médicaments et des Produits de Santé
AIFA	Agencia Italiana del Farmaco (Italian Medicines Agency)
AIMDD	Active Implantable Medical Devices Directive
ALK	Anaplastic lymphoma kinase
AMNOG	Arzneimittelmarkt-Neuordnungsgesetz (Reform of the market for medicinal products)
ANSM	Agence nationale de sécurité du médicament et des produits de santé
AQuAS	Agència de Qualitat i Avaluació Sanitàries de Catalunya (Catalan Agency for Health Quality and Assessment)
ATMPs	Advanced therapy medicinal products
ATV	Added therapeutic value
CCI	Commercially Confidential Information
CD33	Myeloid Cell Surface Antigen CD33
CE	Conformité Européenne (European Conformity)
CEAR	Clinical Evaluation Assessment Report
CECP	Clinical Evaluation Consultation Procedure
CED	Coverage with evidence development
CENELEC	European Committee for Electrotechnical Standardization
CER	Clinical Evaluation Report
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organizations of Medical Sciences
CJEU	Court of Justice of the European Union

CMA	Conditional Marketing Authorisation
CMV	Cytomegalovirus
CNEDIMTS	Commission Nationale d'Evaluation des Dispositifs Médicaux et Technologies de Santé
CONSORT	Consolidated Standards of Reporting Trials
CORE-MD	Coordinating Research and Evidence for Medical Devices
CRM	Commission for reimbursement of Medicines
CRPS	Complex regional pain syndrome
CT-College	Clinical Trial College
CTD	Clinical Trials Directive
CTIS	Clinical Trials Information System
CTR	Clinical Trials Regulation
CURIA	European Court of Justice database
DFS	Disease-free-survival
DoH	Declaration of Helsinki
DRG	Diagnosis related group
EB	Expected benefit
EC	European Commission
EEA	European Economic Area.
EEC	European Economic Community
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
ENCEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report

EQ-5D-5L	Euroqol Five dimensions of health Five severity levels
ESMO	European Society for Medical Oncology
ESMO-MCBS	European Society for Medical Oncology - Magnitude of Clinical Benefit Scale
EU	European Union
EUDAMED	European Union Database on Medical devices, version under MDR
EudraCT	EU Clinical Trials Register
Eurlex	European regulations databases
FAMHP	Federal Agency for Medicines and Health products
FDA	Food & Drugs Administration
FPG	Fasting plasma glucose
G-BA	German Federal Joint Committee
GLP-1	Glucagon-like peptide-1
GRADE	Grades of Recommendation Assessment Development and Evaluation
HAI	Health Action International
HAS	Haute Autorité de Santé (French National Authory for Health)
HbA1c	Hemoglobin A1c
HDE	Humanitarian device exemption
HIV	Human immunodeficiency viruses
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
HVB	Main Association of Austrian Social Security Institutions
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDE	Investigational Device Exemption
IDEAL	Idea, Development, Exploration, Assessment, Long-term study

IEB	Improved expected benefit
IMD	Implantable medical device
IMPs	Investigational medicinal products
IQR	Inter-Quartile Range
IQWIG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ISDB	International Society of Drug Bulletins
ISO	International Organization for Standardization
IVD	In vitro diagnostic medical devices
LBI-HTA	Ludwig Boltzmann Institute for Health Technology Assessment
MA	Meta-analysis
MD	Medical Device
MDCG	Medical Devices Coordination Group
MDD	Medical devices Directive
MDR	Medical devices Regulations
MEA	Managed entry agreement
MEL	Medizinische Einzelleistungen
MHRA	Medicines and Healthcare products Regulatory Agency
MiEF	Medicines in Europe Forum
MRD	Minimal residual disease
MRI	Magnetic Resonance Imaging
NAGS	N-acetylglutamate synthase
NCAs	National competent authorities
NGO	Non-governmental organization
NICE	National Institute for Health and Care Excellence

NJR	National Joint Registry's
NRCT	Non Randomised Controlled Trial
NSCLC	Non-small cell lung cancer
OJ	Official Journal
OJEU	Official Journal of the European Union
OCEBM	Oxford Centre for Evidence-Based Medicine
ODEP	Orthopaedic Data Evaluation Panel
OS	Overall Survival
PDL1	Programmed Cell Death Ligand 1
PFS	Progression Free Survival
PICO	Population, Intervention, Comparator, Outcome
PICOTS	Population, Intervention, Comparator, Outcome, Time periods, Study designs
PM	Pacemaker
PMA	Pre-market approval
PMCF	Post-market clinical follow-up
PMS	Post-market surveillance
POP	Pelvic organ prolapse
PRIME	Priority medicines
QALYs	Quality-adjusted life years
QoL	Quality of life
RCT	Randomised Controlled Trial
REA	Relative effectiveness assessment
RIZIV - INAMI	National Institute for Health and Disability Insurance – Rijksinstituut voor ziekte- en invaliditeitsverzekering – Institut national d'assurance maladie-invalidité
SMC	Scottish Medicines Consortium

SMR	Service Médical Rendu
SNSA	Simultaneous National Scientific Advice
SR	Systematic review
SSCP	Summary of Safety and Clinical Performance
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
TFEU	Treaty on the Functioning of the European Union
TLV	The Swedish Dental and Pharmaceutical Benefits Agency
TRIP	Turning Research Into Practice
UDI	Unique Device Identification
US	United State
USA	United States of America
WEPAR	Withdrawal assessment report
WHO	World Health Organization
WMA	World Medical Association
ZIN	Zorginstituut Nederland (Care Institute Netherlands)

SCIENTIFIC REPORT

1 INTRODUCTION, AIMS AND SCOPE OF THIS REPORT

1.1 Background

This project has been selected by the KCE board as part of the annual work programme of KCE.

Healthcare has an ethical dimension as it aims to prevent and alleviate human suffering. Healthcare has also developed into an important economic sector, with sales of services and products. Total EU expenditure on healthcare (public and private) amounts to around € 1.3 trillion annually, including €220 billion for medicinal products and €100 billion for medical devices. Healthcare spending represents about 10% of EU GDP.[1] The role of governments in this medical market is unique. First, the safety of patients and the public should be assured. Second, public health insurance systems cover a major part of the bill in Europe.

The pathway from the development to the introduction of innovations into the routine healthcare system is currently not as smooth as it could be.[2] Citizens and patients expect their government to facilitate the path from scientific invention to usual care, maximizing health in an efficient and evidence-based way. Governments are expected to streamline the regulation of medical product market access (by the regulators) and the coverage of innovations in routine care

Governments have typically split the roles between bodies that grant market access and manage vigilance (the regulators) and those that pay, the (public healthcare payers), who decide on coverage via public health funds supported by internal or external bodies for Heath Technology Assessment, HTA. In Europe, this split was made more explicit when a common market was created: the European Union legislator would be responsible for guaranteeing free circulation of goods and services. The marketing authorisation of medicinal products in Europe is nowadays mainly controlled by the European Medicines Agency (EMA) and is based on the evaluation of quality, safety and efficacy. Medical devices are placed on the European

market based on the CE marking system, whereby a Notified Body assesses the device's conformity with EU safety and performance requirements. For drugs and devices the benefit-risk is also evaluated. Reimbursement or coverage of drugs and devices is at member state level, sometimes regional level. The Joint Scientific Assessment part of HTA is moving to EU level under the forthcoming HTA regulation.

In this report the focus is on innovative new medicinal products and high-risk therapeutic medical devices (class IIb/III). Innovative does not mean better but the word is often used to imply that the new product is intended to be better. It has been reported that only 10% of the new medicinal products are a notable therapeutic advance.[3] These sobering results are in line with a recent KCE report on 40 new oncology drugs introduced over the past 15 years in 12 advanced cancer types. When outcomes were assessed using linked national cancer registry data and the literature no detectable impact on survival was found for half of the tumour types and only a small effect was found for the other half.[4]

How can this be explained? The regulatory function and the payer/HTA function are both government-controlled but currently operate mainly independently, sometimes even moving in opposite directions. In addition, both at EU level and member state level there is a delicate balance between industrial policy and health policy while commercial clinical development is more and more global and needs clear regulatory and HTA/payer framework.

Legal and regulatory changes in Europe and the USA have created a complex mix of expedited programmes aimed at facilitating faster access to new drugs.[5] We did not study what pressures (political, perceived demand by patients, industry, competition between regulators,…) or evolutions in regulatory science have caused this lowering of the bar for clinical evidence requirements. Patients may be willing to tolerate greater uncertainty about drug benefits to be able to access investigational/untested products sooner but there is little evidence to support this general statement. On the other hand, patients and even clinicians may not always be aware of the limited level of evidence required by the regulators for drugs and devices.[6]

Under the current reimbursement practices, companies have an incentive to only generate the data needed to pass the regulatory hurdle. Time to market/reimbursement is a key element in the calculation of return on investment. From a company perspective the conduct of a confirmatory trial that generates comparative evidence can be more risky, more costly or take longer. The regulatory initiatives to approve drugs more rapidly and more frequently based on observational data or non-validated surrogate endpoints, means that their efficacy may remain unknown. The result is that the trials with a patient population, comparators, and outcomes that are accepted by the regulatory authorities may not be suitable for performing an HTA, nor for informing physicians wanting to practice evidence-based medicine.

The split in objectives and responsibilities of the two government-controlled bodies, the regulators and the HTA bodies/payers combined with a gradual erosion of regulators' evidence standards over the past few decades[7] can thus be seen as reason for the growing evidence gap (from an HTA/payer perspective) that remains after the private sector has provided the evidence needed for bringing their product to the market. In this regard it is important to stress that **health technology assessment is always comparative in nature, focussing on comparative evidence, on the evaluation of added therapeutic benefit, especially when this is part of the product claim (and pricing).** Clinicians in the field of oncology,[8] multiple sclerosis,[9] severe athma,[10] and other therapeutic areas have also reported the need for more comparative effectiveness trials.[11]

In cases where comparative evidence is not generated in the pre-market phase there may be options to generate comparative evidence demanded by regulators or required by HTA/payers in the post-market phase. **The options for post-market evidence generation however have major limitations in delivery**.[12] It would be naïve to think that without legal or financial consequences, industry would generate data that could potentially cut their sales. The delivery of comparative evidence in the post-market period may not happen within the next 5 years, may be delayed or in cases where no effectiveness is shown, no action may follow. It is still unknown whether there is any benefit in overall survival for about half of the oncology drugs on the market for a median of 5 years.[13] Following EMA conditional

marketing authorisation more than half of post-market obligations imposed on companies are delayed.[14, 15] In 6 out of 18 cases, no FDA action was taken after the oncology drug in the post-market phase failed to show an effect on overall survival.[16] The lack of comparative evidence generated under local coverage with evidence development initiatives or managed entry agreements generally does not allow hard evidence-based decision making.[17, 18]

The CE marking system for medical devices relies mainly on post-market collection of clinical data. However, it has been shown that for medical devices the assumption that high-quality studies will occur in the post-market setting is not true and that evidence regarding clinical effectiveness may thus remain unknown.[19] Spontaneous safety reporting for medical devices is also not up to standard, with significant underreporting of adverse events making it difficult to weigh up benefits versus risks.[20, 21] Physicians implanting cardiovascular or orthopaedic devices may consider the reporting of adverse medical device events as unnecessary, not possible or futile due to multiple factors, leading to severe underreporting.[22]

In this report we have tried to cover the pre-market evidence gaps in terms of the PICOTS elements:[23] population, intervention, comparison, outcomes, length of follow-up (time), and study design. This analysis was performed based on the gaps reported for a series of reimbursement dossiers by the assessors at the Belgian healthcare payer RIZIV-INAMI (chapter 4). This covers both high-risk devices and drugs claiming added therapeutic benefit. This was completed with a literature review trying to identify general trends with regard to the level of evidence (and the gaps) for new high-risk medical devices or medicinal products entering the market. (chapter 5).

Postponing comparative evidence generation also implies postponing access for patients to an evidence-based treatment choice. This is part of the discussion in section “Discussion and possible solutions” (chapter 6), together with **more efficient and more pragmatic ways to generate comparative evidence** using, for example, registry-based randomized trials[24-27] or adaptive platform trials.[28] The shortcomings of the current post-marketing research landscape highlight the importance of generating meaningful evidence on new drugs and devices before they enter the market. This is the main reason why in this report the pre-market comparative evidence is studied.

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 (medicines / 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 proceduce 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 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 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**[29] 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 distiction 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 devices 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 trial 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, 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.[30, 31]
- **Horizon scanning:** a process to identify important innovations before they reach the market

1.2 The regulatory system of medicinal products and medical devices

For most new **medicinal products**, market access in Europe and the US is centrally regulated by the EMA and FDA, respectively. It is based on the demonstrated product **quality, safety and efficacy** (termed effectiveness in the US). Typically two pivotal randomised clinical trials are required supporting efficacy. In Europe, a European Public Assessment Report (EPAR) provides a public summary of the clinical data after the marketing authorisation was granted.

For **medical devices**, the regulatory hurdle is generally lower and shows more variation depending on the device risk class and the regulatory system.[6, 32, 33] Access to the European market is provided through the CE marking system, controlled by Notified bodies. Notified bodies are mainly for-profit entities, designated by the local governments. Even for high-risk devices, the clinical trial data supporting the CE mark may be limited. In the EU, only **safety and device performance** need to be demonstrated, together with an **acceptable benefit-risk ratio**. In the US, innovative devices need to demonstrate safety and clinical effectiveness (the FDA uses effectiveness instead of efficacy) under the FDA pre-market approval (PMA) procedure. The PMA is often based on a single randomised trial (e.g. comparing a new invasive procedure versus a sham procedure). In contrast to Europe, the evidence is reviewed during an expert panel meeting and most associated information is publicly accessible through the FDA website. The different regulatory approaches taken in Europe and the US results in devices coming onto the European market earlier but often with little clinical data.[a] In contrast to medicinal products in Europe, no clinical data summary was made public at market entry for medical devices. The reason given was that clinical data are considered confidential company data, and this principle is prioritised over the publication principle. Under the new Medical Devices Regulation (MDR), a summary of safety and clinical performance (SSCP), reviewed by Notified Bodies, will be made available for implantable and class III devices[b] and will include a summary of clinical data.

1.3 Health technology assessment and coverage of healthcare

Whereas the process of marketing authorisation of medicinal products is now mainly through the European Medicines Agency and the certification of medical devices by individual Notified bodies is applicable for the entire EU, this is not at all the case for the pricing of such products and their coverage by healthcare payers. In Europe, the healthcare provision and funding is still within the jurisdiction of the individual member states, resulting in separate healthcare systems, with even varying forms of regional autonomy within a single country. Aiming at a justified and fair coverage of new and sometimes high-priced interventions, the process of **health technology assessment (HTA)** was developed over the past few decades to advise healthcare payers regarding these decisions. Regulators and HTA bodies may be separate bodies (depends on the country) but often evaluate the same clinical data at market entry. Yet, the conclusions of the clinical evaluation can be different.

Health technology assessment is always comparative in nature, focussing on comparing the evidence for a new treatment with current or best practice (comparative evidence). National and regional HTA bodies want to assess the **added patient benefit** and the proposed value for money of the new intervention in the local routine care setting in

[a] The above statement does not mean that the premarket evidence of all medical devices entering the US market is always ideal. In particular, the use and misuse of the lower hurdle 510(k) procedure leading to an 'inherited' approval status based on a marketed 'predicate' device has been discussed in the literature. For example, Heneghan et al. (2017)[34] analysed the transvaginal mesh devices which were originally classified as class II devices by the FDA that required only the 510(k) process for market access. This led to the approval of transvaginal mesh products for pelvic organ prolapse on the basis of weak evidence for 20 years. Based on possible harms observed, these devices were reclassified by FDA in January 2016.

[b] Other than custom-made.

comparison with the standard of care or best practice. In contrast with the evidence required by the regulators, national reimbursement rules for medicinal products and medical devices may need additional evidence regarding the (comparative) effectiveness and added therapeutic benefit, cost-effectiveness and budget impact.[35] In Belgium, for instance, decisions to reimburse medicinal products claiming an added therapeutic value or medical devices claiming a therapeutic or health and economic added value[c] are taken after an evaluation of the five following reimbursement criteria: (i) the therapeutic value of the medicinal product / medical device; (ii) the price and proposed reimbursement basis; (iii) the importance of the medicinal product / medical device for medical practice in relation to the therapeutic and social needs; (iv) the impact on healthcare expenditures; (v) and the relation between the healthcare cost and the therapeutic value of the medicinal product[d] or medical devices[e].

The evidence gaps identified during HTA for devices or drugs may be important as there is currently no clear legal obligation for manufacturers to assess added therapeutic value trough clinical trials. The comparator used in the confirmatory trials may therefore not reflect best practice and the endpoint used may not be easily linked to patients' quality of life or overall survival. This information is not only crucial for making a reimbursement decision but also to optimise clinical care. Clinicians, patients and policymakers are in need of more practice-oriented, comparative and treatment optimisation trial data so as to practice evidence-based medicine.[10] Furthermore, specific patient groups such as the very young or the frail elderly tend to be excluded from registration trials. Yet, they may be most in need of better treatment or they may make up a considerable part of the target population.

The choice of the comparator and the endpoints are also the items about which industry, regulators and HTA bodies tend to disagree during early dialogues or parallel scientific advice (see insert) for medicines under development,[36] and where the uptake by industry of NICE HTA advice has been shown to be low.[37]

Parallel Scientific Advice

In addition to the regulatory scientific advice, since 2010, the EMA has been offering scientific advice in parallel with health technology assessment (HTA) bodies. This parallel regulatory-HTA scientific advice allows manufacturers to receive simultaneous feedback from both the EU regulators (i.e. members of the EMA Committees and Working Parties who provide advice to manufacturers, under the scientific coordination of the EMA) and HTA bodies on their development plans for new medicines. Its aim is to bridge the gap between the evidence requirements for different decision makers and theoretically it can be initiated at any point in the developmental lifecycle of medicines, although it is often requested before the development programme has reached the pivotal phase. According to this process, a manufacturer submits a briefing document that outlines the clinical development plans for the new medicinal product, together with a set of specific questions addressed to the regulators and the HTA bodies and its own position for each question. Of note, for each procedure, the manufacturer selects a set of HTA bodies of choice, which voluntarily participate in the procedure. Furthermore, as part of this process, the manufacturer will meet with both the regulators and the HTA bodies representatives during a face-to-face discussion meeting.

[c] Under Belgian legislation, so-called "Class 1" medicinal products are products claiming an added therapeutic value and the so-called "Class 1" medical devices ar devices claiming a therapeutic or health and economic added value (they can cover risk Class I, IIa, IIb or III devices under the medical devices legal classification).

[d] Article 35bis of the law 14.07.1994 and article 5 of the Royal Decree 01.02.2018. For medicine not claiming added-therapeutic value, only the criteria (i) to (iv) are evaluated.

[e] Article 35*septies* /2, § 3 of the law 14.07.1994 and article 16 of the Royal Decree of 25.06.2015. For medical devices not claiming added therapeutic value, only the criteria (i) to (iv) are evaluated.

Experience shows that the regulatory advice is followed more frequently by industry compared with the advice of HTA bodies.[37]

For medical devices, the lack of robust clinical data in Europe hampers the clinical assessment of patient benefit and the cost-effectiveness analysis in the context of national reimbursement procedures.[38] Similar to medicinal products, typical points of discussion for the reimbursement of devices in European countries concern a lack of direct comparison with the standard of care in a real-world setting and the collection of sufficiently long term patient-relevant endpoints.[39]

1.4 New EU regulations for medical devices and pharmaceuticals

The past EU Directives for the CE marking system for medical devices remained very vague regarding their clinical development and did not provide a clear mandate, nor the authority, for the Notified bodies to demand a demonstration of their clinical effectiveness. The Directives are being replaced from May 26 2021 (May 26, 2022 for in vitro diagnostic medical devices) by new medical device regulations Regulation (EU) 2017/745 (MDR) and Regulation (EU) 2017/746 (IVDMDR). The MDR includes the requirement to evaluate clinical benefit taking into account the state of the art.[40, 41] The new framework also considers that other therapeutic alternatives shall be taken into account in the general clinical evaluation (not necessarily in a trial) of the device. In addition, the term equivalence has now been defined in the MDR,[41], the lack of which was considered a shortcoming in the earlier medical device directives.[42] The regulation also specifies that a clinical data summary will become publicly available for medical devices through the EUDAMED database. The implementation of EUDAMED has however been delayed. Meanwhile companies have been asked to make the clinical data summary available publicly in other ways (e.g. on their website).

The EUDAMED (MDR) database
(https://ec.europa.eu/tools/eudamed/#/screen/home)

The improved European database on medical devices EUDAMED, to distinguish it from the previous EU database, Eudamed2 (which was developed from the original Eudamed database developed as a pilot, neither of which provided public access to data) is one of the key aspects of the new rules on medical devices (Regulation (EU) 2017/745) and on in vitro diagnostic medical devices (Regulation (EU) 2017/746).

EUDAMED will provide a living picture of the lifecycle of medical devices that are made available in the European Union (EU). It will integrate different electronic systems to collate and process information about medical devices and related companies (e.g. manufacturers). In doing so, EUDAMED aims to enhance overall transparency, including through better access to information for the public and healthcare professionals, and to enhance coordination between the different Member States in the EU.

EUDAMED will be composed of six modules related to: actor registration, unique device identification (UDI) and device registration, notified bodies and certificates, clinical investigations and performance studies, vigilance and market surveillance. Once EUDAMED is functional, and for the first time ever, it will be possible to obtain a complete list of all medical devices being made available on the EU market and a list of the manufacturers and suppliers of those devices.

An enhanced collaboration between HTA bodies is planned to be realised by the forthcoming HTA regulation.[43] In addition, the Commission plans to revise the pharmaceutical legislation, namely Directive 2001/83/EC and Regulation (EC) No 726/2004, by the end of 2022.[44] The consideration of the HTA perspective may be timely and relevant in this context. At the July 2021 HTA Network meeting, the European Commission asked: “With the HTA Regulation close to adoption, what policy developments are necessary in terms of pharmaceutical incentives and in cooperation among member

states pricing and reimbursement authorities so that the new EU HTA mechanism can reach its full potential?"[43]

For medical devices too, an enhanced collaboration between HTA bodies, Notified bodies and the medical device industry might not only improve the evaluation of devices[45, 46] but also indirectly stimulate the generation of appropriate evidence for HTA. In this context one should note the whereas clause 19c added by the EU Parliament during their review of the HTA regulation: "Regulation (EU) 2017/745 concerning medical devices and Regulation (EU) 2017/746 concerning in vitro diagnostic medical devices provide for the authorisation of such devices on the basis of the principles of transparency and safety and not on efficacy. However, the gradual increase in the supply of medical devices to address clinical conditions has heralded a paradigm shift towards a new model in which the market is highly fragmented, innovation is chiefly incremental and clinical evidence is lacking, which means that closer cooperation and more frequent exchanges of information between assessment bodies are needed. It is therefore necessary to move towards a centralised authorisation system that assesses devices on the basis of safety, efficacy and quality. It is also one of the areas in which Member States are calling for greater collaboration via a future European HTA. Currently 20 Member States, together with Norway, have HTA systems for medical devices in place and 12 Member States, together with Norway, have established guidelines and are engaging in initial dialogues. EUnetHTA has been conducting high-quality evaluations of the relative efficacy of medical devices based on a methodology that can be taken as a benchmark for this Regulation. [Am. 34]" This call for a new revision of the legislation on medical devices will however probably not be included in the final version of the new HTA Regulation as the Council position has never been in favour of a pre-market centralised authorisation in this sector, even for high risk devices.

1.5 Aims and scope of this project

This project aims to document evidence gaps at market entry from an HTA/payer perspective, therefore the **focus of this project is on evidence gaps present at market entry.** As HTA is always comparative in nature the terms comparative evidence and comparative effectiveness are also appropriate. We refer to new medicinal products claiming added therapeutic value and high-risk medical devices (EU class IIb and III devices) claiming added therapeutic value, submitted over the past years for public payer coverage in Belgium or Europe in general. For healthcare payers, new health technologies with a similar effectiveness provided at a lower cost is also of value. However, the scope here is limited to comparative evidence versus the available alternative, the added therapeutic value. Uncertainties in the cost of downstream activities are also out of scope. Other types of medical interventions are out of scope, such as diagnostic medical devices and in vitro diagnostics for which equivalence testing differs from therapeutic devices.

This project does not focus on the level of evidence for a single medical device or medicinal product but tries to identify general trends. The study of the impact of the level of evidence on the reimbursement decision is out of scope. Studies checking if missing pre-market evidence had become available in the post-marketing phase were also included. However, the focus of this project is not the evaluation of a possible revision or prolongation of reimbursement in the post-marketing phase. Starting from the identified gaps, this project aims to identify solutions to first of all avoid these gaps during future developments and where needed, to remediate in the post-marketing phase.

Our **research questions** are thus the following:

1. What are the evidence gaps for medicinal products and higher-risk medical devices (EU Class IIb and III) in terms of the intended population, the intervention, the comparator, the relevant clinical outcomes, time to follow-up, and necessary study design to provide robust and reliable evidence needed for clinical and reimbursement decision-making at the time of market entry? HTA bodies require this information in order to assess manufacturers' claims of "added value" for their products, medicines or devices, in the dossiers submitted by manufacturers when applying for reimbursement. For this report "added value" should be read as "added therapeutic benefit" and not an equivalent benefit at a lower cost.
2. What are the possible solutions during clinical product development to prevent these evidence gaps in the pre-market phase?

Key points

- **For medicinal products, market access in Europe is mainly regulated centrally by the EMA and is based on the demonstrated product quality, safety and efficacy. A European Public Assessment Report (EPAR) provides a summary of the clinical data.**
- **For medical devices, market access to the European market is provided through the CE marking system, controlled by notified bodies, which are mainly for-profit entities. Safety, performance and an acceptable benefit-risk ratio are to be demonstrated. Currently, newly required clinical data summaries are not made public via the centralised EUDAMED database. Member States are calling industry to make them available by other means (website or upon request) until the EUDAMED is fully functional.**
- **While market access is mainly regulated on a European level, the regulation and funding (coverage) of healthcare has remained a national remit.**
- **If evidence on a new technology allows market entry, but is insufficient for clinical and reimbursement decisions, this evidence gap leads to ill-informed, potentially harmful decisions, both at the bedside and also in the healthcare system.**
- **This project aims to document (comparative) evidence gaps from an HTA/payer perspective for medicinal products and high-risk devices (Class IIb and III), claiming added therapeutic benefit. The project also aims to identify solutions to avoid these gaps in the pre-market phase, and to assess if these gaps are filled in the post-market phase.**
- **From an HTA/payers perspective the gradual erosion of regulators' evidence standards over the past few decades can be seen as a reason for the growing evidence gap remaining after the private sector has performed the trials needed for bringing their product to the market. Under the current reimbursement practices, companies have an incentive to only generate the data needed to pass the regulatory hurdle.**
- **This report may be timely as it coincides with the introduction of the new EU regulation for medical devices, the finalisation of the EU HTA regulation and a planned revision of the pharmaceutical legislation in Europe.**

2 METHODS

This project tries to highlight the evidence requirements and the evidence gaps from different angles using different sources of information, each having a specific methodology, detailed per section. This is illustrated in Figure 1.

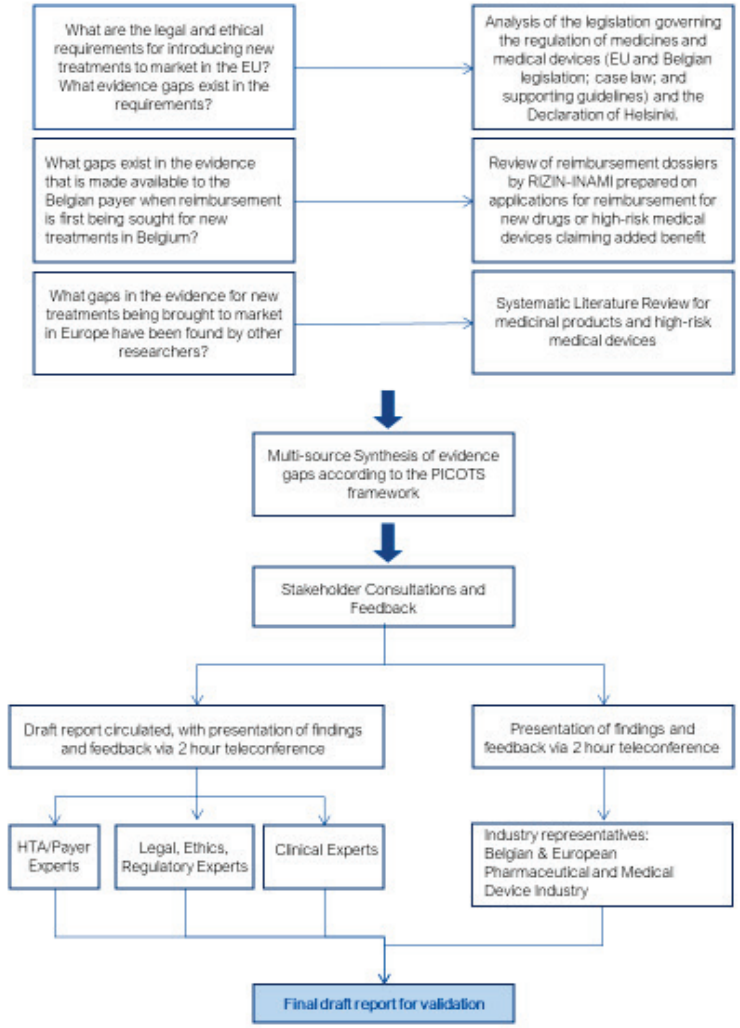
- A review of the legal framework covering the evidentiary requirements for market entry of medicinal products and high-risk medical devices in Europe, based on a combined analysis of legislation, court's decisions and legal literature (Chapter 3). A systematic literature search was not conducted on ethical or legal topics.
- A brief review of evidence gaps reported by assessors as issues in the evaluation dossiers of medical devices or medicinal products submitted for reimbursement to the Belgian National Institute for Health and Disability Insurance (RIZIV-INAMI) claiming added therapeutic value during the past few years (Chapter 4).
- A literature review of articles that studied the level of evidence (and the evidence gaps) of a group of medical devices or medicinal products at market entry or important general trends on the level of evidence.(Chapter 5)
- Chapter 6 discusses the findings and possible solutions are put into context, such as options for post-market data collection. However, no additional systematic search was conducted for this purpose.

In addition, as part of the standard KCE process, external experts and stakeholders were consulted as follows:

- A consultation of a group of experts in medicinal products or high-risk medical devices of selected public HTA/payer institutes from Austria, Belgium, France, Germany, Ireland, Norway, the Netherlands and the UK was conducted, using a two hour videoconference. A draft report was circulated in advance and slides summarizing the main findings were presented during the meeting for discussion and collection of expert opinions and additional references.
- A consultation via a two hour videoconference with a group of experts in ethics, legislation and regulation. A draft report was circulated in advance and slides summarising the main findings were presented during the meeting for discussion and collection of expert opinions and additional references.
- A consultation via a two hour videoconference of a group of clinical experts in medicinal products or high-risk medical devices, mainly authors of publications covering the subject of this report. A draft report was circulated in advance and slides summarizing the main findings were presented during the meeting for discussion and collection of expert opinions and additional references.
- Industry stakeholders representing the Belgian and European medical device and pharmaceutical industry were consulted, also via teleconference, following a presentation of slides summarising the main findings of the report.

Finally, draft policy recommendations were prepared for review by the KCE board.

Figure 1 – Schematic representation of the sources and methods used in this report



3 LEGAL AND ETHICAL CONSIDERATIONS

3.1 Introduction: the legal and ethical frameworks on evidence requirements

Legal requirements governing market access and clinical trials shape the evidence base that support the regulatory approval of new drugs and devices. European market access rules have precise objectives and rely on specific criteria allowing manufacturers a certain flexibility in choosing the appropriate level of evidence to provide in order to place their product on the market.

These criteria and processes are complex and may not always be well known and understood by the general public, by patients, nor even by clinicians who possibly consider the fact that these products are allowed by the regulatory authorities to be made available on the EU market as a confirmation of their efficacy in clinical practice and therefore, do not see why their reimbursement is not immediately granted.[6, 47, 48] It was also shown for health products placed on the US market, that many people do not understand the regulatory processes and criteria, or their implications for product safety.[49]

Therefore, the aim of this chapter is to describe legal requirements governing market access and clinical trials for new medicines[f] and high-risk medical devices[g] in the pre-market phase and to analyse to what extent these requirements are able to ensure appropriate evidence gathering and data transparency, thereby allowing safe and efficient use of innovative medicines and (high-risk) medical devices at market entry. These legal rules, primarily aiming to protect human health, have close links with human rights, in particular the rights to life, to physical integrity and to health. Therefore, they must also be analysed in the light of the ethical rules applicable to clinical research, on which they explicitly rely.

As the focus of this report is the pre-market phase, rules and initiatives contributing to ensure the safety and effectiveness of innovative products in the post-market phase, such as post-marketing requirements, national healthcare organisations' rules (e.g. the use of post-market registries, post-market real-world data analysis) or repeated post-market HTA evaluations (e.g. in the context of managed entry agreements) fall outside the scope of this chapter.

3.2 Methodology

The main purpose of this chapter is to present the legal framework governing market access and clinical trials. Therefore, this chapter uses mainly traditional legal methodology, consisting of the following elements:

- **Analysis of the former and current versions of European and Belgian legislations regarding medicines and medical devices** (including prior parliamentary discussions and subsequent guidelines): the Official European and Belgian legal databases (Eurlex and Belgian Monitor), as well as the websites of European (EMA, European Commission, …) and national competent authorities (FAMHP, NIHDI) and international organisations (Council of Europe, World Health Organization,…) were used to consult policy documents and guidelines.
- **Analysis of the European and Belgian courts' decisions:** the European Court of Justice database (CURIA), as well as wider European regulations databases (Eurlex) and the official (Jurportal) and commercial (Jura) Belgian jurisprudence databases were consulted to identify possibly relevant legal decisions. The case law of the European and national courts are the authoritative interpretations of the legislation.
- **Review of the legal literature**: keyword searches were used in European and Belgian databases (Eurlex and Jura) and in Google, Google Scholar and PubMed to find grey literature dealing with the relevant legal issues. Literature and position papers published by legal journals and publishers and by official bodies (European Commission, EMA, EUnetHTA, MDCG, etc.) and stakeholders (NGO's, industry representatives etc.) were analysed in order to describe the actual implementation of the legislation and to identify main legal issues, bottlenecks, policy options and possible solutions.
- **Discussions (orally or in writing) with experts and stakeholders concerning specific questions** to cross-validate and complete the topics addressed and identified in the chapter.

This chapter also aims to higlight the ethical context supporting the relevant legal rules. In clinical research, there are many ethical standards which are issued by many different actors including national or international professional associations or research institutions, international organisations,… This chapter is limited to the analysis of the most universally referenced ethical rules which are included in the Declaration of Helsinki. The moral authority of this Declaration is so important that most of the ethical rules adopted in the area of clincial research as well as the legal texts refer to this Declaration. Consequently, an analysis of the literature (identified using the methods described above) was conducted regarding

[f] Specific rules for paediatric, homeopathic, orphan or advanced therapy medicinal products are out of scope.

[g] In vitro diagnostic medical devices are out of scope.

the relationship between the Declaration of Helsinki and the legal framework.

These sources were mainly consulted between May and September 2021.

3.3 Applicable rules

Clinical evidence regarding medicines and medical devices at the market entry is regulated by both legal and ethical provisions that have different aims and scopes.

European legal framework

The Treaty on the Functioning of the European Union (TFEU) stipulates that a high level of human health protection shall be ensured in the definition and implementation of all Community policies and activities[h]. While primary responsibility for health protection and, in particular, healthcare systems, continues to lie with the Member States, the European Union (EU) has, a complementary competence (i.e. both the EU and Member States are able to enact laws). In order to meet common health safety concerns, article 168.4 (c) of the TFEU gives the EU the authority to adopt harmonised standards of quality and safety for medicinal products and medical devices. In addition, the TFEU also gives the EU the authority to adopt harmonised measures to guarantee the functioning of the internal market, bearing in mind the compelling requirement to safeguard and protect public health[i].

The recitals of the **European Directive 2001/83 on medicinal products for human health**[j] recall that the **essential and primary aim of any rules governing** the production, distribution and use of **medicinal products must be to safeguard public health** but that this objective (health protection) must be attained **by means which will not hinder the development of the pharmaceutical industry or trade** in medicinal products within the Community. The Court of Justice of the European Union considers that rules regarding medicines seek to reconcile *the aim* of protection of public health with *the principle* of free movement of goods[k].

With regard to **medical devices**, the recitals of the new **European Regulations 2017/745**[l] on medical devices and 2017/746[m] on in vitro diagnostic medical devices (which are progressively replacing European Directives on medical devices[n], in vitro diagnostic medical devices[o], and active implantable medical devices[p]) state that the aim of rules for medical devices is to ensure the **smooth functioning of the internal market** as

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h Article 168(1) of the TFEU.

i Article 114 of the TFEU. The EU can pursue public health objectives *through* the integration of the internal market.EU health policy initially originated from health and safety provisions, and later developed as a result of the free movement of people and goods in the internal market, which necessitated the coordination of public health issues. See also European Commission “Blue Guide on the implementation of EU products”, 2014.

j Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use. O.J. L 311, 28/11/2001.

k CJEU, *European Commission vs. Germany*, C-319/05 (15.11.2007). On the safeguard of public health as primary objective see also CJEU, *Abcur,* C-544/13 (16.07.2015); CJEU, *Antroposana and Others*, C-84/06 and CJEU, *Commission v Poland*, C-185/10.

l Regulation 2017/745 of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. O.J. L117, 5/05/2017.))

m Regulation 2017/746 of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU. O.J. L117, 5/05/2017. IVD medical devices are out of scope.

n Directive 93/42/EEC concerning medical devices. O.J. L169, 12.07.1993.

o Directive 98/79/EC of 27 October 1998 on in vitro diagnostic medical devices. O.J. L331, 07.12.1998.

p Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices. O.J. L189, 20/07/1990.

regards medical devices, **taking as a base a high level of protection of health for patients** and users and that **both objectives** are being pursued simultaneously and are inseparably linked whilst **one not being secondary to the other.**

The tension between the promotion of a European market where goods can circulate freely and the essential and primary aim to safeguard public health is frequently observed in the discussions between the European Parliament, the European Commission and the European Council that precede the adoption of the legal texts in the area of health.

As an example, numerous discussions illustrating this tension took place in the process leading to the adoption of the Medical Devices Regulation (MDR)[50]. This was also the case in the very recent discussions for the adoption of the European HTA Regulation (see infra section 3.4.3.6). The first recitals of the draft Regulation proposed by the Commission referred very strongly to the need to harmonise the rules with a view to promote socioeconomic growth and innovation in the European internal market[q]. This position was criticised by the European Parliament which in its amendments proposed a much stronger focus on health protection[r]. In this context, the European Economic and Social Committee (specific advisory body in the EU regulatory process) recalled that the primary aim of this new HTA Regulation is to safeguard the health of all citizens. This Committee also importantly draw attention to the fact that "the mandate (for the EU legislator) refers to health as a market, whereas health is a common good and should be addressed from a general interest point of view"[s].

Directive 2001/83 on medicines is complemented by **Directive 2001/20 on clinical trials** of medicines[t], which harmonised rules to **protect human subjects'** rights in clinical trials involving medicines and aimed to ensure the **reliability and robustness of the data** generated by those trials. It is soon to be replaced by the clinical trials Regulation[u]. The European legislator integrated a similar framework on clinical trials in the new medical devices Regulations.

Finally, the **cross-Border health care Directive**[v], currently under revision in the context of the creation of a new European HTA mechanism[w], defines common rules applicable to **patients' right in cross-border health care** and promotes **cooperation** between Member States **in the field of health**.

Human rights to health, physical integrity and life (including those rights of the patients and study subject in clinical trials) are enshrined in various legal texts including in the **European Convention on human rights**[x] and additional protocols (Council of Europe) and in the **Charter of Fundamental**

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q COM/2018/051 final - 2018/018 (COD) https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM%3A2018%3A0051%3AFIN.

r P8_A(2018)0289 (Report) https://www.europarl.europa.eu/RegData/seance_pleniere/textes_deposes/rapports/2018/0289/P8_A(2018)0289_EN.pdf.

s https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CONSIL:ST_8330_2021_INIT&from=FR

t Directive 2001/20/EC of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

u Regulation (EU) No 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, O.J. L158, 27.5.2014. This text will enter into force in January 2022.

v Directive 2011/24/EU of 9 March 2011 on the application of patients' rights in cross-border healthcare O.J. L88, 04.04.2011.

w Proposal for a Regulation of the European Parliament and of the Council on health technology assessment and amending Directive 2011/24/EU : https://eur-lex.europa.eu/legal-content/EN/HIS/?uri=celex:52018PC0051.

x European Convention on human rights. Available at: https://www.echr.coe.int/Pages/home.aspx?p=basictexts&c

Rights[y] (European Union). As explained in this chapter (see section 3.4.2), recognition of fundamental human rights implies general government obligations, but the concrete legal consequences of these obligations are not always straightforward.[51]

National legal framework

Member States remain competent (i.e. they retain authority and responsibility) for the definition of their health policy and for the organisation and delivery of health services and medical care, including the allocation of the resources they assign to these. They can decide freely on the pricing and reimbursement criteria applicable in their country, including by requiring evidence of added therapeutic value, as long as these criteria are objective and verifiable and provided that they implement the requirements (including deadlines) set up by the Transparency Directive[z]. This allows them to take into account their own national context and resources.

Ethical rules

In addition to European and national legal rules, ethical standards require health care professionals to ensure patients' health, well-being and rights, including in the conduct of clinical trials. Ethical rules are a set of moral principles regulating individual's behaviour. In the context of medical research, ethical rules are moral principles guiding health care professionals in making choices about medical care and medical research. Unlike laws, the authors of ethical norms are not strictly limited: ethical standards can be presented as such by a whole range of actors from the World Health Organisation (WHO) to local or international professional associations, business associations, etc. The moral value and recognition of an ethical standard is defined by its addressees; in other words, the more an ethical standard is followed and accepted by its addressees, the stronger its moral value is and the more of an ethical imperative it is. In contrast, laws are structured rules utilised to govern all society, issued by legislators and interpreted by judges.

Ethical standards are not sanctioned except when the law incorporates an ethical standard and sanctions its violation (see infra section 3.4.1.1).

In clinical research, which is the focus of this report, the Declaration of Helsinki remains the most universal reference. This text was adopted based on the Nuremberg Declaration that was enacted after the horrors committed during the Second World War, including in the area of scientific experiments on humans. Numerous other ethical texts have since been adopted in this area and generally refer to the Declaration of Helsinki. The moral authority of this Declaration is so important that legal texts also explicitly refer to it.

Key points

- **Legal requirements governing market access and clinical trials shape the evidence base that support the regulatory approval of new drugs and devices.**
- **The European market access rules have precise objectives and rely on specific criteria and processes which allow manufacturers a certain flexibility in choosing the appropriate level of evidence.**
- **These criteria and processes are complex and may not always be well known and understood by the general public, by patients, nor even by clinicians who might wonder why reimbursement is not immediately granted after market entry.**[6, 47-49]

[y] Charter of Fundamental Rights of the European Union, O.J. C326, 26.10.2012.

[z] Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems, O.J. L40, 11.02.1989.

- **Legal requirements governing market access and clinical trials, which primarily aim to protect human health, have close links with human rights, in particular the rights to life, to physical integrity and to health. They must also be analysed in the light of the ethical rules applicable to clinical research, on which they are explicitly based.**

3.4 Evidentiary requirements for medicinal products and medical devices

Before placing innovative medicines and high-risk medical devices on the market, manufacturers are, in principle, required to perform clinical trials (though this is not always the case for medical devices – see infra section 3.4.4.2). The definition of appropriate level of evidence and of the appropriate clinical trial elements to generate this evidence (comparator, endpoints, studied group, …) is a controversial debate between regulators and HTA. Relying on the requirements of their legislations, regulatory authorities, like the FDA or the EMA, support a flexible approach and do not require active control trials as the default standard in all clinical trials. This view is criticised by many clinicians, patient and professional associations and by HTA agencies who believe that more demanding study designs and more relevant clinical evidence are needed to ensure that patients are safe and that public money for drug or device reimbursement is appropriately spent.[52, 53]

The following sub-sections examine the relevant ethical and legal rules applicable to clinical evidence in the pre-market phase.

3.4.1 Ethical rules for the conduct of clinical trials

3.4.1.1 The declaration of Helsinki

The Declaration of Helsinki (DoH), initially enacted by the World Medical Association (WMA)[aa] in 1964[bb], constitutes one of the cornerstones of medical research ethics.[54] In fact, it is the most referred to "code of ethics" regarding medical research and it has served as a foundation for national and international legislation governing medical research across the world. It contains the core ethical principles for physicians to protect human participants in medical research. The Declaration has been revised several times (1975, 1983, 1989, 1996, 2000, 2004, 2008, and 2013).

Box 1 – Binding character of the Helsinki Declaration (DoH)

The Declaration of Helsinki is referred to in most of the European Directives and Regulations on medical devices and medicines and related clinical trials (see Appendix 1). ISO standards and clinical trial protocols also usually refer to this Declaration.

Ethical rules constitute, strictly speaking, a separate set of rules. In Europe, legal rules are enacted by both European and national authorities. Ethical rules are issued by moral authorities. The legislations for medical devices and medicinal products have absorbed certain ethical principles by copying them in full in the legal texts. Legal rules also recognise specific competences for ethics committees regarding the evaluation of requests for approval of clinical trials on certain medical devices and medicines.

[aa] The World Medical Association is an international organization founded after the Second World War. This organization brings together 95 national physicians associations and is funded by the annual contributions of its members. The Association Belge des Syndicats Médicaux (ABSYM) is one of their members.

[bb] Based on the Nuremberg Code of 1947.

However, ethical rules that are not explicitly mentioned in full in the legislation are, in most countries, not legally binding. In Belgium, this has been confirmed by the highest administrative court (Council of State): in order to recognise a binding character to the Declaration of Helsinki, the Council advised the Belgian legislator to add this entire Declaration in full in the text of the legislation or in an appendix. A mere referral, even explicit, to ethical rules is thus not sufficient to ensure legal authority (see Appendix 1).

Despite its limited direct legal authority, the Declaration of Helsinki has indisputably a considerable moral authority all over the world. [54, 55]

The protection of patients' health, well-being and rights are the fundamental values underlying the Declaration of Helsinki. Consequently, article 8 states that while the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects. In addition, article 16 states that medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

According to Wendler et al. (2017)[56] and Habet et al. (2014)[57], the Declaration is one of the texts that supports the principle that clinical research is ethically acceptable only when it has social value, in the sense that the data to be collected have the potential to improve health. The authors consider clinical research that exposes participants to risks and burdens, but lacks social value, as unethical no matter what other positive features it might possess. They see a major role for ethics committees to assess this aspect and ensure that it is upheld.[cc]

The DoH does not impose a specific study design and does not define specific criteria for the choice of clinical endpoints, but it does contain a key principle concerning the choice of comparator and the possible use of placebo (old article 29, current article 33). The initial provision, introduced in 1996, stated that "*in any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists*".

This provision was strengthened and rephrased as follows in 2000: "*The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not preclude the use of placebo, or no treatment in studies where no proven prophylactic, diagnostic, and therapeutic methods exist*" (article 29).

This change provoked strong protests from the American and European regulatory authorities.[58] In reaction, the EMA adopted in 2001, a "Position Statement on the Use of Placebo in Clinical Trials with Regard to the Revised Declaration of Helsinki" nuancing the statement of article 29 and defending a case-by-case approach for the choice of the comparator[dd].

In this position paper, the EMA recalled that marketing authorisations can, legally, be granted to new drugs provided that they demonstrate quality, safety and efficacy and that their benefit-risk balance is favourable. However, this does not mean for the EMA that new and established therapies always need to be actively compared and that placebo control arms shall be ruled out when other therapeutic methods exist. Without being very specific, the EMA generally states that in some cases the "judicious use of placebo remains essential to demonstrate the value of new medicinal products". From a regulatory perspective, the use of placebo may indeed present some relevance, for instance to ensure assay sensitivity in studies, which test for efficacy/safety in the regulatory context.[59, 60]

[cc] Nuremberg Code: research is acceptable only when it has the potential to yield "fruitful results for the good of society".

[dd] https://www.ema.europa.eu/en/documents/position/emea-position-statement-use-placebo-clinical-trials-regard-revised-declaration-helsinki_en.pdf

According to the EMA, the legal provisions prohibiting the causing of additional risks or irreversible harm to study participants and the provisions requiring patient's consent regarding the clinical trial are sufficient to avoid the unethical use of placebo. The remit to ethically evaluate this unethical use falls, according to the EMA, to the ethics committees. Given the importance of clinical studies in the marketing authorisation process for medicines, the task of ethics committees is key in this process (see infra section 3.4.3.2, 3.4.4.2 and 3.4.5). As analysed later in the text (see section 3.4.5), this imposes a huge responsibility on the ethics committees which, in addition, are regulated nationally and might not be organised (or funded and supported) identically everywhere in Europe (running the risk of competition that may lead to cost-cutting activities such as reduced time to assess clinical trial applications or reduced oversight). It could even be argued that it is naive (and potentially dangerous) to accept ethics committee approval alone as evidence that ethical concerns have been appropriately reviewed, with the trial appropriately designed, best evidence considered, and harms minimised.[61] In addition, Mendel et al. (2016)[61] call for more transparency to access the details of the ethical reviews and the actual information given to patients. The authors reported substantial barriers to accessing the relevant documents.

As a result of the EMA and FDA reactions, an explanatory note was first added to article 29 of the DoH in 2002[ee] and then integrated in 2008 in the new phrasing of article 33 of the DoH, which currently states that:

"*The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:*

- Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

- Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option."

Despite those changes, the Declaration of Helsinki still considers active control trials as the standard or normal case in clinical trials, and it considers placebo-controlled trials or trials with a less effective or no intervention only as possible exceptions within narrow circumstances, and under specific conditions.[53]

In 2010, the EMA stated in a discussion paper that where ethical and feasible, a placebo control arm should be included in the pivotal trial(s) used to support marketing authorisation application, which seems to imply that placebo-controlled arms are the standard for marketing authorisation, while the need for an active control must be considered on a case-by-case basis[ff]. To date, the EMA has not drastically changed its opinion and still defends a flexible approach (see infra section 3.4.3.1).

3.4.1.2 Other ethical provisions

Ethical recommendations on study design, comparators and endpoints in clinical trials are published by a very large number of different actors: ethical rules can be enacted by medical associations or by national or international scientific or professional associations. It is not possible to describe all these ethics codes here.

[ee] https://ordomedic.be/fr/avis/deontologie/secret-professionnel/declaration-d-helsinki

[ff] https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-need-active-control-therapeutic-areas-where-use-placebo-deemed-ethical-one-more_en.pdf

However, the International Ethical Guidelines for Health-related Research Involving Humans adopted by the WHO and the Council for International Organizations of Medical Sciences in 2015 should be mentioned because they are particularly overarching and detailed[gg] [hh]. Guideline 5 of this document concerns the choice of control in clinical trials. It contains similar provisions to the Helsinki Declaration but provides concrete definitions (such as established intervention, compelling scientific reasons, etc.) and provides concrete behavioural rules for researchers.

Key points

- **The Declaration of Helsinki (DoH) enacted by the World Medical Association (WMA) constitutes one of the cornerstones of medical research ethics and has considerable moral authority worldwide. It recalls that in any research involving humans the rights and interests of individual research subjects take precedence over all other interests.**
- **European rules on medical devices and medicines and on clinical trials refer to this declaration. A mere referral is, however, not sufficient and this Declaration is not, in itself, legally binding.**
- **The DoH does not impose a specific study design and does not define specific criteria for the choice of endpoints, but it does contain a key principle concerning the choice of an active comparator.**
- **Article 33 of this Declaration considers comparative trials against best proven interventions as the standard or normal case in clinical trials (regardless of the phase of the trial) and the use of placebo-controlled trials or no intervention / less effective intervention as possible exceptions, to be used under strict conditions and interpreted narrowly. In any case, the patients who receive any intervention less effective than the best proven one, placebo, or no intervention must not be subjected to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.**
- **The EMA considers that new and established therapies do not always need to be actively compared and that placebo control arms shall not necessarily be ruled out when other therapeutic methods exist. Without being very specific, the EMA generally states that in some cases the "judicious use of placebo remains essential to demonstrate the value of new medical products".**
- **The remit to ethically evaluate unethical use of placebo falls, according to the EMA, to the ethics committees. This imposes a huge responsibility on the ethics committees, which are regulated nationally and might not be organised (or funded and supported) identically everywhere in Europe (thus risking competition that may lead to cost-cutting and reduced oversight of applications). It could even be argued that it is naive (and potentially dangerous) to accept ethics committee approval alone as evidence that ethical concerns have been appropriately reviewed, trials appropriately designed, best evidence considered, and harms minimised.**

gg The World Health Organization guidance also adopted in 2011 Standards and operational guidance for ethics review of health-related research with human participants. They contain however very broad provisions.

hh https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf

3.4.2 Research and human rights

Recognition of fundamental human rights implies general positive government obligations (i.e. the government must take all necessary measures, including legislation, to give effect to the right) or even negative government obligations (i.e. the government must respect and ensure the right) even if the concrete legal consequences of these obligations are not always straightforward.[51]

The **European Convention on Human Rights** enshrines fundamental human rights, including the right to life and to physical integrity. Adopted by 47 states, including all EU Member States, it is legally binding (in contrast to purely ethical rules). The Convention on Human Rights and Biomedicine (ETS No 164), also called the Oviedo Convention, draws on the principles established by the European Convention on Human Rights, in the field of biology and medicine and sets out fundamental principles applicable to daily medical practice and to biomedical research. The provisions of the Oviedo Convention are further elaborated and complemented by several protocols, including an additional Protocol Concerning Biomedical Research which contains general provisions regarding the study design, endpoints and comparators in clinical trials. However, they illustrate the strong connection between research ethics and human rights and reaffirm the primacy of the interest and welfare of the human being. The Oviedo Convention and its additional protocols are also legally binding instruments. However, this binding character remains rather theoretical as a significant number of countries did not ratify (and sign) these international conventions. Belgium, for instance, did not sign the Oviedo Convention nor its additional protocol.

The European Court of Human Rights (ECtHR) is the international court which interprets these conventions. While no ECtHR case law has been identified regarding market access rules for medicines or medical devices or clinical trials legislations specifically, several health-related case law analyses the compliance of a State legislation (and its effective application) with human rights. For instance, the ECtHR ruled that a State violated the right to life by failing to efficiently control health care professionals who had been carrying out unlicensed medical activities in violation of domestic law, causing damages to a patient. The Court ruled in that case that "*while there was a legal framework for supervising compliance with the relevant licensing requirements, the respondent Government had not clarified how its implementation had been ensured in practice, if at all. There had therefore been a violation of the State's substantive positive obligation to provide an effectively functioning regulatory framework that would ensure compliance with the applicable regulations geared to the protection of the patients' lives*.[ii] In other words, if a State fails to ensure the effective implementation of legislation aiming at the protection of patients' lives, it could violate the right to life.

Some authors also argue that the right to health enables to make legal arguments for the national implementation of strong mandatory trial registration, broad results reporting and extended data transparency.[51]

Fundamental rights are also protected at the European Union level. The right to life (article 2) and the integrity of the person (article 3) are enshrined in the **European Charter of Fundamental Rights**, which became legally binding on EU Member States and institutions of the European Union when the Treaty of Lisbon entered into force in December 2009. In the fields of medicine and biology, article 3 of the Charter explicitly contains the prohibition on making the human body and its parts as a source of financial gain. In addition, article 35 of the Charter enshrines the right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices. It also recalls that a high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities.

As part of its mission, the Court of Justice of the European Union can review the legality of the acts of the institutions of the European Union, ensure that the Member States comply with obligations under the Treaties, including the European Charter on human rights, and interpret European Union law at the

[ii] ECtHR, Sarishvili-Bolkvadze v. Georgia, 58240/08, judgment 19.7.2018.

request of the national courts. The Court could for instance appreciate, in the context of a question raised by a national court in a specific litigation, whether the national and European legislation regarding medical devices and medicines or the decisions of the European Commission or national authorities regarding medicines comply with the right to life, to health or to physical integrity.

Key points

- **The right to health (article 35), to life (article 2) and to the integrity of the person (article 3) are enshrined in the European Charter of Fundamental Rights (and in the European Convention on human rights), which is legally binding on EU Member States.**
- **Recognition of fundamental human rights implies general positive government obligations (the government must take all necessary measures, including legislation, to give effect to the right) or even negative government obligations (the government must respect and ensure the right).**
- **If a State fails to ensure the effective implementation of legislation aiming at the protection of patients'lives, such as, for instance, certain parts of the legislation on clincial trials or on market access of medicinal products and medical devices, it could violate the right to life or other fundamental rights.**
- **The Court of Justice of the European Union has authority, in the context of a question raised by a national court in a specific litigation, to judge whether the national and European legislation regarding medical devices and medicines or the decisions of the European Commission or national authorities regarding medicines comply with the prohibition against making the human body and its parts a source of financial gain or other rights enshrined in the European Charter.**

3.4.3 *Evidentiary requirements in the marketing authorisation process for medicines*

In Europe, market access for a medicinal product is allowed when a marketing authorisation is granted by the European Commission after the scientific evaluation performed by the European Medicines Agency (EMA) or when a marketing authorisation is granted by the national authorities after their own scientific evaluations. In both cases, medicines must demonstrate quality, safety and efficacy.

The process of gaining market access for innovative medicines generally includes several phases:

- research and development (first in the laboratory and then in healthy volunteers and in patients in clinical trials)
- eventually, and depending on the type of procedure (centralised or not), scientific advice by European or national (if any) authorities
- evaluation by the European (EMA) or national authority, depending on the type of procedure (centralised or not)
- marketing authorisation
- access[jj]

[jj] https://www.ema.europa.eu/en/documents/other/laboratory-patient-journey-centrally-authorised-medicine_en.pdf

3.4.3.1 The general criteria for market access

The medicines legislation does not limit the type and design of trials required for market access[kk].

The authorisation of medicines builds on three key criteria laid down in Directive 2001/83, namely pharmaceutical **quality, safety and efficacy.** Market authorisation is granted in the case of a favourable benefit-risk ratio, meaning that the expected benefits (e.g. efficacy, intended effect) outweigh the risks (e.g. safety concerns, unintended effects) when patients are exposed to the product.

Efficacy is the therapeutic, preventive, or diagnostic effect for an average patient that falls within the claimed therapeutic indication, considering ideal conditions. Practical considerations about how the treatment is expected to perform under real conditions of use ("effectiveness") or about the value of such treatment in terms of societal considerations ("cost-effectiveness"), whether in absolute or relative terms, are outside the scope of the benefit-risk assessment.

Article 1. 28a. of the Directive 2001/83 defines the risk-benefit balance as "*an evaluation of the positive therapeutic effects of the medicinal product in relation to the risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health"*. Marketing authorisations can be granted to new medicinal products if they are better than a placebo, even if these new drugs are inferior (or not compared at all) to established therapies. Superiority or equivalence to other products or treatments is thus not a regulatory requirement.

The only place where the study design is currently mentioned in the Directive 2001/83 on medicines is annex I of the Directive, in the description of the clinical study report, which forms part of the marketing authorisation dossier (Annex I – Module 5 - 5.2.5. Reports of efficacy and safety studies - 5.2.5.1. Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication). This section states that:

> *"In general, clinical trials shall be done as 'controlled clinical trials' if possible, randomized and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value; any other design shall be justified. The treatment of the control groups will vary from case to case and also will depend on ethical considerations and therapeutic area; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.* [ll]

This approach seems not entirely different but more flexible than the one included in article 33 of the Declaration of Helsinki. Indeed, under this ethical principle, comparative trials against best proven interventions are the standard or normal case in clinical trials and the use of placebo-controlled trials or no intervention / less effective intervention as possible exceptions, to be used under strict conditions and interpreted narrowly. When there is another proven intervention, less effective intervention, the use of placebo, or no intervention can be used provided that compelling and scientifically

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kk https://www.ema.europa.eu/en/documents/position/emea-position-statement-use-placebo-clinical-trials-regard-revised-declaration-helsinki_en.pdf

ll "Initially, the old directive 75/318 concerning the marketing authorisation dossier (replaced by the Directive 2001/83 and then the by the CTR) mentioned that "*in general clinical trials **must** be carried out in the form of "controlled clinical trials". The design of the trials will vary from case to case and also will depend on ethical considerations ; thus it may, in some instances, be more pertinent to compare the therapeutic effect of a new proprietary medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo*".

See Directive 75/318 of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products. O.J. L 147 (09.06.1975).

sound methodological reasons justify that it is necessary to determine the efficacy or safety of an intervention. In any case, the patients who receive any intervention less effective than the best proven one, placebo, or no intervention must not be subjected to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. In law, when exceptions to a principle are listed, these must be interpreted narrowly.

Under the current legal framework for medicines, the comparison shall (and not must) in general be done "as appropriate" (thus not necessarily as an exception duly justified by compelling scientific reasons) versus a placebo and another medicine.

Box 2 – EMA statements

In line with the 2001/83 Directive, the EMA considers that the legislation provides for flexibility in the type and design of trials required for the demonstration of efficacy and safety[mm].

In 2009, the CHMP of the EMA started a reflection on benefit-risk assessment methods[nn]. It appears from the consultation of the Member States in 2011 some national competent authorities consider that this balance includes the demonstration of effectiveness in the real world and others not[oo]. Based on these discussions, the EMA issued a guidance document for assessment by the authorities in 2011, which only advises the evaluator of a marketing authorisation to "shortly summarize" the main available treatment options and the unmet need, if any[pp].

In 2010, the EMA's Committee for Medicinal Products for Human Use (CHMP) published a discussion paper on the need for active control in certain situations[qq]. This discussion paper mentions that:

"Where feasible, three-arm trials including experimental medicine, placebo and active control represent a scientific gold-standard and there are multiple reasons to support their use in drug development. However, there are situations where such trials are not required by CHMP for a properly informed decision on benefit-risk.

It is the position of CHMP that, where ethical and feasible, a placebo control arm should be included in the pivotal trial(s) used to support marketing authorisation application. The need for an active control must be considered on a case-by-case basis. CHMP consider it to be particularly important for estimated benefits and risks to be contextualised through comparison to active control where:

- *the experimental medicine might be associated with safety concerns which impact mortality or morbidity, markedly impair quality of life or cause active treatment to be discontinued or delayed leading to significant, long-term or irreversible harm.*
- *treatment with a medicine of inferior efficacy might conceivably lead to significant, long-term or irreversible harm for the patient.*

mm https://www.ema.europa.eu/en/documents/position/emea-position-statement-use-placebo-clinical-trials-regard-revised-declaration-helsinki_en.pdf

nn https://www.ema.europa.eu/en/about-us/support-research/benefit-risk-methodology

oo https://www.ema.europa.eu/en/documents/report/benefit-risk-methodology-project-work-package-1-report-description-current-practice-benefit-risk_en.pdf

pp https://www.ema.europa.eu/documents/template-form/day-80-assessment-report-overview-d120-loq-template-guidance-rev-05-21_en.docx

qq https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-need-active-control-therapeutic-areas-where-use-placebo-deemed-ethical-one-more_en.pdf

In both scenarios, the comparison to active control will usually need to be 'direct' (i.e. within the same trial). There are few circumstances where an indirect comparison might be considered sufficiently reliable."

This discussion paper contains an unresolved ambiguity since it recognises on the one hand that "given the impact on the complexity, duration and cost of drug development, there will be circumstances where such (three arm) trials should not be required, a*s a properly informed decision on benefit-risk can be made without such data*" and on the other hand that "*without a direct comparison to active control it may not be possible to properly gauge and understand the magnitude of benefit or risk from a clinical perspective and hence to make a properly informed decision on benefit-risk*."

Meaningful endpoints are also needed to evaluate the added therapeutic value of a new medicine. Surprisingly, this requirement is only explicitly mentioned in the Directive 2001/83 for advanced therapy medicinal products[rr]. For those medicines, "*the efficacy of the proposed indications shall be supported by relevant results from clinical studies using clinically meaningful endpoints for the intended use. In certain clinical conditions, evidence of long-term efficacy may be required. The strategy to evaluate long-term efficacy shall be provided."*

In addition to the marketing authorisation dossier requirements, manufacturers shall take into account the scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use as adopted by the CHMP or, as it was formerly known as, the Committee for Proprietary Medicinal Products (CPMP) and published by the EMA and the other Community pharmaceutical guidelines published by the Commission in the different volumes of the rules governing medicinal products in the Europe.(EudraLex Volume 3). Guidance ICH E10 on the choice of control group describes the consequences of each study design. It only indicates that *"the choice of the control group should be considered in the context of available standard therapies, the adequacy of the evidence to support the chosen design, and ethical considerations*[ss]."

A very large number of specific guidelines also exist regarding the demonstration of clinical efficacy and safety of different therapeutic classes and some of them address the study design[tt]. These documents contain guidance on what could be, according to the EMA, the design, "preferred primary endpoint" or other "relevant endpoints" for a specific condition (ex: acute heart failure[uu]) or for specific medicines (ex: anticancer medicinal products[vv]) during the different phases of clinical trials, but these guidelines usually cover a very large number of possible endpoints and designs and do not depart from the flexible approach of the EMA; other choices can always be made if justified by the manufacturers.

While the flexibility offered by the legislation does not preclude a robust study design being chosen by the manufacturer, and some guidelines promote this type of design, the situation on the ground seems to indicate that this is not generally the case. Indeed, as analysed in the next chapters (see chapters 5 and 6), a number of studies have shown weaknesses and insufficiencies in the pre-market evidence leaving patients, clinicians and HTA bodies with no answers regarding the real added therapeutic value of these medicines. In 2010 Van Wilder also already observed that "*In fact, studies have shown that between 1999 and 2005, only 48% of the approved*

rr Advanced therapy medicinal products (ATMPs) are medicines for human use that are based on genes, tissues or cells.

ss https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-10-choice-control-group-clinical-trials-step-5_en.pdf

tt All guidelines: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-efficacy-safety-guidelines.

uu https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-acute-heart-failure_en.pdf

vv https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-evaluation-anticancer-medicinal-products-man-revision-6_en.pdf

new medicines were compared with existing medicines at the time of their marketing authorisation.[ww] *In cases where a comparison is made between new and existing medicines, the prevailing criterion is not that of an added therapeutic value, but rather that of non-inferiority*[xx]*. Instead of assessing whether a new treatment does more good than harm compared to other already existing and approved intervention alternatives, the EMA uses trials to establish whether a new treatment has more benefits than risks. In case of comparisons with alternatives, the principle of non-inferiority sets limits to any difference in clinical effect to ensure the investigational compound is "not unacceptably worse" than the control treatment.* [35]

With regard to these gaps, three former staff members of the EMA, including one of its former heads, defended, in an online article published by Nature review in 2019, that the risk-benefit balance assessment in the current legal framework necessarily includes "comparative efficacy". According to them, *"any good or bad effects of a treatment must necessarily be described by comparing it with a counterfactual scenario; the concept of 'absolute' benefits or harms is a commonly held misconception. The counterfactual may be treatment with another drug or no treatment (or placebo treatment), the latter corresponding to the natural history of the disease. Regulators could perhaps be more explicit about this fact and in quantifying comparative effects.*

Moreover, benefit-risk is not assessed in a therapeutic vacuum. Even with placebo-controlled trials, benefits and risks are necessarily contextualized. For example, in therapeutic indications where treatment with a medicine of inferior efficacy would risk increasing mortality or may delay more effective treatment, leading to irreversible harm, the benefit-risk balance may be deemed negative even when the comparison with placebo seems favourable. We have heard from external stakeholders that more emphasis should be placed on contextualizing the effect of new medicines and to be more explicit about negative, neutral or positive added benefit where possible in relevant patient subgroups. The EMA is now engaged in dialogues with HTA bodies and payers to explore how best to serve these information needs."[yy]

They support the proposal to address added benefit by putting a "*more explicit focus on regulatory assessments and communications on the comparative efficacy part of benefit-risk assessments*".

As acknowledged by the authors, the legal texts could be more explicit. One could, even go further and make head-to-head comparisons as the gold standard and require any other design to be justified allowing the use of placebo arms or other types of comparisons (e.g. mixed treatment comparisons) when justified.

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ww Van Lujin, J.C., Gribnau, F.W. & Leufkens, H.G., 2007, Availability of comparative trials for the assessment of new medicines in the European Union at the moment of marketing authorisation, British Journal of Clinical Pharmacology, 63(2), p. 159-162 (cited by Van Wilder).

xx Wieseler, B., 2011, Comparisons enable better treatment – evaluating therapeutic advances in patients' best interest, p. 2. (cited by Van Wilder)

yy https://www.nature.com/articles/d41573-019-00068-x.

3.4.3.2 The conduct of clinical trials

Directive 2001/83 on medicines is complemented by Directive 2001/20 relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (CTD) [zz]. The Directive is about to be replaced by a new clinical trials Regulation (CTR) which is expected to enter into force on 31.01.2022[aaa], setting up a single authorisation procedure for all clinical trials and strengthening transparency for clinical trials data.

Under the market access rules, the aim is to ensure that the benefit-risk balance is favourable before licensing and that the overall ethical conduct is acceptable, the focus is thus on the individual medicine. The clinical trial rules also focus on the protection of the rights, safety and well-being of trial subjects and on aspects related to the quality of the data of the trials.

In line with the DoH, article 3 of the CTR recalls that a clinical trial may be conducted "*only if (a) the rights, safety, dignity and well-being of subjects are protected and prevail over all other interests; and (b) it is designed to generate reliable and robust data*" .

Under both the CTD and the CTR, the approval of clinical trial applications is the responsibility of the Member States. The national competent authorities are responsible for authorising all clinical trials, regardless of the phase, taking place in their Member State. A prior positive advice of an ethics committee is also required.

Articles 6 (Part I) and 7 (Part II) lists the different aspects that the national competent authority shall assess when evaluating a trial application.

Article 6 states that:

"1. The reporting Member State shall assess the application regarding the following aspects:

(a) Whether the clinical trial is a low-intervention clinical trial, where claimed by the sponsor.

(b) Compliance with Chapter V with respect to the following:

*(i) The **anticipated therapeutic and public health benefits** taking account of all of the following:*

- *the characteristics of and knowledge about the investigational medicinal products.*
- ***the relevance of the clinical trial**, including whether the groups of subjects participating in the clinical trial represent the population to be treated, or if not, the explanation and justification provided in accordance with point (y) of paragraph 17 of Annex I to this Regulation; the current state of scientific knowledge; whether the clinical trial has been recommended or imposed by regulatory authorities in charge of the assessment and authorisation of the placing on the market of medicinal products; and, where applicable, any opinion formulated by the Paediatric Committee on a paediatric investigation plan in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council (2);*
- *the reliability and robustness of the data generated in the clinical trial, taking account of statistical approaches, design of the clinical trial and methodology, including sample size and randomisation, comparator and endpoints;*

(ii) The risks and inconveniences for the subject, taking account of all of the following:

[zz] Directive 2001/20/EC of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

[aaa] Regulation (EU) No 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, O.J. L 158, 27.5.2014. This text will enter into force in January 2022.

- *the characteristics of and knowledge about the investigational medicinal products and the auxiliary medicinal products.*
- ***the characteristics of the intervention compared to normal clinical practice;***
- *the safety measures, including provisions for risk minimisation measures, monitoring, safety reporting, and the safety plan;*
- *the risk to subjects' health posed by the medical condition for which the investigational medicinal product is being investigated;*

The competent Member State must assess all the above-mentioned aspects including the risk for the study subjects taking into account normal clinical practice which is defined by the CTR as "the treatment regime typically followed to treat, prevent, or diagnose a disease or a disorder". However, the referral to normal clinical practice is here not a study design requirement but a component of the risk assessment for the study subjects.

According to article 7, the Member State must also assess Part II covering more practical aspects such as compliance with informed consent, compensations, and study recruitment methods.

The involvement of ethics committees is contained in article 4 of the CTR which states that the review by the ethics committee **may** encompass aspects addressed in Part I of the assessment report for the authorisation of a clinical trial as referred to in Article 6 and in Part II of that assessment report as referred to in article 7 as appropriate for each Member State concerned. This departs from the CT which did not contain this possibility for Member States to limit the review by the ethics committees. It also departs from the Declaration of Helsinki which foresees that protocols have to be reviewed by ethics committees.

Some EU Member States (apparently France, Greece and Italy) have already decided to narrow the scope of the ethics review.[62] Lukaseviciene et al (2020)[62] emphasises this could weaken the protection of research subjects. While national competent authorities will still assess all part I and II elements, it remains of utmost importance that research ethics committees can issue negative advice, for instance when a clinical trial exposes research participants to an inferior treatment (for example, the use of placebo control) as compared with normal clinical practice in the Member State concerned.

As underlined by Lukaseviciene et al (2020) "research ethics committees' experience with poorly designed clinical trials in conjunction with COVID-19 has shown the enormous importance of Part I ethical review for the protection of research participants."

3.4.3.3 The different marketing authorisation procedures

Once a medicinal product has successfully gone through the clinical trial period, it may either be required or selected for the centralised authorisation procedure, which – if successful – allows the medicinal product to circulate on the European market.[35] Concrete procedures and organisation of the EMA are covered by Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

The centralised procedure is compulsory for medicinal products manufactured using biotechnological processes, for orphan medicinal products and for human products containing a new active substance (not authorised in the EU before May 2004) that are intended for the treatment of certain specified diseases, such as diabetes and cancer. For other medicines "*that are a significant therapeutic, scientific or technical innovation, or whose authorisation would be in the interest of public health*", companies may opt for using the centralised marketing authorisation procedure[bbb].

[bbb] http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp.

The EMA's Committee for Medicinal Products for Human Use (CHMP) will deliver its opinion on the granting of a marketing authorisation and submit it to the European Commission, which alone has the authority to grant the authorisation. If approved, the document containing the body of evidence analysed by the Committee, called the European Public Assessment Report (EPAR), is made publicly available by the EMA through its website.

Box 3 – Composition of the CHMP

The CHMP consists of a chairperson and one member nominated by each of the EU Member States, one member and an alternate nominated by Iceland and Norway, up to five co-opted members, chosen among experts nominated by Member States or the Agency and recruited, when necessary, to provide additional expertise in a particular scientific area.

The EMA Policy on the Handling of declared Interests for Agency scientific Committees members and experts is applicable[ccc] and annual reports on conflicts of interest are published by the EMA[ddd]. In 2020, 617 declarations of interest of new experts were checked, and an error was noted in 22 of them (3.6%). The nature of the errors in 2020 (16 out of 22) was that the experts failed to declare their recent employment (in the past 3-year period) within a pharmaceutical company.

It should be noted that conflicts of interest rules also apply to external experts. An example of that is the judgment of 28 October 2020[eee] of the CJEU annulling the Commission Decision refusing the granting of a Marketing Authorisation for Aplidin on the basis that two external experts on the Scientific Advisory Group had conflicts of interest since they are employed by an institute that controls and exercises a significant influence on a university hospital which hosts a cell therapy centre manufacturing a product competing with Aplidin, as well as on a clinical research centre which performs development activities for pharmaceutical companies.

As a consequence of this judgment, external experts that are employed by universities or university hospitals performing development or manufacturing activities in respect of any medicinal products actually or potentially competing with the (candidate) product under review, are not allowed to be involved in the procedure.

The EMA is of the view that this judgment will have an adverse impact on the EMA's operations, and also on the national competent authorities, because it will make it more difficult to find the best specialist expertise and may lead to decreasing the robustness of the scientific assessment and possibly cause significant delays in the assessment of medicines.

In order to obtain a marketing authorisation for two or more Member States at the same time, manufacturers may also use the decentralised procedure or the mutual-recognition procedure (unless the new medicine falls within the above mentioned categories for which the centralised procedure is compulsory). They may also choose to apply for a national authorisation, which is then limited to a single Member State.

Looking at all available medicines (including very old ones), the majority of medicines authorised in the EU were authorised under the decentralised

ccc https://www.ema.europa.eu/en/documents/other/policy-44-european-medicines-agency-policy-handling-competing-interests-scientific-committees_en-0.pdf

ddd https://www.ema.europa.eu/en/documents/report/2020-european-medicines-agency-annual-report-independence_en.pdf

eee https://curia.europa.eu/juris/document/document.jsf?text=Aplidin&docid=233013&pageIndex=0&doclang=EN&mode=req&dir=&occ=first&part=1&cid=5007434#ctx1

procedure[fff]. However, when we look at newer medicines, most of them are authorised under the centralised procedure[ggg].

Regulatory requirements regarding the safety and efficacy are the same, irrespective of the authorisation route for a medicine[hhh]. They are also the same for orphan drugs.

3.4.3.4 The possibility of seeking scientific advice and early dialogues

Scientific advice by the EMA

One of the possibilities available for manufacturers to improve the study design of a trial in the pre-market phase is to ask the EMA during a medicine's development to give product-specific scientific advice on the best methods and study designs required to generate robust information on how well a medicine works and how safe it is, regardless of whether the medicine is eligible for the centralised authorisation procedure or not[iii].

The content of this advice does not bind the EMA or the manufacturer and does not pre-evaluate the results of the studies. Advice is delivered in exchange for fees[jjj].

The scientific advice or protocol assistance outcome given by the EMA for a medicinal product is considered confidential and will not be made public prior to the submission of an application for a marketing authorisation nor during the assessment of such marketing authorisation. In the case of a subsequent centralised marketing authorisation, scientific advice or protocol assistance given by the CHMP will be included in the European public assessment report (EPAR), after deletion of commercially confidential information.

The expert Group in charge of delivering this advice includes members of the different committees of the EMA and external experts. Experts must declare their interests before being involved in the scientific advice and the declared interests will be handled in accordance with the EMA Policy on the Handling of declared Interests for Agency scientific Committees members and experts. According to this policy, which focusses on links with industry, scientific advice provided by the national competent authority experts of a Member State is not considered a consultancy activity leading to a conflict of interest[kkk].

Many NGO's and HTA bodies have argued for an integration of some HTA elements in these pieces of scientific advice.[lll] They have also denounced the inherent risk of regulatory capture with this procedure, accentuated when the members of the committee responsible for providing advice on marketing

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fff https://www.ema.europa.eu/en/documents/leaflet/european-regulatory-system-medicines-european-medicines-agency-consistent-approach-medicines_en.pdf

ggg https://toolbox.eupati.eu/resources/marketing-authorisation/ see also https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines

hhh https://www.ema.europa.eu/en/documents/leaflet/european-regulatory-system-medicines-european-medicines-agency-consistent-approach-medicines_en.pdf

iii Legal basis for this advice is article 57-1 of the Regulation 726/2004 of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

jjj https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance

kkk https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-guidance-applicants-seeking-scientific-advice-protocol-assistance_en.pdf

lll https://epha.org/wp-content/uploads/2017/11/A2M-new-model-for-scientific-advice.pdf

authorisation procedures are concomitantly involved in the provision and endorsement of scientific advice.[mmm] In this investigation, opened in 2017, the EU Ombudsperson expressed the view that " *to the greatest extent possible, EMA should ensure that there is a separation between those responsible for providing scientific advice to a medicine developer and those subsequently involved in evaluating an MAA for the same medicine*."

Regulatory scientific advice can also be given by national competent authorities (e.g. FAMHP in Belgium[nnn], MHRA in the UK, and the German authorities). The EU Innovation Network started a pilot for Simultaneous National Scientific Advice (SNSA) from national competent authorities (NCAs) in February 2020 to enable innovators to access scientific advice simultaneously in different EU Member States. The pilot has been extended to the end of 2021.

Early dialogues

The above mentioned (European or national) scientific advice aims to provide scientific support in the course of the regulatory process. Unlike the parallel scientific advice obtained from the EMA and EUnetHTA/national HTA bodies, they do not include assessments or advice on the classic HTA assessment criteria[ooo]. These pieces of parallel scientific advice on the clinical development of (mainly) drugs and (a few) medical devices have been issued by selected EUnetHTA member HTA bodies. In addition, between 2017 and 2020, the EMA and EUnetHTA have offered Parallel Consultations on evidence generation plans. These contained feedback from regulators and HTA bodies. A new call has been opened by the European Commission to replace this procedure[ppp]. In this EUnetHTA21 initiative the parallel scientific advice is referred to as Joint Scientific Consultation (JSC).

3.4.3.5 Accelerated assessment and conditional marketing authorisations

There are several marketing authorisation flexibilities in the current legal framework for the centralised procedure that enables early access to medicines responding to unmet medical needs[qqq]. Accelerated assessment[rrr] and conditional marketing authorisations are two possibilities[sss].

The accelerated assessment procedure[ttt] reduces the timeframe for the EMA Committee for Medicinal Products for Human Use (CHMP) to review a marketing-authorisation application[uuu]. Applications may be eligible for accelerated assessment if the CHMP decides the product is of major interest for public health and is a therapeutic innovation.

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mmm https://haiweb.org/wp-content/uploads/2015/10/EMA-Consultation-Response-Conditional-Approval-Accelerated-Assessment.pdf

nnn https://www.famhp.be/en/human_use/medicines/medicines/scientific_technical_advice/generalites

ooo https://www.eunethta.eu/services/early-dialogues-for-pharmaceuticals/.

ppp https://etendering.ted.europa.eu/cft/cft-display.html?cftId=7416.

qqq https://www.ema.europa.eu/en/human-regulatory/overview/support-early-access

rrr Article 14(9) of regulation (EC) No 726/2004.

sss Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) N 726/2004

ttt Article 14(9) of regulation (EC) No 726/2004 and the Guideline on the scientific application.

uuu Evaluating a marketing-authorisation application under the centralised procedure can take up to 210 days, not counting clock stops when applicants have to provide additional information. On request, the CHMP can reduce the timeframe to 150 days if the applicant provides sufficient justification for an accelerated assessment. https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/accelerated-assessment

To help developers in the marketing-authorisation application, the EMA has launched a specific voluntary scheme (PRIME) to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on reinforced dialogue on clinical trial design with developers of promising medicines, with the aim of optimising development plans and speeding up evaluation so that these medicines can reach patients earlier. PRIME medicines can expect to be eligible for accelerated assessment and can also be selected for HTA by EUnetHTA within the scope of its remit under the pending HTA regulation. The majority of applications for this programme come from micro-, small- and medium-sized enterprises (SMEs) and "others" rather than academia. Most of the selected drugs for this program are in oncology and neurology[vvv] (see 5 for more details).

In the interest of public health, applicants may be granted a **conditional marketing authorisation**[www] for such medicines on the basis of less comprehensive clinical data than normally required, where the benefit of immediate availability of the medicine outweighs the risk inherent in the fact that additional data are still required. Medicines for human use are eligible if they are intended for treating, preventing or diagnosing seriously debilitating or life-threatening diseases. This includes orphan medicines.[xxx] Conditional marketing authorisations are valid for one year and can be renewed annually. Once a conditional marketing authorisation has been granted, the marketing authorisation holder must complete ongoing or conduct new studies or collect additional data to confirm that the medicine's benefit-risk balance remains favourable[yyy].

In addition to these two procedures, "**compassionate use**" mechanisms are available in many Member States. They allow physicians and patients to apply for access to an unapproved therapy, or one that is still under consideration for approval if they have a life-threatening condition and approved treatments have failed, or there are no treatments currently approved[zzz].

3.4.3.6 The proposal to create common European HTA

The relationship between HTA requirements and market access requirements have been discussed for decades. Initiatives such as HTA Joint Action 1 and 2 (including EUnetHTA) have been put in place by the EU to facilitate cooperation on HTA between Member States.

In 2015, on the request of the European Parliament, a research team investigated the feasibility and opportunity of introducing a harmonised EU approach concerning the assessment of the added therapeutic value (ATV) of medicines in the European Union.[35] This study confirms the existence of evidence gaps but does not propose regulatory changes in the current marketing authorisation process. It concludes that it would be desirable and possible for the Member States to agree on a shared definition and assessment methodology for HTA if this is based on clinical criteria, rather than social and economic considerations. A shared definition would also clarify the expected benefits of new medicinal products, incentivising the production of innovative medicines and hopefully reducing the burden of unmet medical need.

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vvv https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines#key-figures-section.

www Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004.

xxx The legal basis is Article 14(7) of Regulation (EC) No 726/2004. The provisions for granting a conditional marketing authorisation are further elaborated in Regulation (EC) No 507/2006.

yyy See also https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/medicines-under-additional-monitoring

zzz https://haiweb.org/wp-content/uploads/2015/10/EMA-Consultation-Response-Conditional-Approval-Accelerated-Assessment.pdf

Several recent attempts have been made to ensure a better synergy between the regulatory process (market access) and the HTA process. These discussions are still ongoing[aaaa].

On 31 January 2018, the Commission submitted a proposal for a Regulation on health technology assessment and amending Directive 2011/24/EU[bbbb]. This proposal aims to introduce a common, EU funded, clinical HTA assessment at Union level for certain medicines authorised through the centralised procedure, new active substances and existing products for which the marketing authorisation is extended to a new therapeutic indication and for certain medical devices selected by the MDR expert panels[cccc]. It also intends to ensure that the methodologies and procedures applied in HTA are more predictable across the EU and to avoid duplication of the work of HTA bodies.

The initial proposal was substantially amended by the European Parliament at the end of 2018[dddd] and was discussed within the European Council more than three years[eeee]. Parliament's amendments concerned key issues (e.g. HTA definition, binding character of the advice, confidentiality, etc.).

The proposal foresees two different mechanisms: the Joint scientific consultation (JSC) and the Joint clinical assessment (JCA) conducted by the same expert group called the Coordination Group. The JSC and the JSA of the same intervention are however preferably performed by different experts to avoid regulatory capture.

- The JSC is a preliminary advice for medicines in the planning stage and eligible medical devices. It can be requested voluntarily by the technology developers for the purpose of obtaining scientific advice concerning data and evidence likely to be required as part of a JCA. This can be made in parallel with a request for EMA scientific advice for medicines. This advice is not binding. However, any deviation from the recommended evidence should be duly justified by the manufacturer. If there are too many requests given the budget and work plan of the Coordination Group, there will be a selection process based on unmet needs, with criteria such as: first in class; potential impact on patient, public health and health care systems; cross-border dimension; EU priorities; major added value.
- The JCA is a mandatory assessment procedure applicable to certain medicines and medical devices selected by the coordination group on the basis of the priorities set by European authorities. The JCA focusses on the core aspects of HTA: the comparative analysis of the available clinical evidence on the new technology (medicine or medical device) in comparison with one or more other health technologies or existing procedures, based on the description of the health problem, the current use of other health technologies, the description and technical characteristics of the health technology, the relative clinical effectiveness, and the relative safety of the health technology. Member States must however give due consideration to the published joint clinical assessment.

aaaa https://www.ema.europa.eu/en/partners-networks/health-technology-assessment-bodies; https://www.ema.europa.eu/en/documents/other/ema-eunethta-work-plan-2017-2021_en.pdf

bbbb Proposal for a Regulation of the European Parliament and of the Council on health technology assessment and amending Directive 2011/24/EU : https://eur-lex.europa.eu/legal-content/EN/HIS/?uri=celex:52018PC0051.

cccc Medicinal products undergoing the centralised marketing authorisation procedure, new active substances and existing products for which the marketing authorisation is extended to a new therapeutic indication, and certain classes of medical devices and in vitro diagnostic medical devices which would be selected by a coordination group set up at European level.

dddd https://www.europarl.europa.eu/RegData/seance_pleniere/textes_adoptes/definitif/2019/02-14/0120/P8_TA(2019)0120_FR.pdf

eeee https://eur-lex.europa.eu/legal-content/EN/HIS/?uri=celex:52018PC0051.

For medicines, these procedures are meant to run in parallel with the regulatory process for (centralised) market access. Due to the specificities of the medical devices regulations (which doesn't involve a pre-market authorisation but rather a certification process through a decentralised certification system that takes a life cycle approach, which implies that evidence may only become available after the medical device has been placed on the market) these procedures could also take place following their placing on the market.

As recalled by the European Commission in the initial proposal : "*regulatory and HTA processes will remain clearly separated due to their different purposes*". However, there are "*opportunities to create synergies, through mutual information-sharing and better alignment of the timing of procedures between the proposed joint clinical assessments and the centralised marketing authorisation for medicinal products. Synergies are also expected between joint clinical assessments of medical devices and some of the provisions in the new EU Regulations for medical devices and in vitro diagnostics (e.g. strengthened rules on clinical evaluation and clinical investigation; EU-level expert panels for high-risk medical devices).*"[ffff]

Box 4 – Scope of the common HTA

All medicines falling under the centralised procedure are potentially eligible but they have to be selected and included in the Coordination Group's work program (filter). New substances, orphan drugs and ATMPs are not in scope in the first phase.

Medical devices classified as class IIb and III pursuant for which the relevant Expert panels have provided a scientific opinion in the framework of the clinical evaluation consultation procedure (see section 3.4.4.3) and selected by the European Commission (double filter) based on the following criteria:

(a) unmet medical needs;

(b) first in class;

(c) potential impact on patients, public health or healthcare systems;

(d) incorporating software using artificial intelligence, machine learning technologies or algorithms;

(e) significant cross-border dimension

(f) major Union-wide added value.

The Coordination group would be composed of members appointed by the Member States amongst their national authorities and bodies responsible for HTA. Members of the Coordination Group and their appointed representatives shall respect the principles of independence, impartiality, and confidentiality.

Between the initial version and the latest amended publicly available texts, some differences exist. At the time of writing, based on public texts, uncertainties exist regarding the extent of the European Commission's powers, the means available, or the existence of a concrete and secure process for the sharing of confidential information. In the latest public documents, which might have been substantially amended or completed during the discussions with the Council, the text does not list the documents that must be shared with HTA bodies by technology developers. The preferred methodology for these JCA is also not yet public and is a topic of the EUnetHTA21 project.

[ffff] COM/2018/051 final - 2018/018 (COD) https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM%3A2018%3A0051%3AFIN.

3.4.3.7 *The Pharmaceutical strategy*

In parallel, in 2021, the Commission launched a public consultation to revise the pharmaceutical legislation.[gggg] The aim of this consultation is to revise legislation in order to create a future-proof and crisis-resistant medicines regulatory system.

This project takes place in the more global context of the Pharmaceutical Strategy for Europe[hhhh]. The following flagships of this strategy are relevant to the topic of improving clinical efficacy of medicines [iiii]:

- Enable parallel scientific advice on clinical study design for medicines by HTA bodies and the EMA, as provided for by the proposed HTA Regulation – 2021. (Flagship on unmet needs)
- Enhance dialogue among regulatory and other relevant authorities in the area of medicines and medical devices to increase cooperation on evidence generation within their respective fields – 2021. (Flagship initiatives on innovation)
- Full implementation of the regulatory framework for clinical trials, which supports innovative trial designs and a more patient-oriented medicines development – 2021. (Flagship initiatives on innovation)
- Propose revision of legislation to give regulatory authorities more power to adapt on their own initiative the terms of marketing authorisations on the basis of scientific evidence – 2022. (Flagship initiatives on regulatory efficiency)
- Work at global level, with the EMA and the network of national regulators, in international fora and through bilateral cooperation to promote regulatory convergence to ensure access to safe, effective, high-quality and affordable medicinal products globally – ongoing. (Flagship initiative on international cooperation)
    - Advance international harmonisation by proactively proposing topics in line with the latest scientific developments; promoting the uptake and implementation of international standards, and ensuring a level playing field for operators on the international market by enhancing the EU's bilateral and multilateral relations - ongoing. (Flagship initiative on international cooperation)

Key points – evidence requirements for medicinal products

- **The authorisation of medicines builds on three key criteria laid down in Directive 2001/83, namely pharmaceutical quality, safety and efficacy.**
- **This legislation provides for flexibility in the type and design of trials and outcomes required to demonstrate efficacy and safety. Indeed, under this legal framework (Module 5) it is stated that a new medicinal product shall (and not must) in general be compared (in a randomised trial) "as appropriate" (thus not as an exception) with a placebo and another medicine (not another intervention).**
- **This differs slightly from article 33 of the Declaration of Helsinki, along with other ethical rules and international legal provisions implementing human rights in the field of biomedical research, which consider that new interventions must, as the standard or normal case, be tested against those that are the best proven intervention(s), and consider placebo-controlled trials or trials**

gggg https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Evaluation-and-revision-of-the-general-pharmaceutical-legislation

hhhh https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM%3A2020%3A761%3AFIN&qid=1606303953523 See also https://ec.europa.eu/commission/presscorner/detail/en/ip_20_2173 and https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12421-Pharmaceutical-Strategy-Timely-patient-access-to-affordable-medicines

iiii https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52020DC0761.

with no control (or using an intervention that is less-effective than best practice) as a possible exception in narrow circumstances.

- **European authorities consider that the purpose of regulatory approval is not to determine clinical practice. Marketing authorisations can be granted to new medicinal products if they are better than a placebo, even if these new drugs could in theory be inferior to established therapies. Such new medicines can be cheaper or may have a different side effects profile. There is, legally, no limit to the number of medicines that can be licensed for any given therapeutic indication providing the benefit-risk balance of each is favourable.**
- **The EMA's guidance documents and working papers regarding the benefit-risk balance and appropriate comparators adopt a case-by-case approach: they acknowledge the scientific value of comparing new interventions against available treatments in some situations but do not establish this as the gold standard.**
- **According to European legislation, the responsibility and task of evaluating clinical trial compliance with ethical rules, including the use of an appropriate study design, study outcomes/endpoints, and comparators, and to ensure that the unethical use of placebo is prohibited, falls to the national ethics committees and national competent authorities.**
- **The rules regarding clinical trials for medicines states that rights, safety, dignity and well-being of trial subjects shall prevail over all other interests. However, these rules only contain general provisions for the conduct of clinical trials and do not require specific study designs.**
- **The Clinical Trial Regulation (CTR) allows Member States to narrow the scope of the ethics committee's review, which could potentially weaken the protection of research subjects.[62]**
- **A proposal for a Regulation on health technology assessment is currently reaching the last steps of the EU legislative process. Under this proposal, HTA and market approval remain two separate frameworks, but synergies are created.**

3.4.4 *Evidentiary requirements in the CE-marking process for high-risk medical devices*

In accordance with the general European policy for consumer's products[jjjj], and unlike the framework for medicines which are subjected to a pre-market authorisation, medical devices can circulate freely on the European market via a certification system. The compliance of medium and high-risk medical devices with European general safety and performance requirements is assessed prior to their market entry by Notified Bodies which are usually for-profit and private organisations. After their entry on the market, these products are monitored by their manufacturers, under the surveillance of the national competent authorities.

[jjjj] European Commission 'Blue Guide' on the implementation of EU products rules 2016. O.J. C272/1, 26/07/2016.

Box 5 – CE marking

Regardless of the risk classification of a device, its manufacturer must, in order to obtain a CE marking, demonstrate that this device is **safe and performs as intended** and that the risks which may be associated with its use constitute acceptable risks when weighed against the benefits to the patient (acceptable benefit-risk balance).

Depending on the risk classification of the device, Notified Bodies will audit the manufacturer's quality system and, depending on the type of device, perform a review of the evidence provided by the manufacturer before approving a CE marking.

Once placed on the market, the device is the responsibility of the manufacturer who markets it. However, the CE marking has a limited period of validity and the Notified Body must periodically reassess the relevance of the evidence and the organisation of the manufacturer and re-certify the device. The manufacturer must monitor the performance and safety, check that the benefit-risk balance remains acceptable and, if necessary, take preventive or corrective actions. The national competent authorities for medical devices are responsible for market surveillance. These authorities are also designated to authorise national clinical trials.

However, the national competent authorities are not the regulators of the notified bodies *per se* (unless they have a dual role, which is true for approximately half of all EU national competent authorities). This is the role of the Notifying Authorities (also called Designating Authorities), who assess the competence of an organisation to become (and remain) a Notified Body and monitor its activities through audits and reviews. Notifying Authorities may be assisted in this task by national Accreditation Bodies. Belgian Notified Bodies are monitored by the Belgian Accreditation Body (Belac) in consultation with relevant competent authorities, including the Belgian Competent Authority for Medical Devices, the FAMHP.

To meet major safety concerns affecting certain devices and to reflect the technological and scientific progress in the medical devices sector, the former three Directives on medical devices[kkkk], in vitro diagnostic medical devices[llll], and active implantable medical devices[mmmm] are progressively being replaced since 2017 by two Regulations[nnnn] [oooo] which, in contrast to Directives, do not need to be transposed into national law. The Regulation 2017/745 (hereafter "MDR"), which is relevant for the present study[pppp], replaces Directive 90/385 on active implantable medical devices and Directive 93/42 on medical devices (hereafter "AIMDD" and "MDD").

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kkkk Directive 93/42/EEC concerning medical devices. O.J. L169, 12/07/1993.

llll Directive 98/79/EC of 27 October 1998 on in vitro diagnostic medical devices. O.J. L331, 07/12/1998.

mmmm Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices. O.J. L189, 20/07/1990.

nnnn Regulation 2017/745 of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. O.J. L117, 5/05/2017.

oooo Regulation 2017/746 of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU. O.J. L117, 5/05/2017.

pppp The Regulation on in vitro diagnostic medical devices is not applicable in the context of our study and will therefore not be analysed.

These new rules largely contain the same basic regulatory requirements for manufacturers and devices as the former Directives. The MDR however adds clarification of the already existing safety and performance requirements regarding connected devices and more stringent rules in terms of risk classification, oversight provided by notified bodies and control of these entities by the public authorities. The MDR also places more emphasis on clinical evidence requirements for placing high-risk medical devices on the market and adds a pre-market scrutiny procedure by EU Expert Panels.

New rules also increase traceability and transparency and include an obligation for the manufacturer to summarise the clinical evidence for any high-risk device in a Summary of Safety and Clinical Performance (SSCP) that will be publicly available in a new version of the European Union Database on Medical Devices (EUDAMED). The critical question is whether the SSCP data will be detailed enough to support clinical decisions, HTA, guidelines, or other purposes.

The MDR entered into force in May 2017 and became applicable during the drafting of this report, on 26 May 2021. However, transitionallyqqqq, CE markings approved under the MDD and AIMDD remain valid until the expiry date of the certificate or until 26 May 2024 at the latestrrrr. During this transitional period, medical devices certified under the MDD and AIMDD, called "legacy devices", will be subject to a mixed regime (See Appendix 5). Basically, all post-market vigilance and surveillance obligations under the MDR are in force, while all other certification rules regarding clinical trials, transparency rules (including the drafting of a SSCP) will be applicable at the end of the transition period.

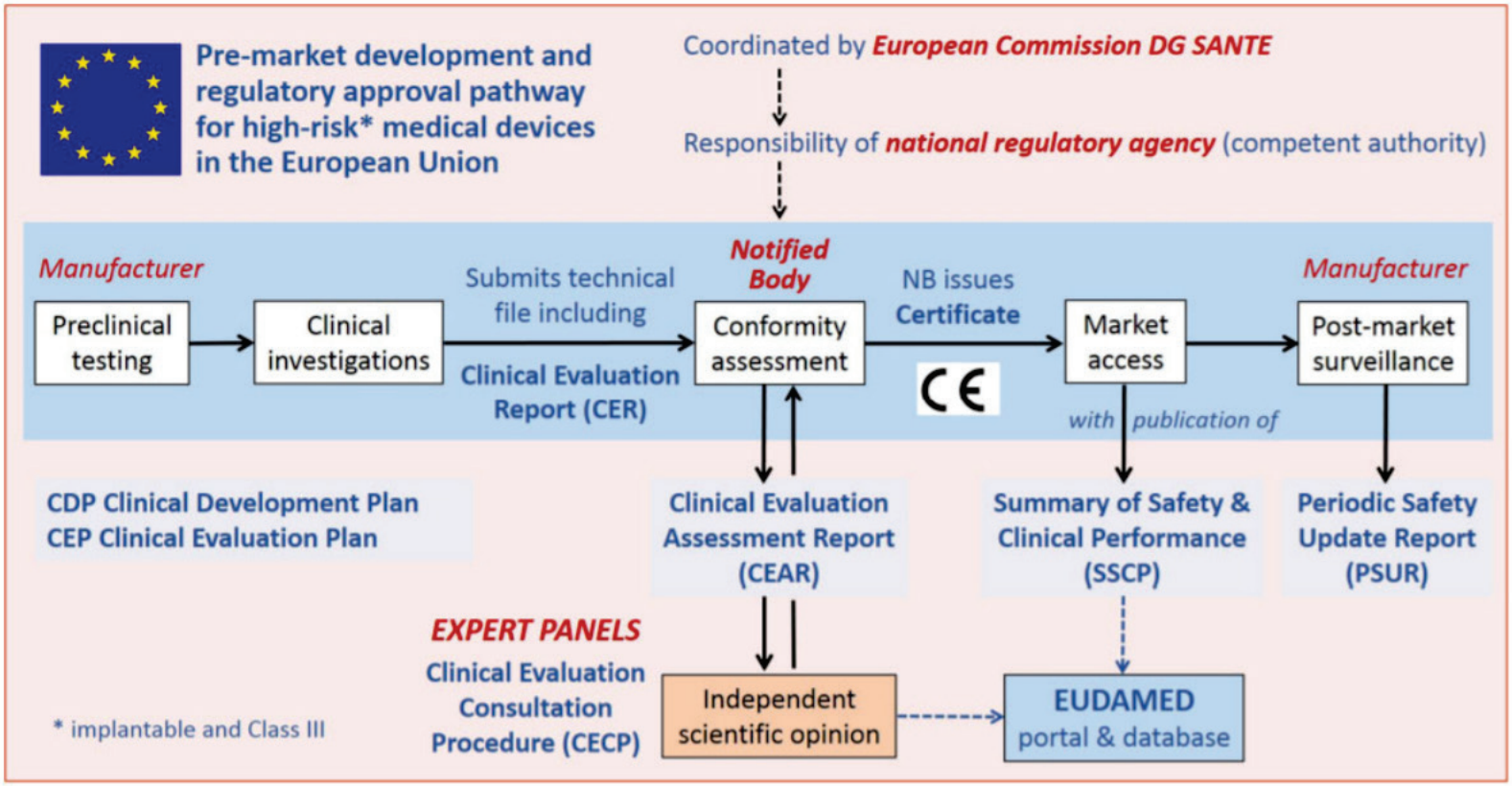
Steps for market access of medical devices include:

- the research and development phase,
- the preparation and submission of the technical files
- the conformity assessment, which in some cases may include a non-binding scientific opinion of an independent expert panel
- approval of CE marking and issuance of a conformity assessment certificate
- market access

qqqq Article 120 MDR.

rrrr Some medical devices will have to comply with the new regulation by 2022 (if they obtained their CE marking under a specific EC verification procedure).

Figure 2 – Schematic representation of the approval process and the Clinical Evaluation Consultation Procedure for high-risk medical devices.[63]



3.4.4.1 The general criteria for market access

According to Annex I of the MDR, medical devices shall achieve the performance intended by their manufacturer for the device's intended purpose and shall be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose. They shall be safe and effective and shall not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art.

Clinical performance means the ability of a device, resulting from any direct or indirect medical effects which stem from its technical or functional characteristics, including diagnostic characteristics, to achieve its intended purpose as claimed by the manufacturer, thereby leading to a clinical benefit for patients, when used as intended by the manufacturer.

In sum, like the previous Directives, the MDR requires, prior to entry on the market, the demonstration that a device is safe and performs as intended and that the risks which may be associated with its use constitute acceptable risks when weighed against the benefits to the patient (acceptable benefit-risk balance) However, the new MDR specifies that clinical benefit means the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health. As developed in the next section (3.4.4.2), in some cases, the demonstration of performance, clinical benefits and clinical safety of medical devices requires a clinical investigation.

This further definition of the clinical benefit could lead certain Notified Bodies to put more focus on real added value for patients in their assessment of medical devices. In addition, as developed hereunder, under the MDR, comparison with other therapeutic alternatives must be taken into consideration in the clinical evaluation (which is different from clinical investigation see 3.4.4.2) and these alternatives must be mentioned in the public documentation for the device (see 3.4.4.5).

The new MDR puts more emphasis on sufficient clinical evidence, based on clinical data, for demonstrating the conformity of medical devices (see next sections on clinical evaluation and investigation).

In accordance with article 9 of the MDR, the European Commission is entitled to establish or enact technical and/or clinical requirements (common specifications) other than a standard, that provide a means of complying with the legal obligations applicable to a device, process or system.

In addition, compared to the MDD where the "state of the art" is only mentioned in Annex I General Requirements[ssss], the MDR strongly emphasizes the importance of the "state of the art", which is mentioned in several sections on standards/common specifications (article 106) and in sections on the evaluation of the benefit-risk balance and clinical requirements (mainly article 62.4 annex IX and annex XV).

Box 6 – State of the art

There are different sources providing references (see Appendix 2), definitions and practical examples on the "state of the art", all of them non-legally binding

In the context of clinical investigations with medical devices, the MDR expressly states that the clinical investigation plan must include a description of "the current state of the art in clinical care in the relevant field of application and the proposed benefits of the new device."

The clinical investigation report, sent to the competent authorities of the Member States in which a clinical investigation was conducted, shall

[ssss] "the solutions adopted by the manufacturer for the design and construction of the devices must comply with safety principles, taking into account the generally acknowledged state of the art"

contain a critical evaluation of all the data collected during the clinical investigation, and shall include any negative findings (art 77).

Under the previous MDD, the MEDDEV Guideline defined the state of the art as "the current knowledge/ state of the art in the corresponding medical field, such as applicable standards and guidance documents, information relating to the medical condition managed with the device and its natural course, benchmark devices, other devices and medical alternatives available to the target population"[tttt]. Under the new MDR, the MDCG defines the state of the art as follow: *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 (guidelines on legacy devices)*[uuuu].

To enable more rapid adjustment to technical advances both the previous Directives and the new Regulations set out general principles and allow the details to be worked out by international and/or European standardisation bodies, such as the International Organization for Standardization (ISO), the European Committee for Standardisation (CEN), the European Committee for Electrotechnical Standardisation (CENELEC), and the European Communications Standards Institute (ETSI). The European Commission may request the European standardisation bodies (ESBs) to develop 'harmonised standards' in relation to specific aspects in a particular directive or regulation required for CE marking, which when published in the OJEU are official harmonised standards, the compliance with which confers a presumption of conformity with the applicable aspect of the legislation in question. This means that if a manufacturer chooses to use the harmonised standard to fulfil a specific requirement then the Notified Body is required to presume that the device is in conformity with that aspect of the legislation.[vvvv]

However, due to the non-legal status of the concept of "state of the art" and its complexity, with so many different and dynamic aspects to be taken into account, mere compliance with "state-of-the art" standards do not confer any presumption of conformity if their references are not cited in the EU official journal, as harmonised European standards on the basis of a standardisation mandate or request issued by the Commission. [wwww]

3.4.4.2 The conduct of clinical evaluations and investigations

A. Evidence in the clinical evaluation

Before placing the device on the market, the manufacturer shall confirm that it has sufficient clinical evidence to ensure that the device is safe and performs well under the normal conditions of intended use and that the clinical benefit-risk ratio is acceptable.

To demonstrate that, manufacturers of all classes of medical devices are required to perform a clinical evaluation. A clinical evaluation does not mean a clinical trial but instead means 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 (article 2. § 44).

The clinical evaluation aims to assess the residual risks that remain after the manufacturer has implemented all available risk mitigation methods and then decide whether the anticipated clinical benefits of the device under consideration outweigh its risks. This clinical evaluation shall follow a

[tttt] MEDDEV 2.7/1 rev.4 Clinical Evaluation.

[uuuu] https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_mdcg_2020_6_guidance_sufficient_clinical_evidence_en.pdf

[vvvv] MDD articles 5 and 6; MDR articles 8 and 9.

[wwww] https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_mdcg_2021_5_en.pdf

defined and methodologically sound procedure based on a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device, a critical evaluation of the results of all available clinical investigations.

In addition, a clinical evaluation shall **consider currently available alternative treatment options** for that purpose, if any.

After placing the device on the market, the clinical evaluation must be updated regularly if a change has an impact on the benefit-risk ratio of the device.

B. Evidence in the clinical investigation

Clinical investigations are, in principle, only required for class III and implantable devices. Clinical investigation means any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device (article 2. § 45).

According to article 62 of the MDR, the purpose of clinical investigations under the Regulation are:

- to establish and verify that, under normal conditions of use, a device is designed, manufactured and packaged in such a way that it is suitable for one or more of the specific purposes listed in point (1) of article 2, and achieves the performance intended as specified by its manufacturer;
- to establish and verify the clinical benefits of a device as specified by its manufacturer;
- to establish and verify the clinical safety of the device and to determine any undesirable side-effects, under normal conditions of use of the device, and assess whether they constitute acceptable risks when weighed against the benefits to be achieved by the device.

The dossier of the clinical investigation (Clinical investigation plan, submitted to the national competent authority and ethics committee in charge of their authorisation) must demonstrate that clinical investigations will be performed on the basis of an appropriate plan of investigation reflecting the latest scientific and technical knowledge and defined in such a way as to confirm or refute the manufacturer's claims regarding the safety, performance and aspects relating to benefit-risk of devices. The rationale for the design and chosen statistical methodology shall be presented. **The endpoints shall be determined and assessed using scientifically valid methodologies** and shall address the intended purpose, clinical benefits, performance and safety of the device. The primary endpoint shall be appropriate to the device and clinically relevant (annex XV of the MDR).

In addition, “normal clinical practice” shall be considered to evaluate the risks for the study subjects[xxxx]

The clinical investigation report, signed by the investigator, shall contain a critical evaluation of all the data collected during the clinical investigation, and shall include any negative findings.

All these new requirements considerably reinforce the trial setting for medical devices. However, an important nuance undermining this improvement lies in the exceptions to the requirement for clinical investigations:

- A clinical investigation is not required if the new device has been designed by modifications of a device already marketed by the same manufacturer, the modified device is equivalent to the marketed device, and the clinical evaluation of the marketed device is sufficient to demonstrate conformity of the modified device with the relevant safety and performance requirements under the MDR or MDD (article 61.4)

  In this context, a marketed device is considered to be a device already placed on the market and CE marked with respect to either the MDR or the directives 93/42/EEC or 90/385/EEC. The CE marking should still

[xxxx] MDR article 72, 78, Annex XV (CIP) 3.4 and 3.6.5.

be valid, should be based on an updated clinical evaluation, and the benefit/risk ratio for this device should be favourable[yyyy].

- A clinical investigation is not required if a new device is equivalent to a device marketed by another manufacturer and the clinical evaluation of the already marketed device is sufficient to demonstrate conformity of the modified device with the relevant safety and performance requirements under the MDR and the two manufacturers have a contract in place (or, most probably via a merger) that explicitly allows the manufacturer of the second device full access to the technical documentation on an ongoing basis; (article 61.5)

The demonstration of equivalence is endorsed by a Notified Body. To be considered equivalent a device must be of similar design, use similar materials in construction, and be used by the same kind of user for the same condition[zzzz].

From the MDR Section 3 Annex XIV, the device must be considered equivalent in terms of technical, biological **and** clinical characteristics.

- **Technical** means having the same or similar design, specifications and properties, conditions of use, principles of operation and critical performance characteristics.
- **Biological** means the device having the same materials or substances in contact with the same body parts for a similar kind and duration of contact, with similar release of substances (e.g. degradation products or leachables).
- **Clinical means** that the device is used for the same purpose, in the same condition, with a similar stage or level of severity, in a similar population, and is used by a similar kind of user (e.g. clinicians versus lay persons), and has a similar performance relevant to the expected clinical effect for the specified intended purpose, with 'no clinically significant difference in the safety and clinical performance of the device'.

In addition, clinical investigations are not required for a class III device which has been lawfully placed on the market in accordance with Directive 90/385/EEC or Directive 93/42/EEC and for which the clinical evaluation is based on “sufficient clinical data”. Ultimately, the notified bodies will evaluate whether these data are sufficient. In this regard, the MDCG states that when this type of device is compared against the ‘state of the art’, this must be supported by recognised guidelines by scientific societies or educational bodies[aaaaa]. After the transition period, these devices will have to be certified under the rules of the new MDR, including the obligation to conduct clinical trials (unless they fall under one of the two above mentioned exceptions).

Manufacturers and notified bodies also apply recommendations from the International Organization for Standardization (ISO 14155.2020) and the International Electrotechnical Commission (IEC), and their counterparts, i.e. the European Committee for Standardization (CEN) and the European Committee for Electrotechnical Standardization (CENELEC). About 300 of their standards were formally recognised in the Official Journal of the EU in November 2017 and updated more recently in 2020[bbbbb]. As mentioned previously, standards published in the EU Official Journal are called harmonised standards. Compliance with harmonised standards means that

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yyyy MDCG 2020-5

zzzz Section 3 of Annex XIV of the MDR. https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_mdcg_2020_5_guidance_clinical_evaluation_equivalence_en.pdf

aaaaa MDCG 2020–6 on clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC. A guide for manufacturers and notified bodies . 2020 Available from: https://ec.europa.eu/docsroom/documents/40904

bbbbb https://eur-lex.europa.eu/legal-content/EN/TXT/?toc=OJ%3AL%3A2020%3A090I%3ATOC&uri=uriserv%3AOJ.LI.2020.090.01.0001.01.ENG

Notified Bodies must assume that the device conforms to the safety and performance requirements.

The MDR gives the European Commission authority to publish common technical specifications. In addition, certain professional associations, funded under the CORE-MD (Coordinating Research and Evidence for Medical Devices) project are working on guidance on study design, for instance in cardiology[ccccc]. As the Regulation does not define good clinical practices, each member state is allowed to define them. In Belgium, good clinical practices are defined as the ISO standard 14155:2020[ddddd] (private – standards are available in exchange for a fee).

The methodology and the extent of the evidence used by the manufacturers to place medical devices on the market is not made public. Unfortunately, it is currently not possible to know what clinical investigations were conducted in order to place a medical device on the market, if any, or whether new clinical investigations are ongoing for regulatory purposes because there is no comprehensive public database containing this information. This will, in principle, improve when the new version of EUDAMED developed to implement the MDR requirements becomes fully operational (which is not expected before 2024) (see section 3.5.3).

C. Procedure and involvement of national competent authorities and ethics committees

The MDR brings several changes to the procedure of clinical investigations. It requires sponsors of clinical investigations to apply for a prior authorisation by submitting relevant data and documentation, such as a clinical investigation plan, to the electronic EUDAMED database, after which it is assessed by the Member State.

This assessment by national competent authorities must be conducted by qualified persons who must not have any conflict of interest. Article 71 describes the aspects that should be assessed by the Member State. With regard to study design, the competent authority should make sure that the study design ensures that potential remaining risks to subjects or third persons, after risk minimisation, are justified when weighed against the clinical benefits to be expected. The competent authority should also scrutinise, among other things, **the reliability and robustness of the data generated in the clinical investigation, taking into account statistical approaches, the design of the investigation and methodological aspects, including sample size, comparator and endpoints and verify compliance with annex XV requirements** (requirements for the conduct of the clinical investigation see supra A).

Even though there are no instructions on how the reliability of the data should be assessed, the fact that the design should also be assessed for medical devices implies that the reliability of clinical investigations has received more attention.[50]

Both the MDD and the MDR require that **an ethics committee**, in accordance with the law of the Member State concerned, **has not issued a negative opinion on the clinical investigation**, after performing an ethical review of the clinical investigation application. In comparison with the current MDD though, the proposed MDR puts more emphasis on ethical principles. The Regulation adds for example that clinical investigations shall be designed and conducted in a way that the rights, safety, dignity and well-being of the subjects participating in a clinical investigation are protected and prevail over all other interests. Recital 64 mentions that the MDR rules "should be in line with the most recent version of the World Medical Association Declaration of Helsinki".

The concrete organisation and division of tasks between national competent authorities are a matter of internal organisation for each Member State.

ccccc https://www.escardio.org/The-ESC/Press-Office/Press-releases/EU-assessment-of-high-risk-medical-devices-faces-in-depth-review

ddddd Article 2 of the Royal decree of 18.05.2021 on clinical trials with medical devices.

In Belgium, the clinical trial procedure for medical devices is implemented through the law of 22 December 2020 on medical devices[eeeee] and the Royal Decree of 18 May 2021 on clinical investigations of medical devices[fffff].

The royal decree on clinical trials with medical devices defines the clear division of tasks between the competent authority (AFMPS-FAGG-FAMHP) and the ethics committees (see Appendix 3). Ethics committees are responsible for among other aspects, verifying that all stages of the clinical investigation, from the initial reflection on the need and justification for the clinical investigation to the publication of the results, will respect recognised ethical principles. However, both the competent authority and the ethics committees are responsible for (a.o.): the assessment of the expected benefits for the participants in the clinical investigation; the assessment that the clinical investigation will be conducted according to an appropriate investigation protocol corresponding to the latest state of science and technology, as well as the assessment that the clinical investigation includes a sufficient number of observations to ensure the scientific validity of the conclusions.

After the Member State concerned has authorised the clinical investigation (in contrast with Belgian law, no timelines are set for this in the MDR), the sponsor and the investigator are responsible to ensure that the clinical investigation is conducted in accordance with the approved investigation plan. Article 72 (5) of the MDR states that "Member States shall inspect, at an appropriate level, investigation site(s) to check that clinical investigations are conducted in accordance with the requirements of this Regulation and with the approved investigation plan". Inspectors can therefore check that clinical investigations are conducted within the framework of their approval and in compliance with the European Regulation, the law of 22/12/2020 and the Royal Decree of 18/05/2021.

In accordance with article 81 of the MDR, the European Commission is entitled, to enact implementing acts to promote a uniform application of the requirements related to the clinical evidence or data needed to demonstrate compliance with the general safety and performance requirements. This could indeed also help to improve study designs in the pre-market stage.

It should also be noted that clinical investigations that are not covered by the MDR must also be authorised but according to the requirement of each Member State. This legislation is not covered by this report.

3.4.4.3 The extra scrutiny procedure for high risk medical devices and the links with common HTA

The MDR creates a formal scientific advisory structure at the EU level (article 106). For the first time, independent advice will be available to EU regulators and notified bodies concerning individual high-risk devices, through the **Clinical Evaluation Consultation Procedure** (CECP) conducted by **Expert Panels**. These experts must observe the principles of highest scientific competence, impartiality, independence and transparency. The MDR also clearly states that members of expert panels shall not have financial or other interests in the medical device industry, which could affect their impartiality. They shall undertake to act in the public interest and in an independent manner. They shall declare any direct or indirect interests they may have in the medical device industry and update that declaration whenever a relevant change occurs. The declaration of interests shall be made publicly available on the Commission website (article 107).

These experts can be consulted voluntarily by an individual manufacturer if it wishes to obtain independent expert advice. In addition, Expert Panels can issue advice on the clinical evaluation of certain devices without being requested thereto by their manufacturer. Basically, when a Notified Body finishes the clinical evaluation of a Class III implantable device or a class IIb active device intended to administer and/or remove a medicinal product, **and before it delivers a CE marking**, it is obliged to notify its clinical evaluation assessment report to the competent authorities, the authority responsible for notified bodies and the Commission via EUDAMED (MDR article 54). This report sets out the conclusions of the Notified Body concerning the clinical

[eeeee] Law of 22 December 2020 on medical devices. Royal Decree of 18 May 2021 on clinical investigations of medical devices. M.B. -B.S. 18.01.2021.

[fffff] Royal Decree of 18 May 2021 on clinical investigations of medical devices. M.B.-B.S. 25.05.2021.

evidence provided by the manufacturer, in particular concerning the benefit-risk determination, the consistency of that evidence with the intended purpose, including the medical indication or indications and the post-market clinical follow-up plan (PMCF). The European Commission will immediately transmit those documents to the relevant expert panel. This panel will, under the supervision of the European Commission, select the devices to review, on the basis of all of the following criteria:

- the device is novel or may have possible major clinical impact,
- where there has been a significantly adverse change in the benefit-risk profile in a specific category or group of devices
- a significantly increased rate of serious incidents (MDR Annex IX, paragraph 5.1.c).

For the selected devices, the relevant expert panels will scrutinise the clinical evidence submitted by manufacturers and issue scientific advice within 60 days, and its report will be published in the EU Database on Medical Devices (EUDAMED). The Notified Body has to wait for the advice of the Expert Panel before approving the CE marking and has to take it into consideration (not mandatory). The Notified Body remains responsible of its own assessment; if it does not follow the advice of the Expert Panel, it must however justify its decision in a document that will also be published.

The MDCG and, where applicable, the Commission, may, based on reasonable concerns, request scientific advice from the expert panels in relation to the safety and performance of any device (article 55).

The devices for which the relevant expert panels have provided a scientific opinion will be eligible for selection by the European Commission in the context of joint clinical assessments (common HTA) (see supra on joint clinical assessments in section 3.4.3.6). [63]

3.4.4.4 Early dialogues for medical devices

As mentioned previously, certain medical devices are eligible for the EUnetHTA program. (see supra section 3.4.3.4). However, no Joint Scientific Consultations for medical devices are planned under the EUnetHTA21 programme.

3.4.4.5 The summary of safety and clinical performance

Interestingly, the comparison with other therapeutic alternatives comes back in a section that does not primarily concern clinical investigations but patient information.

The manufacturer of each Class III medical device or Class II implantable device approved under the MDR should summarise and update the main safety and performance aspects of the device and the outcome of the clinical evaluation as well as the therapeutic alternatives (MDR Recitals 48 and 49[ggggg]). This document, called the Summary of Safety and Clinical Performance, or 'SSCP' (MDR article 32), will be publicly available on the EUDAMED portal.

The MDCG has recently issued a guidance on the content of this document[hhhhh]. This document mentions, regarding therapeutic alternatives, that:

> *"Regarding therapeutic alternatives, the SSCP should contain a review of how the device relates, in terms of benefit-risk, to*

ggggg Recital 49 of the MDR states that "the summary of safety and clinical performance for a device should include in particular the place of the device in the context of diagnostic or therapeutic options taking into account the clinical evaluation of that device when compared to the diagnostic or therapeutic alternatives and the specific conditions under which that device and its alternatives can be considered".

hhhhh MDCG 2019-09 https://ec.europa.eu/docsroom/documents/37323.

diagnostic or therapeutic alternatives and the specific conditions under which the device and its alternatives can be considered

If reference is made to the "state of the art", that statement should be supported for example by referring to relevant recognised guidance documents generated by specialty medical societies or educational bodies.

In the part of the SSCP intended for patients the text should include a recommendation to discuss any possible diagnostic or therapeutic alternatives with a healthcare professional who can take into consideration the individual patient's situation (…)."

It should be noted that such a requirement does not exist in the legislation on medicines where the leaflet and summary of the product characteristics must legally include information on the composition of the medicine, how it needs to be used, possible side effects, properties, special warnings, etc. but not on the clinical evidence that was used (available in the EPAR but not understandable by lay people) or its place in clinical practice.

Once the new version of EUDAMED is made available, the general public will be able to access, for each implantable and class III medical device, a Summary of Safety and Clinical Performance (SSCP) drawn up by the manufacturer. In the meantime, the MDCG consider that the manufacturers should make this document available by other means (on their website, or upon request)[iiiii]. This summary must contain general information on the device and specifically a description of the clinical evaluation and the possible diagnostic or therapeutic alternatives. This summary shall be written in a way that is clear to the intended user and, if relevant, to the patient. The MDR indicates that patients are also intended recipients of the information in the SSCP, "if relevant". Devices for which information will be especially relevant for patients include:

- implantable devices for which patients will be given implant cards, and
- class III devices that are intended to be used directly by patients. For these devices, a part of the SSCP specifically intended for patients should be provided.

For other devices not in one of these two groups, manufacturers need to evaluate themselves if "relevant to the patient" is applicable.

This summary will facilitate patient information and choice. Manufacturers will have to carefully weigh each word in explaining other alternatives and misleading information could be grounds for a legal claim. However, this article does not require that patients are provided with overall survival statistics explaining which option is the best. This will remain under the responsibility of the physicians/public authorities/scientific societies.

3.4.4.6 Evidence in the post-market vigilance and surveillance

The post-market phase is in principle out of scope for this report. However, the main principles of this phase are briefly summarised here because it is one of the most common arguments in the debate on evidence gaps that this gap will be filled in the post-market phase for those products. The post-market phase is specifically crucial in the regulatory framework for medical devices as the placing on the market relies precisely on the fact that data will be collected during the product life cycle, that is after it becomes available and used, even for high-risk devices.

The MDR requires more follow up during the post-market phase, including more post-market studies, and has created new obligations for manufacturers.

"Market surveillance" (performed by the national competent authorities) covers the set of activities carried out and the measures taken to verify and guarantee that the devices that are on the market are compliant with medical device rules and do not endanger health and safety.

[iiiii] MDCG 2021-1 https://ec.europa.eu/health/sites/default/files/md_sector/docs/2021-1_guidance-administrative-practices_en.pdf

"Post-market surveillance" (PMS), which is performed by the manufacturer, is a proactive and systematic process, designed to monitor the safety and performance of a medical device by collecting and analysing information relating to its use in the field. Under the new MDR, post-market surveillance must be based on a PMS plan which should include the post-market clinical follow-up plan. Manufacturers of middle and high risk devices must submit a Periodic Safety Update Report (PSUR) to the notified body that issued the conformity certificate for its device, at least every two years for Class IIa devices and at least every year for Class IIb and III devices. For Class III and implantable devices, these PSURs need to be submitted through EUDAMED and the notified body should add its assessment in the EUDAMED database. Only competent authorities and Notified Bodies have access to these documents.

Finally, "vigilance" (performed by the manufacturer and the national competent authority) is a reactive process and consists in reporting serious incidents and field safety corrective actions (FSCA) to the competent authorities involved. The FSCA is a corrective action (e.g. a recall, software-update, etc.) while a serious incident is a specific failure event causing harm to a specific patient. It should be noted that expected and foreseeable side effects must not be reported by manufacturers if they meet all the following criteria:

- clearly identified on the labelling,
- are clinically well known as being foreseeable and having a certain qualitative** and quantitative predictability when the device is used and performs as intended,
- documented in the device master record, with an appropriate risk assessment, prior to the occurrence of the incident
- and clinically acceptable in terms of the individual [jjjjj]

Under the MDR, manufacturers must however report adverse events trends, as well as trends of expected unwanted accidents that are not classified as serious. Notification obligations are broader in Belgium since they also require healthcare professionals, and professionals that use devices to notify incidents involving medical devices based on a national decision tree[kkkkk].

All FSCAs in which Belgium is concerned (affected devices or in cases where the manufacturer or authorised representative is located in Belgium) need to be reported by the manufacturer to the FAMHP, the Belgian national competent authority for medical devices. Based on the FSCA, the manufacturer shall draw up a field safety notice for users (FSN) summarising the identified problem, the potential risks that may arise for patients and users, and/or actions to be taken by the user to minimise the risks. It should also include the actions taken by the manufacturer to resolve the problem and/or minimise the risks. Only the FSNs are "public". However, unlike in other countries (e.g. UK, Germany), in Belgium, FSNs are not systematically classified in a specific database allowing product or key-word searches. Therefore, they are not easily accessible. In the future fully functional EUDAMED database, the FSNs will be publicly available. Additionally, also a limited dataset of the reported serious incidents will be available to the public.

In the US, the MAUDE[lllll] database summarises some data-elements of the reports made by manufacturers and mandatory reporters. Occasionally, the FDA publishes recommendations on specific safety issues affecting medical devices[mmmmm].

jjjjj MEDDEV 2.12-1 rev.8, section 5.1.3.5 .

kkkkk These definitions were taken from https://www.thema-med.com/en/what-is-the-difference-between-market-surveillance-post-market-surveillance-pms-and-vigilance/

lllll https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm

mmmmm https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm

Publicly available safety information only gives an idea of the possible safety issues affecting medical devices but does not give information on the scale or the frequency of these events. This will not change with the new version of EUDAMED.

Key points – evidence in the CE marking process for high-risk medical devices

- **Previous rules governing medical devices (MDD and AIMDD) are being progressively replaced by the Medical Device Regulation (MDR) which introduces more stringent rules, particularly with regard to clinical evidence for Class III medical devices.**
- **Like the previous Directives, the MDR requires, prior to entry on the market, the demonstration that a device is safe and performs as intended and that the risks that may be associated with its use constitute acceptable risks when weighed against the benefits to the patient (acceptable benefit-risk balance). The new MDR specifies that clinical benefit means the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health.**
- **To demonstrate that these criteria are met, manufacturers of all classes of medical devices are required to perform a clinical evaluation. Clinical evaluation does not mean clinical trial but constitutes a broad collection and analysis of all kinds of clinical data. This clinical evaluation shall follow a defined and methodologically sound procedure based on a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device, a critical evaluation of the results of all available clinical investigations. In addition, a clinical evaluation shall be based on a consideration of currently available alternative treatment options for that purpose, if any.**
- **Under the MDR, clinical investigations are obligatory for all Class III medical devices. This positive improvement is mitigated by the fact that this requirement does not apply, under certain conditions, namely if the device is equivalent to a device already marketed by the same manufacturer under the MDR or the MDD or to an equivalent device marketed by another manufacturer under the MDR provided that access to the data of the existing device is ensured by a contract. In addition, clinical investigations are not required for a Class III device which has been lawfully placed on the market in accordance with Directive 90/385/EEC or Directive 93/42/EEC and for which the clinical evaluation is based on "sufficient clinical data".**
- **The design and conduct of these investigations must reflect the latest scientific and technical knowledge. The endpoints shall be determined and assessed using scientifically valid methodologies and shall address the intended purpose, clinical benefits, performance and safety of the device. The primary endpoint shall be appropriate to the device and clinically relevant.**
- **Despite the fact that these requirements are relatively broad and that there is no explicit regulatory requirement imposing a specific study design or specific endpoints, the further definition of clinical benefit and the inclusion of consideration for the therapeutic alternatives in the clinical evaluation as well as a strong emphasis on the state of the art in the MDR confirm that the MDR places more emphasis on the real added therapeutic value of medical devices for patients.**
- **In addition, the manufacturer of each Class III medical device or Class II implantable device must summarise and update the main safety and performance aspects of the device and the outcome of the clinical evaluation in a document that should be publicly available. This will include in particular a description of the device's place in therapy in the context of available diagnostic or therapeutic options taking into account the clinical**

evaluation of that device when compared to the diagnostic or therapeutic alternatives.

- **The MDR also adds the possibility for the manufacturer to ask EU-level expert panels to issue scientific advice on the best study design to initially test a device's performance and safety, and to assess the manufacturer's clinical file. This advice is scientific advice provided in the context of the regulatory process and does not include HTA evaluation.**
- **A proposal for a Regulation on health technology assessment is currently reaching the last steps of the EU legislative process. This proposal includes the possibility of performing a common HTA on high-risk medical devices at EU level that would need to be taken into consideration by all EU Member States.**

3.4.5 The role of ethics committees in reviewing the evidence and the Belgian situation

The new CTR (applicable to clinical trials with an investigational medicinal product (IMP) from January 2022) and MDR (applicable to clinical trials called clinical investigations) of medical devices with a regulatory purpose) both aim to enhance simplification and independence of national review by ethics committees and national competent authorities. Therefore, they both reviewed previous legislations (Clinical Trials Directive for clinical trials with an IMP and Medical Devices Directives for clinical investigations with medical devices).

In the current situation, sponsors submit their dossier to their own ethics committees. Under the new regulation, the CTR, each Member State is made responsible for setting up a national system for an independent and central ethics review. This may result in narrowing down the scope of ethics review, which is considered a risk.[62]

In Belgium, a specific college (CT-College) has been established, whose remit is to choose which ethics committee will examine an application to ensure that the ethical evaluation of clinical trials of medicines for human use or medical devices is carried out with the necessary quality and is performed independently of the sponsor, the location of the clinical trial, the investigators and any other undue influences. The chosen ethics committee cannot be the one for the clinical trial site(s) concerned (art. 7 of the Law on Clinical Trials).

This independent College, established within the Belgian Federal Public Service (FPS Public Health), will act as a single point of contact for all communications between the 'Ethics Committees' and the Federal Agency for Medicines and Health Products (FAMHP) with regard to clinical trials of medicinal products for human use that fall within the scope of the European Regulation but also clinical investigations of medical devices (and in the future, also IVDs).

Under these new legislations, the key principle remains that national competent authorities should authorise the clinical trial / clinical investigation after an ethics committee has issued a favourable opinion on each application for a clinical trial of a medicine or a medical device.

This review (by an ethics committee and a competent authority) aims to ensure the reliability of the data to be generated and the protection of the study subject. As underlined by Mendel et al (2016),[61] this aim is not always achieved. The authors give the example of trials where over 10 000 people with rheumatoid arthritis have been randomised to control groups receiving ineffective treatment in trials of biological disease modifying antirheumatic drugs, risking "irreversible deterioration in condition". The authors of this study tried to analyse the process of ethical review and experienced enormous difficulties in accessing ethics committees' advice (which is not public). According to them, the reasons for failure in this case can be linked to: failure in the risk mitigation; failure of the sponsor to communicate the risks of using placebo to the study subjects during the informed consent process; and failure of the sponsor to communicate methodological shortcomings and the results of previous research. There have also been criticisms of the ethical review process for studies conducted during the Covid-19 pandemic. [62]

As already mentioned (see supra sections 3.4.3.2 & 3.4.4.2), both the CTR and the MDR describe (with various degrees of detail) the different elements of this review. The division of tasks between national competent authorities

and ethics committees and the extent of the control of ethics committees may however vary in each Member State.

- **For medicines**, Parts I (scientific part including protocols etc.) and II (covers more practical aspects such as compliance with informed consent, compensations, arrangements for participant recruitment, etc.) of the assessment must be assessed by the Member State. The CTR states that the review by the ethics committee **may** encompass aspects addressed in Part I of the assessment report for the authorisation of a clinical trial as referred to in article 6 and in Part II of that assessment report as referred to in article 7 as appropriate for each Member State concerned (article 4). As mentioned previously, this possibility to narrow the scope of ethics review could weaken the protection of research subjects.[62]

  In Belgium, trials with medicines (until the CTR is in force) are regulated by the law of 2004 on human experimentation (which has a broader scope than the MDR and CTR) and will be regulated by the law of 2017 when the CTR comes into force. Art. 5 of the law of 2004 states that an experiment may only be undertaken or continued if several conditions are met, including that:

  1. the experimentation is scientifically justified and based on the latest scientific knowledge and on sufficient pre-clinical experimentation;
  2. the purpose of the experimentation is to broaden man's knowledge or to find ways to improve his condition
  3. there is no alternative method of comparable efficacy that would allow the desired results to be obtained;

- **For medical devices**, the MDR states that a clinical investigation under the scope of the MDR can only be conducted if authorised by a national competent authority and if no negative opinion has been issued by an ethics committee with regard to the clinical investigation[nnnnn]

The MDR describes the review by the national competent authorities (article 71 MDR) which must include, amongst other things, the review of the reliability and robustness of the data generated in the clinical investigation, taking account of statistical approaches, the design of the investigation and methodological aspects, including sample size, comparator and endpoints.

However, the MDR does not further define the involvement of ethics committees regarding the review of the trial application. Indeed, under the MDR, it should be left to the Member State where a clinical investigation is to be conducted to determine the appropriate authority to be involved in the assessment of the application to conduct a clinical investigation and to organise the involvement of ethics committees within the timelines for the authorisation of that clinical investigation as set out in this Regulation. Member States should however ensure the involvement of laypersons, in particular patients or patients' organisations. They should also ensure that the necessary expertise is available.

In Belgium, the King adopted a list of respective competences for FAGG and the ethics committees. This list only mentions as a joint competence of both the national competent authorities and the ethics committees (i.e. both have legal authority), the assessment of whether clinical investigation participants will benefit from appropriate protection in accordance with the MDR and of whether the expected benefits to study participants or to public health justify the foreseeable risks and inconveniences. In contrast to the text of the MDR, no reference is made in the Belgian law to normal clinical practice However, the content of the MDR is directly applicable to national law.

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nnnnn Under the MDD ethics committee concerned has issued a favourable opinion on the programme of investigation in question including its review of the clinical investigation plan.

In Belgium, the involvement of an ethics committee regarding the review of clinical investigations with medical devices is thus broad.

The legislation imposes a huge responsibility on the ethics committees which are organised nationally and might not be organised (or funded and supported) identically everywhere in Europe. This responsibility also means that they are accountable for the tasks assigned to them (for medicines, see Mendel et al., 2016).[61]

In addition, the transparency that should correspond to such accountability and make ethics committees truly accountable for the opinions that they issue is not assured (Mendel et al., 2016).[61] The authors claim that the following principles should be followed for all clinical trials and that ethics committees should ensure them:

- Systematically review evidence relating to current and proposed treatments;
- Assess the quality of the proposed research, and tell patients about this;
- Ensure that risks are appropriately mitigated, including the risks associated with placebo;
- Give patients a summary of existing evidence and of any risks of participation;
- Make all documentation around ethical approval and consent freely available;
- Blank consent forms should be made publicly available alongside trial registration, accompanied by the participant information sheet.

The Ethics Committee and the competent authority may refuse or withdraw their approval (Art. 22 and 23) if the conditions for a favourable opinion are no longer met. In 2019, 92% of the opinions of the ethics committees were favourable (only 1% were unfavourable) and 7% were without an opinion)[ooooo]. No remarks concerning the design of the study were reported in 2019. It should however be underlined that these numbers do not take into account application withdrawals by the sponsors.

Decisions of the ethics committees are not made public. Yet, article 12 of the CTR (medicines) specifies that in the case that an application is withdrawn, the reasons for the withdrawal must be made known. The MDR does not contain a similar provision.

According to some of the stakeholders consulted, the organisation and funding of ethics committees in Belgium may not always allow a comprehensive review of the protocol, including an in-depth discussions or analysis of the relevant endpoints. This will depend on each ethics committee. Despite their important responsibilities, ethics committees in Belgium are not sufficiently funded. However, the Council of Ministers has just approved an “avant-projet de loi” (i.e. a draft bill) that should allow a better financing of the ethics committees[ppppp].

Key points- ethics committees

- **Ethics committees and national competent authorities play a major role in the assessment of the appropriate study design for trials as they have, in principle, the authority to review protocols and evaluate endpoints.**

  The new CTR and MDR aim to enhance the simplification and independence of national review by ethics committees and competent authorities but the CTR potentially endangers the role of ethics committees by allowing Member States to narrow the scope of their review.

[ooooo] https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/210208_rapportcem_2019.pdf.

[ppppp] https://news.belgium.be/fr/modification-de-la-loi-relative-aux-dispositifs-medicaux-et-de-la-loi-concernant-lafmps.

- **The organisation and funding of ethics committees in Belgium does not always allow for a comprehensive review of the protocol, including an in-depth discussion or analysis of the relevant endpoints. This will depend on each ethics committees.**
- **Available Belgian statistics show that only 1% of the opinions are not favourable. It should however be underlined that these numbers do not take into account withdrawals by the applicants and that, in practice, the FAMHP discusses its comments in advance with the applicants, eventually allowing them to withdraw their proposal before it is refused.**
- **Decisions of the ethics committees are not made public. Yet, article 12 of the CTR (medicines) specifies that in case of withdrawal, the reasons for the withdrawal must be made known. The MDR does not contain a similar provision.**

3.5 Transparency requirements for clinical data

In order to improve the quality of scientific research, both by industry and by independent researchers, the existence and the results of all studies should be known, regardless of whether the outcomes are positive or negative. Some obligations exist in the European regulations, but they rely largely on the goodwill and collaboration of the study sponsors. In addition, enforceability of these obligations seems to be a general problem, not only in Europe, but also in the United States[qqqqq] because of the lack of sanctions or application thereof or because of the application of confidentiality exceptions. The functionality of the EU dedicated (mandatory) portals to ensure this transparency are also a barrier[rrrrr].

As a consequence, healthcare providers and patients do not always have access to appropriate information to make informed choices, and researchers do not have access to sufficiently detailed data to allow independent re-analysis of trials, limiting their potential to contribute towards improving post-market comparative effectiveness assessment.[64]

3.5.1 *Ethical rules regarding the transparency on clinical trials data*

Article 35 and 36 of the Declaration of Helsinki states that:

> *"35. Every research study involving human subjects **must be registered** in a publicly accessible database before recruitment of the first subject.*
>
> *36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available **the results of their research** on human subjects and are accountable for the **completeness and accuracy of their reports**. All parties should adhere to accepted guidelines for ethical reporting. **Negative and inconclusive as well as positive results must be published or otherwise made publicly available**. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication."*

These rules are applicable to all research studies involving human subjects. As analysed in the following sections, European legislation contains similar requirements (with some gaps and enforcement problems).

qqqqq https://www.sciencemag.org/news/2020/01/fda-and-nih-let-clinical-trial-sponsors-keep-results-secret-and-break-law

rrrrr https://haiweb.org/wp-content/uploads/2021/09/Lessons-Eudamed-and-CTIS-2021.pdf

3.5.2 *Transparency requirements in the regulatory framework for medicines*

Some clinical data regarding medicines are made publicly available both in the context of the marketing authorisation process (via a specific EMA webpage) and in the context of clinical trials rules (via a dedicated platform for the mandatory registration of clinical trials with all IMPs and publication of study results). Other platforms, used on a voluntary basis in Europe[sssss], are also a useful source of information such as ClinicalTrials.gov or WHO International Clinical Trials Registry Platform.

3.5.2.1 *Evolution of transparency rules in the context of clinical trials on medicines*

The provisions of the Clinical Trial Regulation, which will replace the CTD, were adopted in 2014 but are expected to take effect only at the beginning of 2022. This delay is due to technical challenges concerning the implementation of the single EU portal and database system foreseen by the Regulation. In the interim, the Clinical Trials Directive 2001/20/EC8 and the Paediatric Regulation (EC) No. 1901/2006 remain applicable. The Directive and the Regulation apply to interventional clinical trials on medicinal products for human use performed in the EU and exclude non-interventional studies or studies of medical devices (unless the devices are part of a clinical trial involving a medicinal product).

The Clinical Trials Regulation constitutes an improvement as it not only requires clinical trials with IMPs to be registered but also makes it mandatory to publish the results of those clinical trials, both favourable and unfavourable within one year after the end of a clinical trial (or within six months for a paediatric trial). It is the responsibility of sponsors to ensure that the protocol information and results of all clinical trials are submitted to EudraCT[ttttt];

The CTR now obliges the sponsor to submit a summary of the results of the clinical trial to the EU database (a template for this purpose is annexed in Annex IV and is extensive):

- Irrespective of the outcome of a clinical trial
- Within one year from the end of a clinical trial
- It shall be accompanied by a summary written in a manner that is understandable to laypersons (Annex V)
- However, where, for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results within one year, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification.
- This obligation is directly applicable in all Member States

The sponsor can also voluntarily decide to share all the raw data in EudraCT (guidance of the European Commission is announced but does not yet exist).

According to the European Commission, "*as of April 2019, the EudraCT database included 57,687 clinical trials in total, out of which **27,093 were completed**. Out of these completed trials, **18,432 should have had results posted**; **sponsors** were in compliance with the publication requirements for **68.2% (12,577)** of the trials, however **results were still lacking for 31.8% of them (5,855).** The reporting compliance of **non-commercial sponsors** (e.g. academia) **was much lower than for commercial sponsors** (i.e. companies), with 23.6% of results posted for non-commercial sponsors vs 77.2% for commercial sponsors. Academic sponsors or smaller companies often lack awareness or incentives to post clinical results, therefore EU authorities are taking various steps to ensure sponsors are aware of their obligations and can act on them*". [uuuuu]

[sssss] ClinicalTrials.gov is mandatory in the USA for certain interventional trials.

[ttttt] Articles 37, § 4 of the CTR.

[uuuuu] https://www.ema.europa.eu/en/news/call-all-sponsors-publish-clinical-trial-results-eu-database

Other sources also point to the extent of this problem generally [vvvvv] and in Belgium[wwwww] . Cochrane Belgium, Test Aankoop and Kom op tegen Kanker joined forces with TranspariMED to report on the transparency of clinical trials in Belgium. The report is based on clinical trial registration data in EudraCT.

The report shows that 22% of trial registrations that are verifiably due to have results do not yet have those results. However, this is probably an underestimation as only 292 of the 1098 registered Belgian trials have been marked as completed. The register contains many trials that started more than 10 years ago but that have not yet been marked as completed. It is unlikely that these studies are still ongoing.

Commercial organisations have published their results much more often than non-commercial organisations such as universities and hospitals. The current report was published after reaching out to Belgian organisations last year asking them to register their results. Several organisations took this to heart and added results, but not all of them. There is certainly still room for improvement. Moreover, a more accurate picture needs to be formed of the trials that have been completed. This needs to be done by the national medicine's regulator, FAHMP, together with the funding organisations. Results will be evaluated again in 6 months. TranspariMED, in collaboration with Kom op tegen Kanker, Test Achats and Cochrane Belgium urge the FAHMP to enforce the MDR transparency rules.

EUDRACT and EU Clinical Trials Register (current Directive on Clinical Trials)

Before starting a trial, the sponsor has to register its study and to obtain a unique EudraCT number. The national competent authorities are responsible for entering protocol-related information that has been submitted to their Member State into the EudraCT database. The authorities also add to this information the authorisation of the clinical trial and the opinion from the relevant ethics committee. Once entered, a sub-set of this information is made publicly available through the EU clinical trials register website[xxxxx].

The EudraCT database is currently used to store information on clinical trials performed in the EU/EEA (i.e. those that have a EudraCT number) or on all trials associated with regulatory applications in the EU/EEA or that need to be disclosed because they are part of the Paediatric Investigation Plan (PIP) – such as those trials performed outside of the EU/EEA, in the so-called "third countries". It covers non-commercial and commercial (interventional) trials.

It does not cover

- Other trials (e.g. non interventional)[yyyyy]
- Medical devices
- Trials on medicines that are not commercialised in Europe

The contents of this register are summarised and compared with the contents of the CTIS in Table 1 below.

[vvvvv] See also https://eu.trialstracker.net/2021;

See also: https://www.transparimed.org/single-post/european-medicines-regulators-set-to-tackle-missing-clinical-trial-results

[wwwww] https://www.test-aankoop.be/gezond/ziekten-en-geneesmiddelen/geneesmiddelen/nieuws/klinischestudies & https://www.test-aankoop.be/gezond/ziekten-en-geneesmiddelen/geneesmiddelen/pers/2021/resultaten-van-klinische-studies-met-geneesmiddelen-vaak-stilgehouden

[xxxxx] https://www.clinicaltrialsregister.eu/natauthorities.html.

[yyyyy] For non-interventional clinical trials, refer to ENCEPP database https://www.encepp.eu/. Registration on the ENCEPP database is on a voluntary basis.

Clinical Trials Information System (CTIS, new regulation on clinical trials)

The new CTR creates a new Clinical Trials Information System (CTIS) that will contain the centralised EU portal and database for clinical trials with medicines. The EMA will set up and maintain CTIS, in collaboration with the Member States and the European Commission.

This database will include:

- the **main characteristics of the trial** comprising **design, scientific and, where applicable, therapeutic intent**, title, identification of the investigational medicinal products (IMPs), treatment arms, treatment population and number of subjects, inclusion and exclusion criteria and the **main objectives and endpoints**.
- the conclusion of the assessment and decision on the trial [zzzzz]
- information updated during the trial to indicate the start of the trial and the start and end dates for recruitment.
- any substantial modifications to the trial.
- the end date of the trial, with reasons for which trials are ended prematurely where applicable, and, 12 months later, the summary of results and a summary in lay language.
- **clinical study reports for clinical trials on medicines** for which a marketing authorisation has been granted, the procedure completed, or the marketing authorisation application withdrawn.

In accordance with the Regulation, the EU database shall be publicly accessible unless, for all or part of the data and information contained therein, confidentiality is justified on any of the grounds outlined in article 81(4).

The confidentiality exemption protects:

- personal data;
- commercially confidential information, in particular the marketing-authorisation status of the medicine, unless there is an **overriding public interest;**
- confidential communication between Member States in the preparation of their assessment of clinical trials by Member States.

The "overriding public interest in disclosure" may prevail in some particular ad hoc situations over and above the general disclosure rules established for the CTIS database. Documents and data not usually made public may be published or made public at an earlier point in time than would be normally the case.

In addition, while the trial and results registration obligations apply to all trials with an investigational medicinal product (IMP) regardless of the phase, information regarding phase 1 trials will only be visible to national competent authorities, the EMA, and the European Commission and will not be disclosed to the public.

3.5.2.2 Information available at the EMA and the debate on commercially confidential information[aaaaaa]

Since 2015, for medicines authorised centrally, the EMA publishes certain document (including clinical study reports) submitted to EMA by pharmaceutical companies to support their request for marketing authorisation[bbbbbb].

[zzzzz] For a medicine that is authorised by a Member State, details on the assessment of the medicine are also available in a Public Assessment Report. https://www.ema.europa.eu/en/medicines/download-medicine-data#periodic-safety-update-report-single-assessments-(psusas)-section

[aaaaaa] https://www.ema.europa.eu/en/glossary/commercially-confidential-information

[bbbbbb] https://clinicaldata.ema.europa.eu/web/cdp/home

Clinical data normally include:

- the clinical overview, providing a critical analysis of the clinical data in the submission package, including the conclusions and implications of the clinical data;
- the clinical summary, which provides a detailed factual summarisation of all the clinical information submitted;
- the study reports on the individual clinical studies;
- three appendices to the clinical study reports, namely the study protocol, the sample case report form used to record information on an individual patient, and documentation of the statistical methods used to analyse the data.

The EMA also publishes a European public assessment report (EPARs) providing public information on a medicine, including how it was assessed by the EMA (after the marketing authorisation was granted or denied). In accordance with the legislation, EPARs should be updated periodically to reflect the latest regulatory information on medicines. This means for instance that if the original terms and conditions of a marketing authorisation are varied (European Commission decision), the EPAR is updated to reflect such changes with an appropriate level of detail.

However, the EMA cannot disclose commercially confidential information unless there is an overriding public interest in disclosure. The EMA has published several implementing rules describing the practical implementation of the general transparency rules[ccccc] and two policies nr. 0043[ddddd] and 0070 [eeeee]. According to the traditional EMA position, commercially confidential information is information whose publication might prejudice the commercial interests of individuals or companies to an unreasonable degree.

However, the agency has recently stated that clinical data cannot, in principle, be considered commercially confidential information (CCI) and that there are limited circumstances where information could constitute such confidential information. Companies must justify the redaction of any CCI which, in limited circumstances, may be contained in study reports.

According to the European Ombudsman, when the information contained in a document has implications for people's health (such as information on the effectiveness of a medicine), the public interest in disclosure will generally outweigh any claim of commercial sensitivity. Public health should always take precedence over commercial interests.

In the judgments in *PTC Therapeutics International* v *EMA* (C-175/18 P) [fffff] and *MSD Animal Health Innovation and Intervet International* v *EMA* (C-178/18 P), delivered on 22 January 2020, the Court of Justice was required to examine, for the first time, the question of access to European Union documents submitted in the context of marketing authorisation (MA) applications. In this instance, it dismissed the appeals brought by, on the one hand, PTC Therapeutics International and, on the other, MSD Animal Health Innovation and Intervet International against the judgments of the General Court dismissing their actions for annulment of the decisions by which the EMA had granted access to documents containing information submitted in the context of the procedure relating to MA applications for medicinal products[ggggg].

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ccccc https://www.ema.europa.eu/en/documents/report/questions-answers-european-medicines-agency-policy-publication-clinical-data-medicinal-products_en.pdf

https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/clinical-data-publication

ddddd https://www.ema.europa.eu/en/documents/other/policy-43-european-medicines-agency-policy-access-documents_en.pdf

eeeee https://www.ema.europa.eu/en/documents/other/european-medicines-agency-policy-publication-clinical-data-medicinal-products-human-use_en.pdf

fffff https://curia.europa.eu/juris/document/document.jsf?text=&docid=199044&pageIndex=0&doclang=fr&mode=lst&dir=&occ=first&part=1&cid=5277192

ggggg https://curia.europa.eu/juris/document/document.jsf;jsessionid=69C64867D99DA23E963715F89B5300DD?text=&docid=223126&pageIndex=0&doclan

Both cases concern the legality of the EMA's decisions to grant, under Regulation No 1049/2001, access to a number of documents, namely toxicology reports and a clinical study report, submitted by the appellants in the context of their MA applications relating to two medicinal products, one for human use (Case C-175/18 P) and the other for veterinary use (Case C-178/18 P). In the present case, after authorising the placing on the market of those medicinal products, the EMA decided to disclose the content of those reports to third parties, subject to some redactions. Unlike the appellants, who claimed that those reports should benefit from a presumption of confidentiality in their entirety, the EMA contended that, apart from the information that had already been redacted, those reports were not confidential.

The Court of Justice has concluded that the application of a general presumption of confidentiality is merely an option for the institution, body, office or agency concerned, and the latter always retains the possibility of carrying out a specific and individual examination of the documents in question to determine whether they are protected, in whole or in part, by one or more of the exceptions laid down in article 4 of Regulation No 1049/2001. Consequently, the Court of Justice rejected the appellants' plea that the reports at issue were covered by **a general presumption of confidentiality**, **noting that the EMA was not obliged to apply such a presumption to those reports** and that the EMA had carried out a specific and individual examination of those reports, which had led it to redact certain passages.

3.5.3 *Transparency requirements for Medical devices*

Under the MDD, most of the information related to medical devices is confidential. Confidentiality extends to data resulting from clinical investigations of medical devices as well as claims submitted by manufacturers to Notified Bodies, assessment reports, and evaluation of the device by Notified Bodies.[50, 63]

Information contained in the original version of Eudamed (and the subsequent Eudamed2) is only accessible by national competent authorities in charge of the implementation of the medical device's legislation. This platform is a platform for information exchange and storage (e.g. of vigilance information, national competent authority Reports (NCARs) and manufacturer information) but the content of this database is rather limited.

Overall, transparency will improve with the MDR and the further development of the public EUDAMED database[hhhhhh], which will include certain data on registration, (of economic operators and devices), certificates, clinical investigations, vigilance, and a system for market surveillance. Once the new version of EUDAMED is fully available, the general public will also be able to access, for each implantable medical device and class III devices, a Summary of Safety and Clinical Performance (SSCP) drawn up by the manufacturer.

The new version of the EUDAMED database is not fully functional yet and has been repeatedly delayed. As a consequence of this delay, the registration obligation imposed by the MDR has been postponed to a later date (Art. 123(3) and 122 4th indent). This notice is estimated to be published in mid-2023. Actors (i.e. manufacturers, distributors, importers and any other relevant economic operators) will therefore only be obliged to register at the end of 2023. As far as medical devices (and their clinical data) are concerned, they need to be registered 18 months after the full functionality of EUDAMED; this would be around 2025.

g=FR&mode=req&dir=&occ=first&part=1&cid=15466592 (Tribunal) • https://curia.europa.eu/juris/document/document.jsf?text=%2522Commercially%2Bconfidential%2Binformation%2522%2B%2522medicines%2522&docid=222502&pageIndex=0&doclang=FR&mode=req&dir=&occ=first&part=1&cid=2011230 (Court)

[hhhhhh] Article 33 of the MDR.

Not all device trials are required to be registered in EUDAMED. Trials that are not being conducted for the purpose of CE marking or for an extension of the indications for CE marking, such as early academic trials (e.g. first in man), are exempt from the requirement to be registered in EUDAMED. These unregistered trials are potentially the highest risk trials, and as they may not ever be published, particularly if they're discontinued due to safety reasons, they run the risk of being repeated and exposing even more people to unnecessary risk of harm. In principle, industry early phase trials, if conducted for regulatory purposes, are covered by the registration obligation[iiiiii].

In accordance with ISO 14155 (Good clinical practice for clinical investigation of medical devices for human subjects), which is not integrated in the MDR nor in the Belgian legislation, a description of the clinical investigation shall be registered in a publicly accessible database before the start of recruitment activities and the content shall be updated throughout the conduct of the clinical investigation and the results entered at completion of the clinical investigation.

Regarding the results, article 77 of the MDR requires the clinical study report and lay summary of the study to be uploaded to EUDAMED 12 months after the end of the study or 3 months after early termination. At this stage these documents are not yet public. Both documents will be public (except confidential information) at the latest when the device is registered in EUDAMED for completed trials. For early terminated trials, both documents will be available when the manufacturer applies for conformity assessment and CE marking. If the device is not registered (thus also if CE marking is not requested) within one year after the uploading of early terminated trials reports and summary, then both documents will become public.

According to Annex XV Chapter I §2.8 of the MDR « The clinical investigation report, signed by the investigator, shall contain a critical evaluation of all the data collected during the clinical investigation, and shall include any negative findings. The minimum requirements for content of the clinical investigation report (which will be made public according to article 77 of the MDR) are defined in Chapter III point 7 of Annex XV to the MDR.

The standard ISO 14155:2020, Annex D also has information which is relevant regarding the content of a clinical investigation report. It is important to note that the summary of serious adverse events, adverse device effects and device deficiencies should only present aggregated information related to these events.

With respect to confidentiality, the article in the proposed Regulation has changed quite a bit from the current article in the MDD. Where the MDD wants Member States to ensure that 'all the parties involved in the application of this Directive are bound to observe confidentiality with regard to all information obtained in carrying out their tasks,' the proposed Regulation requires all parties involved in the application of this Regulation to respect the confidentiality of information and data obtained in carrying out their tasks in order to protect a) personal data, b) commercially confidential information and trade secrets, or c) the effective implementation of the Medical Devices Regulation, in particular for the purpose of inspections, investigations or audits.

In the MDR, confidentiality thus needs to be protected as long as it serves particular goals. Interestingly, these goals might be in conflict, since a disclaimer is added to goal b), that commercially confidential information might be disclosed if it is in the public interest.[50]

iiiiii https://ec.europa.eu/health/sites/default/files/md_sector/docs/mdcg_2021-6_en.pdf

Table 1 – EU databases containing publicly accessible clinical information on medicinal products and medical devices[jjjjjj]

	EU CTR	CTIS (31.01.2022)	EUDAMED (MDR)
Scope	Interventional clinical trials using IMP conducted in the EU (or outside the EU if PIP) The scope is thus not limited to trials with regulatory purposes	Interventional clinical trials using IMP conducted in the EU (or outside if PIP) The scope is thus not limited to trials with regulatory purposes	Clinical investigations on medical devices for regulatory purposes
Remarks	EU CTR is the portal allowing the publication of certain information published in Eudract (platform not accessible directly by the public). Phases I to IV trials (and results thereof) are registered in Eudract but there is no public information on Phase I trials in the EU CTR. Since Brexit, no further information is completed by UK authorities and UK sponsors conducting trials in the UK	Information on applications which are only for assessment of Part I of the dossier (article 11- applications) will not be made public. Information on applications which are not validated or those withdrawn by the applicant before a decision is made will not be made public. In exceptional circumstances the above mentioned information may be made public if there is an overriding public interest in disclosure.	Potentially all classes are covered in trials that are conducted for regulatory purposes (but they are only mandatory for Class III) EUDAMED covers other modules (manufacturer, devices etc.) and serves as an exchange platform between MFs, NBs and NCAs. (not public) Clinical investigations on a CE labelled device that is used within the scope of its intended use are not covered (i.e. no obligation to register and publish in EUDAMED).
Available information	Summary information on the trial (including summary of the protocol) based on a predefined template dataset including data on : • the design of the trial • the sponsor • the investigational medicine (trade name or active substance) • the therapeutic areas	Description of the trial based on a predefined template dataset including data on : • the main characteristics of the trial comprising design, scientific and, where applicable, therapeutic intent, title, identification of the IMPs, treatment arms, treatment population and number of subjects, inclusion	• Clinical Investigation Application: Annex XV, Chapter II, 1 • Clinical Investigation Plan (CIP): Annex XV, Chapter II, 3 • Investigator's Brochure (IB): Annex XV, Chapter II, 2 • CIP must describe policy on the publication of results (Annex XV, Chapter II, 3.17).

[jjjjjj] Without prejudice of redactions due to confidentiality rules.

	• the status (authorised, ongoing or complete) • administrative status of the trial • the sponsor • the use of placebo • the objective of the trial • endpoints • scope • design • trial subjects • end of the trial	and exclusion criteria and main objectives and endpoints • protocol • conclusion of the assessment and decision on the trial (not the reasoning and arguments) • information updated during the trial to indicate the start and end dates of recruitment. • substantial modifications to the trial. • the end date of the trial, with reasons for which trials are ended prematurely where applicable • Information on clinical trials which are refused will be made public, in which case the date of the refusal decision will be taken as equivalent to the date of the end of the trial (see Table one for further details).	• A Clinical Investigation Report (CIR) will be prepared within one year of the end of the clinical investigation or within three months of the early termination or temporary halt, irrespective of the outcome (article 77, 5). • The CIR is accompanied by a summary easily understandable by the intended user (article 77, 5).
	Results • Summary of the results (including negative)	**Results** • Clinical study reports for clinical trials on medicines for which an MA has been granted, the procedure completed, or the MA application withdrawn. • Irrespective of the outcomes, within 12 months, summary of results in scientific and lay language	**Results** • Clinical investigation report and lay summary of the study including positive and nefgative results • 12 months after the end of the study or 3 months after early termination

CA = competent authorities for the authorisation of trials; EC = ethics committees; IMP = investigational medicinal product; MA= marketing authorisation; MFs = manufacturers; NBs = notified bodies; NCAs = national competent authorities; PIP = pediatric investigation plan; PSUR = Periodic Safety Update report;

3.5.4 Transparency of national reimbursement decisions

At national level, the transparency of certain other public documents could also be enhanced and could serve the interest of comparative effectiveness research. In Belgium, a summary of the motivations regarding the reimbursement decisions for medicines is, in principle, published.

However, if we compare this information with the information published by our neighbouring countries, Belgium only publishes very limited information. Indeed the RIZIV-INAMI database for decisions on reimbursement of medicines is not up to date and only contains the main reason for reimbursement and not the whole HTA reasoning[kkkkkk]. The reports of the Commission evaluating the reimbursement requests and the conflicts of interest are not made public either.

Surprisingly, similar decisions for medical devices are not published at all. These documents can be requested and disclosed upon individual request[llllll] (passieve openbaarheid van bestuur / publicité passive de l'administration).

In Germany, this transparency goes even further. The Arzneimittelmarkt-Neuordnungsgesetz (AMNOG, English translation: "Pharmaceuticals Market Reorganisation Act") is a German law relating to the marketing of pharmaceutical products in Germany. It requires drug manufacturers to submit evidence to the Federal Joint Committee (in Germany) to show that their new products are more effective than previous products. AMNOG reports (https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/) are publicly available (but unfortunately not in English) and contain more results by subgroup compared with the EPARs.[65]

3.5.5 Enforcement and penalties

Article 94 of the CTR (medicines) states that "Member States shall lay down rules on penalties applicable to infringements of this Regulation and shall take all measures necessary to ensure that they are implemented[mmmmmm]". The MDR foresees similar obligations in article 113.

The penalties provided must be effective, proportionate, and dissuasive. The article however does not state to whom the penalties are allowed to be applied, nor what the penalties are allowed to entail. Neither does the Regulation define penalties for Member States if they transgress their powers, violate their obligations, or turn out to be negligent in performing their duties.

For medicines, penalties in case of violation of the CTR or law of 17 May 2017 are described in articles 44 to 46 of the Belgian law of 7 May 2017. These provisions do not provide for sanctions in case of violations of transparency obligations. In addition, no actions were taken in the past several years to promote voluntary compliance despite the persistent demands of patients' and consumers' associations[nnnnnn].

In answer to a question in the context of this report, the FAMHP declared that the Agency was aware of the importance of publishing the results of clinical trials and that it has planned various initiatives to ensure the consistency of data and compliance with timelines for registration in EudraCT:

- At the end of June 2021, the FAMHP published a communication in the form of "News" on its website to inform clinical trial sponsors of their responsibilities and to provide guidance on how to proceed correctly in EudraCT.

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kkkkkk https://www.riziv.fgov.be/nl/toepassingen/Paginas/applicatie-rapporten-ctg.aspx

llllll It is the citizen who takes the initiative to request administrative documents that are not actively published by the administrative authorities.

mmmmmm https://belgium.cochrane.org/en/news/cochrane-belgium-participates-report-trial-transparency

nnnnnn https://www.test-aankoop.be/gezond/sitecore/content/lobbyandpressta/pers%20informatie/persberichten/2019/klinische-studies.

- Every year, the EMA provides a list of clinical trials for which no results have been uploaded to EudraCT within one year of the end of the trial (6 months for paediatric clinical trials). Based on the latest list provided, the FAMHP recently (June 2021) took action and wrote to the responsible sponsors (commercial and non-commercial) to remind them of this obligation.
- The ethics committees of the largest hospitals were recently asked to give their opinion in accordance with the regulations. They have also been asked to remind their investigators to send the End-of-Trial (EoT) to the FAMHP when the clinical trial is completed and to upload their results into EudraCT within one year (or 6 months for a paediatric trial).

Under the current legislation, proof of trial initiation is not required by the FAMHP. However, a notification of the end of the trial, with the effective date of the end of the trial in Belgium, must be sent to the FAMHP. The results of the clinical trials must be published directly by the sponsors in EudraCT but are not required to be sent to the FAMHP.

This is different in other countries**.** Denmark has recently introduced criminal sanctions for non-reporting of clinical trial results.[oooooo]

Unlike for medicines, the recent Belgian legislation on medical devices foresees sanctions in case of non-compliance with the requirements of the MDR regarding clinical investigations, including the publication requirements (article 88. 5) of the law of 22 December 2020 on medical devices.

Key points – transparency

- **Clinical trials of medical devices and medicines that are conducted for regulatory purposes must be registered in publicly accessible databases.**
- **The study results shall also be summarised and published regardless of the direction of the results.**
- **While the EPARs (including the evaluation by the EMA) are publicly accessible for centrally authorised medicines, it remains to be seen how detailed the public Summary of Safety and Clinical Performance (SSCP) will be for medical devices, once uploaded in the EUDAMED database.**
- **The presumption of confidentiality of the regulatory process documents is not automatically applicable.**
- **However, severe hurdles still prevent a satisfactory transparency on medicines and medical devices data: the effective functioning of public databases intended to make this information available is constantly delayed. This is especially a concern for medical devices.**
- **In addition, concrete enforcement of transparency rules and the imposition of infringement sanctions for sponsors is lacking in the large majority of countries.**
- **In Belgium, sanctions exist for non-compliance with transparency obligations for medical devices (in the context of CE marking under the MDR) but not for medicines.**

[oooooo] https://www.transparimed.org/single-post/2020/03/10/denmark-eudract-clinical-trial-regulation.

3.6 Conclusion / Discussion regarding legal framework

As recently recalled by the European Economic and Social Committee, health is not a market; health is a common good and should be addressed from a general interest point of view[pppppp]. This is also the position of ethics[qqqqqq].

Patient health should come first: given this central place of the patient, it should be remembered that medicines and medical devices are not products like any others: for some of them, their use in the absence of proven added therapeutic value can increase mortality in the long term. For others, the lack of efficacy is an unacceptable opportunity cost, since it means that they have foregone a potentially effective treatment, or at least have foregone the opportunity of avoiding the usually acceptable harms (e.g. surgery) as well as being subjected to the risk of unacceptable harms associated with the ineffective treatment.

In accordance with article 168.1, a high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities[rrrrrr]. Therefore, under article 168.4 TFEU, the European legislator is allowed to adopt measures setting high standards of quality and safety for medicinal products and devices for medical use in order to meet common safety concerns.

As mentioned in recital 2 of the Directive 2001/83 on medicines, the essential aim of any rules governing the production, distribution and use of medicinal products and medical devices must be to safeguard public health[ssssss], but this objective (health protection) must be attained by means that will not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community.

Medicines and medical devices are indeed “goods” under the Treaty of the European Union and must benefit, in accordance with article 114 TFEU, from the principle of free movement of goods. European rules aiming to ensure the smooth functioning of the internal market under this article 114 TFEU must however always take as a base a high level of protection of health for users (patients)[tttttt].

Nevertheless, the European industrial policy objectives may conflict with European health policy objectives.

The regulatory frameworks for medicines and medical devices provide for a “flexible approach” regarding the study design and contain “indications” (but no formal requirements) stating that comparative studies are important/ the gold standard. However direct comparative data are not required to place these products on the market despite the fact that they are needed to make informed treatment decisions and to perform cost-effectiveness analyses.

This regulatory framework relies heavily on national ethics committees issuing advice and national competent authorities authorising trials to evaluate that the study design is appropriate prior to the conduct of a study. Thus, they play an important role in evaluating the study design and appropriate endpoints. In accordance with article 33 of the DoH, they should make sure that the benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s) and that exception to these principles should be interpreted narrowly. However, the lack of resources and time, as well as the competition between ethics committees of the different Member States, raises doubts regarding

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pppppp https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CONSIL:ST_8330_2021_INIT&from=FR.

qqqqqq https://haiweb.org/wp-content/uploads/2015/10/EMA-Consultation-Response-Conditional-Approval-Accelerated-Assessment.pdf; https://www.fda.gov/files/science%20&%20research/published/Accelerating-development-of-scientific-evidence-for-medical-products-within-the-existing-US-regulatory-framework.pdf.

rrrrrr Article 168.1 TFUE.

ssssss See also confirmation by the CJEU : Abcur AB, C-544/13 and C-545/13; see also judgments in Antroposana and Others, C-84/06, EU:C:2007:535, paragraph 36, and Commission v Poland, C-185/10, EU:C:2012:181, paragraph 27.

tttttt Article 114.3 TFEU.

the success of this approach. If we look at how they actually operate, the enormous potential of these committees is often not met.[66]

The actual work of ethics committees is organised at the national level. Paradoxally, the new regulation on clinical trials of medicines decided to allow the Member States to narrow the scope of the ethics review.[62] This could weaken the protection of research subjects. While national competent authorities will still assess all part I and part II elements, it remains of utmost importance that research ethics committees can still issue negative advice when a clinical trial exposes research participants to an inferior treatment (for example, the use of placebo as a control) as compared with normal clinical practice in the Member State concerned

They should, therefore, be made fully aware of their responsibility in the regulatory process and should not be bypassed in this important role.

In addition, severe hurdles still prevent satisfactory transparency of data on medicines and medical devices:

Firstly, the application of several confidentiality rules reduces transparency. Secondly, the effective functioning of public databases intended to make this information available is constantly delayed. Effective sanctions in case of non-compliance with publication obligations (registration or results) are also lacking in most of the Europeans countries.

4 ANALYSIS OF RIZIV-INAMI DOSSIERS

4.1 Methods

KCE requested and obtained (July 2019) **from the public national payer institute RIZIV-INAMI the most recent evaluations of dossiers submitted** for medicinal products and medical devices for a specific indication or for a specific intended use, independent of the reimbursement outcome of the evaluation. **Only dossiers with an intervention claiming added value as indicated by the company** were considered.

Evaluations of medicinal products performed by RIZIV-INAMI (Commission for reimbursement of Medicines, CRM) should be made public on the RIZIV-INAMI website and, in the day 90 evaluation report, which includes the company's feedback. There is however a delay in this publication process. For the purpose of this project, KCE also received the recent evaluations not yet made public. The evaluations studied in this project concern 8 dossiers for class 1 (innovation with proven added benefit) and 10 orphan drug dossiers. The evaluation reports were mainly produced during the first half of 2019.

Evaluations of medical devices performed by RIZIV-INAMI are not accessible using a public database, nor is the company's feedback on the evaluation report made public. KCE received both the evaluation report as well as the feedback from the company for a total of 20 device evaluations performed during 2018 and the first half of 2019. In this report we coded or aggregated the information as the purpose of this project was to identify general trends and not to discuss individual dossiers. Two out of 20 device dossiers were incomplete at the time of report writing and were not included in the analyses.

Each RIZIV-INAMI evaluation report and the corresponding company feedback was read by two of the three KCE researchers (CPdJ, FH, MN). For each product (medicine or device), the medicinal product or device description, trade name, dossier number(s) and indication/intended use were recorded in a table together with the design and primary endpoint of the clinical studies submitted and evaluated (retrospective or prospective cohort, RCT with placebo/sham or versus active standard of care). Gaps

identified by RIZIV-INAMI were listed and grouped by PICO (Population, Intervention, Comparator, Outcome). Other weaknesses of study design were added as described by the RIZIV-INAMI evaluator. Efficacy and effectiveness results were grouped into quality of life (QoL) related endpoints, overall survival (OS), and surrogate endpoints, with the option of recording 'no data' or 'no indication of effect', where appropriate. Specific side-effects or safety issues of high importance were also added. The health economist also recorded remarks made on evidence limiting the economic evaluation.

Where needed, the coding in the final table was the result of a consensus among the two KCE researchers.

The final draft table was circulated for review to RIZIV-INAMI as an additional check and to make sure no confidential information was made public.

4.2 Findings

4.2.1 Applications for reimbursement of 18 medicinal products

In total, for 8 out of 18 medicinal products, the RCTs included an active control.

For 7 out of 18 drugs there was no active control group RCT, the studies were placebo-controlled.

For 3 out of 18 medicinal products there were no RCTs. These were all orphan drugs.

Issues with patient population: in 6 out of 18 dossiers, the exclusion of a significant part of the target population from the trials was considered an issue.

Issues with control group: in 9 out of 18 dossiers, issues were raised with the comparator group being lacking (eg no RCT or placebo-controlled RCT) or the comparator not reflecting standard of care.

Issues with outcomes: in 8 out of 18 dossiers, issues were raised for the outcomes assessed in the trials, mainly the use of only short term surrogate marker results without assessment of long term hard outcomes (functional outcomes related to quality of life, overall survival).

Table 2 – Analysis of 18 RIZIV-INAMI dossiers on medicinal products

Class demanded	Indication	Trials (placebo/active controlled RCTs, prospective / retrospective cohorts) ; Primary endpoint	Methodological gaps (PICO)	Remarks on effects on quality of life (QoL) and/or on overall survival (OS) and/or surrogates
class 1	Migraine prevention	4 placebo controlled RCTs; days with headache	**P:** Exclusion of patients without respons to existing drugs **C:** No active comparator RCT **O:** No long term	**QoL:** Limited but clinically relevant effect (days with headache) **OS:** no data
class 1	First line ALK+ NSCLC	2 RCTs vs crizotinib, 1 single arm; primary endpoint: PFS	**O:** Not powered for OS	**QoL**: data, improved **OS:** data, no significant effect **Surrogate:** PFS improved
class 1	Grass pollen (mono)allergy in adults and children >5y	Placebo controlled RCTs in adults and children; symptoms and medication use	**C:** No comparison versus relevant comparator, also in class 1 procedure.	**QoL**: symptoms improved, long term **OS:** no data; surrogate: less medication use
class 1	PDL1+ (>1%) stage III NSCLC no progression under cisplatinum	Placebo controlled RCT; PFS and OS	**C:** no active comparator	**QoL:** data, no impact **OS:** data, improvement PFS: improvement, but similar drugs are marketed and reimbursed without PDL1 test
class 1 (refused)	Grass pollen (mono)allergy	2 single season and 1 long term placebo-controlled RCTs 1 retrospective cohort study; primary endpoint: symptoms	**P:** in the trial the two groups are not comparable (different severity; proportion of children) **C:** not relevant comparator in RCT (placebo instead of symptomatic treatment) Retrospective cohort analysis is biased	**QoL:** data, very limited symptom reduction versus placebo, even lower after 3 seasons **OS:** no data
class 1	Adults with diabetes type 2	7 RCTs including active-control RCTs Primary Endpoint: HbA1c	**P:** Limited experience in elderly over 75 or in severe liver or renal failure	**QoL:** data, no difference **OS:** no data

			C: No cardiovascular comparative trials versus other GLP-1 analogues	**Surrogate:** reduced HbA1c versus metformine, sitagliptine, insuline glargine, exenatide, dulaglutide, similar as liraglutide, another GLP-1 analogue
class 1	Schizophrenia with negative symptoms in adults	Placebo and risperidone controlled RCTs.		**QoL:** data**,** small but statistically significant negative symptoms improvement over risperidone 3-6mg at 6 months. in the economic model, there is no reliable approach to the inclusion of quality of life data. **OS:** no data
class 1 (refused)	Treatment of diabetes in children and adults	RCTs versus insulin treatment; retrospective cohort Primary Endpoints: Effect on HbA1c and FPG, number of hypoglycemias, impact on weight.	C: Superiority claimed based on cohort data	**QoL:** no data **OS**: no data **Surrogate:** No benefit versus other insulin treatment in RCT for HBA1C or hypoglycemia
orphan	Cerebrotendineous xantomatosis	Two retrospective cohorts Primary endpoint: serum level of cholestanol	**C:** missing	**QoL:** no data **OS:** no data *Note: Substance used for compounding had >1% impurities. However in EPAR: Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.*
orphan	Acquired thrombocytopenic purpura in adults	One placebo-controlled RCT; time to platelets >150000	**M:** only one trial **O:** no long term data	**QoL:** no data, no effect on hard endpoints **OS:** data? no effect **Surrogate:** shorter stay in hospital
orphan	X-linked hypophosphatemia, children and adolescents	Prospective cohort plus one RCT versus SoC (oral phosphate plus active vit D); radiology	**P: low number, no data >12y** **C:** compliance in SoC ok? **O:** only surrogates short term	**QoL:** no data **OS:** no data **Surrogate:** radiological improvement
orphan	De novo CD33+ acute myeloïd leukemia, in combination with anthracycline and cytarabine.	Open label investigator initiated RCT; event free survival	**P:** cytogenetics take 2 weeks so stop if cytogenetics are contraindication	**QoL:** no data **OS:** no effect (underpowered?) **Surrogate:** improved event free survival, no effect on peripheral blood MRD

orphan	Primary biliary cholangitis, second line	3 placebo-controlled RCTs; laboratory values Primary Endpoint: biochemical criteria	**P:** early stage only **C:** alternatives bezafibrate and budesonide not even mentioned in EPAR	**QoL:** no data **OS:** no data **Surrogate:** biochemistry
orphan	Transthyretin amyloidosis with neuropathy stage 1 or 2 (not 3)	1 placebo-controlled RCT Primary endpoint: neurological symptoms	**P:** long list of exclusion criteria **O:** no long term **C:** no comparison versus tafamidis (in stage 1), neurotersen (in stage 1 or 2), nor liver transplant nor off-label diflunisal	**QoL:** Unclear, short term effect vs placebo limited to neuropathy scale **OS:** no data
orphan	Prevention of CMV reactivation post stemcel transplant	1 RCT prevention versus reactive treatment; clinical CMV infection	**P:** only in transplant receptors CMV+ (not donors CMV+) treated **C:** ongoing trial versus gancyclovir	**QoL:**data, no effect **OS:** data, no effect **Surrogate:** effect on clinical reactivation stronger in cyclosporin compared with tacrolimus treated patients
orphan	Nephropathic cystinosis	Prospective cohorts; biochemistry	**O:** no hard endpoints	**QoL:** no data **OS:** no data **Surrogate:** No advantage over standard (same molecule), total dose 75% but more capsules
orphan	Chronic hyperammonemia because of reduced activity of enzymes in urea cycle (excl NAGS)	RCT vs sodium fenylbutyrate	**C:** no data versus sodiumbenzoate **O:** no clinical outcomes	**QoL:** no data **OS:** no data **Surrogate:** minimally lower urea compared with fenylbutyrate
orphan	Hypophosphatasia (perinatal/infantile form has high medical need)	cohort data in children, radiology; 1 RCT vs wait in >12y, biochemistry	**P:** few data on juvenile form or >12y, unclear criteria to start treatment	**QoL:** no data **OS:** no data **Surrogate:** Limited to radiology, link with functional endpoints unclear

4.2.2 Applications for reimbursement of 18 medical devices

In two applications the reimbursement dossier assessor mentioned as an issue that the population studied did not match the target population for which reimbursement was requested.

For most devices, only prospective cohort data was available. For one device only a retrospective cohort comparison was available. For 12 devices no RCTs were performed. In two of these 12 dossiers the absence of a RCT was raised as an issue by the reviewer.

Randomized trials were performed for 6 of the 18 devices. In two of these applications it was mentioned as an issue that the device studied differed from the device for which reimbursement was requested.

In 9 out of 18 dossiers no quality of life data nor functional/patient relevant outcome data were included. In one of the evaluation dossiers this was mentioned as an issue.

In two applications the absence of sufficiently long term outcome data was mentioned as an issue.

Table 3 – Analysis of 18 RIZIV-INAMI dossiers on medical devices

Device description	added value class demanded	Intended use	Trials (placebo/active controlled RCTs, prospective / retrospective cohorts; primary endpoint)	RCT	methodological gaps (PICO)	QoL	Remarks on effects on quality of life (QoL) and/or on overall survival (OS) and/or surrogates
Retinal Prosthesis System	1a	Adults with retinitis pigmentosa with very low vision	Prospective cohort n=30, patient is own control (device switched off)	N		Y	**QoL:** data: improved vision and very limited increase in utility score; **OS:** no data
Flow and pressure readings for specific lobes in the lungs to assess collateral ventilation	1a	Select patients for endobronchial valve therapy	Cohorts comparison with MRI; used to select patients in 4 RCTs wih endobronchial valve therapy	N	**O**: no patient relevant outcomes	N	**QoL**: no data; **OS:** no data; **Surrogate:** may be of use in grey zone MRI
Cochlear implant	2a	Severe deafness (extending indication from 85DB loss to 70 in adults, why not children?)	Published retrospective and prospective cohorts	N	**P**: population in cohorts does not match target population for reimbursement expansion	N	**QoL:** no data; **OS:** no data; **Surrogate:** better hearing
Prosthetic attachment sutures secured with automated fasteners	1a	Minimally invasive heart valve replacement or reconstruction	Restrospective cohort comparisons with standard technique.	N		N	**QoL:** no data; **OS:** no data; ICU/hospital stay, bleeding or regurgitation: no effect
Dorsal Root Ganglion neurostimulator	1a	Complex regional pain syndrome (CRPS I or II)or neuropathic pain in area	RCT in CRPS patients (with other DRG versus spinal cord stimulation)	Y	**P:** no trial in neuropathic pain; **I:** other device used; **O:** limited to 12 months	Y	**QoL and pain:** data, improved; **OS:** no data
Monitoring hemodynamic parameters		Monitoring of high risk surgery (non	RCTs versus pulmonary artery catheter, RCTs versus	Y	**I:** previous model	N	**QoL:** no data; **OS:** data, no effect; surrogates: fewer

		cardiac, non neurosurgical)	standard (none used current version)				complications and maybe shorter hospital stay, not to be used for cardiac output monitoring
Iliac Branch Endoprosthesis	1a	(Aorta)-iliac aneurysm	Prospective multicenter cohort, 3 single centre cohort (one is retrospective)	N	**M:** no RCT	N	**QoL:** no data; **OS:** data, favorable but no comparative data; **Surrogate:** probably fewer complications
Stent between gastrointestinal tract and a neighboring fluid-filled cavity.	1a	Endoscopic drainage of a pancreatic pseudocyst or a walled-off necrosis	Cohorts mostly multicentre, one RCT versus plastic stent			N	**QoL:** no data; **OS:** no data; **Surrogates:** short procedure and low complication rate (but increased in RCT if stent > 3 weeks)
Triangular pins for fusion sacroiliac joint	1a	Stabilize sacro-iliacal junction	2 RCT versus conservative treatment; 1 prospective cohort	Y	**O:** crossover allowed already after 6 months only; not blinded	Y	**QoL and pain:** data, improved; **OS:** no data; **Surrogate:** composite score treatment succes
Implant replacing anterior cruciate ligament (ACL) without removing ACL, with spring	1b	Rupture of ACL < 21 days	Prospective and retrospective cohorts; tests for ACL	N	O: no long term data (5y only 10 patients)	N	**QoL:** no data; **OS:** no data; **Surrogates:** ACL scores
Drug eluting balloon, paclitaxel coated	2	Peripheral artery disease	1 RCT versus non-coated balloon; prospective cohort	Y	**M**: patient relevant outcome claim based on posthoc subgroup analysis	Y	**QoL:** data, no effect; **OS:** no data; **Surrogates:** in RCT no difference in re-interventions (only in post hoc subgroup)
Leadless pacemaker implanted in right ventricle	1a	One chamber PM requiring free venous access	Prospective cohort	N	**C:** no RCT; **O:** no long term data >12m; lifespan 12y	Y	**QoL:** data, improved; **OS:** no data; **Surrogate:** shorter procedure

					but only 6y guaranteed		
Device for percutaneous transluminal removal of occlusive material	1a	critical limb ischemia after thrombosis (in-stent occlusion)	multiple single site cohorts prospective and retrospective; endpoint revascularisation	N	**P:** unclear if target population was studied in cohorts; **C:** no RCT comparison versus thrombectomy	N	**QoL:** no data; **OS:** no data; **Surrogate:** revascularisation no comparative data
Stent-retriever for intracerebral revascularisation		Mechanic thrombectomy for revascularisation of ischemic intracerebral event in case of no use or no response to IV-tPA	5 RCTs mainly after tPA versus control	Y		Y	**QoL/function:** improved
Biopsy needle	1a	Macro-biopsy of soft tissue	Prospective and retrospective cohorts	N	**C:** no RCT, no clear advantages over existing biopsy needles	N	
Cellulose based sterile material to promote hemostasis	2a	Additional hemostasis during operation	RCTs point to inferior efficacy versus expensive medicinal products for local hemostasis	Y		N	
Implanted vagus nerve stimulator	1b	Chronic or recurrent treatment resistant depression	2 RCTs and 1 prospective cohort study;	Y		N	**QoL/function**: no significant effect on depression scores in RCTs
Endobronchial valve		Severe pulmonary emphysema	5 RCTs versus medical treatment; multiple endpoints	Y	**O:** max 12 months only	N	**QoL/function:** small benefit

Key points

- **We analysed the assessments by RIZIV-INAMI reviewers (2018-2019) of dossiers submitted for the reimbursement of medicinal products (n=18) and medical devices (n=18) with a claim of added value, irrespective of the reimbursement outcome.**
- **Gaps identified were listed and grouped by PICO and study design.**
- **For medicinal products, for about half of the dossiers, an active control RCT was available. In about half of the dossiers, issues were raised for the outcomes assessed in the trials, mainly the use of only short term surrogate marker results without assessment of long term hard outcomes (e.g. quality of life and/or overall survival).**
- **Most devices were evaluated using prospective cohort data. RCTs were only performed for 6 of the 18 devices. In half of the dossiers, no quality of life data nor functional/patient relevant outcome data were included.**
- **Overall, based on reimbursement dossiers introduced at RIZIV-INAMI the main evidence gaps identified by the assessors concerned**
  1. **Use of a surrogate endpoint without evidence of effect on patient relevant outcomes such as overall survival or quality of life,**
  2. **Use of a comparator in the trials not reflecting usual care or**
  3. **Use of a trial population not reflecting the full target population.**

5 LITERATURE REVIEW

This chapter provides a review of studies published on evidence gaps at market entry in different therapeutic areas of groups of medicines or devices. Publications dealing with a single product were not considered. The articles could focus on the marketing authorisation stage or on the reimbursement decision step or describe the remaining gaps in the post-market phase. In addition, examples of evidence gaps could be identified in the grey literature or be suggested by experts consulted during the project. We consider medicinal products with an added value claim and higher risk devices (class II and III with an added value claim) submitted over the past several years for public payer coverage. The added value claimed by the manufacturer was considered in a broad way for the literature search and the term 'novel' or 'innovative' were assumed to also cover such products.

5.1 Methods

5.1.1 Search strategy

In September 2019, an initial search strategy was developed in PubMed by KH as part of her PhD on medical device safety that included a work placement with KCE. The search strategy combined text words and controlled vocabulary terms (medical subject headings - MeSH) for the concepts of (reimbursement[uuuuuu] OR market approval) AND evidence gaps

[uuuuuu] The search strategy for the reimbursement concept drew on a search strategy developed by KH with help from Isabelle Delaunois, Medical Librarian at University Hospital Limerick, Dooradoyle, Ireland in the context of a rapid review that KH conducted for the Irish Health Technology Assessment Group (HTAG) on collaboration between HTA and procurement.

AND Europe AND medical devices[vvvvv]. (Appendix 8) In December 2019, the search strategy was amended for medicines, combining the concepts of reimbursement AND market approval AND evidence gaps AND Europe AND medicines.(Appendix 9)

Covid-19 interrupted progress but the study recommenced in January 2021 with searches being devised by Nicolas Fairon, Information Specialist at KCE, for the Cochrane Database of Systematic Reviews (CDSR), Cochrane Central, Ovid MEDLINE, and EMBASE databases. (Appendices 2.3-2.4) The searches were later updated and revised by KH and NF to cover the entire period of interest, from June 2011 (the date of the last KCE search for a previous review of this topic) to October 2021, combining the searches for medicines and medical devices into a single search strategy for each of the three databases (Ovid MEDLINE, EMBASE, and the Cochrane Library), thus the final searches combined the concepts as follows: (reimbursement or market approval) AND evidence gaps AND Europe AND (medicines OR medical devices).

In addition, HTA websites were searched using key phrases, and additional ad hoc searches, such as internet searching using key phrases and Google's search engine, were conducted for medical devices since the numbers for inclusion were small. Reference and citation searching of the included medical device articles were also conducted in Google Scholar.

The articles had to be available in English, French, Dutch or German.

5.1.2 Selection procedure

Titles were screened by two researchers independently to exclude those that were out of scope. The final set of search results was screened by just one researcher due to time constraints. Using RAYYAN QCRI, the abstracts were screened independently by two researchers, the results were compared and disagreements discussed until consensus was reached regarding articles for inclusion. This process was repeated for each of the updated search results, until finally 46 articles were selected for inclusion, of which 16 were relevant to medical devices, and 30 were relevant to medicines. In addition, over 60 other articles were found to be relevant for informing the background and discussion to the report. (see table 1).

The initial searches in 2019 identified 1,177 hits (282 for medicines and 895 for medical devices). Subsequent searches focussed primarily on medical devices and these identified 2154 hits across three databases - Ovid MEDLINE (n=1345), EMBASE (n=425, excluding MEDLINE), and the Cochrane Library (n=384; 56 from CDSR, and 328 from Cochrane Central). The final search strategy, which searched for studies relevant to medicines and medical devices identified 4076 hits across all three databases (Ovid MEDLINE, n=2950; EMBASE, n= 783, excluding MEDLINE; and the Cochrane Library, n=343). Citation searching resulted in screening 277 additional titles, which identified 5 additional studies (four for medical devices and one for medicines).

Combining the results of the database searches yielded 7407 hits in total. 2328 duplicates were removed, leaving 5079 titles and abstracts for screening. Overall,128 full texts were selected for screening. 82 full texts were excluded as they did not meet the inclusion criteria (not reviewing evidence at the time of market entry; not focussed on medicines or high risk medical devices; no claims being made for added therapeutic value; the study wasn't focussed on the evidence available for devices/medicines marketed in Europe; or not within the timeframe of interest). This resulted in 46 full texts for inclusion in the review, including the 5 additional studies identified through citation searching.

[vvvvv] The search strategy for the medical devices concept was adapted from a search strategy developed by the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) in the context of a systematic review that they conducted for the WHO on the needs for medical devices of the ageing population, see p.11.

5.1.3 Selection criteria

The inclusion and exclusion criteria for texts to be selected for the review are described in Table 4.

Table 4 – Inclusion and exclusion criteria

Concepts	Inclusion criteria	Exclusion criteria
Population/ Products	A group of new drugs. A group of class IIb and III medical devices.	Not medicines or higher risk medical devices. A single medicine or medical device. In-vitro diagnostic devices.
Intervention/ Interest	At the time of market entry. At the time of the reimbursement decision. Early post-marketing phase.	Post-market period beyond market entry or/and the initial reimbursement time.
Comparator/ Context	European market.	Non-European contexts.
Outcome	Types of study outcomes/endpoints and the quality of evidence available.	Focus is on the evidence available for a single, specific medicine or medical device.
Time period	From 1st June 2011- October 2021	Published before June 2011.
Study design	Review of evidence.	Conference abstracts, individual trials, opinions.

5.2 Overview of the literature on medicinal products

5.2.1 Introduction

The literature search (including updates) identified 28 articles on drugs published between 2011 and 2021. These articles concerned, in most cases, the lack of evidence of the effectiveness of new drugs either at the time of the European Medicine Agency's approval,[9, 65, 67-71] in the first years of the post-marketing phase [13, 72] or at the time of reimbursement or evaluation by HTA bodies.[73-76] Many publications include suggestions for improvement of the relative lack of evidence.

The following table provides an overview of the different articles. They studied, in most cases, anti-cancer drugs [13, 67-69, 71, 72, 75, 77, 78] and orphan drugs .[70, 74] Five articles studied several therapeutic areas.[36, 65, 73, 76, 79-81] Three articles studied medication related to a specific condition, namely multiple sclerosis,[9] Alzheimer's disease[82] and psychotropic medication.[83]

Over the last ten years, the authors made similar observations:

- the evidence on clinical efficacy of medicinal products may be limited at the time they are allowed to enter the market; issues in studies often concern the comparator (lack of an active comparator), the lack of patient-relevant endpoints and their efficacy in patient population subgroups;
- the outcome measure used to justify clinical efficacy is often a surrogate measure lacking validation for the specific class of drugs and indication;
- (costly) medicinal products, often in the field of oncology or orphan drugs, are increasingly benefiting from accelerated marketing approval procedures with the promise of providing post-marketing efficacy results;
- additional required evidence of efficacy may not become available five or even 10 years after approval.

All of these evidence gaps represent a real challenge for HTA bodies having to advise on the reimbursement of these medicines.

The data sources used by the studies were mainly the decisions published by the EMA (EPARs, etc.), HTA reports available on the agencies' websites, clinical trial data available on www.clinical.trials.eu or available in scientific publications.

Our review of the literature is grouped according to a number of topics which were addressed in the publications.

Table 5 – Overview of selected articles on medicinal products

Publications (1st Author, date)	Type of drug or therapeutic area	Aim	Method(s)	Sources	Study period
Ferrario et al. (2015) [79]	Antineoplastic and immunomodulating products	Design a conceptual framework for MEAs and test it by investigating variations in MEAs implementation across countries and over time as well as their governance structures	Comparative analysis	Publicly available data from HTA agencies Survey data from the European Medicines Information Network	2003-2012
Dupont et al. (2011) [74]	Orphan drug	To analyse reimbursement decisions for orphan drugs compared to innovative drugs (focus on the quality of clinical evidence)	Statistical analysis Five point scale parameter 'Service Médical Rendu (SMR)' Qualitative analysis of the clinical evidence in the orphan reimbursement files	RIZIV-INAMI dossiers	2002-2007
Köhler et al. (2015) [65]	Oncology Hepatitis C HIV Acute coronary syndrome Multiple sclerosis Thrombosis after surgery Renal graft rejection	To determine the information gain from AMNOG documents compared with non-AMNOG documents for methods and results of studies available at market entry of new drugs.	Reporting quality assessment (using reporting rates for combined methods and results items)	IQWIG dossiers	2011-2013
Onakpoya et al. (2015) [70]	Orphan drug	to evaluate the clinical effectiveness of orphan drugs at market entry in Europe, determine their annual costs (branded orphan drugs compared to generic ones), and explore any relationships between the prevalence of orphan drugs diseases and annual costs.	Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence Checklist adapted from the Grades of Recommendation Assessment Development and Evaluation (GRADE) criteria	EMA database PubMed, EMBASE, the Clinical Trials database National Electronic Library for Medicines	2002-2014
Winstone et al. 2015 [71]	Oncology	To evaluate the pivotal clinical evidence available in the European Public	Treatments comparison in terms of patient-years (accumulated duration	European Public Assessment Report (EPAR)	2007-2014

		Assessment Report (EPAR) for orphan-designated treatments	of follow-up), the number of patients in the pivotal trials and disease prevalence.		
Liberti et al. (2015) [84]	Oncology	To assess three key properties of endpoints (type of endpoint [hard/surrogate], magnitude of endpoint outcome, and its statistical significance) used in preauthorization trials and whether they are associated with a positive regulatory outcome	Statistical analysis	EMA public assessment reports (EPARs) Withdrawal assessment reports (WEPARs)	2009-2013
Pauwels et al. (2015) [75]	Oncology	To examine the relative importance of different criteria for oncology drugs' reimbursement in Belgium	Multivariate logistic regression	Reimbursement dossiers	2002-2013
Grössmann et al. (2016) [67]	Oncology	To quantify the level of the clinical benefit of oncological therapies at the time of marketing authorisation.	Calculation of the point estimates median OS and PFS (to assess the benefit of new interventions) Calculation of the difference between the control and the intervention arm (to evaluate the clinical benefit of oncological therapies).	Approval documents provided by EMA Assessments from the Austrian Horizon Scanning program	2009-2016
Hatswell et al (2016)[85]	Excluded: generics, biosimilars, vaccines, antimicrobial products, blood products, diagnostic agents or combinations of existing drugs	To evaluate the use of randomised evidence for drugs approved by EMA or FDA.	Check if RCT data available	EMA website and the 'Drugs@FDA' database	1999-2014
Tafuri et al. (2016) [36]	Oncology/immunology central nervous system respiratory system cardiovascular system infectious drugs for blood or blood forming organs alimentary tract and metabolism musculoskeletal system	To investigate the functioning of the parallel scientific advice system and the levels of similarity between EU regulators and the HTA, and between HTAs.	Retrospective qualitative analysis 2 levels of comparison: the answers of the HTABs vs. those of the regulators, and between the answers of the participating HTA agencies.	Minutes of parallel EMA-HTA advice procedures	2010-2015
Bittner et al (2016)[86]	Neurology (multiple sclerosis)	To see if early evaluation of the additional benefits by the Federal Joint Committee (FJC, Gemeinsamer Bundesausschuss, G-BA) has met its goals.	Analysis of dossiers at G-BA	Information submitted to the G-BA	12/2010 - 10/2015

Davis et al. (2017) [13]	Oncology (solid tumours and haematological malignancies)	To determine if data on overall survival and quality of life benefits were available both at time of approval and in the postmarketing period.	Assessment of the clinical value of the reported gains in published studies of cancer drugs (using validated European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)) Evaluation of the magnitude of benefit of drugs	EPARs	2009-2013
Kleijnen et al. (2017) [87]	Oncology	To investigate the role of health-related quality-of-life (QoL) data in relative effectiveness assessments (REAs) of new anti-cancer drugs across European jurisdictions	Retrospective comparative cross-sectional analysis	HTA Guidelines Publicly available assessments produced by HTA bodies	2011-2013
Maignen et al (2017)[37]	Antineoplastic and immunomodulating Agents Cardiovascular system Alimentary tract and metabolism Dermatologicals Musculo-skeletal system Nervous system Respiratory system Systemic hormonal preparations, excluding sex hormones and insulins	to identify the differences between scientific advice procedures of the NICE and the EMA-HTA parallel ones	Mapping of the questions asked by the companies which contain the original clinical development proposals and the summary points highlighted in the NICE advice reports to individual paragraphs of the NICE methods guide to the technology appraisals	Scientific advice procedures undertaken by National Institute for Health and Care Excellence (NICE) Scientific Advice	2009-2015
Blome et al (2017)[88]	All new drugs undergoing early benefit assessment 4 years after introduction of the AMNOG in Germany	to determine methodological requirements for QoL measurement and data presentation in the early benefit assessment in Germany	Qualitative content analysis. a systematic qualitative approach	Documents concerning early benefit assessment publicly available on the G-BA website	2011-2014
Tafuri et al. (2018) [81]	Oncology/immunology central nervous system respiratory system cardiovascular system infectious drugs for blood or blood forming organs alimentary tract and metabolism musculoskeletal system	To investigate the degree of uptake of the recommendations made during such meetings with respect to the primary endpoint and comparator	Rate of uptake of the advice provided by regulators and HTA bodies regarding the primary endpoint and the comparator/s.	Minutes of parallel EMA-HTA advice procedures EU Clinical Trial Register National Institute of Health portal for clinical trials AdisInsight database	2010-2015
Wallerstedt et al. (2018) [78]	Hemato-oncology Oncology	To investigate the clinical and cost-effectiveness evidence underpinning	Systematic review	EPARs Published pivotal studies	2011-2016

		reimbursement decisions of 3 HTA agencies (TLV, SMC and NICE)		TLV, Scottish Medicines Consortium and National Institute of Health and Care Excellence decisions Guidance documents	
Gerardi et al. (2018) [9]	Multiple sclerosis	To assess the evidence of multiple sclerosis medicines at European market entry and investigate if post-marketing research fills information gaps at the time of authorisation.	Descriptive statistics	EPARs Medline Embase Cochrane Library Trial registries	2006-2017
Lexchin et al. (2018) [80]	HIV/AIDS Stroke Cancers (breast, lung, etc.) Relapsed multiple myeloma Chronic myeloid Paroxysmal nocturnal haemoglobinuria Myelodysplastic syndromes Parkinson's disease Central neuropathic pain Clotting disorders Kidney cancer Influenza	To examine the characteristics of the studies that led to the granting of marketing authorisation for certain products that received conditional approval	Cohort study	clinicaltrials.gov PubMed Embase	1998-2017
Naci et al. (2019) [69]	Oncology	To examine randomised pivotal trials of anti-cancer drugs (design, risk of bias, etc.) approved by the European Medicines Agency (EMA)	Cross-sectional analysis	EPARs European Clinical Trials Database: EudraCT ClinicalTrials.gov PubMed	2014-2016
Dekker et al. (2019) [82]	Alzheimer's disease	To evaluate similarities and differences in evidence requirements between regulatory and HTA bodies of Alzheimer's disease approved products.	Data extraction from the HTA reports and from regulatory assessments	European marketing authorisation application dossiers EPARs Assessment reports of NICE and ZIN	2003-2013
Grössmann et al. (2019) [72]	All solid cancer therapies Lymphoid Haematopoietic and related tissue cancer	To review ambiguous benefit-risk profiles' therapies and identify any EMA's post approval updates on median OS 3 years later	Statistical analysis	clinicaltrials.gov EPARs PubMed	2009-2015
Schuster-Bruce et al. (2019)[89]	All drugs approved through EMA conditional marketing authorisation or accelerated assessment	To determine the extent to which surrogate endpoints are used and to assess whether their validity had been confirmed according to published hierarchies.	Literature search for validity of surrogate if identified as the primary endpoint in the pivotal trials	EPARs	2011-2018
Vreman et al. (2019) [76]	Oncology drugs Infectious disease drugs Central Nervous System drugs Ophthalmologic drug	To assess whether the presence or absence of controlled data is decisive in HTA evaluations of CMA drugs	Retrospective analysis of available HTA reports	HTA conclusions of reimbursement dossiers	2006-2016

Vreman 2020 [90]	All drugs	To quantify and compare the uncertainties that regulators and HTA bodies (in Europe and the US) raise during their evaluations of clinical evidenc	Retrospective analysis of available regulatory and HTA reports	EMA and FDA reports; HTA reports of ICER for the US and of two of the four HTA bodies (NICE, IQWIG, ZIN, EUnetHTA) for Europe.	1995-2018
Anderson et al. (2019) [73]	Oncology Hepatology Rheumatology Immunology	To review comparative clinical effectiveness estimates using non-RCT data vs those using RCT data in NICE's appraisals	Comparative analysis	All publicly available guidance documents from NICE	2000-2016
Lasala et al. (2020) [68]	Oncology	To provide an overview of the pivotal trials of cancer drugs authorized for marketing in Europe since 2014	Cross-sectional analysis	EMA website	2014-2019
Grössmann et al. (2020) [77]	Oncology	To identify cancer indications where no information on HRQoL was publicly available at the time of approval by the EMA and monitor HRQoL evidence updates 3 years later	Statistical analysis	EMA website clinicaltrials.gov PubMed [72]	2009-2015
Grössman et al. (2021)[91]	Solid cancer	To study the Magnitude of Clinical Benefit Scale (ESMO-MCBS) and an adapted version for solid cancer drugs	Descriptive statistics	EMA website and literature search	2009-2020
Erhel et al. (2021)[83]	Psychotropic medication	To check the use of an active control arm in trials leading to EMA approval of psychotropic drugs.	Descriptive statistics	EPARs	Until 2017
Farina et al. (2021)[92]	Solid or hematological tumors	Check for presence of RCT, OS as endpoint pre and post-approval	Descriptive statistics	EPAR; for indications without RCTs in the EPAR at the time of first approval also PubMed and SPC search.	2010-2019

Abreviations : MEA: Managed entry agreements; HTA: Health Technology Assessment; HTAB: HTA Body; SMR: Service Médical Rendu'; AMNOG: reform of the market for medicinal products (in German Arzneimittelmarktneuordnungsgesetz); IQWIG: Institute for Quality and Efficiency in Health Care (in German Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen); OCEBM: Oxford Centre for Evidence-Based Medicine; GRADE: Grades of Recommendation Assessment Development and Evaluation; EMA: European Medicines Agency; EPARs: EMA public assessment reports; WEPARs: Withdrawal assessment reports; OS: Overall Survival; PFS: Progression Free Survival; EU: European Union; ESMO-MCBS: European Society for Medical Oncology Magnitude of Clinical Benefit Scale; QoL: quality-of-life; REAs: relative effectiveness assessments; NICE: National Institute for Health and Care Excellence; TLV: The Swedish Dental and Pharmaceutical Benefits Agency; SMC: Scottish Medicines Consortium; ZIN: Zorginstituut Nederland; CMA: Conditional Marketing Authorisation; RCT: Randomised Controlled Trial; HRQoL: Health-related quality of life.

The publications listed in the overview are briefly discussed below. They are grouped by broad themes:

- Evidence gaps at market entry, some papers report a re-evaluation of the evidence in the postmarket-period
- Evidence gaps and considerations for reimbursement decisions
- Need for more collaboration, eg between regulators and HTA bodies
- Use of surrogate endpoints
- Early patient access and conditional marketing authorisation

5.2.2 *Evidence gaps at market entry (and in the post-market period)*

Different methods are used in the publications to assess the lack of evidence of certain drugs at market entry:

Onakpoya et al. (2015)[70] **focused on orphan drugs and effectiveness data available at market entry.** They searched the EMA database for all orphan drugs that had been approved by the EMA between May 2002 and April 2014. For each orphan drug the authors determined the level of evidence available for efficacy using the Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence. The quality and strength of the body of evidence for each orphan drug was then assessed using a checklist adapted from the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) criteria. The authors identified 74 orphan drugs (corresponding to 63 indications) approved by the EMA over a 12-year period. **For none of the 74 orphan drugs was there high-quality evidence of their effectiveness.** Using the GRADE criteria, the overall quality of evidence could be judged moderate for 54 drugs (73.0%) and low or very low for the other drugs. In addition, the authors pointed out that one out of five of the orphan drugs studied could potentially be dangerous because of side effects.

Winstone et al. (2015)[71] focussed on the European Public Assessment Report (EPAR) of **30 orphan drugs approved for the treatment of 41 cancer indications** between 2007 and February 2014. Four drugs were excluded as approval was based on literature only. Five drugs were excluded as only surrogate endpoints (different from PFS) rather than clinical survival-based endpoints had been studied. Of the remaining 21 drugs, 14 were supported by comparative trial data with at least one survival-based clinical endpoint. Eligible treatments were compared in terms of patient numbers in the pivotal clinical trial, duration of follow-up in the pivotal clinical trial and the prevalence of the orphan condition. The quality of the pivotal trials, as assessed by Jadad scores, was moderate. **Overall more than a third of the trials for the orphan drugs reviewed in this study were nonrandomised, and less than 40% were appropriately randomised or blinded.** With one exception of 4068 patient-years, the duration of follow-up ranged from 308 to 2906 patient-years, median 1796 patient-years. The authors noticed that some pivotal trials of treatments for orphan conditions were approved by the EMA despite methodological limitations such as a lack of randomization or blinding, low patient numbers, and a limited follow-up. The authors also warn that these problems had already been raised in a 2006 publication by Joppi et al. (2006).[93]

Hatswell et al (2016)[85] showed that some of the drugs are approved by the EMA or the FDA without any supporting randomised evidence. They analysed drugs (excluding generics, biosimilars, vaccines, antimicrobial products, blood products, diagnostic agents or combinations of existing drugs) approved by the EMA or the FDA between 1 January 1999 to 8 May 2014. Over the period of the study, 76 unique indications were granted without RCT results (44 by the EMA out of 795 approvals and 60 by the FDA out of 774 approvals). Haematological malignancies (34) and other oncology indication (15) accounted for most indications, as well as metabolic conditions (15).

Grössman et al. (2016)[67] checked **all 134 anticancer drug-indication pairs the EMA approved between 2009 and April 2016**. Supportive drug therapies were excluded. Hemato-oncology accounted for 25% of the indications. The authors extracted and quantified clinical benefit using the gain in median overall survival and median progression-free survival. For 37 out of 134 indications (27%), no data were available for PFS nor for OS. A positive difference in median OS between treatment arms was shown for 76 out of 134 indications (55.5%). **Only 22 out of 134 (16%) showed a**

difference in OS of more than 3 months. Note that in six approved indications there was a decrease in overall survival. Regarding PFS, an improvement was shown in 90 out of 134 indications (65.2%). The authors conclude that **for a large number of oncology treatments no valid knowledge about the overall survival benefit was available at the time of approval.** These conclusions confirm the findings of a study published in 2007 by Bertele et al., [94] showing that a third of the haematological anticancer drugs did not have demonstrated added value either due to a lack of robustness of the endpoint and/or for methodological reasons.

Three years after their first evaluation, Grössman et al. (2019)[72] re-evaluated the same oncology drugs to see if new evidence of efficacy had been recorded. The authors sought to examine the availability of **median overall survival data at least three years after EMA approval**. In total, the authors identified 102 eligible therapies that were approved by the EMA between January 2009 and May 2015. Despite the fact that much evidence was generated and published after approval, **the authors still found a lack of information on overall survival in about a third of all identified therapies at least three years after approval.** Furthermore, three years after approval, drugs with a decrease in overall survival had still not been withdrawn from the market. Grössman et al. (2019)[72] confirmed the results of Davis et al. (2017)[13] discussed hereunder.

Davis et al. (2017)[13] performed a systematic evaluation of **approvals of 48 oncology drugs for 68 indications by the EMA in the period 2009-2013**. A drug was judged to have a survival advantage in its indication if, as reported in the EPAR and the study publications, overall survival (OS) was the primary or secondary endpoint in a randomised controlled trial, and if the difference in OS between the experimental and control groups was significant according to a predefined statistical analysis. The authors considered that a drug had shown a benefit regarding quality of life (QoL) for its approved indication when a significant difference was reported using a validated QoL instrument. Almost all the drugs (i.e. 61 out of 68 or 90% of the drugs) were approved for use in a non-curative setting. Yet **none of the pivotal studies supporting the approval of oncology drugs from 2009 to 2013 had used quality of life as the primary outcome measure.** Of the 68 drug indications, 37 included the evaluation of quality of life but this was always as a secondary outcome. QoL results were reported only for 35 out of these 37 drug indications. Only 29 out of 68 (57%) drug indications entered the market with evidence of improved OS orQoL. Eight indications (12%) were approved on the basis of a single-arm study. In 24 out of 68 (35%), there was a significant prolongation of OS, ranging from 1.0 to 5.8 months, median 2.7 months. **For 42% of oncology drugs no OS data were available at marketing authorisation and this was still 28% after a median follow-up of 5.4 years**, ranging from 3.3 to 8.1 years. Of 23 oncology indications associated with a survival benefit that could be **scored with the ESMO-MCBS tool, the OS benefit was judged to be clinically meaningful in less than half** (11 out of 23, 48%). Improvement in QoL was shown in only 10% (7 out of 68) at market entry and this increased post-market to 18% (12 out of 68). A significant improvement in OS or QoL at market entry was shown in 29 out of 68 indications and this increased to 35 out of 68 indications after a median of 5.4 years' follow-up. **This means that for about half of the drug indications on the market for over three years, any improvement in OS or QoL remained uncertain.**

Maignen et al (2017)[37] analysed all the **scientific advice procedures undertaken by the National Institute for Health and Care Excellence (NICE)** between 1 January 2009 and 3 December 2015 for a total of 122 investigational medicinal products, including 27% (44) for antineoplastic and immunomodulating products; 18% (30) for nervous system disorders; 15% (25) for musculoskeletal conditions; 12% (20) for the cardiovascular system; and 8% (14) for the alimentary tract and metabolism. Disagreements with the plans of the companies as discussed in the HTA scientific advice mainly concerned the choice of comparator, the generalisability of the clinical trial evidence to NHS practice and the impact of the clinical trial outcomes on quality of life and survival. It is difficult to assess the extent to which companies are following the scientific advice given by NICE as the study protocols may not be made public in case a drug development is discontinued. Despite the fact that quality of life was the most frequently discussed topic during the scientific advice, for products that later received marketing authorisation **the measurement of quality of life was only reported in 25% of public assessment reports** of the products included in the study. **This suggests that the uptake of the HTA advice by industry remains low. The reasons why companies seek HTA scientific**

advice remain unclear and it could be a strategic move by companies to gauge their likelihood of success and may be part of a longer-term market access and commercial strategy. Of note, the proportion of orphan drugs for which the EMA and/or NICE scientific advice is requested is only about 20% whereas they represent 50% of new drug approvals. It is unclear whether this is related to the company size.

Blome et al (2017)[88] analysed the publicly available Pharmaceutical Market Restructuring Act (AMNOG) documents concerning inclusion of quality of life measures in early benefit assessment performed during the first 4 years (2011-2014). **QoL data were not included in 23 out of 91 benefit dossiers.** Manufacturers often had a wider understanding of QoL than the IQWiG or G-BA and trials had been set-up before AMNOG. As a consequence, there was often a lack of QoL data for benefit assessment**. In only five benefit dossiers, the G-BA stated an added benefit regarding QoL.**

Bittner et al (2016)[86] analysed eight dossiers of new neurology drugs (five to treat **multiple sclerosis**) submitted to G-BA for early benefit assessment under the first five years of the AMNOG law (12/2010 to 10/2015). G-BA concluded that there was an added therapeutic benefit in only 2 out the 8 drugs. The **AMNOG procedure is reported to be quite demanding** in terms of their methodology for accepting quality of life measures, indirect comparisons and analysis of subgroups. The comparator selected for the (indirect) analysis is also questioned.

Gerardi et al. (2018)[9] investigated **new drugs to treat multiple sclerosis**, trying to define their place versus other MS drugs in patient management (based on head to head comparisons) and their role in slowing disease progression (using long term disability outcomes). The authors searched the EPARs, and the publication of pivotal trials, as well as trial registries, for pre- and postmarket RCTs of 8 out of the 10 multiple sclerosis drugs reviewed by the EMA from 2006 to 2017 (after approval of interferon and glatiramer). Two molecules were excluded because they were copies of Betaferon, and laquinimod, a drug that was refused marketing authorisation. The 8 drugs studied were alemtuzumab, daclizumab, dimethyl fumarate, fampridine, fingolimod, peginterferon-β-1a, natalizumab, and teriflunomide. **Out of the 16 pivotal trials, 11 compared the new multiple sclerosis drug to placebo, and 5 to interferon-β-1a.** Annualized relapse rate was the primary outcome in two-thirds and co-primary with disability progression in the 2 studies of alemtuzumab. Of the 52 post-marketing trials, 24 reported final results and 28 were ongoing, terminated, or completed but no results were available. **No trial was published directly comparing the new approved multiple sclerosis drugs, thus leaving their respective therapeutic values unknown.** Data on the prevention of disease progression were scarce. Only 3 RCTs were conducted in people with solely progressive forms of MS. **None of the disease-modifying drugs showed any effect on disability progression.** The authors conclude that the lack of comparative evidence and data on clinical effectiveness hamper the assessment of therapeutic value and their place in therapy of drugs approved for MS. Also in the post-approval phase, placebo was used as a comparator in 34 out of 52 (65%) of the RCTs. It should be no surpise in this case that HTA bodies are struggling to see the therapeutic added value of each drug for relapsing-remitting MS, leading to significant variations in interpretation and acceptance of evidence, as was demonstrated by Visintin et al (2018).[95]

Pilette et al. (2018)[10] report on the **absence of comparative trial results among the four monoclonal antibodies introduced to treat severe asthma** (omalizumab, mepolizumab, reslizumab, benralizumab) and some more being in phase 2/3. **Many treatment questions for clinicians remain unanswered because comparative trials are lacking**, for example,which monoclonal antibody is most effective in which patient. A first (academic) comparative trial has been started. The authors indicate the need for independent multidisciplinary patient-centred clinical research, possibly coordinated by the European Respiratory society. This could be similar to the European Organisation of the Treatment of Cancer initiative for oncology treatment optimization.

Naci et al. (2019)[69] analysed all randomised controlled **pivotal trials of new cancer drugs approved by the EMA between 2014 and 2016** for their design characteristics, risk of bias (using the revised Cochrane tool, RoB 2.0, version 2016), and reporting adequacy. This was based on scientific publications and EPARs. The authors identified 54 pivotal studies performed for 32 new cancer drugs. Of 32 new cancer drugs, 27 entered the European

market with at least one randomised trial. **Of the 27 cancer drugs with randomised controlled trials, only seven were evaluated in trials powered to measure overall survival as a primary or co-primary endpoint. The 54 pivotal studies included 41 RCTs (76%), of which 39 had been published.** Based on the literature review, **around half of the RCTs were at high risk of bias** based on characteristics of their design, conduct, or analysis. Only 10 of 39 randomised controlled trials (26%) evaluated overall survival as either a primary or co-primary endpoint. A high risk of bias was seen in 2 out of these 10 RCTs versus in 16 (55%) out of the 29 RCTs that evaluated surrogate measures of clinical benefit. **There were concerns about missing primary outcome data and the assessment of the primary endpoint.** The content and consistency of reporting varied between the scientific publications and the EPAR. For example, the methods adopted in generating and concealing the allocation sequence were more readily available in the scientific literature than in regulatory documents (n=15). In contrast, major protocol deviations were only explicitly reported in regulatory documents, albeit inconsistently (n=3). In the EPARs additional deficits were described for 10 drugs (31%) that were not reported in the trial publications. These deficits included magnitude of clinical benefit, inappropriate comparators, and non-preferred study endpoints.

Lasala et al. (2020)[68] highlighted that efficacy and safety of new drugs usually must be demonstrated in at least 2 well-controlled studies. The authors evaluated this rule for **pivotal trials of cancer drugs authorized by the EMA between January 1, 2014 and May 31**, 2019. The authors evaluated 38 drugs, 6 of which were classified as orphan, and a total of 96 pivotal trials. **The rule of 2 well-controlled trial was met in just over 50% of authorised medicines.** In cases where there was only one pivotal trial to support authorisation, the trial itself was not necessarily well-controlled: Furthermore, **most trials consider progression-free survival (PFS) as the primary endpoint, less than 30% of trials include OS as a primary endpoint, and less than 40% of trials report quality of life**. This is surprising as anti-cancer drugs aim to increase the life span and the quality of life of the patient.

Grössman et al. (2020)[77] in their 2020 publication studied **anticancer drugs approved by the EMA between January 2009 and October 2015** and assessed available data on overall survival benefit and health-related quality of life (HRQoL). Their article's aim was to identify cancer indications where no information on HRQoL was publicly available at the time of approval by the EMA (and monitor HRQoL evidence updates 3 years later). Among the 110 cancer indications identified, **53% were lacking publicly available information on HRQoL outcomes at the time of approval and at least three years post-approval there was still a lack of published quality of life data in 34 out of 110 indications (31%).** No evidence on median overall survival nor on HRQoL was available at the time of approval in 33 (30%) out of 110 cancer drug indications. After at least three years this was still the case for 15 (14%) out of 110 indications.

Erhel et al. (2021)[83] searched all EPARs and identified 27 approved psychotropic medications until March 2017. For 10 out of 27 drugs no trials with an active control were identified. Of the 17 drugs with active control trials: 5 showed superiority (for 3 this was in a single trial), 8 showed non-inferiority (for 7 this was in a single trial), 3 presented a negative (i.e. non-significant) result and for one drug non-inferiority was based on pooled analyses of different superiority trials. For 20 out of 27 drugs (74%) there was superiority versus placebo in two or more trials.

For 9 drugs an active comparator arm was presented without any comparison with the investigation drug (this was described in the EPARs as 'internal positive control for assay sensitivity'). **"Interestingly, some EPARs presented studies with an active comparator but did not report the results of the comparison, and the CHMP did not consider this evidence in the decision process."** "In fact, most of the approvals were solely based on evidence of superiority against placebo, which appears to be the standard for the EMA. As a consequence, **our meta-analyses revealed that in most of the cases, there was no added benefit with the most recent drugs and some approved doses for some drugs were less effective than those of already marketed drugs**." The authors therefore conclude that in general the evidence for psychiatric drug approvals by the EMA is low, especially when comparative effectiveness issues are considered.

Farina et al. (2021)[92] studied all new drugs and/or new indications for the treatment of solid or hematological tumors approved by EMA in the period 2010–2019. The EPAR database search was completed for indications without RCTs in the EPAR at the time of first approval with a PubMed and SPC search for post-approval randomized studies. Of 199 approvals, 63 (32%) had at least one RCT with OS as the primary or co-primary endpoint. In most cases, OS was included among the secondary endpoints. Of the 40 approvals (20%) not supported by any RCT, 9 (22%) were followed by a post-approval RCT. The authors state "**Our results show that about one of five approved drugs was based on uncontrolled studies and that only 25% of these cases had at least one randomized study after an average time of about 3.6 years from approval."** Recently an issue was raised by Gyawali et al (2021)[16] for oncology drugs approved using FDA accelerated approval and that failed to improve the primary endpoint in post-approval trials. In only 12 of 18 cases (where post-approval studies failed to demonstrate improvement in the primary endpoint) was their subsequent marketing actually discontinued.

Grössman et al. (2021)[91] studied the Magnitude of Clinical Benefit Scale (MCBS) developed by the European Society for Medical Oncology (ESMO) for 144 originator solid cancer drugs and indication extensions that were approved between 1 January 2009 and 31 October 2020 by the European Medicines Agency (EMA). This was done for the version 1.1 of the original scale and a locally adapted version of the ESMO-MCBS that is used by the Austrian Institute of Health Technology Assessment (AIHTA). A meaningful clinical benefit (MCB) was found using the original scale in 48/144 (33%), and in 27/144 (19%) using the adapted scale. Over time there was no significant change in these proportions.

5.2.3 Evidence gaps and reimbursement decisions

The focus of this report is on the identification of gaps for relative evidence, not on the reimbursement decision that is finally taken.

Dupont et al. (2011)[74] analysed the **25 orphan drug files submitted between 1 January 2002 and 31 December 2007** to the Belgian National Health Insurance Agency (RIZIV-INAMI) and compared them with the 117 added therapeutic value drug dossiers for more common but equally severe diseases, with special emphasis on the quality of the clinical evidence. The criteria used by the authors to assess the quality of the trials were: the presence or absence of randomised controlled trials (RCTs) with or without active control, dose-finding studies, clinical and/or surrogate endpoints, adequate trial sample size (taking into account the rarity of the disease), and the presence of long-term safety and efficacy data. According to the authors, the clinical data submitted for orphan drugs leave many questions unanswered regarding long-term efficacy, safety and optimal dosing. At least in some of the cases of orphan drugs, they report that more robust evidence could have been generated. The duration of drug exposure was in most cases far too short in relation to the natural history of the disease. Twenty-two of 25 (88%) submissions for orphan drugs were granted reimbursement as opposed to 74 of the 117 (63%) non-orphan innovative medicines, indicating that the benefits of orphan treatment are valued more highly. **Only 52% of the 25 orphan drug files included a randomized controlled trial** as opposed to 84% in the control group, which was a random sample of 25 non-orphan innovative submissions ($P < 0.01$). **The authors therefore conclude that the authorities deciding on the reimbursement of drugs are prepared to accept a very high degree of uncertainty regarding the clinical efficacy and safety of orphan drugs.** The authors recommend that the evidence gap at market authorisation should be reduced by post-marketing structured programmes, in which the centralised regulatory and the local reimbursement authorities collaborate in an efficient way across the European Union member states.

Köhler et al. (2015)[65] looked at **the impact of the German law/act on the reform of the market for medicinal products (Arzneimittelmarkt-Neuordnungsgesetz, AMNOG) on the completeness of the publicly available information on new drugs.** This German law requires drug manufacturers to submit evidence to the Federal Joint Committee (GBA) to show that their new products are more effective than previous products. GBA generally commissions the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the evidence contained in the **HTA dossier, which should include all reports on all clinical studies.** This information is extracted and integrated in the AMNOG document, creating a novel public source of information, which was compared with the information in other publicly accessible documents such as EPARs, journal publications, and study reports added to trial registries. For that purpose, the authors selected the evaluations conducted by IQWIG between January 1, 2011 and February 28, 2013. A total of 27 files were submitted during this period. Among the 27 dossiers, 15 dossiers contained 22 studies that were eligible for the authors' study. The dossiers concerned different therapeutic areas such as oncology, infectious diseases (hepatitis C and HIV), and multiple sclerosis, amongst others. The data on all the populations studied were very well documented in the AMNOG documents (90%) and a little less in the non-AMNOG documents (75% for elements relating to methods). The authors found similar results for the data on the analysis of sub-populations: the method was detailed similarly (90% in AMNOG documents vs. 75% for non-AMNOG documents). Finally, concerning the reporting of results, while approximately 70% of the results were fully reported in the AMNOG documents, only 11% were fully reported in the non-AMNOG documents. The authors therefore conclude that **data from EPARs, journal publications and registry reports provide insufficient information on new medicines, particularly on relevant patient outcomes in approved sub-populations. The authors, therefore, suggest using AMNOG documents at the international level as a comprehensive publication model for clinical studies**. The authors conclude that EPARs could be improved by paying more attention to the reporting of secondary endpoints and subgroups of relevance for HTA.

Finally, **Anderson et al. (2019)**[73] reviewed technologies appraised by NICE based on non-RCT data from 2000 to 2016 and compared the appraisals with technologies appraised based on RCT data. The aim was to see whether there was a difference in the NICE committee's final recommendation. The authors identified 309 technology assessments comprising 489 individual pharmaceutical products. Of these 489 products, 4% (N=22) representing 20 technology assessments were based on non-RCT data. Methods for establishing external controls in such studies varied: 13 (59%) used published trials, 6 (27%) used observational data, 2 (9%) used expert opinion, and 1 (5%) used a responder vs nonresponder analysis. Only 5 (23%) used a regression model to adjust for covariates. **The HTA recommendation was similar for technologies evaluated on the basis of non-RCT data versus those with RCT data with a NICE decision "recommended"** 10/22 vs 289/467 (45% vs 62%) or "not recommended" 3/22 vs 81/467 (14% vs 17%). According to the authors, the committees explicitly highlighted their **concerns about the clinical evidence of the 22 technologies.** These concerns related to the immaturity of the data and the uncertainty associated with the lack of a direct comparator. Nevertheless, they considered other factors when evaluating technologies with non-RCT data, such as significant unmet need (11/22, 50%), a small patient population (6/22, 27%), and cases when early trials had shown substantial benefit (2/22, 9%). A limitation is that technologies from 2000 to 2009 were missed if NICE considered the comparator arm of some trials to be irrelevant for the decision scope during this period.

5.2.4 Need for more collaboration (e.g. between regulators and HTA bodies)

Different stakeholders are involved in the process of a new drug's arrival: the EMA is responsible for approving most innovative new drugs for the European market, while the national HTA bodies and payers are responsible for the reimbursement of the drug. As Dupont et al. (2011)[74] and Grössman et al. (2016)[67] pointed out, the expectations and objectives of the involved parties are different. Clinicians are interested in the potential benefits of the drug for individual patients and they are also interested in the side effects. The EMA bases its decision to grant a marketing authorisation on the assessment of the quality, safety and efficacy of drugs. Whereas, reimbursement decisions are based on the risk-benefit of the new drug (and the cost) compared to existing treatment options.

A growing number of publications recommend more cooperation between the different stakeholders [13, 36, 67, 76, 82, 90] in order to achieve a better understanding of the perspectives and sustainable evidence-based decisions.

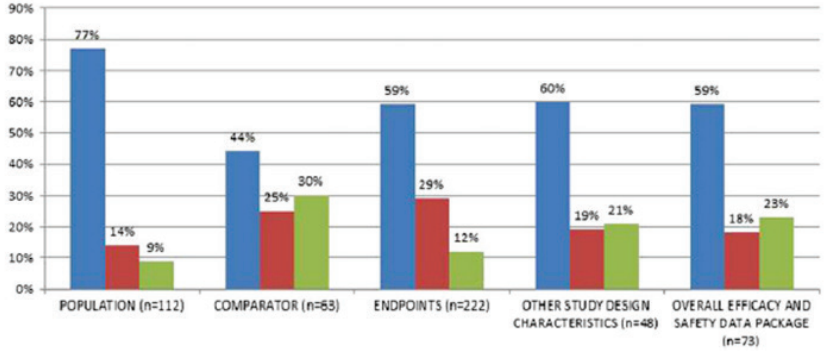
Dekker et al. (2019)[82] compared the EMA assessment reports with the assessments of HTA bodies (i.e. NICE or ZIN) for the marketing authorisation of Alzheimer's disease drugs (donepezil, galantamine, rivastigmine, and memantine). In their article, the authors determined the differences in terms of evidence requirements between the EMA and the HTA bodies for Alzheimer's disease drugs. They observed slight differences: “In the regulatory assessments the focus was on cognitive and global outcomes, and to some extent on function. In the HTA assessments of clinical effectiveness other domains were also covered including: function, behaviour and mood, and, occasionally, quality of life.” The authors believe that reducing the differences in evidence requirements between regulators and HTA/payers would facilitate more efficient drug development and allow faster access to medicines for the patient.

According to Grössman et al. (2016),[67] regulators (the EMA) and HTA bodies represented by scientific institutions should exchange information on their methodology and jointly develop tools at the European level. Some tools already exist to assess the strength of evidence of effectiveness (ESMO, JADAD, OCBME, etc.). It would therefore be appropriate, as proposed by Köhler et al. (2015),[65] to use some of these tools at an international level. Grössman et al. (2016)[67] go further by stressing the need for a systematic tool to assess the benefits of new medicines in a standardised and transparent way. According to Vreman et al. (2019),[76] research has shown that the lack of alignment on evidentiary standards between regulators and HTA bodies has hampered the implementation of adaptive licensing strategies by regulators.

For the last ten years, initiatives have multiplied to encourage collaboration between the EMA and HTA bodies: in 2010 the EMA launched a pilot project on parallel scientific advice, followed by several initiatives such as PRIME in 2016, and the EMA-EUnetHTA parallel consultation in 2017. All of these initiatives enable manufacturers to obtain feedback on their development plan from regulators and also from HTA bodies.[81]

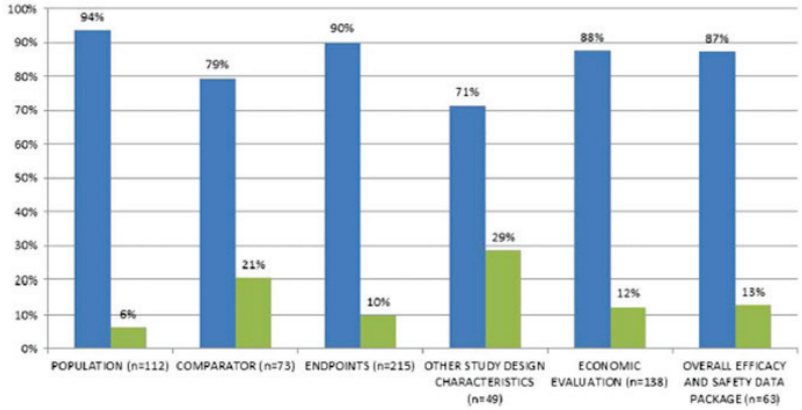
Tafuri et al. (2016)[36] studied the 31 procedures of parallel scientific advice at EMA between 2010, when parallel advice was launched, and 1 May 2015. The authors studied the differences and similarities not only between regulators and HTA bodies but also between the HTA bodies themselves. In particular, the authors focused on the content of the discussions that took place during the final stage of the parallel scientific advice: this is a meeting attended by the applicant, the HTA bodies and the regulators. Multiple health technology assessment bodies participated in one or more meetings: the Italian Medicines Agency (AIFA), the Catalan Agency for Health Quality and Assessment (AQuAS), the German Federal Joint Committee (G-BA), the National Authority for Health (HAS, France), the Main Association of Austrian Social Security Institutions (HVB), the National Institute for Health and Care Excellence (NICE, England), the National Institute for Sickness and Invalidity Insurance (RIZIV-INAMI, Belgium), the Dental and Pharmaceutical Benefits Agency (TLV, Sweden). As illustrated in the **figures** below (copied from Tafuri et al. (2016)[36]) the proportion of partial agreement and disagreement combined were 23% for study population, 56% for study comparator, 41% for study endpoints. The disagreement on study comparator between regulators and HTA bodies illustrates their difference in perspective. The authors also noted some level of disagreement (on the comparartor) between the opinions of the different HTA bodies, in some cases probably reflecting local differences in usual care.

Figure 3 – Level of agreement between HTA bodies and regulators by topic



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

Figure 4 – Level of agreement between HTA bodies



Level of agreement among Health Technology Assessment bodies (HTABs) for each domain (based on 30 procedures). *n* represents the number of multiple comparisons among HTABs expressing an opinion for each domain. agreement disagreement

In a 2018 publication, Tafuri et al.[81] investigated the degree of uptake of the recommendations made during parallel scientific advice meetings with respect to the primary endpoint and comparator. Uptake was tracked using the EU Clinical Trial Register (https://www.clinicaltrialsregister.eu/), the National Institute of Health portal for clinical trials (https://clinicaltrials.gov/) and the AdisInsight database (http://adisinsight.springer.com). The cut-off date for data retrieval was 31 December 2016. The unit of analysis was each individual clinical study for which the advice was sought. In total, the authors assessed 23 studies for the uptake of the advice by the manufacturer with regard to the primary endpoint and 21 studies with regard to the comparator. The advice of regulators and of at least one HTA body regarding the comparator was followed in only 12 of 21 studies. **For the choice of the study comparator, manufacturers seemed to be slightly more inclined to satisfy the regulatory advice (and not the HTA advice).** The authors conclude that parallel scientific advice can facilitate the integration of both regulatory and HTA perspectives into clinical development, potentially reconciling their data requirements. The review by Naci et al(2020)[5] includes a study of drugs approved by the EMA with at least one active-comparator RCT. From 2015 to 2018, this proportion ranged annually between a quarter and one-half. Of course for some new drugs no active comparator may be available.

Wang et al. (2018)[96] studied the evidentiary requirement of regulators and HTA bodies using a survey of stakeholders' perceptions. Both companies and agencies reported the same areas in which divergences were observed and potential alignment could occur: acceptable primary endpoints, inclusion of an active comparator arm in the trial, and the choice and use of surrogate end points. **Company respondents pointed out that the evidentiary requirements from HTA agencies on conditional approvals showed the biggest divergence compared with regulatory requirements.** With regard to the joint scientific advice meetings, **company respondents pointed out that the input was more regulatory-focused and the advice received was diverse rather than an aligned view from both stakeholders.** One should note that since the roles and remits of regulators and HTA bodies are different this difference in advice will remain even if there is better collaboration between the two.

Vreman et al. (2020),[90] studied the variation in clinical evidence assessment between regulators and health technology assessment bodies in the United States and Europe. US and European regulators report uncertainties related to safety for almost all drugs (85–94%), whereas HTA bodies reported these less (53–59%). **HTA bodies raised uncertainties related to effects against relevant comparators for almost all drugs (88–100%), whereas this was infrequently addressed by regulators (12–32%).** Regulators as well as HTA bodies reported uncertainties related to the patient population for 60–95% of drugs. The patterns of regulator-HTA misalignment were comparable between the United States and Europe. The authors indicate that increased coordination between these complementary organisations is necessary to facilitate the collection of necessary evidence in an efficient and timely manner.

Some authors such as Dupont et al (2011)[74] mention the relevance of more **cooperation between the European Commission and the Member States**. The authors suggest that conditional pricing and reimbursement could be linked to the creation of registers of all patients receiving treatment using coordinated efforts within and between EU Member States.

5.2.5 Use of surrogate endpoints

5.2.5.1 Introduction to surrogate endpoints, focus on oncology

Overall survival and patient quality of life are the two most important patient relevant endpoints. Randomised clinical trials in oncology may need a long follow-up period to allow for the assessment of the effect of the studied intervention on overall survival (OS). Treatment effects on OS are diluted by risks of death unrelated to the cancer or related to treatment toxicities. Effects on OS are potentially confounded by the further lines of treatment a patient will receive after failing on the new agent.

For all these reasons, so called surrogate endpoints have been used that are observed earlier, specifically disease-free-survival (DFS) in the adjuvant setting and progression-free survival (PFS) in the advanced disease setting. DFS is defined as the time from randomisation to a cancer recurrence, second cancer, or death from any cause, while PFS is defined as the time from randomisation to the time of progression or death from any cause.

Surrogate endpoints need to be validated for each indication and each intervention. [97] Each time a new drug is introduced having a substantially different mode of action, another prospective evaluation of surrogacy may be needed. As Buyse et al stated, “The more we understand about surrogates, the more we realize how difficult it is to formally “validate” them”.[98]

An association between the potential surrogate and the clinical endpoint is desirable but is not sufficient. What is required to replace the clinical endpoint (OS) by the surrogate (PFS) is that the effect of the treatment on the surrogate endpoint reliably predicts the effect on the clinical endpoint(OS).[98] The surrogate should be biologically plausible and ideally lies on the causal pathway of the treatment effect for the true endpoint.

The most adequate method to validate a surrogate is a meta-analysis of individual patient data from the clinical trials.[97] As recommended by Buyse et al, “When data are available from several trials, one can additionally assess the "trial level association" between the treatment effect on the surrogate and the treatment effect on the true endpoint. In the latter case, the "surrogate threshold effect" can be estimated as the minimum effect on the surrogate endpoint that predicts a statistically significant effect on the clinical endpoint.”

In general, the quality of studies evaluating the surrogacy of PFS and their reporting can be improved. In addition, the surrogate threshold effect is often poorly reported. A systematic review found 91 studies evaluating the validity of PFS as a surrogate for OS in 24 cancer localisations. Only half of studies concluded on the validity of PFS as a surrogate for OS. However, among these, for 15, this conclusion was not supported by the results, with no quantitative argument in favour of surrogacy given. Therefore, the interpretation of the results of surrogacy studies should be made with care. [97] Belin et al. (2020) made the sobering conclusion, **“A mapping of the localisations and treatments for which PFS has been validated as a surrogate for OS would help in planning future trials. Unfortunately, this mapping is currently not possible because of the heterogeneity of methods used.”**

This study confirmed the conclusions by Ciani et al. (2014)[99] who found in a systematic review of solid tumors that according to IQWiG's framework, only PFS achieved acceptable evidence of surrogacy for OS in metastatic colorectal and ovarian cancer treated with cytotoxic agents.

Making abstraction of the methodological challenges and as an example, Gyawali et al. (2020)[100] searched correlation studies of surrogate measures of OS for breast cancer, in particular the endpoints FDA considered appropriate for accelerated or regular approval: event-free survival (EFS), disease-free survival (DFS), objective response rates (ORR), and progression-free survival (PFS), and in addition, pathological complete response rates (pCR) which was listed as appropriate only for accelerated approval. (https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure) The results from correlation studies evaluating pCR, DFS, ORR, and PFS suggest that the treatment effects on none of these surrogate measures were strongly correlated with treatment effects on OS ($r<0.85$ or $R2 < 0.7$), except for DFS in HER2 positive early breast cancer ($R2 = 0.75$).

Can PFS be considered as a surrogate for quality of life? In addition to OS, one may wonder if PFS could be considered a surrogate of quality of life. Hwang et al. (2019)[101] checked the association between PFS and quality of life for the phase III clinical trials of drugs for advanced or metastatic solid tumors published between 2010 and 2015. QoL was included as an endpoint in 190 out of the 352 trials (54%), but reported only for 147 of 190 trials (77%): 106 (56%) in the main paper, 36 (19%) in a subsequent publication, or 5 (3%) in a conference abstract. For the trials with QoL reported, the overall trial-level correlation between positive PFS and positive quality of life was of low strength ($r = 0.34$). The hazard ratio for PFS was not a strong predictor of positive quality of life (AUC, 0.72; 95% CI, 0.59–0.84). The association between PFS and improvement in any domain of quality of life was also weak.

In general, Dawoud et al. (2021)[102] have argued for a more selective use of surrogate endpoints when evaluating new drugs, restricting their use to chronic diseases, especially when collecting data on patient relevant clinical outcomes requires trials with unattainably long follow up.

5.2.5.2 *Surrogate endpoints in the publications selected*

Surrogate endpoints are more and more used in clinical trials for regulatory approval of new drugs, whereas they do not reliably predict clinically meaningful outcomes such as overall survival or quality of life .[13] Indeed, according to Wallerstedt et al. (2018),[78] the validity of the pivotal studies is hampered in particular by the use of surrogate primary outcomes.

Despite the EMA's statement that overall survival is the most convincing outcome for studies of the clinical safety and efficacy of new oncology medicines and new uses of its medicines, European regulators generally accept the use of surrogate endpoints of benefit as the primary endpoint in pivotal trials for both the conditional and regular routes to market authorisation .[13] Indeed, according to Grössman et al. (2016),[67] progression-free survival (a surrogate endpoint for overall survival) is one of the most commonly used endpoints in cancer clinical trials.

In the Davis et al. (2017)[13] study, the authors report that recent studies in the United States have shown that only a small proportion of cancer drugs approved by the FDA improved survival and/or quality of life. In the same way, most of the new cancer drugs approved by the EMA in 2009-2013 came to market without clear evidence that they improved overall survival or quality of life for patients. In the Dupont et al (2011)[74] study, which evaluated efficacy data submitted at the time of marketing of orphan drugs, in half of the cases, the main parameters were surrogate endpoints with very little evidence of benefit for clinical outcomes.

Schuster-Bruce et al. (2019)[89] studied the use of validated and nonvalidated surrogates as the primary endpoint in 26 EMA conditional marketing authorisations and 25 accelerated assessments. Half of the indications were in oncology. Five products (10%), all accelerated assessments, were authorised based on pivotal trials reporting clinical outcomes, and 46 (90%) were authorised based on surrogate endpoints. According to the published hierarchies the surrogates were 'reasonably likely' (n = 30; 61%) or had 'biological plausibility' (n = 46; 94%) to predict clinical outcomes. The EPARs did not, however, consistently explain whether surrogate endpoints were validated or not, or describe the endpoints to be reported in the confirmatory postmarketing studies. The authors conclude “EPARs and summary product characteristic documents, including patient information leaflets, need to state consistently the nature and limitations of endpoints in pivotal trials supporting expedited authorisations so that prescribers and patients appreciate shortcomings in the evidence about actual clinical benefit. For products supported by nonvalidated surrogate endpoints, postauthorisation measures to confirm clinical benefit need to be imposed by the regulator on the marketing authorisation holders.”

5.2.6 *Early patient access, conditional marketing authorisation and managed entry agreements*

Vreman et al. (2019)[76] focussed on drugs with **EMA conditional marketing authorisation (CMA)**. In particular, the authors assessed the 92 HTA recommendations by five HTA bodies for such drugs by the type of studies available in the dossier (presence of controlled studies or not). Of the 30 CMA drugs approved by the EMA until June 2016, 27 were included in the final analysis. Two drugs were excluded because the CMA was withdrawn by the marketing authorisation holder, and one product was excluded because it was not assessed by any of the five HTA organizations. Five HTA jurisdictions were included: NICE for England; HAS for France; IQWIG for Germany; SMC for Scotland, and ZIN for The Netherlands. **Common evidence limitations identified for CMA drugs were the use of surrogate end points and uncontrolled studies.** The HTA recommendations were categorized into positive, restricted, and negative. Thirty of 62 (48%) and 17 of 30 (57%) of the recommendations were negative for drugs with and without controlled studies, respectively. **Reasons for negative recommendations were for economic (i.e. price), clinical, or organisational reasons.** In all jurisdictions, the proportion of negative recommendations was rather similar for drugs with or without controlled data. This suggests that the presence of controlled data is not the only decision-making factor in these HTA evaluations and that expedited regulatory pathways may not always lead to earlier patient access. The authors conclude **“Earlier collaboration between stakeholders is advised in order to improve patient access.”** To ensure adequate patient access to novel drugs, manufacturers, HTA bodies, and regulators should collaborate more efficiently early on during drug development in order to improve the alignment of evidence generation strategies so as to satisfy both

regulatory and HTA evidence requirements. The parallel consultations, in which manufacturers can engage in scientific advice from the EMA and multiple HTA institutions in parallel, may provide such a platform that would help to ensure a better aligned vision on which data are necessary for market authorisation and reimbursement.

Some diseases do not have effective drug treatment. This is, for example, the case for certain orphan diseases. As a result, there is a very high expectation from patients' associations and physicians as to the arrival of a drug. The drug may obtain an accelerated marketing authorisation even if there is not enough information on its efficacy and safety. Measures such as managed entry agreements (MEA) and value-based pricing are options that are increasingly being implemented to facilitate access to new therapies in the face of uncertainty and to enforce pricing rules.[67] In addition to accelerated authorisation strategies, two other pathways allowing early and, therefore, faster access to patients have been introduced by the EMA: adaptive pathways and Priority MEDIcine.[72]

Ferrario et al. (2015)[79] analysed the case of 3 countries (Belgium, England and Sweden) which have implemented the process of 'managed entry agreements' (MEAs). The authors included in their analysis all the MEAs existing since the date of implementation of the first official MEA in each country until December 2012. The authors found a decrease in MEAs in the Netherlands between 2008 and 2011, while Belgium and England continued to increase their MEAs between 2010 and 2012. In Belgium, the MEAs have been the subject of a KCE report .[103] The report showed that **in Belgium the use of MEAs has increased over time and is no longer exceptional.** The lack of transparency of MEAs has disadvantages however, and hampers the conduct of health economic evaluations. In particular health economic comparisons with products under a MEA become impossible if the correct healthcare payer cost of that product cannot be made public. A more recent overview of MEAs, again illustrating their impact on budget rather than on comparative evidence generation is provided in a 2019 OECD report.[104]

Key Points

- **Medicinal products are mainly regulated at EU level whereas HTA bodies and payers operate at member state level. In many cases the clinical evidence that was sufficient to obtain marketing authorisation is considered incomplete by HTA body standards, leading to uncertainties for the reimbursement decision.**
- **Compared with regulators, HTA bodies and payers want to see pivotal trials with overall survival and quality of life as endpoints (instead of non-validated surrogates) and with usual care as direct active comparator. According to industry, this divergence in viewpoint is most pronounced in the case of conditional regulatory approvals.**
- **Efficacy and safety of new drugs usually must be demonstrated in at least 2 well-controlled studies. The rule of 2 well-controlled trials was met in little more than 50% of authorised medicines. More alarming for HTA is that annually (2015 to 2018) half to three-quarters of the new EMA approved drug dossiers do not include any active-control trial.**
- **Only 16% of the new anticancer drugs showed an overall survival gain of at least 3 months. For 42% of oncology drugs no overall survival data were available at marketing authorisation and this was still 28% after at least three years of follow-up. Improvement in quality of life, also of importance, is only reported in 10% of the oncology dossiers. For about half of the oncology drugs on the market, for a median of 5 years, it is still unknown whether there is any benefit in overall survival or QoL.**

- **Similarly, high quality evidence is lacking for orphan drugs at market entry, but also when assessed many years after marketing. Methodological limitations often relate to a lack of randomisation or blinding, low patient numbers and limited follow-up.**
- **Expedited regulatory pathways have lead to smaller, shorter and less cost-intensive trials, and an increasing use of surrogate primary endpoints. About half of the conditional marketing authorisation dossiers received a negative HTA recommendation for reimbursement, citing not only clinical evidence but also pricing and organisational reasons. Clinical uncertainty concerns the use of surrogate end points and uncontrolled studies. Conditional marketing authorisation may, therefore, not lead to earlier reimbursement and patient access.**
- **As the evidentiary requirements of regulators differ from those of HTA bodies and payers, and as there may be differences in usual care between member states, Vreman et al. (2019)[76] proposed that regulators and the different HTA bodies need to better align their evidentiary requirements before having a parallel scientific advice meeting with industry.**
- **In addition, Dupont et al (2011)[74] state that alignment of post marketing data collection is needed between the regulatory (EU) level and reimbursement (member state) level.**
- **Köhler et al. (2015)[65] found that the reporting of trial results may be incomplete and that the AMNOG documents in Germany provide more complete trial results.**

5.3 Overview of literature on medical devices

5.3.1 Introduction

In Europe, the regulatory framework for medical devices, including high risk medical devices, differs greatly from the regulatory framework for medicinal products, and it also differs greatly from the FDA's approach to regulating medical devices in the United States. The issues associated with high risk medical devices have been the subject of two previous KCE reports and related papers[32, 105] They particularly addressed the lack of sufficient evidence for HTA purposes when a device is CE marked as well as the lack of evidence transparency. In contrast to medicinal products, under the medical device directives there was no legal obligation to register device trials. As there may be aspects that are specific for medical devices (e.g. a learning curve), a stepwise introduction of innovative devices has been proposed.[105]

Compared with medicinal products there are fewer publications analysing the premarket evidence of groups of medical devices in Europe. In contrast to the EPARs, often used as starting point for studies on medicinal products, there is no such public document available yet (awaiting EUDAMED) that summarises the clinical studies when a medical device enters the European market.

The articles on MDs concerned cardio-vascular devices,[106], orthopedics, surgery [107], urology [108] or several areas .[19, 42, 109, 110]

All articles started from the same observation: that despite the lack of evidence of clinical efficacy, MDs are entering the market. As a result, several unsafe and/or ineffective devices had to be withdrawn from the market. All authors raised similar issues that could explain the lack of evidence of effectiveness of MDs:

- absence of clinical studies when reference is made to an equivalent device and problems in interpreting the equivalence of MDs
- a poor methodological quality of clinical studies with a low level of evidence

- safety and performance are being assessed instead of efficacy/effectiveness
- a lack of transparency in trial registration and publication

Table 6 – Overview of selected articles on medical devices

Publications (1st Author, date)	Therapeutic area	Aim	Method(s)	Sources	Study period
Huot et (2012)[111]	Implantable medical devices, several areas	This study aimed to ascertain the level of evidence available for implantable medical devices (IMDs) access to reimbursement in France.	Review of evidence contained in 'opinions' published by the Commission Nationale d'Evaluation des Dispositifs Médicaux et Technologies de Santé (CNEDIMTS) following assessment of evidence for new medical devices for 'sufficient expected benefit'	102 CNEDIMTS 'opinions' on applications for reimbursement of new (previously unlisted) medical devces	2008
Kynaston-Pearson et al. (2013)[112]	Orthopaedics	To determine the extent to which prostheses with no readily available evidence to support their use are being implanted in primary total hip arthroplasty.	Systematic review	PubMed, Cochrane, Embase, OVID, and Google databases	2011
Boudard et al. (2013)[42]	Cardio-vascular disease Orthopaedic surgery Digestive surgery Thoracic surgery Plastic and reconstructive surgery Gynaecologic surgery	To quantify the level of evidence available for innovative medical devices in the context of hospital-based HTA	Screening and classification of the clinical studies according to the Sackett 5-point level-of-evidence scale	Medline, Embase and Cochrane Library databases	2008-2012
Nieuwenhuijse et al. (2014)[113]	Orthopaedics	To determine the evidence of effectiveness and safety for introduction of five recent and ostensibly high value implantable devices in major joint replacement to illustrate the need for change and inform guidance on evidence based introduction of new implants into healthcare.	Systematic review and review of FDA documents and registry reports	PubMed (Medline), Embase, Web of Science, Cochrane Library, CINAHL and Academic Search Premier. Reference lists of trials and reviews were assessed for additional studies. FDA summaries of safety and effectiveness of PMA trials and FDA-mandated PMS studies. Orthopaedic registry annual reports and studies	Search up to April 2014

Wild et al. (2014)[106]	Cardio-vascular disease	Analyse the differences between Europe and USA in dealing with risks and benefits of new cardio-vascular devices	Comparison between EU and US data	Data from Austrian pre-reimbursement assessments. Clinical data available at time of market approval by FDA in the USA.	2008-2014
Sauerland et al. (2014)[107]	Surgery	Provide an overview of the latest developments in the regulation of medical devices and give recommendations on how surgeons can make the best use of medical devices, while avoiding potential harm or liability issues.	Recommendations review	Literature search	2010-2013
Krüger et al. (2014)[109]	Pulmonology Cardiology Orthopedics Ophthalmology Oncology	Explore the authorisation and reimbursement processes and associated evidence requirements for high-risk medical devices in four regions: Europe, the United States, Australia and Canada.	Case studies	publicly available summaries of the authorisation agencies Controlled Clinical Trial Database Information from HTA and reimbursement organizations	2013
Kisser et al. (2016)[114]	Several areas	To analyse which factors impact MD reimbursement decisions within the Austrian appraisal programme on “extra medical services” (procedures reimbursed in addition to case flat rates) for inpatient care over the past eight years.	Review of evidence contained in medical device appraisals conducted by LBI-HTA for the in-patient medical device additional reimbursement, “Medizinische Einzelleistungen” (MEL), list	78 appraisals covering 59 medical devices (includes 19 updates on the same device groups)	2008-2015
Garfield et al. (2016)[115]	Molecular diagnostics	Review diagnostic-specific HTA programs and identifying elements representing common and best practices.	Representative case studies of test evaluations	Published HTAs on molecular diagnostics	2013
Chaverri-Fierro et al. (2017)[116]	Orthopaedics, hip replacement	To assess the evidence supporting the use of implants used in Catalonia for primary total hip replacement	Orthopaedic Data Evaluation Panel (ODEP) database review and a literature review for implants not recorded in ODEP	ODEP, TRIP Database, PubMed, and Google Scholar	2005-2013
Samaniego Alonso et al. (2018)[117]	Orthopaedics, knee arthroplasty	To assess the evidence supporting the use of implants used in Catalonia for knee arthroplasty	Orthopaedic Data Evaluation Panel (ODEP) database review and a literature review for implants not recorded in ODEP	ODEP, literature search	2005-2013

Olberg et al. (2017)[19]	Several areas	Examine the scientific evidence on clinical effectiveness and safety used in HTAs of high-risk MDs in Europe	Extraction of key informations on the clinical evidence considered in the reports (methodologic principles from Drummond's framework)	HTA reports	2010-2015
Chapman et al (2017)[118]	gastrointestinal surgical practice	To check novel implantable devices available for use in gastrointestinal surgical practice	Presence of RCTs and risk of bias, region where marketed, stage in IDEAL framework.	Searches of online catalogues from device manufacturers present at major gastrointestinal conferences held during 2013 or 2014. Then the authors searched the literature and registries for trials supporting these devices.	2013-2014
ANSM (2018) [119]	Urology	To gain an overview of urological mesh implants on the French market by obtaining technical and clinical evaluation data for those devices from economic operators, and analysing device withdrawals from the market	Surveyed economic operators supplying the French market for clinical evaluation, technical, vigilance and sales data.	Dataset of 21 economic operators supplying surgical mesh for urinary incontinence or pelvic organ prolapse created from French medical device suppliers database, manufacturers' websites, advertisements, and data from specialists' conferences.	2014-2017
Te Brummelstroete et al. (2019)[108]	Urology	Review scientific evidence of pelvic floor devices for women	Literature review	Annual meetings abstracts analysis and literature search	2016 and 2017
Sauerland et al. (2019)[110]	Several areas	Assess the methodological quality of premarket clinical studies performed on medical devices (MDs) in Europe	Retrospective cross-sectional analysis	MD study applications requiring approval by an ethics committee and the competent federal authority	2010-2013

5.3.2 The selected publications

Huot et al. (2012)[111] analysed the 'opinions' of the **Commission Nationale d'Evaluation des Dispositifs Médicaux et Technologies de Santé (CNEDIMTS)**. Opinions are issued publicly following the assessment of clinical evidence on new (not already listed) implantable medical device (IMD) applications for reimbursement from the French Health insurance system. They provide information on the level of evidence available at reimbursement. CNEDIMTS assessments are based on the evidence submitted by applicants for reimbursement and 'in-house' literature reviews. Opinions are device and indication specific, thus changes to the device or the indication require another application, and applications to remain on the list must be made every five years. The assessment of the clinical benefit, the efficacy/safety ratio, and the public health benefit of the new IMD when compared with the current standard of care are summarised, and each application is categorised into one of two categories, namely insufficient or sufficient 'expected benefit' (EB). Sufficient benefit is further categorised into five levels of 'improved expected benefit' (IEB), with levels I to V being major, significant, moderate, minor, and no improvement respectively. The authors extracted the study with the highest level of evidence of efficacy provided in each 'opinion' issued by CNEDIMTS, (whether it was specific or non-specific to the device), and categorised each according to their study design, number of included patients, number of study sites, and the significance of the results. Studies were also categorised into four levels of evidence (1: meta-analysis of randomised controlled trials (RCTs); 2: RCTs; 3: non-randomised comparative studies; 4: non-comparative studies (i.e. meta-analysis of non-comparative studies, prospective observational registries, prospective case-series, and retrospective case-series). Applications were categorised into new (which included first and subsequent new applications, where there was insufficient EB at first application) or renewals (demonstrating the observed benefit). Devices were categorised into into six levels of expected benefit (i.e. insufficient EB, and IEB I-V). **The authors reviewed 102 opinions covering 93 IMDs, 79 of which were considered to have sufficient benefit**. Two thirds of the opinions were issued on first new applications (n=67), 21 of which were deemed to have insufficient EB, despite the median time from CE marking to a first new application opinion being five years. Only one device was deemed to be IEB level I, and its highest level of evidence was an RCT with 40 participants. Less than half (28/79) of the applications were supported by RCTs or meta-analyses. Twenty-nine percent (30/102) of opinions did not include a clinical study, and for the 72 that did, half of the device applications were supported by two or less clinical studies. For those clinical studies (72) that were considered to be the highest level of evidence for a particular device, 27 were studies of a predicate rather than of the device itself (previous model, n=15; similar device, n=12). Of the 30 opinions that contained no clinical studies, for 16 the highest level of evidence was 'expert-based analysis', 9 were based on a previous opinion (deemed to be IEB level V), and 5 reported no data (4 rated as having insuffient EB and one as IEB level V). Overall, 23 were judged to have insufficient EB, 50 no improvement, and 15 minor improvement in EB, comprising 86% (88/102) of all opinions. The authors conclude that **"[t]his study confirmed that level of evidence of clinical evaluation of IMDs is low and needs to be improved, since less than half of clinical studies with the highest level of evidence assessed by CNEDIMTS in 2008 were RCTs or meta-analysis of RCTs."** The authors recommend that **clinicians and authorities collaborate with small-to-medium firms** to investigate **"the determinants and the solutions needed to improve quality of clinical evaluation of medical devices"**.

Kynaston-Pearson et al. (2013)[112] reviewed the **National Joint Registry's (NJR) 9th annual report** to identify primary hip replacement prostheses implanted in 2011 that had an Orthopaedic Data Evaluation Panel (ODEP) rating of pre-entry (i.e. less than three years of evidence of any kind) or was unclassified (i.e. no evidence had been submitted by manufacturers to the ODEP database for comparison against specific revision rate benchmarks), identifying 118 (45%) such implants (femoral stems or acetabular cups). They conducted **a systematic literature review** of those prostheses, searching PubMed, Cochrane, Embase, OVID, and Google databases, and identified 157 relevant papers. These were categorised by the level of evidence they contained according to the simplified Oxford Centre for Evidence-Based Medicine evidence levels (i.e.1a: Systematic reviews of RCTs; 1b: Individual RCTs; 1c: All or none RCTs; 2a: Systematic reviews of cohort studies; 2b: Individual cohort study or low quality RCTs; 2c: Outcomes' research; ecological studies; 3a: Systematic review of case-control studies; 3b: Individual case-control study; 4: Case series; 5: Expert

opinion without explicit critical appraisal/pre-clinical biomechanical data), and identified the highest available level of evidence for each device. They contacted manufacturers where no evidence was identified requesting evidence, and any that was received was also rated according to its evidence level. They found that 48% (57/118) of these implants had no evidence of clinical effectiveness, which accounted for 10,617 prostheses, 8% of all primary hip replacements implanted in 2011. The authors conclude that "**This study shows that the need still exists for an improved and more rigorous approach to regulation of devices to avoid devices with no available evidence being used in a widespread and uncontrolled manner."**

Boudard et al. (2013)[42] analysed **the published clinical data supporting 32 innovative medical devices requested for hospital use by surgeons or clinicians at a single university hospital in France during the period 2008-2012 period**. Overall, 28 out of the 32 (87.5%) innovative medical devices belonged to the high-risk classes (IIb and III). The authors classified the level of evidence of clinical studies into 4 categories, referring to Sackett et al. : cat 1: RCT; cat 2: prospective non-randomized studies with some control group; cat 3: other prospective studies; cat 4 : retrospective studies and cat 5 : case report. Cat 1 and 2 were considered by the authors as high quality data. This can be considered optimistic as it is difficult to show evidence of efficacy or effectiveness, or added value, using a non-randomized design. Clinical studies with a level of evidence of 3, 4 or 5 were considered to have poor-quality data. Among the 215 trials supporting the 32 innovative medical devices, 33 were RCTs (15%). Two RCTs were conducted for the 6 class IIb devices and 27 RCTs for the 22 class III devices. The report unfortunately does not specify the number of devices for which RCT data are available. Another 14 trials (7%) were prospective non-randomized controlled studies. Overall, 47 clinical studies (22%) were considered to provide high-quality data. Only 18% of the clinical studies relating to high-risk medical devices provided high-quality data. The authors state **"Our results suggest that the level of evidence does not necessarily increase with the level of risk and that the clinical evidence used to demonstrate safety and efficacy for high-risk medical devices is actually based on clinical studies with poor-quality data."** Among the 47 RCTs and non-randomized controlled studies, only 30% reported on missing data and 39% reported on sample size calculation. For the primary outcome, 29% of the prospective randomized controlled studies and 89% of the prospective nonrandomized comparative studies had more than one primary outcome or no primary outcome. For implantable medical devices, 84 studies (71.8% of the total) specified the follow-up period. The mean follow-up period was 18.9 months, which the authors considered very short given the long duration of use of such devices. Only few articles reported on the learning curve or the volume–outcome relationship. As the directive did not really define the criteria to be used to determine equivalence, the authors reported difficulties with the interpretation of equivalence for several of the medical devices studied.

Nieuwenhuijse et al. (2014)[113] **selected five innovative hip and knee replacement prostheses in widespread use**, each with a reference safety benchmark and with good reason to expect additional clinical benefit over standard treatment, in order to conduct a **systematic literature review** to assess the evidence supporting their use. They identified 118 studies (94 unique cohorts) across six databases comparing the selected devices with a relevant alternative that assessed functional or patient-reported outcomes. They assessed study quality based on the CONSORT, STROBE, or Cochrane criteria (though they didn't provide details on how they did this), rating it as low (high risk of bias), low to moderate, moderate, moderate to high, or high (low risk of bias) quality. They used registry data to assess implant survival and complication rates, and the clinical study data to assess effectiveness. The authors concluded that **"new technologies are being introduced to the commercial market without sufficient high quality evidence for improved benefit over existing, well proven, and safe alternative implant solutions. Furthermore, the safety of several new technologies could be (substantially) compromised. Combined with recent disasters, we advise that actions should be undertaken by all stakeholders to prevent patients from being further exposed to new device related technologies without proper evidence of improved clinical benefit and safety."**

Wild et al. (2014)[106] investigated **27 newly CE approved medical devices used for ten cardio-vascular interventions identified using Austrian pre-reimbursement HTA reports (2008 to 2014).** The authors compare the

situation in Europe with the US and challenge the argument that earlier provision of new devices is always of benefit to the patient. They graded the clinical evidence using the Oxford Centre for Evidence-based Medicine hierarchy: level 1 is SR (systematic review) or MA (meta-analysis) based on several high quality RCTs (randomized clinical trials); level 2: at least 1 RCT of high quality; level 3: controlled trials without randomisation; level 4: prospective case–control and cohort studies; and level 5: case reports and retrospective case series.

- For 12 of the 27 devices introduced for reimbursement in Austria at least one RCT had been performed.
- For one device (CYPHER® Select), marketing was discontinued in Europe. A large group of 12 CE marked cardio-vascular devices are neither PMA approved nor hold (yet) an investigational device exemption (IDE) allowing trials to be conducted for FDA. This means that they are produced solely for the European market or that the IDE will be applied for at a later stage.
- For about half of the devices marketed in Europe (14 out of 27), an IDE allowing trials under FDA regulations had been obtained. However, for 4 out of these 14 devices the FDA market application or the approval-trial was either suspended due to efficacy or safety concerns (Cotovance™, Ventana™, Symplicity™), or market authorisation was denied (Watchman®). For three devices the trials under IDE were still ongoing. Finally, only 7 out of the 27 CE-marked devices had obtained FDA market approval (6 PMA, 1 HDE) about 3 to 7 years after receiving a CE mark.
- Note that some additional medical devices in this field obtained a CE mark but were not included in the analysis set of 27 devices as they posed problems before the start of the pre-reimbursement assessment. Such devices include ProRhytm® and HD Mesh Ablator® for the treatment of atrial fibrillation.

Including these two cases would yield a proportion of **24% (7 out 29 cardio-vascular devices) with clear issues after being CE marked versus a similar proportion of 24% of medical devices that succeeded to pass the FDA hurdle** for safety and effectiveness. Only for 3 out of the 15 remaining devices are trials ongoing to obtain FDA approval.

The findings reported by Wild et al. (2014)[106] are in agreement with the 2012 FDA report entitled “Unsafe and Ineffective Devices Approved in the EU that were Not Approved in the US” (https://kce.fgov.be/en/news/market-introduction-of-high-risk-medical-devices-in-the-eu-vs-us-0)

Sauerland et al. (2014)[107] lists the highest level of evidence available for **16 new medical devices on the market in Europe and used in surgical indications**. The method to assess the level evidence is not detailed. For 7 out of 16, no RCTs had been performed and for all 7, the conclusion on effectiveness was unclear. **For the 9 cases with RCTs performed, only one showed minor advantages in effectiveness, for three there was no relevant difference in effectiveness and the effectiveness, remained unclear for the other 5 cases**. Moreover, the authors highlighted the fact that **follow-up products just have to demonstrate equivalence in order to enter the market.**

Krüger et al. (2014)[109] analysed the **authorisation and reimbursement processes and associated evidence requirements for high-risk medical devices in Europe, USA, Australia and Canada**. Performing a literature search, they selected seven high-risk medical devices as examples in the areas of Pulmonology, Cardiology, Orthopedics and Ophthalmology. The authors observed that there were major differences in the approval of MDs between Europe and the USA: **some devices, which are considered either unsafe or not effective for the market in the United States, may be legally marketed two to three years earlier in Europe.**

Kisser et al. (2016)[114] reviewed the **medical device appraisals conducted by LBI-HTA over eight years (2008-2015)** to inform the addition or retention of a device on the “Medizinische Einzelleistungen” (MEL) list, which authorises additional payments to the hospital for the device on top of the DRG-based procedure fee. For those devices that receive a ‘preliminary rejection’ decision based on the identified gaps in the evidence the appraisal report contains a description of the rationale and the evidence reviewed. Appraisal reports on generic device classes were considered to be ‘one’

device, except where there were subgroups of devices that had different mechanisms of action, in which case they were considered to be separate devices. Data were extracted and categorised according to the study characteristics, the level of evidence presented regarding efficacy and safety (controlled or uncontrolled; non-inferiority, equivalence, or superiority)), device characteristics, population characteristics, assessment year, recommendations made by the LBI-HTA, and the reimbursement decision made. 78 appraisals covering 59 medical devices (which includes 19 updates on the same device groups) were reviewed. Of these 59 devices, 32 had no RCTs, 57 had no NRCTs, with 26 having 2 or fewer case series. Devices belonged to classes IIa (n=1), IIb (n=36), and III (n=22). 27/59 had one or more RCTs, and of these eleven failed to use standard current care as the alternative, and 5 used surrogate outcomes. Two demonstrated inferior efficacy, and six were shown to be less safe than standard care. The authors found that Class III devices were more likely to be reimbursed in the absence of an RCT. Using regression analysis, they found that only for Class II devices did superior efficacy predict a positive reimbursement decision, which means that low levels of evidence regarding safety and efficacy were accepted for the reimbursement decision. The authors conclude that "**our data indicate that the combination of high risk characteristics and a low evidence base are factors that favour a positive reimbursement decision of MD, albeit with restrictions." "Actions on national level may help contain the risks associated with access to technologies without robust evidence base, provided that the imposed restrictions or conditions effectively lead to an improved evidence base."**

Garfield et al. (2016)[115] reviewed the current **evaluation processes of several HTA agencies for MDs** by analysing case studies. They highlighted that evidence expectations varied between agencies (clinical utility, patient outcomes, mortality, and quality of life) and they observed the **lack of transparency in the selection and acceptance of evidence and in reimbursement decision making.**

Chaverri-Fierro et al. (2017)[116] analysed the 18816 acetabular cups and 19595 implanted stems used for primary hip arthroplasty and reported in the Catalonian registry for hip arthroplasty between 2005 and 2013. The level of evidence for the 74 acetabular cups and 75 implanted stems with at least 10 records in the registry was analysed. These models accounted for 99% of the total number of registered implants. The evidence was retrieved from the Orthopaedic Data Evaluation Panel (ODEP) in the UK or if not available, the evidence was scored according to the Oxford scale, ranging from level 1a for a systematic review of RCTs to level 4 (case series) and level 5 (expert opinion). For over half of the cups and stems implanted there was strong evidence according to ODEP with at least 5 years of follow-up. The clinical evidence was found outside of ODEP and consisted mainly of level 4 (case series) for 16 cup models accounting for 12.6% of the volume and 16 stem models accounting for 19.1% of the volume analysed. No clinical evidence was found for 18 cup models accounting for 13.6% of the volume and 16 stem models accounting for 9.5% of the volume analysed. **In conclusion, over a quarter of the hip implants used in Catalonia either had no published evidence or only case series to support their use.**

Samaniego Alonso et al. (2018)[117] used the Catalonian knee arthroplasty register (Registro de Artroplastias de Catalun˜a (RACat)) to identify **total knee prostheses implanted in Catalonia between 2005 and 2013**. They used the Orthopaedic Data Evaluation Panel (ODEP) to identify those implants rated according to the ODEP criteria, and conducted a literature review on the remaining implants to identify all clinical studies conducted on those implants. They classified the identified studies for each model according to the Oxford Centre for Evidence-Based Medicine's evidence levels. **The authors analysed data on 74 different implant models representing 41,497 implant procedures notified to RACat. 25 models were rated by the ODEP, of the 49 that were not, no clinical evidence was found for 13 models, and the quality of evidence for the remaining models varied but most were rated at evidence level IV**. The authors concluded that though **"there are clinical studies that vouch for the use of most of the prostheses used, there are some prostheses (11.24%) implanted in Catalonia between 2005 and 2013 for which we found no scientific evidence."** Further for knee arthroplasty, Gagliardi et al (2016)[120] checked the primary studies included in health technology assessments (HTA) on total (TKA) and unicompartmental knee arthroplasty. The authors identified 265 eligible primary studies published between 1986 and 2014. Many studies were uncontrolled single cohorts (58.5%) or enrolled fewer

than 100 patients (66.4%). Most devices were evaluated in only one study (55.3% TKA implants, 61.1% unicompartmental knee implants).

Ciani et al. (2017)[121] **searched HTA reports published in English between 2003 to 2014 on medical devices and medicinal products with a cardiovascular primary indication.** The researchers identified 18 HTA reports on drugs and 27 HTA reports on medical devices of which 19 (70%) were class III. The reports were from UK, Canada, US, Ireland and Australia. Whereas 17 out of 18 (94%) drug evaluations contained RCT data, **only 12 out of 27 (44%) device evaluations were supported by randomized trials.** Device HTA reports were less likely than drug HTA reports to provide a detailed description of the technology and associated disease indication.

Mayer et al. (2018)[46] report on the experiences gathered with 6 joint rapid assessments of medical devices within the European Network for Health Technology Assessment (EUnetHTA) Joint Action 2 (JA2). The authors have observed the specificities of medical devices: absence of comparative clinical trials at market entry, incremental product changes during the product life cycle and the learning curve of users. **They conclude that HTA should continue during the life cycle beginning with early dialogues. Sharing of best practice among HTA bodies was found important by the authors:** "The concrete benefit of European collaboration for stakeholders is manifold:

- uncertainties with regard to the actual added value of a technology, caused by a lack of evidence, may be reduced by Early Dialogues;
- harmonised and transparent assessment processes throughout Europe increase the reproducibility and quality of reports;
- the division of work among the health technology assessment (HTA) organisations allows a resource efficient assessment of a larger amount of technologies."

Olberg et al. (2017)[19] identified **93 HTA reports on high-risk medical devices (as defined in the German health care regulation §137h) published during the period 2010-2015 by the European HTA institutions.** Based on the HTA reports, the authors evaluated the evidence base, the type of evidence and the level of evidence established by the Cochrane Collaboration: high is 1a Evidence obtained from meta-analysis or systematic review of RCTs, or 1b Evidence obtained from at least one RCT; moderate is 2a, Evidence obtained from at least one well-designed controlled study without randomization, or moderate is 2b Evidence obtained from at least one other type of well-designed quasi-experimental study, without randomization; and low includes 3, Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, and case studies and 4, Evidence obtained from expert committee reports, or opinions and/or clinical experiences of respected authorities. "Cardiac disorders were the most frequently evaluated (49 reports [53%]), followed by diseases related to the central circulatory system (36 reports [39%]). Eight reports assessed high-risk MDs used for diseases of the central nervous system (9%). All evaluated devices were technologies for therapeutic use. In only three reports (3%), the technologies evaluated also served a diagnostic purpose. The most evaluated group of technologies were implantable devices (e.g. cardiac stents) (62 reports [67%]), which mainly belong to risk class III (37 reports [40%])." The 93 HTA reports identified included 898 primary studies which were classified by the authors as follows: 83 studies had a level 1a (with 17 (20%) systematic reviews and 73 (28%) RCTs); 264 studies had a level 1b; 60 were level 2a; 41 were level 2b; 25 were level 3 and 425 studies had a level of evidence of 4. The report unfortunately does not specify the number of devices for which RCT data were available. The authors conclude "In more than half the identified studies considered in the reports, clinical evidence for demonstration of effectiveness and safety was of moderate or low quality. **Even when systematic reviews and randomized controlled trials were available for assessment, most studies showed an unclear or high risk of bias**." The authors also make an important remark: **"Our findings could not confirm the assumption that high-quality studies will occur in the postmarket approval setting and consequently will be available when it comes to decisions on reimbursement."**

Chapman et al (2017)[118] studied 116 novel implantable devices available for use in gastrointestinal surgical practice identified using searches of online catalogues from device manufacturers present at major gastrointestinal conferences held during 2013 or 2014. Then the authors searched the literature and registries for trials supporting these devices. They identified

246 trials, of which 128 (52%) were published, 95 (39%) ongoing and 23 (9%) unpublished. Of the 99 devices available in the UK and/or USA, 31 (31%) were supported by at least one published RCT. For the 17 devices not available in either the UK or USA, significantly fewer devices were supported by a published RCT (only 2 out of 17). Overall, only 10% of the devices were supported by an RCT at low risk of bias. The highest stage of innovation according to the IDEAL Framework was stage 1 for 11 devices, stage 2a for 23 devices, stage 2b for one device and stage 3 for 33 devices. For 48 devices (41%) no relevant clinical evidence was identified. The authors state "**The present study showed that few devices were supported by RCTs, which may have been because these devices have not yet progressed into the later stages of assessment, as described by the IDEAL Framework. If so, it is arguable that they should not be available in unrestricted practice. Integration of such frameworks into regulatory bodies may add a strong evidence basis throughout the total product life cycle and may incentivize manufacturers to follow more effective processes.**"

The report by ANSM (2018)[119] drew on manufacturers' websites, advertisements, data from specialists' conferences, and the French database of medical devices placed on the market **to identify 21 economic operators supplying surgical mesh devices** intended for the treatment of urinary incontinence or pelvic organ prolapse (POP) in France. **They surveyed these economic operators twice, requesting technical, clinical evaluation, vigilance, and sales data for surgical mesh devices specifically for these clinical indications**, and available on the French market in July 2016 (with sales volumes being requested for 2016 and 2017) to gain an overview of urological mesh implants available on the French market. 139,704 female slings, 4,624 male slings and 77,218 surgical meshes for Pelvic organ prolapse (POP) were sold in France over a four year period. Most of these devices received CE marking prior to 2011. Clinical evaluations for CE marking can be based on data for the device in question or from a literature review of data on another predicate device. ANSM report that 37,633 of the 38,477 (98%) of slings (for female urinary incontinence) sold in France in 2017 had specific clinical data, suggesting that 2% still had no direct clinical evidence after at least 5 years of being on the market. For surgical implants used to treat POP, in almost two thirds of the transvaginal implants no clinical studies were conducted prior to CE marking and none of the transabdominal implants were subjected to a clinical study prior to CE marking. The report states that more than 80% were the subject of a clinical study after CE marking. Overall, **the authors conclude that "Though this market review shows that clinical data are available for surgical mesh implants used to treat urinary incontinence and those used to treat pelvic organ prolapse, one cannot overlook the many questions now being considered internationally."**

Te Brummelstroete et al. (2019)[108] studied devices designed to support the diagnosis and/or treatment of any pelvic floor dysfunction in women. First, **devices were identified in abstracts presented in 2016 and 2017 at annual meetings** of the International Continence Society, the International Urogynecological Association, the European Association of Urology, and the American Urological Association. The exhibition floor of the 2017 International Continence Society was also searched. Second, literature was searched for studies of these devices, and a level of evidence was determined according to the pyramid of evidence (this is not further specified in the publication). The authors identified 11 eligible pelvic floor devices, with urinary incontinence being the most common indication. Seven devices were commercially available to patients of caregivers. For 7 out of the 11 devices, a total of 10 original full-text publications were found. Five RCTs were reported as abstract, all with a small sample size (58, 55, 40, 80 and 47 patients, respectively), but only a few were published in full in a peer reviewed journal supporting only one device. The authors conclude **"Sample sizes were small and there was a lack of convincing evidence for most devices. Despite this, many devices were available on the market."**

Sauerland et al. (2019)[110] reviewed the methodological quality of all **medical device studies submitted between March 2010 and December 2013 to a large ethics committee in Berlin, Germany** and which also required approval by the competent federal authority. A total of 122 study applications were identified including 84 (69%) pre-market studies. The other applications were post-CE marking studies requiring federal authority approval because the study entailed additional invasive or otherwise burdensome components. Therapeutic use devices accounted for 80% of all

study applications. The proportion of studies on Class I, IIa, IIb and III devices was 10%, 15%, 28% and 39%, respectively. 10 studies (8%) investigated IVD MDs. A randomised controlled trial (RCT) was planned in 70 (57%) of the 122 applications with the proportion of RCTs steadily increasing from 46% in 2010 to 55%, 61% and 66% in 2011, 2012 and 2013, respectively. The study design was not associated with the risk class of a therapeutic medical device. For the 70 RCT applications, 33 (47%) contained an adequate description of how randomisation sequences had been generated,in 50 (71%) the method of allocation concealment was explained and was adequate, and 37 (53%) incorporated at least some form of blinding. Among the 62 studies on efficacy, in addition to standard treatment, the control interventions consisted of another medical device (n=34), no medical device (n=11), a sham intervention (n=11), drug therapy (n=7), active surveillance (n=5), a different standard treatment (n=3) or a pharmaceutical placebo (n=1). All 12 studies using sham or placebo controls were RCTs.

In the sub-group of pre-market studies on therapeutic devices, the proportion of RCTs was 66% (43/65). Among all 122 studies, the overall median sample size was 120 participants or samples (IQR 53–229). The median study duration was 24 (14–38) months. Patient-relevant outcomes were assessed in 87 of 122 studies (71%). **The primary outcome was patient-relevant in 44 of 122 (36%) studies.** No primary outcome at all was defined in eight studies, including two RCTs. The authors conclude **"A large proportion of MD studies in Germany apply a randomised controlled design, thus contradicting the industry argument that RCTs on MDs are commonly infeasible."** The medical device industry argument that the conduct of randomised trials with medical devices is often not possible or ethical is also contradicted by a publication by Neugebauer et al (2017).[122] The authors have published solutions for these issues, allowing the generation of evidence based on RCTs

5.3.3 *Recurring issues in the articles:*

As we have seen in the section on medicines, RCTs are the gold standard for evaluating the efficacy of a product. But in the case of medical devices several problems arise. Medical devices entering the market for the first time must **prove their safety and performance but are not required to demonstrate their effectiveness**. This makes it difficult to judge benefit-risk. According to Sauerland et al. (2014)[107] among the large number of medical devices with unknown effectiveness, some may turn out to be ineffective or even harmful. Furthermore, the lack of assessment of the effectiveness of medical devices entering the European market is an issue at national level when reimbursement decisions have to be made. Even when some manufacturers make the effort to perform RCTs, **most RCTs evaluating medical devices to obtain CE marking are of low methodological quality** with thus a lower level of evidence. Our review of the literature showed us that, whatever the tool used to evaluate this lack of evidence (Sackett, Cochrane, Oxford Centre for Evidence-based Medicine hierarchy), high level evidence based on randomised trials was rarely reached. The sample size of the trials was often less than 30 patients and many trials are underpowered.

Manufacturers, since the 2007/47/EC directive, can use clinical data from other similar medical devices to support applications for CE marking. Indeed, only the first innovative product has to prove safety and technical performance on the basis of clinical data; follow-up products can be CE marked "on the basis of their technical equivalence to the first product".[107] It means that a CE marking is thus often delivered after a simple demonstration of equivalence with another device subjected to clinical evaluation. Boudard et al.(2013) [42] highlighted this issue and reported a French Senate report on the safety of medical devices which stated that **90% of the medical devices on the French market obtained their CE marking after a demonstration of equivalence.** But the criteria used to determine equivalence were not really defined by the 2007/47/EC directive. This may have consequences because medical devices without clinical trial data could potentially be harmful for patients: Wild et al. (2014)[106] highlighted that **recalls are not uncommon, especially for those devices that have been cleared via the "substantial equivalence" process. Heneghan et al**

(2017)[34] have shown that it is entirely possible for multiple generations of devices (e.g. transvaginal mesh devices for pelvic organ prolapse) to be approved on the basis of 'generations' of equivalence claims, and that this is possible even when some of the claimed equivalent devices, the predicates, have been removed from the market due to adverse patient outcomes, device failure, or more stringent evidence requirements.

There is still a lack of transparency related to the entry of medical devices on the market. Indeed, data are not always publicly available. According to Wild et al. (2014),[106] there is a lack of transparency regarding the way devices are approved and the information gathered by Notified Bodies. Sauerland et al.(2014) explains **"When trying to find data on a single device or a group of medical devices, surgeons will often have difficulties in finding information, because preclinical and clinical data on medical devices may exist but are kept on file by the manufacturer." Heneghan et al (2017)[34]** conclude **"A publicly accessible registry of licensed invasive devices, with details of marketing status and linked evidence, should be created and maintained at the time of approval." Fraser et al (2018)[123] clearly demanded: "The evidence submitted by manufacturers when seeking approval of their high-risk devices must be publicly available, including technical performance and premarket clinical studies. Giving physicians access to this information supplements the peer-reviewed scientific literature and might be essential for comparing alternative devices within any class. Interested patients should be encouraged to review the evidence for any device that has been recommended for them."**

Key points

- **The regulatory context for medical devices in Europe differs greatly from the regulatory framework for medicinal products. Medical devices for the European market are certified by Notified Bodies based on device performance and safety. Comparative trials evaluating the efficacy or added therapeutic benefit of a new medical device are not required for this purpose. RCTs may or may not be performed. When a randomised trial is performed, the quality may not be high enough. This evidence gap leads to uncertainties for reimbursement decisions at member state level.**
- **Under the medical device directives there was no legal obligation to register device trials. Furthermore, medical device trial results may be considered confidential and may not be made public. Compared with medicinal products, relatively few studies have reported on the level of evidence and methodological shortcomings of clinical evaluations of medical devices. Given the fact that a central database of new medical devices with a summary of their trial results is not yet available, authors had to find other ways to define a group of medical devices for their evaluation. Such a central database is urgently needed.**
- **The literature review indicates that many high risk devices are still marketed without any peer reviewed publication of a controlled trial evaluating patient benefit. Over the years there is a tendency towards more RCTs, contradicting the industry argument that RCTs on medical devices would not be feasible. However, many RCTs of devices are underpowered, do not well define the primary endpoint or do not describe the handling of missing data. For implants, the study observation period (also for observational studies) is often short compared with their long duration of use. Few articles report on the learning curve or the volume–outcome relationship.**
- **As the medical device directive (in place until 2021) did not really define the criteria to be used to determine equivalence, multiple authors reported difficulties with the interpretation of equivalence for several of the medical devices studied.**
- **The assumption that high-quality studies will occur in the postmarket approval setting was shown to be incorrect by Olberg et al. (2017)[19]**

6 DISCUSSION AND POSSIBLE SOLUTIONS

This report is about the gaps in comparative evidence from an HTA/payer perspective. In contrast to their intention, the expedited regulatory approvals risk delaying rather than speeding up patient access to evidence-based innovations. This report is also about efficiency gains, it is about bringing not just innovation but evidence-based innovations more rapidly to patients. It is about making randomised trials more acceptable to patients, guaranteeing that they will get the best possible treatment options, independent of the arm they get randomised to. It is about collecting outcomes that matter for patients. It is about enrolling most, if not all, patients in RCTs. As has been demonstrated in the Upsala registry-based RCT in cardiology[26], this can result in a very short recruitment time and an even larger reduction of the trial cost. In 2022, the use of routinely collected data in RCTs should become the norm and lawmakers could and should facilitate this. Sometimes a helicopter view is needed to see possible solutions, leaving the silo of the stakeholder. This report is mainly focussing on the roles of regulators and HTA bodies. However, clinicians and their scientific societies have an equally important role to promote the timely generation of the comparative data needed to practice evidence-based medicine. Multistakeholder initiatives could help, such as the EU-funded CORE-MD initiative (www.core-md.eu).[27] Finally, it is key to also involve patient representatives and to explain the importance of comparative evidence generation.

6.1 The tension between business priorities and patient benefit

6.1.1 The healthcare economy, important but not the scope of this project

Healthcare has an ethical dimension as it aims to prevent and alleviate human suffering. Healthcare has also developed into an important economic sector, with sales of services and products. Total EU expenditure on healthcare (public and private) amounts to around € 1.3 trillion annually, including €220 billion for medicinal products and €100 billion for medical devices. Healthcare spending represents about 10% of EU GDP.[1] Garattini et al (2021)[3] state “According to the European Federation of Pharmaceutical Industries and Associations (EFPIA), it contributes with more than €110 billion to the EU trade balance and employs almost 800 000 people across Europe. In 2019, it invested an estimated € 37 500 million in R&D in Europe. However, despite these investments, the drug market is not without some low-value drugs and alleged innovations, resulting in an excess of public and private spending that could be reduced in favour of other health-related activities. A survey by the independent scientific journal Prescrire found that only 10% of the new authorisations in 2019 presented a notable therapeutic advance, a view shared by the German Institute for Quality and Efficiency in Health Care (IQWiG).” A recent KCE report studied 40 innovative drugs used between 2004 and 2017 to treat advanced stages of 12 types of cancer in Belgium. Overall survival data linked to billing data were analysed for over 800 000 cancer patients in Belgium. No change in overall survival over the period 2004-2017 was seen for about half of the tumor types studied, despite a very strong increase in investment of public money to cover the innovative drugs. Overall Belgian healthcare payer expenditures for drugs to treat cancer increased from €140 million in 2007 to more than €1 billion in 2019. These sobering observational real-world findings were in line with published RCT results, which in most cases did not report on quality of life.[4] Tay-Teo et al. (2019)[124] have argued that the returns from cancer drugs have been so high that they might have over-incentivized the pharmaceutical industry to dedicate a substantial and perhaps disproportionate level of investment

toward the development of cancer drugs, possibly at the expense of research in other disease areas.

The healthcare sector is a specific market as a large fraction of the bills are paid by healthcare insurance systems. Intellectual property and data protection measures aim to reward investments made by companies. However, de facto monopoly situations may result, leading to maximisation of product prices and profit margins. The analysis and a possible rework of the healthcare economy are not the focus of this report. For pharmaceuticals, the interested reader is referred to the KCE-ZIN report[125] or the policy brief 29 by the European Observatory on Health Systems and Policies[126] for discussions on changing the current system including the benefits and harms of the current intellectual property system on true innovation. The number of possible alternatives for product development is limited and most would require a major rework of the current system.

During the course of this research project, a key paper appeared by Naci et al (2020)[5] very clearly describing the topic of this report: **"The uncertainty associated with the paucity of well designed active-comparator trials has been compounded by legal and regulatory changes in Europe and the USA that have created a complex mix of expedited programmes aimed at facilitating faster access to new drugs. Comparative evidence generation is even sparser for medical devices. Some have argued that the current process for regulatory approval needs to generate more evidence that is useful for patients, clinicians, and payers in health-care systems."**

6.1.2 Hard law or ethical rules to manage business priorities versus patient benefit?

It might help to remind all researchers, scientific societies and in particular hospitals working with the industry of their ethical responsibilities: all parties are not only expected to apply the legislation but also the ethical rules which may have a broader scope. Ethically responsible research remains a collective responsibility.[54] Nevertheless, it is naïve to expect ethical rules or weak agreements to be sufficient to counter business priorities. Despite a reference to the Declaration of Helsinki (sometimes an older version) many new drugs are still evaluated in phase 3 versus no active treatment when a standard of care treatment exists, contrary to the requirements of the Declaration of Helsinki. It should be noted that Ethics Committees also fail to check these ethical requirements or take action. Ethics Committees and other deontological authorities should be reminded that they are not only there to apply the regulation criteria but also to apply the Declaration of Helsinki. This also applies for the use of an active comparator in the trial design, as applicable. **As long as the legislation does not change, Ethics Committees may de facto be the only ones able to impact study design and relevant endpoints.**

Despite a reference to the Declaration of Helsinki in each protocol and in the regulatory provisions on medical devices, many of the medical device study protocols were never entered in a public registry nor were the results published. A reason often mentioned by the device industry is that a publication, even of the protocol, will give other companies a competitive edge. Here also Ethics Committees fail to check these ethical requirements or take action. In theory, ethics committees could even refer specific cases to a deontological body. The EUDAMED when operational will provide a registry of trials and a summary of results, but only for device trials conducted in the context of obtaining the CE marking. Negative trials not leading to CE marking may not be published, and trials conducted for other purposes are not required by the regulation to be registered in EUDAMED.

Business priorities and a lack of hard consequences may also explain why early dialogues between HTA bodies and industry or joint scientific advice with regulators have shown little impact so far of the HTA body advice on the actual trial design.

Despite 'best efforts' clauses or very broad legal requirements in the post-marketing agreements, in many cases no evidence is generated which is hard enough to decide on the continuation or discontinuation of marketing or reimbursement. Also in this case it would be naïve to think that without very robust contractual clauses or consequences, industry would generate data that could potentially cut their sales. The EMA has cited constraints in resources as a reason why little action is taken in case post-authorisation requirements are not met after a conditional marketing authorisation.[5]

Unfortunately, it often takes a tragedy before legal changes are put in place. Regulatory change for medicinal products in Europe had been triggered by the thalidomide tragedy now 60 years ago. One could argue that no such tragedy was observed for medical devices. However a variety of device issues associated with human suffering or death have surfaced, for example metal on metal hip prostheses, surgical meshes for pelvic organ prolapse, and specific catheter ablation devices that had to be withdrawn from the EU market. In addition, an insufficient level of regulatory control has been linked to the Poly Implant Prothèse (PIP) breast implant scandal. The harms associated with not knowing what device or drug (or combination of drugs or dose or duration) to best use in a specific patient are more difficult to estimate but are likely very real. Hence the need for a timely generation of comparative evidence.

6.1.3 The assessment of true innovation requires a direct comparison of patient benefit

Researchers who identify a new pathway or overcome a major technical challenge in the development of a candidate drug or device will consider this as innovation in healthcare.[127] On the other end of the spectrum are the researchers assessing the added value of the new drug or device for the patient's health. They do not consider the technical challenges that had to be overcome but merely focus on the patient benefit that can be expected after the introduction of the innovation in the routine healthcare system. In between these two extremes lies an evidence gap. The focus of this report is on the available clinical evidence for pharmaceuticals and medical devices when these products are entering the market in Europe.

Before covering the intervention, payers increasingly want to see evidence that the innovation brings added benefit to the patient compared with the standard of care. Randomised trials are feasible for medical devices[122] and drugs and have been conducted even in extremely rare conditions.[128] Previous management of the EMA has discussed the merits and pitfalls of proposals with regard to the role of regulatory agencies in establishing added therapeutic benefit.[129] Regulators however run the risk of focussing on the wrong discussion. **The real issue for HTA bodies and clinicians is the lack of comparative evidence generation, it is not an obligation to show the superiority of a drug over the standard of care in order to enter the market.** Over the past decades governments have failed to increase the evidentiary requirements of regulators to a level that meets the needs and expectations of the payers and clinicians, that is the demonstration of added therapeutic value, as has been demanded for many years.[11] Instead, governments have opted to install HTA bodies to judge whether the output of the regulatory system meets the needs of the public healthcare payers. Non-transparent central purchase agreements at EU level without any preceding HTA are an exception to the rule and should be restricted to actual emergency situations.

It can be argued that this split between regulators and HTA bodies has delayed instead of shortened access for patients to evidence-based innovations. The development of comparative clinical evidence for a new product has a cost and poses a risk for the company. It may demonstrate that the innovative product is not superior to a lower cost standard of care therapy, or a trial assessing patient-relevant endpoints might take longer and delay the time to market. These economic aspects are part of the problem and appropriate financial incentives need to be considered as part of the solution.

The successful demonstration of added therapeutic benefit has been associated with a positive reimbursement decision of medicines in Belgium[130] and medical devices in France[131] but in Austria this correlation was not always present for the coverage of medical devices used in hospitals.[114] In the UK and Canada, the availability of overall survival benefit data instead of surrogates did not seem to significantly impact the final reimbursement decision of cancer drugs approved from 2012 to 2016.[132] However, the scope of this report did not include the study of the final decision taken by the healthcare payers when faced with limited evidence.

6.1.4 Horizon scanning and current limitations affecting the impact of early dialogue and common scientific advice

Horizon scanning initiatives (e.g. https://beneluxa.org/horizonscanning) allow HTA bodies and healthcare payers to make preparations (also in budget allocation) before the request to cover the innovation is submitted. In addition, horizon scanning is relevant for early HTA activities. HTA bodies may provide advice on the pivotal trial design and data to be collected for the HTA. Early HTA has a different meaning for different stakeholders.[133] Early dialogues among stakeholders aim to inform the clinical development programme such that it meets the expectations of the parties involved. The advice can be given jointly by regulators and HTA bodies (common scientific advice or now named joint scientific consultation in EUnetHTA21). Business priorities may play a role when companies tend not to follow the (non-binding) recommendations made by HTA bodies during early dialogue meetings or parallel scientific advice. The reasons why companies seek HTA scientific advice remain unclear. Maignen et al (2017)[37] suggested it could be a strategic move by companies to gauge their likelihood of success as part of a longer-term commercial strategy**.** Companies may not include in their studies the routine target population, the best available active comparator nor the patient-relevant endpoints (overal survival, quality of life) recommended by HTA agencies.[37] Incentives for companies may not compensate for the fact that such confirmatory trials can be more risky, more costly or take longer. The result is that the confirmatory trials with a patient population, comparators, and outcomes that are accepted by the regulators may not be suitable for performing an HTA, nor for informing physicians wanting to practice evidence-based medicine.

An enhanced collaboration between HTA bodies, Notified Bodies and the medical device industry might not only improve the evaluation of devices [45, 46] but also indirectly stimulate the generation of appropriate evidence for HTA. Early dialogues for medical devices in Europe is largely an unexplored field.[134] Companies see the potential of an early dialogue with HTA bodies but are afraid to share confidential data as the intellectual property protection of their product may be weak. Many companies in Europe developing innovative medical devices are rather small and might actually benefit from early HTA advice. More support for this activity could be justified. Smaller country HTA bodies prefer to have an early dialogue together with other HTA bodies as was explored under the EUnetHTA early dialogues. In terms of "regulators" and parallel scientific advice the situation is more complex for medical devices compared with drugs as there is an important role for the notified body in addition to the competent authorities, who do not feel it is their role to provide advice.[134] Under the MDR the Medical Device Coordination Group (MDCG) and expert panels could explore the benefit of HTA input in the guidance given to manufacturers. Blankart et al (2021)[134] conclude "the legislator plays an important role, as the legislator can create the legal basis and set the right incentives for manufacturers to initiate change."

The need to overcome the siloing of drugs versus medical devices is clear for early dialogues and for the HTA of targeted drugs that require companion diagnostic medical devices in order to realise their potential. HTA of such products is based on the combined use of the two interventions.[135]

A final point of relevance in the context of early dialogue and scientific advice is the risk of regulatory capture. According to the HTA regulation, where possible, the experts involved in joint scientific advice (early dialogue) should be different from the team performing the joint scientific assessment. Multiple institutes have expressed a similar recommendation for the EMA scientific advice.[136] Such considerations are not mentioned for the expert group in the MDR.

6.1.5 The failed promise of post-marketing trials, coverage with evidence development and managed entry agreements

Pre-market evidence generation needs are to be balanced with the possibility of generating evidence in the post-market phase. The focus of this report is on pre-market trials. The reason is simple. Reports of post-market evidence generation by industry, be it demanded by regulators or payers/HTA bodies show major uncertainties in delivery.[12] Industry may argue that the lack of alignment between regulators, HTA organizations, and payers leads to a multitude of evidence requirements that the company may not be able to deliver.[137] However, the fact remains that the required evidence is frequently not generated or made publicly available in the post-market phase.

6.1.5.1 Post-marketing evidence generation for medicinal products

It has been recommended that expedited programmes such as conditional marketing authorisation by the EMA or accelerated approval by the FDA should be limited to clearly demarcated circumstances.[5] This should definitely be the case if there are insufficient resources to manage the consequences of conditional marketing authorisations, a reason cited by the EMA for not invoking the power of revoking approval.[5] As stated in a publication by the FDA on accelerated approval of oncology products: "Lack of due diligence in conducting confirmatory trials is a serious concern that has threatened the continuation of the accelerated approval process."[138] In the context of early access initiatives one should also consider that when evidence is developed late in the process and leading to the discontinuation of the marketing or reimbursement of a product, such a decision always remains very difficult for regulators, payers, clinicans, patients and the company. Rupp et al (2017)[139] studied cancer drugs approved by the FDA from 2008 to 2012 on the basis of a surrogate endpoint. The authors concluded "... even when postmarket studies show the new drugs to have no clinically meaningful benefit compared with placebo or observation, most drugs retain FDA approval and remain on the market at prices comparable to those of the most expensive cancer drugs." Gyawali et al (2021)[16] recently studied 18 oncology drug indications that benefited from FDA accelerated approval but failed to improve the primary endpoint in post-approval trials. Only for 12 out of 18 oncology drug indications was marketing discontinued. It has been repeatedly shown that for 30% to 50% of new oncology drugs the data regarding purported benefits to overall survival and/or quality of life remains unknown at least three years after marketing authorisation.[13, 72] Bloem et al (2019)[14] identified 69 obligations for 26 medicines conditionally authorized by the EMA between 2006 and 2016. For 55% of obligations, data submission was delayed, negatively impacting public health by prolonging exposure of patients to unknown risks. Critical time may thus be lost for patients and clinicians if the comparative trial is not started in the pre-market phase. In the post-market phase industry has no real incentive to deliver on time. This paper confirms the observations reported by Banzi et al (2017)[140] showing that the EMA process fails to improve the evidence after early licensing.

Sacher-Konrad et al. (2020)[15] studied 21 cancer drug-indication pairs that received in the period 2009 to 2013 FDA accelerated approval, EMA conditional marketing authorisation, or both. Compared with the FDA, the EMA more often accepted single-arm studies to confirm clinical benefit after approval (75% vs. 29% of indications). Both agencies relied primarily on surrogate measures of patient benefit for postmarketing obligations. After a median follow-up of 7.25 years, 40% of FDA and 61% of EMA postmarketing obligations were delayed for these cancer drug-indication pairs. The authors conclude "…meaningful evidence may not materialize due to shortcomings in study design and delays in conducting required studies with due diligence."

Managed entry agreements and post-market coverage with evidence development initiatives risk remaining limited to coverage without evidence generation. In the Netherlands, outcomes research based on hospital chart review failed to generate the necessary evidence for decision making.[17] In Belgium, fully confidential managed entry agreements (MEAs) for innovative drugs risk becoming the norm for payer coverage.[18] These agreements successfully control budget impact but clearly fail to generate additional clinical evidence. In addition, the lack of transparency of MEAs hampers the conduct of health economic evaluations. In particular health economic comparisons with products under a MEA become impossible if the correct healthcare payer cost of that product cannot be made public. In some countries outcome-based managed entry agreements have started to collect real world data. Low quality of the data collected, lack of (international) standardization and lack of transparency have been reported as hurdles to evaluate these MEAs.[141]

6.1.5.2 *Post-marketing evidence generation for medical devices*

The approval system for medical devices in Europe used to be based mainly on post-market data collection. In the US one has also explored expedited pathways of approval for high-risk devices but the evaluation is not so positive. High-risk medical devices that underwent FDA priority review were reported to have higher recall rates and a shorter time on the market prior to more serious recalls when compared with high-risk devices receiving standard review.[142] In order to cope with the consequences of the FDA Breakthrough Devices Program introduced at the end of 2016, parallel review by regulators and payers (the FDA and Medicare and Medicaid Services) as well as coverage with evidence development have been proposed to reduce delays between marketing approval and subsequent Medicare coverage determinations for medical devices.[143] For medical devices in Europe, it has been shown that the assumption that high-quality studies will occur in the post-market setting is not correct.[19] Clinical evidence on effectiveness may thus remain unknown.[19] Nyholm et al (2016)[144] analysed 77 published studies on implants for the treatment of proximal femoral fracture in use in Denmark in 2014. All 77 studies were either retrospective or very small. The authors conclude "The current system with sporadic evaluation by clinical studies is not sufficient to identify long term problems and continuous performance monitoring of properly registered trauma related implants, possibly in form of national registers, is necessary in the future." Furthermore, good quality registries allow for the conduct of registry-based RCTs with long term follow-up of implants. No public information is available on post-market trials for medical devices demanded by Notified Bodies,[12] Because of the flaws in the EU regulatory system for medical devices France, the UK and Germany[145] have explored temporary funding schemes, so called coverage with evidence development (CED), for specific medical devices. However, challenges remain concerning transparency, timeliness, and predictability for manufacturers.[146] Considerable variation exists between countries in how schemes are initiated, designed, implemented, and evaluated. Frederici et al (2020)[147] state "One general finding across all countries was that relatively little attention was paid to the evaluation of schemes, both during and at their completion." Furthermore, a problem of all these schemes is that they are limited to the national healthcare system. This is a limitation for CED initiatives in rare disease that would require (and deserve) a pan-European trial approach. The role EUDAMED will play as trial registry for post-market trials is unclear.

Another aspect of the evidence concerns medical device safety. Post-market safety follow-up largely depends on spontaneous reporting systems and registries, used for the detection and assessment of product problems and patient harms associated with the use of medical devices.[21] Physicians implanting cardiovascular or orthopedic devices may consider the reporting of adverse medical device events as unnecessary, not possible or futile due to multiple factors.[22] This leads to a severe underreporting of complications in mandatory databases.[20, 22]

Hwang et al (2016) showed that compared with the US, devices approved first in the EU (2005-2010) are associated with an increased risk of post-marketing safety alerts and recalls. Article 90 of the new EU regulation states that the European Commission shall put in place systems and processes to actively monitor medical device safety signals.[21] However, traditionally much of this information is considered confidential and it is not yet clear whether public access to it will actually be substantially improved under the MDR. No global database has been introduced to enable access to spontaneous reports on medical devices. Furthermore, there is inconsistency in post-market reporting requirements (and coding) between regions. For example, expected side-effects are not reportable in the EU, whilst they are subject to event trending in Canada and Australia, and in the US no exemptions are applicable. Pane et al. (2021)[21] conclude "Data quality and coding harmonisation will need to be improved and the Unique Device Identification (UDI) system will need to be fully implemented to benefit from the potential of proactive systems for the safety evaluation of medical devices."

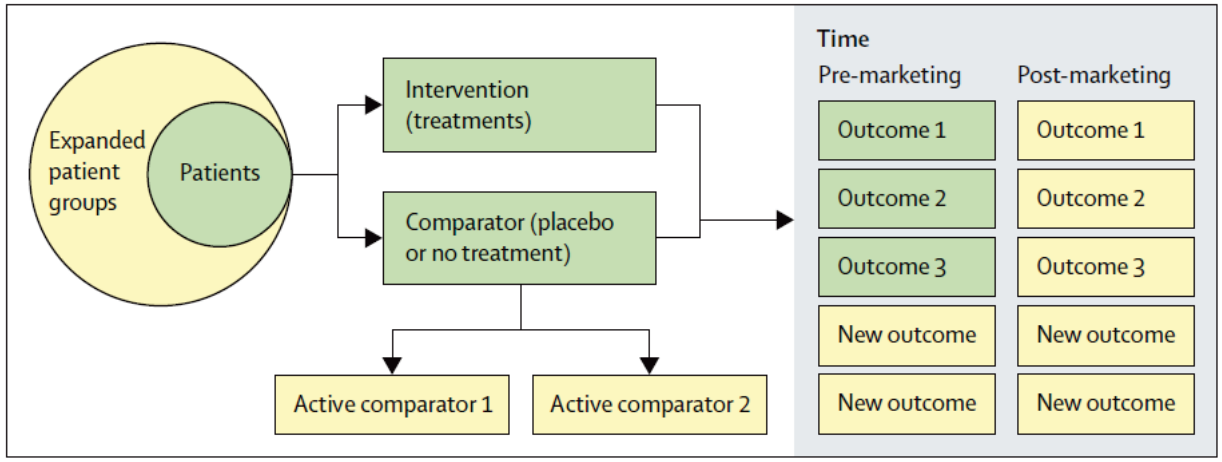
Under the MDR manufacturers must submit a Periodic Safety Update Report (PSUR) to the notified body that issued the certificate for its device, at least every year for class IIb & III devices. For class III & implantable devices these PSURs need to be submitted through EUDAMED and the Notified Body should add its assessment in the EUDAMED database. Only competent authorities and Notified Bodies have access to these documents. Expected and foreseeable side effects need not not be reported by

manufacturers. They must however report side effects trends, as well as trends of expected unwanted accidents that are not classified as serious. Notification obligations are broader in Belgium since they require also healthcare professionals, and professionals that use the device to notify incidents with medical devices based on a decisional tree.

6.1.5.3 Post-market evidence, solutions proposed in the literature

Cipriani et al (2020)[12] have developed 7 key guiding principles for the generation of evidence in the post-market phase,. The authors stress the importance of randomized comparative effectiveness trials and the need for governments to invest in the development of collaborative research networks and data systems that reduce the complexity, cost, and waste of rigorous post-market research. The authors see the pre-market and post-market evidence generation as depicted in figure 4 below.

Figure 5 – The populations, interventions, comparators, outcomes, time periods, and study designs (PICOTS) framework



Framework at present (green) and in the desirable future (yellow).[12]

The seventh guiding principle concerns the use of 'sticks and carrots' to make this happen. 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 postmarketing 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."[12] And also "In terms of penalty mechanisms, regulatory agencies should actively consider licence suspensions, indication restrictions, monetary fines, or even market withdrawal on a case-by-case basis."[12]. Already in 2011, Dupont et al .[74] stated "There is a need for collaboration between the European Commission, competent for market authorisation, and the EU member states, competent for reimbursement, in the collection and assessment of the therapeutic risks and benefits of orphan drugs in the post-marketing phase."

The situation for medical devices is more complex. Essentially, they receive a quality mark but they are not formally licensed. The competent authorities are not responsible for authorising the placing on the market of medical devices. Manufacturers and Notified Bodies are responsible for assuring that the devices continue to meet certain quality standards as set out in the MDR, including the General Safety and Performance Requirements (but clinical effectiveness is not one of those standards).

6.2 Towards a clinical development pathway that better meets the demands of regulators and HTA bodies

6.2.1 The need for a better collaboration between regulators and HTA bodies

For the parallel scientific advice by the EMA and HTA bodies for medicinal products, Tafuri et al. (2016)[36] reported that regulators and HTA bodies showed disagreement or only partial agreement on aspects of the study population (23%), the study comparator (56%) or the study endpoints (41%). The disagreement on the study comparator and endpoints between the regulator and HTA bodies illustrates their difference in perspective. Unfortunately, divergence has also been observed between HTA bodies, although to a lesser extent. According to Kavanos et al (2019), "Europe would improve its negotiating power in global drug design and development if views can be aligned between member states on evidence requirements for HTA. But at the moment they cannot and so the FDA and the USA still dictate to a large extent what clinical studies measure and what endpoints are used."[148]

During parallel scientific advice, comparative data and quality of life measures are typically requested by HTA bodies but not by regulators, as was observed by Maignen et al (2017).[37] Companies traditionally tend to pay more attention to regulatory demands to inform their pivotal trial design compared with the input from HTA bodies, which may furthermore vary by country.

For such parallel scientific advice, companies have reported a large divergence in advice by the EMA and HTA bodies, especially for dossiers on conditional marketing authorisation. The trend to allow constantly faster access to drugs with ambiguous benefit-risk profiles via conditional approval pathways has led to smaller, shorter and less cost-intensive trials and an increasing use of surrogate primary end-points. Expedited regulatory pathways may however not always lead to earlier patient access, especially in the case of conditional marketing authorisation.[76] Vreman et al (2019) recommend that in order to ensure adequate patient access to novel drugs, manufacturers, HTA bodies, and regulators should collaborate more

efficiently early on, during drug development, in order to improve the alignment of evidence generation strategies to satisfy both regulatory and HTA evidence requirements.

For medical devices the communication between HTA bodies, Notified Bodies, national competent authorities, the European Commission, device industry and other parties concerned has started and needs to be continued.[149] Occasionally clinical development input has been provided by HTA bodies to device companies during early dialogues. In contrast to medicinal products, there is no platform yet for a common regulatory/notified body and HTA body scientific advice process on the development of medical devices.

6.2.2 The split between regulators and HTA bodies, an example of inefficient governance?

In most EU member states both the regulator (or for medical devices the authorities controlling Notified Bodies) and the HTA body report to the same minister of health. The EMA (and the FDA) can only operate within their legal frameworks. As stated by Johnson et al (2011)[138]: "The FDA is limited to issues of safety and efficacy when making drug approval decisions." The same considerations apply for the EMA. Therefore, any changes to the system can only be realised with the full support of the EU member states' governments and the EU Commission. These system changes should not only include an obligation for regulators to include in their scientific advice to companies those elements considered essential by HTA bodies, but should also include an obligation for companies to start the HTA required trial in the pre-market phase, preferably continuing in the postmarket phase to assess those long term outcomes that are essential for HTA but may not be essential for marketing approval. If possible, more pragmatic comparative trials could serve as pivotal trials for regulatory purposes. If not, there should be a separate independent pre-market (platform) trial for HTA purposes, possibly co-funded by healthcare payers.

6.3 Evidence gaps grouped according to the PICOTS framework

The elements considered essential by HTA bodies are described below and grouped according to the populations, interventions, comparators, outcomes, time periods, and study designs (PICOTS) framework.[23](www.fda.gov/media/109448/download)

Some PICOTS elements are mainly based on science such as evaluating the appropriateness of using surrogate measures or randomisation in the study design. Other elements such as the selection of the appropriate comparator is both a scientific decision and a context specific decision, as it takes into account for example cost-effectiveness considerations.

Very similar evidence gaps were identified in the literature as those reported by RIZIV-INAMI assessors for drugs and high-risk medical devices. A very special type of evidence gap is present when no trials are performed. This is the case for many medical devices when the new device is considered equivalent with an existing device,[34, 42, 107]For medicinal product reimbursement, the most frequently reported issues in Germany concern the comparator used, patient population subgroups, patient-relevant endpoints and the grading of side-effects.[150] The choice of the comparator and the endpoints are also the items about which industry, regulators and HTA bodies tend to disagree during early dialogues or parallel scientific advice for medicines under development,[36] and where the uptake by industry of NICE HTA advice was shown to be low.[37]

6.3.1 Population: keep the randomization but include the routine care patients, all evidence in patient subpopulations should be detailed

Specific patient groups such as the very young or the frail elderly tend to be excluded from or underrepresented in registration trials. Yet they may be most in need of better treatment or they may make up a considerable part of the target population. Minor subpopulations might have a different efficacy or safety profile. A major advantage of the AMNOG reports is the detailed reporting of all available efficacy and safety data in specific patient subpopulations that are part of the population targeted for reimbursement.[65] The same level of detail could be given in the EPAR. Meanwhile, the AMNOG documents could serve as a more complete source of clinical evidence.

In the RIZIV-INAMI reimbursement dossiers studied, an identified evidence gap concerned the population studied in cases where it differed from the target population for which reimbursement was being requested.

6.3.2 Intervention: knowledge of optimal dose and duration is key, routine care to be reflected as much as possible

Schuller et al.(2019)[151] investigated 49 orphan drugs authorized by the EMA until August 1, 2017. In one out of three orphan drugs no dose-finding trials had been conducted during the pre-market phase. In the post-market phase dose-finding studies were conducted in 18 orphan drugs, but dose changes were applied in only 2 drugs. The optimal dose and duration should best be studied in the premarket phase not only to inform clinicians and patients but also to inform the budget impact calculation of payers. Examples are not limited to orphans drugs but include targeted therapies in oncology (e.g. trastuzumab) and immune checkpoint inhibitor therapy. Dose finding or dose/duration optimization trials that aim to detect clinically relevant differences need to be conducted and have to be well powered. Integration of this research question in the pivotal multi-arm phase 2b/3 trial could be informative for HTA purposes and avoid the need for such a trial in the postmarketing phase. An advantage of a more pragmatic approach for large active control comparative randomized trials is that the recruitment hurdle is lower and extra visits and assessments on top of routine care are reduced to a minimum. Such a trial may better predict the benefits and harms of the intervention when used in a routine care setting.

For medical devices, more than for drugs, it is key that the trial reflects the device's use, education, learning curve, and support as planned for later use in the routine care setting. In the past 90% of the medical devices on the French market obtained their CE marking after a demonstration of equivalence.[42] There was an issue of a broad interpretation of equivalence for medical devices despite clinically relevant differences that were introduced as reported by Heneghan et al (2017)[34]) Another issue that will hopefully be dealt with in the new EU regulation.

6.3.3 The (active) comparator: the Helsinki declaration and the EMA

Both for medicinal products and medical devices, a direct comparison with standard of care in an RCT is key for HTA bodies and payers to assess the added therapeutic value and to inform the calculation of the incremental cost-effectiveness ratio. For this purpose it is clear that HTA bodies will not recommend as comparator an approved drug that is clearly not cost-effective. It is a missed opportunity not to include the best (cost-effective) active comparator (correctly dosed) in the clinical development programme as it hampers the evaluation of added therapeutic benefit[9, 152] and the development of a valid cost-effectiveness model. The uncertainty for the payer is even higher in cases of new regulatory initiatives such as adaptive pathways.

Only half of the new medicines approved between 1999 and 2005 were compared with existing medicines at the time of marketing authorisation.[35] Naci et al(2020)[5] showed that the proportion of EMA drugs approved with at least one active-comparator RCT ranged annually between a quarter and one-half from 2015 to 2018. Of course, for some new drugs no active comparator may be available. However, also in this case best supportive care remains a possible comparator and should always be assured. When alternative treatments exist, choosing an active comparator can be difficult. Furthermore, in comparative trials the (competitor) comparator needs to be correctly titrated and dosed as illustrated by Heres et al (2006)[153] in their

study entitled "Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics."

For 10 out of 27 psychotropic drug approved by the EMA up to March 2017 no pre-approval trials with an active control were identified.[83] For 9 drugs an active comparator arm was presented without any comparison with the investigation drug (this was described in the EPARs as 'internal positive control for assay sensitivity'). Erhel et al. (2021)[83] state "Interestingly, some EPARs presented studies with an active comparator but did not report the results of the comparison, and the CHMP did not consider this evidence in the decision process."

Multiple not for profit organisations in Belgium have recommended that active comparator trials should be the norm for the development of medicinal products.[154] Not only is there a need for these randomized comparative trials to be conducted in the pre-market phase but, in addition, it might be argued that a more independent body should run such commercially sensitive head to head trials. Clinicians struggle with the lack of appropriate comparative and treatment optimisation trials. The clinical need for appropriate comparative trials has been reported for the field of oncology,[8] severe athma,[10] multiple sclerosis,[9] and additional examples documented by Garattini et al. (2021),[11], illustrating the need for (independent) comparative trials. If one has a look at top-selling medicinal products it is clear there is a need for comparative evidence in many, for example, insulin-analogues versus classical insulin, and comparative data between the direct oral anticoagulants, the TNF inhibitors, the angiotensin-converting enzyme (ACE) inhibitors (and versus angiotensin II receptor blockers), atypical antipsychotics, and the bifosphonates, amongst others (examples kindly provided by Marc Bogaert, emeritus Professor UGent). Some of these demands have already been discussed with the EMA, but only the European Commission can take the necessary legal actions.

When checking the regulatory framework it looks like the EMA proposed design for a pivotal phase 3 trial could meet most of the requirements of HTA bodies and the Helsinki Declaration. This is illustrated by the following two citations.

Regarding the study reports of controlled clinical studies, Section 5.2.5.1 of Annex I to Directive 2001/83/EC states *:"In general, clinical trials shall be done as 'controlled clinical trials' if possible, randomized and as appropriate versus placebo* ***and versus an established medicinal product of proven therapeutic value; any other design shall be justified****. The treatment of the control groups will vary from case to case and also will depend on ethical considerations and therapeutic area; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo."*

In 2010, the EMA CHMP issued a document "open to discussion" : "Where feasible, three-arm trials including experimental medicine, placebo and active control represent a scientific gold-standard and there are multiple reasons to support their use in drug development. However, there are situations where such trials are not required by CHMP for a properly informed decision on benefit-risk."

The issue is clearly not the guidance but the lack of adherence to this guidance by manufacturers, making use of the exception stated in the guidance. It would therefore be of great help to HTA bodies if the EMA would be more stringent and only exceptionally allow other designs, and then only after full justification.

The following statements in the guidance might seem somewhat in contradiction, allowing different parties to pick a statement that supports their point of view "*Nevertheless,* ***given the impact on the complexity, duration and cost of drug development, there will be circumstances where such (three arm) trials should not be required by CHMP*** *as a properly informed decision on benefit-risk can be made without such data.*"

However, further in the guidance document it is stated: "***without a direct comparison to active control it may not be possible to properly gauge and understand the magnitude of benefit or risk from a clinical perspective and hence to make a properly informed decision on benefit-risk.****"*

It is clear the EMA guidance leaves (too much) room for interpretation. This seems to be confirmed by EMA staff.[129] In this way the guidance fails to meet the demands of healthcare payers and HTA bodies.

6.3.4 *Outcomes: focus on patient-relevant outcomes instead of surrogates that are not validated*

An evidence gap listed by reviewers at RIZIV-INAMI concerned the endpoint used in the trials both for medical devices and medicinal products. HTA bodies focus on patient-relevant outcomes, the incremental overall survival, functional, symptomatic and quality of life benefits, above and beyond the evidence-based usual care, and covering a long enough follow-up period. Collection of quality of life data using a generic instrument such as EQ-5D-5L (to complement disease-specific QoL measures) at several time points allows for an assessment of quality-adjusted life years (QALYs) gained over a prolonged period.

Quality of life, however, may not be measured or may not be reported, despite being recommended early on by HTA bodies.[37, 155] In contrast to AMNOG reports quality of life information (and even clinical results) may unfortunately be the subject of data redaction in documents supporting the decision of other HTA bodies that use QALYs, such as NICE.[156] Several reports recommend that there should be more alignment between regulators and HTA bodies, and that HTA bodies should insist that QoL is measured and reported in drug trials.[82, 87]

In the field of oncology, as stated by Johnson et al (2011)[138]: “The most common approach used by pharmaceutical companies to gain accelerated approval has been single-arm trials that have an endpoint of response rate in patients who are refractory to all available therapies.” Response rate or progression-free survival may be considered inappropriately as a surrogate for overall survival or quality of life, and evidence of a survival benefit may not become available even years after marketing. The reports on oncology drug-indication pairs show that for only a third of the new oncology drug therapies was a survival advantage demonstrated before approval [13] and in only 16% was the overall survival gain found to be at least 3 months ,[67] For 42% of oncology drugs no overall survival data were available at marketing authorisation and this was still 28% after at least three years of follow-up. Improvement in quality of life, also of importance, is only reported in 10% of the oncology dossiers. Most worrying is the fact that for about half of the oncology drugs on the market for a median of 5 years, it is still unknown whether there is any benefit in overall survival.[13]

Surrogate endpoints can have the advantage that they can be evaluated after a shorter follow-up period, thereby facilitating faster patient access to promising new treatments. Therefore they are preferred in accelerated clinical developments (e.g. the adapted pathways regulatory initiative). However, their use may further magnify the uncertainty associated with the lack of active comparators. Furthermore, surrogate endpoints need to be validated for each indication and each intervention, which strongly limits their use in pivotal trials of innovative interventions.[97] An association between the potential surrogate and the clinical endpoint is desirable but it is not sufficient.[98] Each time a new drug is introduced having a substantially different mode of action, another prospective evaluation of surrogacy may be needed, which remains a challenge.[98] In oncology, progression-free survival is frequently not a valid surrogate for overall survival.[100] Progression-free survival should also not be used as a surrogate for quality of life measures.[101]

The issue is illustrated by Cherla et al. (2021)[157] who studied 93 cancer drug indication pairs that received accelerated approval from the FDA between 1992 and 2017. The authors conclude: “many cancer drug indications that received accelerated approval from the FDA were either not reviewed or denied authorisation or coverage by European regulators and NICE because of insufficient safety, clinical efficacy, or cost-effectiveness, which was likely owing to the use of uncertain evidence derived from unvalidated surrogate measures, which provided the basis for US regulatory approval.” Non-validated surrogates are however also frequently used for regulatory approval by the EMA.

Schuster Bruce et al.(2019)[89] studied the use of surrogates supporting regulatory approval of 51 products assessed through expedited assessment pathways, conditional marketing authorisation (26 products) and accelerated assessment (25 products) by the EMA between 2011 and 2018. The authors checked the literature but failed to find a full validation for any of the surrogate markers used for regulatory approval. Most were rated

according to the published hierarchies as being 'reasonably likely' (n = 30; 61%) or of having 'biological plausibility' (n = 46; 94%) to predict clinical outcomes.

The introduction of the Priority Medicines (PRIME) scheme, launched by the EMA in 2016 to expedite the development and approval of promising products targeting conditions with high unmet medical need was studied by Neez et al. (2020).[158] Until June 2018, the EMA had granted PRIME status to 39 agents, evaluated in 138 studies (102 initiated before and 36 after PRIME eligibility). The authors did not see an immediate impact on the use of a randomised design (about a third of the trials were randomised) nor the use of blinding. However, significantly more efficacy studies included a clinical end point after PRIME designation than before, and significantly fewer included surrogate measures alone.

In the context of oncology trials, the issue of inappropriate cross-over should also be mentioned here. We refer the interested reader to the KCE report on innovative oncology drugs.[4] This report also illustrates that reliance on non-validated surrogates may result in a lack of survival improvements in routine care. In addition, the fact that survival effects for new drugs are not clarified in the post-marketing means that our evidence base is eroding. We will not be able to assess next generation drugs when we do not understand the effects of the current new drugs which might be standard of care / comparators in the coming years.

In addition, the question is raised as to who should pay for new treatments whilst information is being collected as part of any obligations for conditional marketing authorisation. Scheller-Kreinsen et al. (2011)[159] discussed how innovations can be introduced in DRG based hospital financing systems in Europe. It is recommended that the use of generous short term payment instruments are employed only in cases where sufficient evidence is available supporting the innovation.

6.3.5 *Study design and time periods, the opportunities and risks of relying only on observational real-world data*

Clinical trials are most informative for healthcare payers if performed in a population reflecting the routine setting. This can be a strong point for studies based on real-world data. Polak et al. (2020)[160] showed that observational data collected during expanded access programmes approved by the FDA or the EMA (searched up to 2018) increasingly provide pivotal data in the regulatory dossier for drugs with orphan designation and a high medical need. In 13 dossiers (5 approved by FDA and EMA, 2 EMA only, 6 FDA only) the main data supporting approval came from expanded access data while four drugs (2 FDA/EMA and 2 FDA only) were granted marketing authorisation solely based on these data. The use of non-randomised controlled trial data is however discouraged for economic evaluations in the field of personalised medicine and targeted treatments.[161]

Instead of the move towards observational studies, Collins et al (2020)[25] propose to reduce the cost and complexity of RCTs. This vision is also shared by the KCE Trials programme, a publicly funded programme of mainly randomized comparative effectiveness trials, which was started in 2016 based on a KCE report on publicly funded trials.[162] Ideally, as pragmatic trials include a broad patient population they should be powered to allow subgroup analyses of relevance for healthcare payers. Therefore, an appropriate and pre-specified investigation of effect modification should be part of the study design. This is also required for analyses of observational data.

One model for more pragmatic RCTs could be registry based RCTs.[24] Such efficiency gain was nicely illustrated by the Upsala registry-based RCT in cardiology. This RCT was conducted at a very low cost and enrolled over a short period 70% of all registry patients (instead of the 10-15% of patients typically enrolled in RCTs).[26] This type of study does not seem to be part of the discussion of the European Health Data Space, or more specifically of the DARWIN project, which seems to be restricted to observational studies. These initiatives need to be expanded to interventional studies, specifically registry-based RCTs. It does not seem acceptable to spend the substantial resources planned for these projects and to miss the chance to generate

high quality evidence which is urgently required to improve patient care in Europe.

Trial efficiency gains can be also obtained by the re-use of clinical data already collected for other purposes. The famous Oxford RECOVERY trial in Covid-19 patients (www.recoverytrial.net) was conducted as a large simple randomised platform trial with a minimum of data specifically collected for the trial (a single page data entry screen) while most patient data were obtained through linkage of existing databases to the trial database. Also in other area's pre-market randomised adaptive platform trials could help generate comparative effectiveness data, urgently needed for HTA.

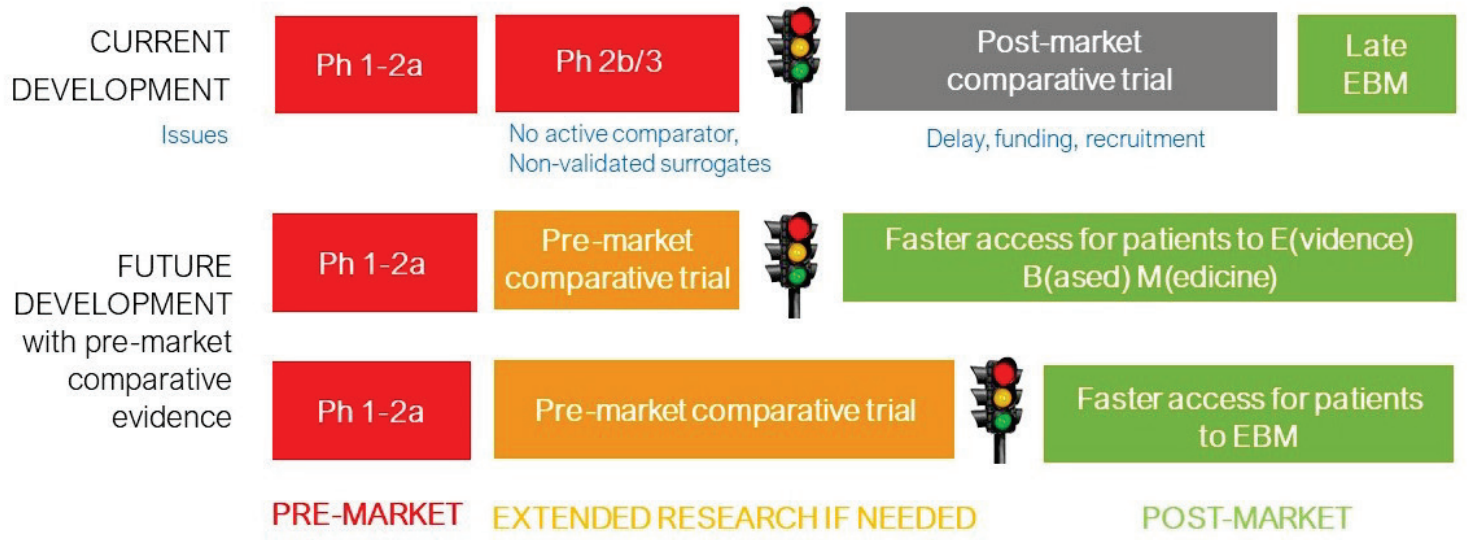
In a more distant future, it would be even more efficient to directly extract the needed data from coded clinical data in standardised electronic health records covering both in-hospital and outpatient care.[2] Governments should facilitate these efficiency gains by providing an appropriate international legal framework, promoting clinical coding standards and the associated information technology infrastructure.

Such big data sets could provide a rapid and systematic overview of the patient population that used the intervention as well as the routinely collected outcomes. This could revolutionise the detection of safety signals both for drugs and medical devices but it remains to be seen if there is any added value for comparative effectiveness analysis if there is no randomisation.[25] In Belgium, the linkage of billing data to the unique device identifier (UDI) will for example allow to systematically assess hospitalisations after a new implant.

Observational real-world data may thus be informative when added to RCTs. However, the push to already replace RCTs by observational data is quite dangerous and is not justified as it requires further breakthroughs in data quality, completeness and big data analysis, to enable the removal of the inherent biases in the data that confound the assessment of clinical effectiveness, which currently make such assessments using 'real world data' unreliable.[25, 163, 164] Currently, many prospective registries are set-up. As for all clinical trials a timely public registration of the protocol and the planned analyses is needed. In addition, there are extra efforts and costs to ensure a correct and complete data entry, costs for companies which may be similar to a (pragmatic) RCT as discussed above. The problem with observational real-world data is that these can only be conclusive if the difference with usual care is exceptionally large, the data set is complete and quality is good. Multiple initiatives are ongoing to produce efficacy conclusions based on observational data[12] but a significant proportion of the efficacy conclusions based on observational data sets may be contradicted when a randomized controlled trial is performed. For example, in a large group of comparisons, Kumar et al. (2020) reported that matching based on propensity score resulted in different inferences regarding therapeutic efficacy 55% of the time when compared with RCTs, that is point estimates were found to be either in a different direction, or nonsignificant in observational research versus significant in an RCT or significant in observational research but nonsignificant in an RCT.[165] Further research is ongoing to make better use of observational data.[166, 167] Today, this means that for the vast majority of novel interventions randomization remains essential to balance both the known and the unknown unknowns, so as to minimise bias and justify inferences made.

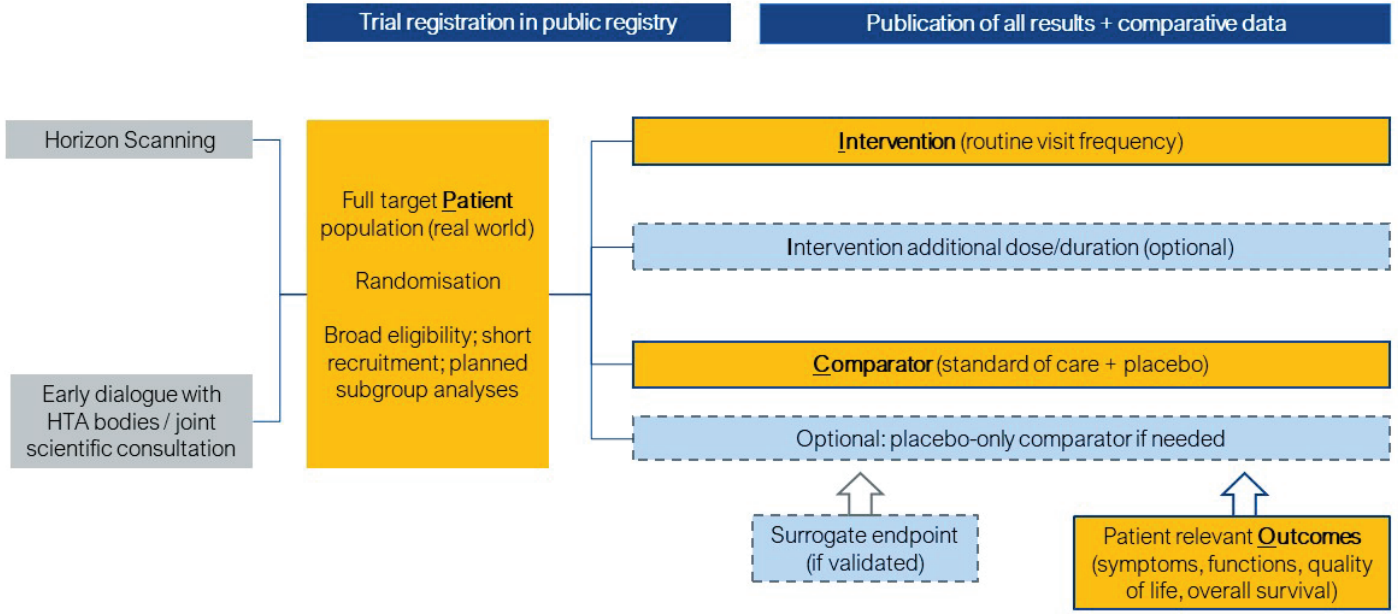
For many post-marketing initiated trials there are two good reasons to initiate such trials already in the pre-market phase as illustrated in figure 5 below. First, precious time is lost for patients and clinicians if the essential questions are not addressed at an earlier stage. Results of post-marketing initiated trials may just arrive too late. By the time results are made public follow-up products may already be introduced as product protection is expiring. Second, trial feasibility may be hampered as the post-marketing trial recruitment has to compete with routine prescription of the same drugs or competing procedures. The G-BA has faced such recruitment difficulties in an effort to generate post-market randomized evidence in the field of urology.[168]

Figure 6 – Towards comparative evidence generation in phase 2b/3



The comparative RCT needed from a healthcare payer perspective should start at 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 7 – The ideal pre-market randomised trial set-up from a healthcare payer (and clinicians) perspective.



For healthcare payers it is key that the essential (direct) comparative evidence is generated in the pre-market phase, possibly with the trial continuing in the post-market phase to assess e.g. long term outcomes that are not essential for marketing approval (but maybe of relevance for the coverage decision). The addition of elements of pragmatic trials to the more classical RCT design could furthermore accommodate many of the healthcare payer concerns, while keeping sufficient rigor to satisfy regulatory demands. This is an area where regulators and HTA bodies could develop common standards and take the lead, for example, in the use of (coded) electronic health records or even certain elements of the billing information for research purposes.[2] For instance, the multi-arm multi-stage platform trial approach may be used to run (simple) pragmatic trials in which multiple interventions (or comparators) are tested simultaneously. Such platform trials would, by definition, lead to harmonised designs for several drugs within a therapeutic area. To make this happen, we need a discussion on how to regulate and organise these trials. This might be a case for an independent third party to take responsibility for the platform (trials).

However, even platform trials may not be able to include all comparators that may be relevant for a given decision problem. In such cases, network meta-analyses may be necessary to address remaining gaps in the evidence base. The only way such analyses can have adequate internal validity is by making sure individual trials that contribute to network meta-analyses are sufficiently comparable in terms of their populations (including sponsor instructions to investigators regarding patient inclusion based on expected study treatment adherence), outcomes, follow-up durations, and other design features. For example, the multitude of companion diagnostic assays and cut-offs used across trials with immune checkpoint inhibitors

lacks harmonisation and leads to difficulties to analyse comparative effectiveness but also hampers patient selection in routine practice.[169] Horizon scanning initiatives may help prepare regulators and HTA/payers to timely prepare guidance on the study design elements that need harmonisation. A straightforward solution would be to make public the advice on these design elements during joint scientific consultations, so other companies preparing their clinical development for the same indication can already take the advice into account.

The standard approach of a single trial testing a medicinal product, sponsored by one marketing authorisation holder is probably too simplistic to address relevant public health needs.[28] Prospectively designed network meta-analyses may also be informative.[5] If a trial design meeting both regulatory and HTA requirements is not possible, two separate trials may need to be performed. Finally, the conduct of more comparative trials in the pre-market phase will not eliminate but could rather accelerate the start of further independent publicly-funded treatment optimisation trials for the benefit of patients. Hurdles for the conduct of such international trials in all therapeutic area's should be further reduced.[170] A pan-European-distributed infrastructure (and funding system) to help investigators overcome barriers for multi-country trials could help improve the situation. However, care must be taken not to introduce the risk of such a platform being used as a mechanism for running seeding trials by industry, which are a marketing strategy to introduce a new technology as widely and as early as possible.[171]

The need for a placebo arm may be justified if the usual treatment is not based on solid evidence. It can be argued that the placebo arm in such a three-arm trial should be dropped as soon as there is sufficient evidence of superiority for one or both active arms. As long term outcomes are often key for HTA, the trial should be continued as appropriate as a two-arm trial with, for example, placebo(only)-treated subjects being randomized to one of the two active arms.

Finally, despite the preference for a superiority design to change practice, a non-inferiority design may be appropriate for active comparator trials. In this case the trial quality deserves extra attention as a sloppy trial may favor non-justified equivalence. The non-inferiority margin is a second point of attention, to be carefully discussed upfront with statisticians and clinicians. If medicines (or devices) are approved based on non-inferiority studies, this can – over successive approvals – lead to medicines (or devices) being accepted without any proof of efficacy compared with placebo (or sham intervention).[126]

6.3.6 Should the evidence bar be lower for medical devices?

Some diseases may be prevented or treated using a public health intervention, a procedure that includes a medical device or/and a medicinal product. HTA experts are confronted with quite different levels of evidence for different types of intervention. Comparing like with like is hampered by the fact that the evidence level is typically lower for medical devices (and public health interventions) compared with medicinal products. Specificities of medical devices concern the possibility of a learning curve associated with the procedure, a volume-outcome relationship, differences in pre-, peri- and post-operative ancillary care, the need for assessment of long term effects of implants, and the need for a better and more strict definition of equivalence of medical devices.[42, 107]

Boudard et al.(2013)[42] highlighted this issue and reported in a French Senate report on the safety of medical devices which stated that **90% of the medical devices on the French market obtained their CE marking after a demonstration of equivalence.** Minimal changes to the device can be necessary and should be justified. The risk is that any harms caused by the change might not be noticed before market entry but may lead to postmarketing safety issues or a device recall.[34] Therefore such minimal changes need to be evaluated carefully on a case-by-case basis to check the possible impact on the clinical benefit and harms. In case of doubt about the equivalence of a device, such doubt might be an indication that there is a need to perform an appropriate premarket clinical trial in order to avoid harm in the routine clinic.

Depending on the healthcare system, the device reimbursement may be part of the coverage of a surgical procedure. In this setting little attention may be paid to differences in evidence level and actual outcomes between the possible alternative devices used for this procedure. Furthermore, HTA experts see indication creep as a problem which may be more difficult to control for high-risk medical devices compared with medicinal products.

Despite the differences in European regulatory systems for medicinal products and medical devices there were similar evidence shortcomings observed during the assessment for reimbursement by RIZIV-INAMI. For implants, evidence of a long term effect on functional outcomes is essential but was sometimes reported as an issue (i.e. an evidence gap) in the reimbursement dossiers assessed at RIZIV-INAMI. Another specificity of medical devices is that the interaction for reimbursement may happen through distributors. As the distributors do not have access to the manufacturer data this complicates answering additional data requests by HTA bodies or payers. In general, the data confirm a rather low level of evidence for implants seen in the 2008 dossiers submitted for reimbursement in France.[111] More recently, according to Tarricone et al (2020),[39] typical points of discussion for the reimbursement of devices in European countries concern a lack of direct comparison with the standard of care in a real-world setting and the collection of sufficiently long term patient-relevant endpoints. The lack of robust comparative clinical data in Europe hampers the clinical assessment of patient benefit and the cost-effectiveness analysis in the context of national reimbursement procedures[32, 38, 105]

Several groups, including KCE, have recommended a stepwise approach to introducing innovative medical devices as proposed in the IDEAL (Idea, Development, Exploration, Assessment, Long-term study) framework, which was developed by a group of surgical experts (the Balliol Colloquium) to improve research and reporting of results[33, 105, 107, 172] Sauerland et al (2014),[107] however warn that all steps of the IDEAL framework should be taken, including the conduct of RCTs: “The pitfall to be avoided is acceptance of preliminary non-randomized data as proof of the new devices or procedure’s superiority.” Based on their study of the distinct regulatory approval pathways for new medical devices, Marcus et al (2016)[173] concluded “Changes in the regulatory approval of devices that would require trials for proof of safety and effectiveness might promote adherence to the IDEAL model.” Chapman et al (2017)[118] make a similar suggestion “Integration of such frameworks into regulatory bodies may add a strong evidence basis throughout the total product life cycle and may incentivize manufacturers to follow more effective processes.” The authors found that only one in ten novel implantable devices available for use in gastrointestinal surgical practice is supported by high-quality RCT evidence. Positive preclinical data are not sufficient evidence to guarantee patient safety; neglecting the IDEAL stepwise introduction in the clinic may lead to harms as shown by Reito et al (2017)[174] for the adoption of Articular Surface Replacement (ASR) hip replacements. HTA experts in the field also comment that safety reporting for medical devices is not yet up to standard, making it difficult to weigh benefits versus risks.

The conduct of RCTs is a standard approach in the clinical development of medicinal products, with discussions focussing on the choice of the comparator and endpoints. Despite a positive trend towards more RCTs,[110] this is still not the standard approach for the clinical development of medical devices in Europe. Because there is no obligation for trial registration and no publicly accessible database of CE marked medical devices with a summary of trial results, relatively few studies have quantified the level of evidence and the methodological shortcomings of clinical evaluations of medical devices.

Do patients deserve the same level of protection against harms when treated with a medical device compared with a medicinal product? The obvious answer is yes, but the reality is different with new devices still entering the market without robust clinical trials or no premarket clinical trials at all if reference is made to an existing device.[19, 34, 106, 107] It has been shown that the selection of products for full evaluation to produce NICE guidance is associated with the claims made for the benefits of products, especially when supported by evidence.[175] Surprisingly, the selection was not significantly associated with the presence of RCTs. In cases of devices supported by little evidence NICE judgements take into account their promise and the plausibility of claims that they will provide benefits in a real-world setting.[176] It is a challenge to do this in a transparent way. The main drivers of the decision-making process are the quality and quantity of the submitted evidence supporting the technologies, as well as the economic evaluation results.

Representatives of the medical device industry have argued that the conduct of randomised trials with medical devices is often not possible or ethical. Each of these arguments have been countered in a paper by Neugebauer et al (2017).[122] The authors have published solutions for these issues,

allowing the generation of evidence based on RCTs. Furthermore, RCTs conducted in the context of pre-market approval (PMA) for innovative high-risk devices in the US proves the contrary.[177] Also in Europe the device trials approved by a large ethics committee in Berlin show a high proportion of the device trials are randomized.[110] The main reason for a paucity of device RCTs seen in the past is most probably the fact that such RCTs were not needed to obtain a CE marking.[178]

A framework to generate comparative evidence has been developed for implantable medical devices, with attention for device-specific critical elements in trial design and conduct.[179-181] In view of the MDR, possible trial designs to investigate medical devices have been reviewed by Wild et al. (2017)[182] in an effort to close the gap between regulatory and HTA needs, also the goal of this report. In addition, HAS 2021[183] has published a guide for the clinical development of medical devices in view of a possible reimbursement, with a focus on comparative evidence needed for innovative devices claiming an added value. The future will tell the impact of the new EU regulation on the level of premarket evidence. During the transition period attention should be paid to the removing from the market of relatively low cost medical devices for commercial reasons because in such cases the cost of meeting the additional regulatory requirements might be more than manufacturers can, or are willing to, pay. As some of these devices can be essential for a group of patients, specific measures may need to be taken by the authorities to ensure their continued availability.

Communication between HTA bodies and Notified Bodies is less advanced compared with the interaction between HTA bodies and the EMA for medicinal products. The legal framework under which the Notified Bodies operate also leaves little room (or incentive) for them to take into account the evidence needs of HTA bodies as no comparative evidence was needed under the device directives.The new device regulation remains unclear regarding the power Notified Bodies will have to require industry to perform a comparative trial versus the state of the art, the term used in the new regulation for the best usual care.

6.4 On transparency and reporting

6.4.1 *The case of medicinal products*

Overall, the level of transparency and publication of drug trial results has improved considerably over the past decades. Actions by regulators have an immediate impact, also for making results of academic trials public.[184] Compared to medical devices, medicinal products have the necessary evidence for a reimbursement decision more readily available at the time of regulatory approval. The clinical development and the results of the pivotal trials for a new drug are summarized in the European public assessment reports (EPARs), available on the EMA website. The completeness of the EPARs (as well as journal publications and trial registry summaries) can still be improved as some evidence was found to be lacking when compared with AMNOG documents in Germany (e.g. on the drug effect in population subgroups and specific endpoints).[65] This is especially the case for orphan drugs, which all lack high-quality evidence regarding their effectiveness. In general, HTA bodies recommend the inclusion of quality of life as an endpoint in clinical trials. This advice is not always followed by the companies.[37] Quality of life endpoints should routinely be included in study protocols and reported accordingly.[155] The lack of recording or reporting of quality of life measures is striking in the field of oncology. The statement sometimes made that QoL data is commercially sensitive and must be kept confidential is difficult to justify in the context of full and transparent reporting of all trial results in the EPARs and scientific publications.[4]

6.4.2 *The case of medical devices*

In contrast to medicinal products, under the medical device directives, there was no legal obligation to register device trials, despite the included reference to the declaration of Helsinki.[105] As noted by Heneghan et al. (2017),[34] the authors were unable to scrutinise the European approval system due to its lack of accessibility. They conclude that there needs to be a publicly accessible registry of licensed invasive devices, with details of marketing status and linked evidence. It is difficult to judge the trial quality if the trial is not made public. Improved transparency for medical devices is needed[123] and is expected with the introduction of the new medical devices

Regulations.[63] Transparency is an aspect for which the medical device trials in Europe lag behind the US device trials, and lag behind the pharmaceutical trials in general. The EU solution promised for providing transparency of medical device trials is the EUDAMED database, at least for those trials that are performed for and result in CE marking for the device. Unfortunately, if a trial is negative and CE marking is not obtained for the device, there is still no legal obligation to make the trial results public. It is also still unclear if the clinical trial summary will be detailed enough to inform clinical and HTA decision making. The launch of the EUDAMED database module with trial data summaries has been delayed. At the EU level, the responsibility for the regulation of medical devices has been moved around between DG Santé and DG Enterprise to come back to DG Santé, illustrating the tension between economic and population health interests.

For now, given the fact that a central database of new medical devices is not available, authors had to find other ways to define a group of medical devices for their evaluation. As illustrated above, the selection started either from publicly available HTA reports, cardiovascular device dossiers introduced for reimbursement, implants entered in a regional hip arthroplasty registry, devices requested by surgeons or clinicians to be used in a hospital, devices recently introduced in general surgery, devices used in post-stroke care starting from an internet search, pelvic floor devices identified using abstracts presented at international conferences, catalogues of distributors or trial applications on medical devices received for review by the ethics committee in Berlin.

6.5 Published policy recommendations

A number of papers have been published on the issues discussed in this report and some have provided recommendations.

Multiple **not for profit organisations in Belgium** (2018)[154] have developed a number of policy recommendations for pharmaceuticals, some also of relevance here.

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

Policy brief 29 by the **European Observatory on Health Systems and Policies** was prepared in support of the 2018 Austrian Council Presidency and is entitled “How to stimulate innovation to meet patients’ needs?”. Panteli et al. (2018)[126] provide 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, Health Technology Assessment). 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)[136] recommended a new model for scientific advice (SA):

- To avoid detrimental efects of confidential SA and simultaneously ensure clariication of scientific and procedural requirements, SA should be conducted in a transparent way. As such, SA would include:
- General guidelines on scientific principles for conducting randomised clinical studies, including comparative trials 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 trials 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 uration). 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 EMA (and/or HTA bodies or payers), which are also answered in writing (without conidential 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, 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, being not part of the marketing approval nor the pharmacovigilance process as well as being independent from industry.

The **European Public Health Alliance (EPHA)** (2020)[28] has provided recommendations to generate better evidence on new drugs.

- 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 randomised trials** 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 randomised trials 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.

Very similar recommendations are supported by two 2020 Lancet papers.[5, 12]

Naci et al. (2020)[5] focussed on pre-market 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)[12] focussed on post-market data and provided seven key guiding principles:

- First, regulators (for drugs and devices), Notified Bodies (for devices in Europe), health technology assessment 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 randomised trials 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 a randomised trial is not feasible.
- Fifth, **efficiency of randomised trials** 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 postmarketing 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**."[12] "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."[12].

7 RECOMMENDATIONS

7.1 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.[14, 15, 17, 18, 140] For high-risk medical devices, the assumptions that device safety can be relied upon based on spontaneous incident reporting[20-22] and that high-quality studies will be conducted in the post-market phase are simply not true.[19] 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.[126] 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 chose 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.[8-11] 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.
    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 authoristion (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.[134, 149] 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[24, 26] or it could be part of an adaptive platform trial.[28, 30, 31] 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.[126] 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.[25, 163-167]

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.[5, 28] 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.[185] 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.

7.2 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.

7.3 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.

7.4 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.[61]

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.

7.5 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.

7.6 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.

7.7 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.[156, 186, 187] 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.[188]

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.

APPENDICES

APPENDIX 1. LISTS OF THE LEGAL TEXTS (EUROPEAN AND BELGIAN) REFERRING TO THE DECLARATION OF HELSINKI

The declaration of Helsinki is very often referred to. In particular the following texts (**whereas or provisions**) refer to this declaration:

EUROPEAN TEXTS

1. **European Directive 2001/20/EC of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (CTD)**

   - Whereas nr. 2 :

     "*The accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration. The clinical trial subject's protection is safeguarded through risk assessment based on the results of toxicological experiments prior to any clinical trial, screening by ethics committees and Member States' competent authorities, and rules on the protection of personal data.*"

2. **Commission Directive 2005/28/EC 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products" (Good Clinical Practice – " GCP Directive").**

   - Article 3:

"*The available non-clinical and clinical information on an investigational medicinal product shall be adequate to support the proposed clinical trial.*

Clinical trials shall be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996)."

3. **Regulation (EU) No 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC**

- Whereas 43 :

  "The members of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) have agreed on a detailed set of guidelines on good clinical practice which is an internationally accepted standard for designing, conducting, recording and reporting clinical trials, consistent with principles that have their origin in the World Medical Association's Declaration of Helsinki. When designing, conducting, recording and reporting clinical trials, detailed questions may arise as to the appropriate quality standard. In such a case, the ICH guidelines on good clinical practice should be taken appropriately into account for the application of the rules set out in this Regulation, provided that there is no other specific guidance issued by the Commission and that those guidelines are compatible with this Regulation."

- Whereas 80:

  "This Regulation is in line with the major international guidance documents on clinical trials, such as the 2008 version of the World Medical Association's Declaration of Helsinki and good clinical practice, which has its origins in the Declaration of Helsinki."

4. **European Directive 2001/83 - first version**

- Annex I (ANALYTICAL, PHARMACOTOXICOLOGICAL AND CLINICAL STANDARDS AND PROTOCOLS IN RESPECT OF THE TESTING OF MEDICINAL PRODUCTS - Part 4 – Clincial documentation - B. Conduct of trials):

  "1. Good clinical practice

  1.1. All phases of clinical investigation, including bioavailability and bioequivalence studies, shall be designed, implemented and reported in accordance with good clinical practice.

  1.2. All clinical trials shall be carried out in accordance with the ethical principles laid down in the current revision of the Declaration of Helsinki. In principle, the freely given informed consent of each trial subject shall be obtained and documented.

5. **European Directive 2001/83 – current version**

- Whereas 8 :

  « All clinical trials, conducted within the European Community, must comply with the requirements of Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (18). To be taken into account during the assessment of an application, clinical trials, conducted outside the European Community, which relate to medicinal products intended to be used in the European Community, shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki."

6. **European Directive 93/42/EEC of 14 June 1993 concerning medical devices**

   - Annex X – Clinical evaluation - 2.2. Ethical considerations

     "Clinical investigations must be carried out in accordance with the Helsinki Declaration adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, as last amended by the 41st World Medical Assembly in Hong Kong in 1989. It is mandatory that all measures relating to the protection of human subjects are carried out in the spirit of the Helsinki Declaration. This includes every step in the clinical investigation from first consideration of the need and justification of the study to publication of the results.

7. **Regulation on 2017/745 of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC**

   - Whereas 64 :

     "The rules on clinical investigations should be in line with well-established international guidance in this field, such as the international standard ISO 14155:2011 on good clinical practice for clinical investigations of medical devices for human subjects, so as to make it easier for the results of clinical investigations conducted in the Union to be accepted as documentation outside the Union and to make it easier for the results of clinical investigations conducted outside the Union in accordance with international guidelines to be accepted within the Union. In addition, the rules should be in line with the most recent version of the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects.»

BELGIAN TEXTS

In Belgian law, the followin texts refer to the DoH:

1. Loi du 7 mai 2004 relative aux expérimentations sur la personne humaine.

   Art. 4.

   Toutes les expérimentations, y compris les essais portant sur les études de bio disponibilité et de bio équivalence, sont conçues, mises en oeuvre et notifiées conformément aux exigences de qualité dans les domaines éthique et scientifique, reconnues au plan international comme devant être respectées lors de la planification, la mise en ouvre, l'enregistrement et la notification des expérimentations et plus particulièrement des essais.

   Le Roi peut déterminer tout ou partie de ces exigences appelées les « bonnes pratiques cliniques »

2. Arrêté royal du 30 juin 2004 déterminant des mesures d'exécution de la loi du 7 mai 2004 relative aux expérimentations sur la personne humaine en ce qui concerne les essais cliniques de médicaments à usage humain.

   Art. 10. Les informations cliniques et non cliniques disponibles sur le médicament expérimental doivent être appropriées à l'appui de l'essai clinique proposé. Les essais cliniques sont menés dans le respect de la déclaration d'Helsinki sur les principes éthiques applicables aux recherches médicales sur des sujets humains, adoptée par l'assemblée générale de l'Association médicale mondiale, dans sa dernière édition disponible

   - *Avis du Conseil d'Etat concernant cette référence :*

     « Si en ce qui concerne la "réglementation des médicaments dans l'Union européenne", il peut se justifier de travailler par référence dès lors qu'il ne s'agit pas de règles contraignantes à proprement parler, ce n'est toutefois pas le cas en ce qui concerne la Déclaration d'Helsinki susmentionnée, les essais cliniques devant obligatoirement être effectués conformément aux règles édictées

dans cette déclaration. Dès lors, il s'impose de transposer ces règles en droit interne et de les publier adéquatement (par exemple dans une annexe jointe à l'arrêté en projet)[wwwwww]

3. Loi relative aux dispositifs médicaux du 20 décembre 2020

- Art. 31. Conformément aux lignes directrices internationales, le Roi détermine les bonnes pratiques cliniques, telles que visées à l'annexe XV, du règlement 2017/745.
- Travaux parlementaires de cette loi :

  L'article en projet habilite le Roi à déterminer les bonnes pratiques cliniques. Le règlement fait en effet référence aux bonnes pratiques cliniques sans cependant les définir, bien que son considérant (64) dispose que "Les dispositions régissant les investigations cliniques devraient être conformes aux lignes directrices internationales bien établies dans ce domaine, telles que la norme internationale ISO 14155:2011 sur les bonnes pratiques cliniques en matière d'investigation clinique des dispositifs médicaux pour sujets humains, afin que les résultats des investigations cliniques menées dans l'Union puissent être plus facilement acceptés ailleurs comme documentation et que les résultats des investigations cliniques menées hors de l'Union conformément aux lignes directrices internationales puissent être plus facilement acceptés dans l'Union. En outre, ces dispositions devraient être alignées sur la dernière version de la déclaration d'Helsinki de l'Association médicale mondiale sur les principes éthiques applicables à la recherche médicale impliquant des êtres humains.". Déterminer en quoi consistent ces bonnes pratiques cliniques en droit belge permettra d'éviter toute discussion quant à leur statut légal, ce dernier ne pouvant en aucun cas être limité à du soft law. Le Roi est habilité à les déterminer dans la mesure où il s'agit de normes techniques qui peuvent évoluer au cours du temps.[xxxxxx]

- *Avis du CE*

  6.12. Conformément à l'article 31 de l'avant-projet, le Roi détermine les bonnes pratiques cliniques, telles que visées à l'annexe XV, du règlement. Interrogés sur le point de savoir quelles sont les divisions de cette annexe précisément visées et sur quel fondement ces bonnes pratiques cliniques peuvent être établies par les États membres, les délégués ont répondu comme suit :

  « Chapitre I, 2.7, chapitre II, 3.12, et chapitre III, 4. et 6. de l'annexe XV. Le chapitre I de l'annexe XV du règlement 745/2017 indique que l'investigateur et le personnel qui participe à la conduite d'une investigation reçoit les instructions et la formation adéquates relative aux bonnes pratiques cliniques. Le chapitre II de l'annexe XV, point 3.12 fait référence à la mise à disposition par le promoteur d'une déclaration de conformité avec les principes éthiques reconnus applicables à la recherche médicale impliquant des êtres humains et avec les principes de bonnes pratiques cliniques. Par ailleurs au point 4 du chapitre III, le promoteur doit désigner une personne indépendante du site d'investigation pour veiller aux principes des bonnes pratiques cliniques et au règlement 745/2017 et le promoteur devra également démontrer le respect de ces bonne pratiques cliniques (point 6). Afin que ces différentes exigences puissent être contrôlées et mises en œuvre, il est nécessaire de déterminer en quoi consiste ces bonnes pratiques cliniques. L'article 31 du projet vise cet objectif. C'est également ce qui ressort du considérant 64 du règlement : 'Les dispositions régissant les investigations cliniques devraient être conformes aux lignes directrices internationales bien établies dans ce domaine, telles que

[wwwwww] Avis 40.219/3 de la section de Législation du Conseil d'Etat concernant le projet d'arrêté royal modifiant l'arrêté royal du 30 juin 200 déterminant des mesures d'exécution de la loi du 7 mai 2004 relative aux expérimentations sur la personne humaine en ce qui concerne les essais cliniques de médicaments à usage humain. http://www.raadvst-consetat.be/dbx/avis/40219.pdf#search=%22D%C3%A9claration%20d'Helsinki%22.

[xxxxxx] https://www.lachambre.be/FLWB/PDF/55/1534/55K1534001.pdf.

la norme internationale ISO 14155:2011 sur les bonnes pratiques cliniques en matière d'investigation clinique des dispositifs médicaux pour sujets humains, afin que les résultats des investigations cliniques menées dans l'Union puissent être plus facilement acceptés ailleurs comme documentation et que les résultats des investigations cliniques menées hors de l'Union conformément aux lignes directrices internationales puissent être plus facilement acceptés dans l'Union. En outre, ces dispositions devraient être alignées sur la dernière version de la déclaration d'Helsinki de l'Association médicale mondiale sur les principes éthiques applicables à la recherche médicale impliquant des êtres humains.'».

Dès lors que le règlement ne définit pas lui-même les bonnes pratiques cliniques en matière d'investigations cliniques des dispositifs médicaux et n'accorde pas non plus de délégation à la Commission sur ce point pour le faire par un acte délégué ou un acte d'exécution, il peut être admis que, dans un souci de sécurité juridique et en exécution des dispositions du règlement précitées, elles soient établies par une règle du droit interne « conformément aux lignes directrices internationales bien établies », eu égard à ce que mentionne le considérant 64 du règlement.[yyyyyy]

4. Arrêté royal du 18 mars 1999 relatif aux dispositifs médicaux

   - Annexe X.2 (relative aux investigations cliniques dans le cadre de l'évaluation clinique) + annexe 7 de l'AR du 5 JUILLET 1997 relatif aux dispositifs médicaux implantables actifs.

Art. 2N10.2. Investigations cliniques.

2.1. Objectifs.

Les objectifs des investigations cliniques sont :

- de vérifier que, dans des conditions normales d'utilisation, les performances du dispositif sont conformes à celles visées à l'annexe I point 3, et;

- de déterminer les éventuels effets secondaires indesirables dans des conditions normales d'utilisation et d'évaluer si ceux-ci constituent des risques au regard des performances assignées au dispositif.

2.2. Considérations éthiques.

Les investigations cliniques sont effectuées conformément à la déclaration d'Helsinki adoptée en 1964 par la dix-huitième assemblée mondiale à Helsinki, Finlande, telle que modifiée en dernier lieu par l'assemblée médicale mondiale. Il est impératif que toutes les mesures relatives à la protection de la personne humaine soient appliquées dans l'esprit de la Déclaration d'Helsinki. Il doit en être ainsi pour chaque étape des investigations cliniques, depuis la première réflexion sur la nécessité et la justification de l'étude jusqu'à la publication des résultats.

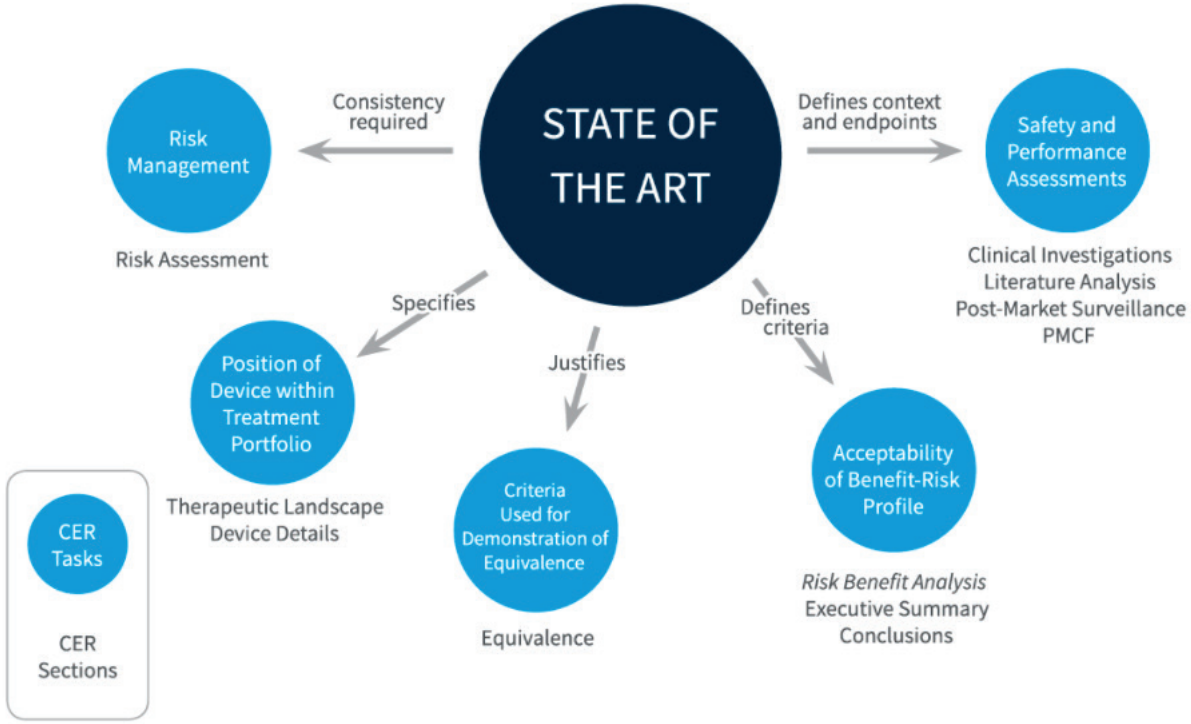
5. ISO 14155:2020

   In Belgium ISO 14155:2020 is mandatory for clinical trials with medical devices (Royal Decree of 18.05.2021)

yyyyyy http://www.raadvst-consetat.be/dbx/avis/67276.pdf#search=%22D%C3%A9claration%20d'Helsinki%22

APPENDIX 2. STATE OF THE ART IN MEDICAL DEVICES

Figure 8 – Core Role of State of the Art



Source *https://www.evidencepartners.com/resources/guides-white-papers/state-of-art-solution-brief-distillersr*

APPENDIX 3. THE DIVISION OF TASKS BETWEEN FAMHP AND ETHICS COMMITTEES

http://www.ejustice.just.fgov.be/cgi_loi/loi_a1.pl?imgcn.x=55&imgcn.y=5&DETAIL=2021051802%2FF&caller=list&row_id=1&*numero*=1&rech=5&cn=2021051802&table_name=LOI&nm=2021041589&la=F&chercher=t&dt=ARRETE+ROYAL&language=fr&fr=f&choix1=ET&choix2=ET&fromtab=loi_all&sql=dt+contains++%27ARRETE%27%2526+%27ROYAL%27+and+dd+%3D+date%272021-05-18%27and+actif+%3D+%27Y%27&ddda=2021&tri=dd+AS+RANK+&trier=promulgation&dddj=18&dddm=05#hit1

N°	Eléments	AFMPS	Comité d'éthique
1	La vérification du fait que le promoteur ou son représentant légal se situe dans l'Union européenne.	X	
2	L'évaluation du fait que les participants potentiellement inclus dans l'investigation clinique bénéficieront, le cas échéant, d'une protection appropriée conformément aux articles 64 à 66 et 68 du règlement 2017/745.		X
3	L'évaluation du fait que les bénéfices attendus pour les participants à l'investigation clinique ou la santé publique justifient les risques et inconvénients prévisibles mais également que le respect de cette condition est surveillé en permanence durant l'investigation clinique.	X	X
4	La vérification du caractère adéquat et complet des informations écrites à fournir au participant ou, s'il n'est pas en mesure de donner son consentement éclairé, son représentant légal pourra donner son consentement éclairé conformément à l'article 63 du règlement 2017/745 et à la procédure d'obtention du consentement éclairé.		X
5	La vérification du fait que le participant ou, si le participant n'est pas en mesure de donner son consentement éclairé, son représentant légal, pourra recevoir les coordonnées d'une entité auprès de laquelle il pourra recevoir de plus amples informations en cas de besoin.		X
6	La vérification du fait que les droits du participant à l'intégrité physique et mentale, au respect de la vie privée et à la protection des données le concernant conformément au règlement (UE) 2016/679, sont préservés.		X
7	L'évaluation du fait que l'investigation clinique a été conçue pour causer aussi peu de douleur, de désagrément et de peur que possible et pour réduire autant que possible tout autre risque prévisible pour les participants, et que tant le seuil de risque que le degré d'angoisse sont définis expressément dans le protocole d'investigation clinique et seront contrôlés en permanence lors de l'investigation clinique.	X	X
8	La vérification et l'évaluation de la compétence de l'investigateur et du fait que les soins dispensés aux participants sont de la responsabilité d'un médecin dûment qualifié ou, le cas échéant, d'un dentiste qualifié ou de toute autre personne habilitée par le droit national à dispenser les soins concernés aux patients dans des conditions d'investigation clinique.		X
9	La vérification du fait qu'aucune contrainte, y compris de nature financière, n'est exercée sur le participant ou, le cas échéant, sur son représentant légal, pour qu'il participe à l'investigation clinique.		X
10	L'évaluation du fait que le ou les dispositifs en question faisant l'objet de l'investigation clinique respecte(nt) les exigences générales en matière de sécurité et de performances énoncées à l'annexe I du règlement 2017/745, sauf pour ce qui est des aspects relevant de l'investigation clinique et, en ce qui concerne ces aspects, que toutes les précautions ont été prises pour protéger la santé et la sécurité des participants. Il s'agit notamment, le cas échéant, de tests portant sur la sécurité biologique et technique et d'évaluation préclinique, ainsi que de dispositions dans le domaine de la sécurité au travail et de prévention des accidents, compte tenu de l'état de l'art.	X	
11	L'évaluation du fait que toutes les étapes de l'investigation clinique, depuis la réflexion initiale sur la nécessité et la justification de l'investigation clinique jusqu'à la publication des résultats, respecteront des principes éthiques reconnus.		X
12	L'évaluation du fait que l'investigation clinique sera conduite selon un protocole d'investigation approprié correspondant au dernier état de la science et de la technique et défini de manière à confirmer ou à réfuter les allégations du fabricant concernant la sécurité, les performances et les aspects relatifs au rapport bénéfice/risque des dispositifs visés à l'article 62, § 1er du règlement 2017/745. L'évaluation du fait que l''investigation clinique comporte un nombre d'observations suffisant pour garantir la validité scientifique des conclusions. La vérification que les raisons du choix de la conception et de la méthode statistique sont exposées dans le plan d'investigation clinique et leur évaluation.	X	X
13	L'évaluation du fait que les procédures et les méthodes d'investigation utilisées pour conduire l'investigation clinique seront adaptées au dispositif faisant l'objet de l'investigation clinique.	X	X
14	L'évaluation du fait que les méthodes de recherche utilisées pour conduire l'investigation clinique seront adaptées au dispositif faisant l'objet de l'investigation clinique.	X	X
15	L'évaluation du fait que l'investigation clinique sera conduite conformément au protocole d'investigation clinique auprès d'un nombre suffisant d'utilisateurs auxquels le dispositif est destiné et dans un environnement clinique qui sera représentatif des conditions normales d'utilisation du dispositif prévues dans la population de patients visée.	X	
16	L'évaluation du fait que toutes les caractéristiques techniques et fonctionnelles pertinentes du dispositif, en particulier celles relatives à la sécurité et aux performances, et leurs résultats cliniques escomptés sont correctement traités lors de la conception de l'investigation clinique.	X	
17	La vérification du fait que les critères d'évaluation de l'investigation clinique portent sur la destination, les bénéfices cliniques, les performances et la sécurité du dispositif, et qu'ils sont déterminés et évalués au moyen de méthodes scientifiquement valides.	X	
18	La vérification du fait que les investigateurs auront accès aux données techniques et cliniques relatives au dispositif et que le personnel qui participe à la conduite de l'investigation a reçu ou recevra les instructions et la formation adéquates au sujet de la bonne utilisation du dispositif faisant l'objet de l'investigation et en ce qui concerne le protocole d'investigation clinique et les bonnes pratiques cliniques.		X
19	La vérification que le formulaire de demande, le protocole d'investigation clinique et la brochure pour l'investigateur répondent aux exigences minimales respectivement établies à l'annexe XV, chapitre II, 1., 2. et 3.du règlement 2017/745.	X	
20	La vérification que le promoteur a contracté une assurance couvrant sa responsabilité pour tout dommage causé aux participants conformément à l'article 69 du règlement 2017/745, et à l'article 32 de la loi du 22 décembre 2020 relative aux dispositifs médicaux.		X

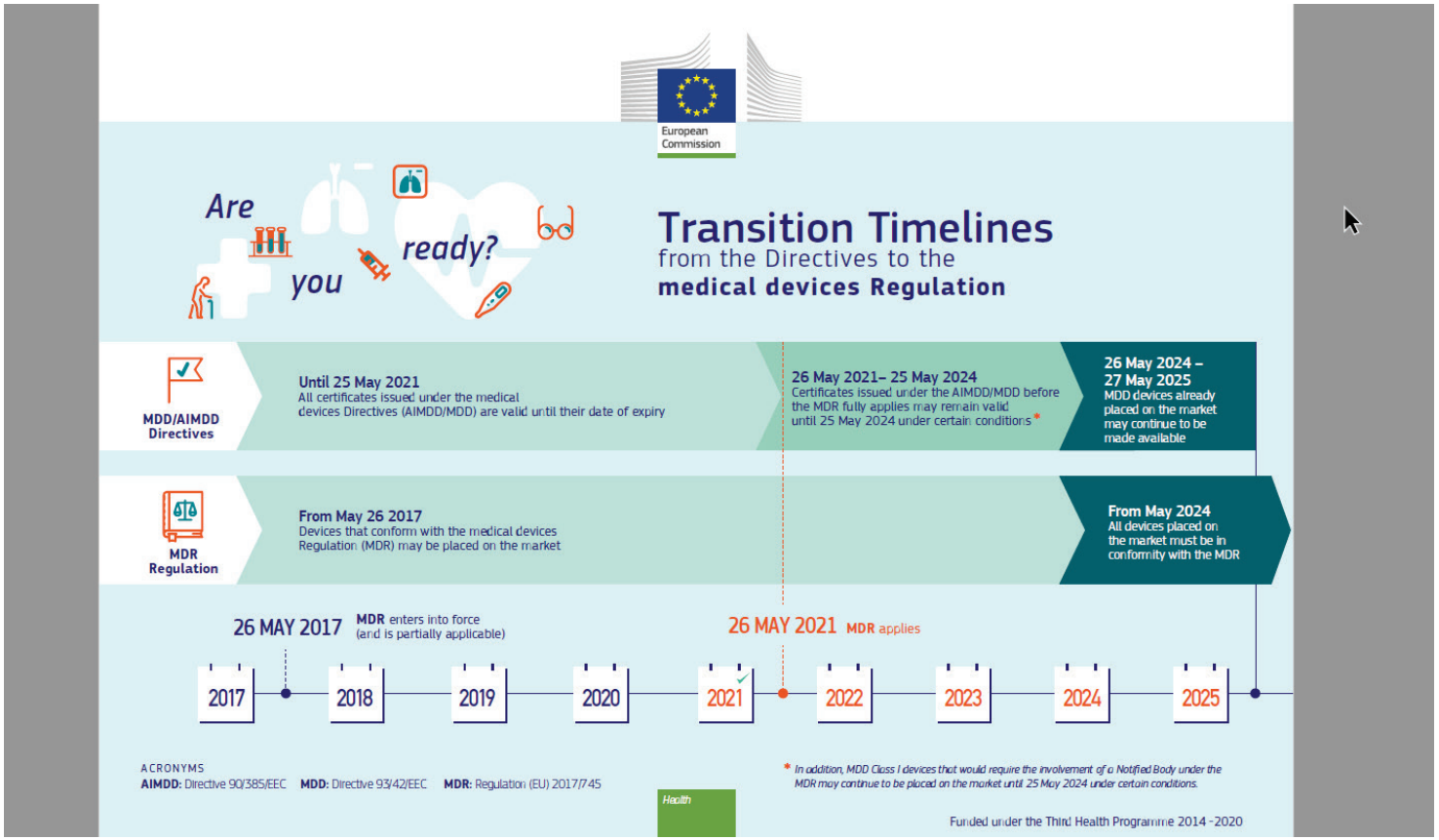
APPENDIX 4. DATA AVAILABLE IN THE SSCP

Table 7 – Data to be publicly available in the Summary of Safety and Clinical Performance (SSCP) on the Eudamed database[18]

Device identification and general information
Device trade name(s), manufacturer
Basic unique device identification code (UDI-DI)
Nomenclature of the medical device, and its risk class
Name of the notified body that issued the certificate for the device
Intended use of the device
Intended purpose
Indications and target populations
Contraindications and/or limitations
Device description
Description of the device
Comparison with previous generation(s) or variants of the device, if any
Description of any accessories to be used in combination with the device
Risks and warnings
Residual risks and undesirable effects
Warnings and precautions
Other relevant aspects of safety, including any field safety actions
Summary of clinical evaluation and post-market clinical follow-up
Summary of clinical data related to equivalent device, if applicable
Summary of clinical data from investigations of the device before the CE marking
Summary of clinical data from other sources, if applicable
An overall summary of the clinical performance and safety
Ongoing or planned post-market clinical follow-up
Possible diagnostic or therapeutic alternatives
Suggested profile and training for users
Reference to any harmonized standards and common specifications applied

Source : https://academic.oup.com/eurheartj/article/41/27/2589/5849536?login=true

APPENDIX 5. TRANSITION TIMELINES MDD- MDR



Source: https://ec.europa.eu/health/sites/default/files/md_newregulations/docs/md_infographic-timeline_en.pdf

APPENDIX 6. COSTS FOR FAMHP ADVICE

Rétributions & contributions AFMPS – RECHERCHE et DÉVELOPPEMENT – Essais cliniques

Due par

A. Promoteurs d'essais cliniques.
B. Centres d'essais cliniques.

Base légale

1. Article 1 de l'Arrêté Royal du 15 juillet 2004 déterminant les mesures d'exécution de la Loi du 7 mai 2004 relative aux expérimentations sur la personne humaine en ce qui concerne les essais cliniques de médicaments à usage humain.
2. Article 30, §6 de la Loi du 7 mai 2004 relative aux expérimentations sur la personne humaine.
3. Article 30, §9/1 de la Loi du 7 mai 2004 relative aux expérimentations sur la personne humaine déterminant les redevances à payer dans le cadre de l'article 26/1, 1er alinéa.
4. Loi portant modification de la Loi du 20 juillet 2006 relative à la création et au fonctionnement de l'AFMPS et portant diverses autres dispositions relatives au financement de l'AFMPS.

Montants applicables au 1er janvier 2020 (indexation)

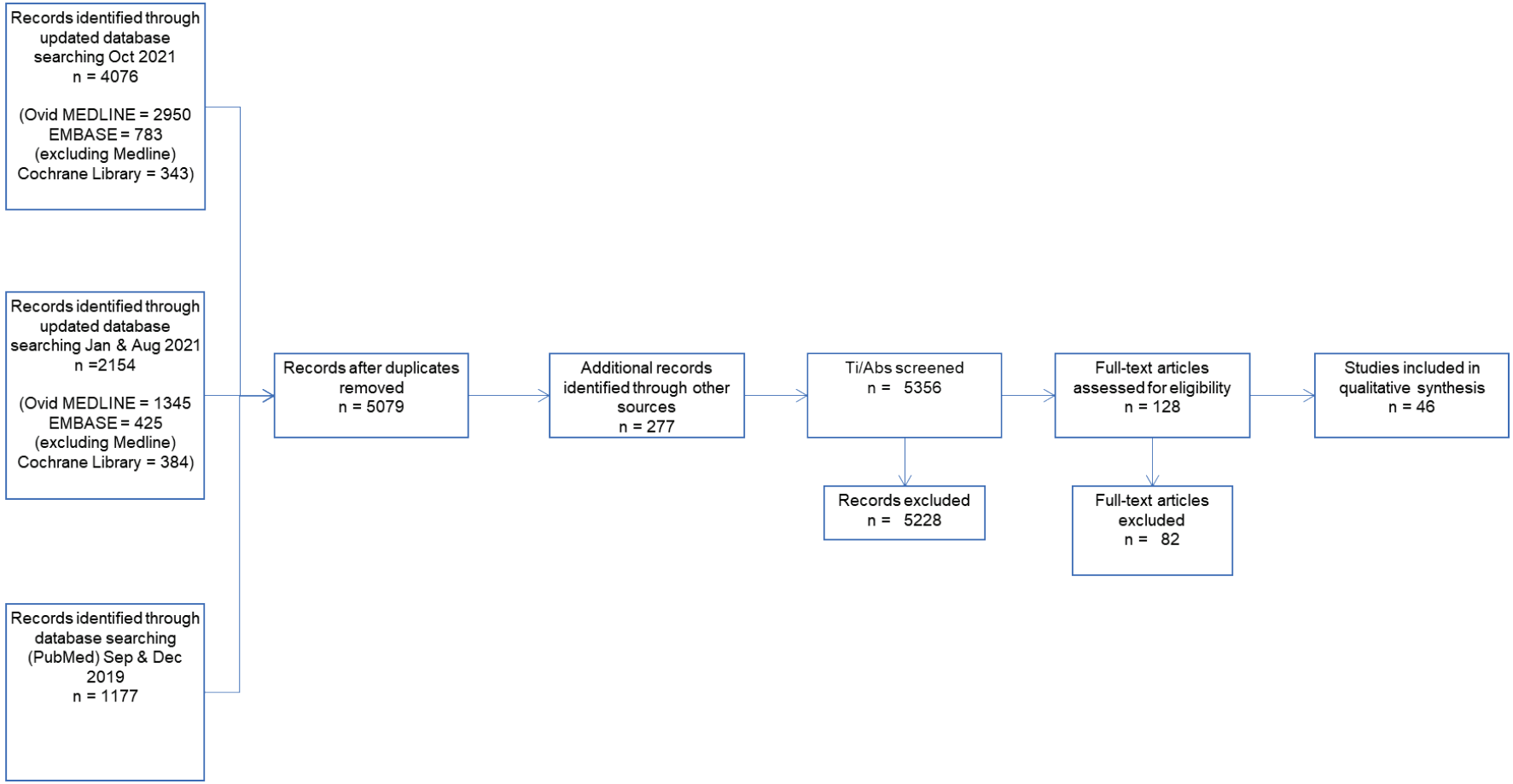
Dossier phase 1 – CTR pilot – Hors CTR pilot	 **0 €** **5.966,68 €**
Dossier autre phase – CTR pilot – Hors CTR pilot	 **0 €** **3.978,58 €**
Investigation GCP (par tranche de quatre heures par inspecteur)	**632,29 €**
Amendement – CTR pilot – Hors CTR pilot	 **0 €** **655,07 €**
Introduction d'une demande d'accréditation pour essai clinique de phase 1	**17.538,59 €**

Paiement

Ces montants doivent être versés au numéro de compte 679-0001514-59 de l'Agence Fédérale des Médicaments et des Produits de Santé
code IBAN : **BE84 6790 0015 1459**
code BIC/Swift : PCHQBEBB

Source: https://www.afmps.be/sites/default/files/content/2020_randd-fr_0.pdf

APPENDIX 7. FLOW CHART OF LITERATURE SEARCH



APPENDIX 8. INITIAL SEARCH STRATEGY FOR MEDICAL DEVICES

20190917 PubMed Search strategy for:

(Market Approval OR Reimbursement) AND Europe AND Evidence AND Medical Devices, date limited from June 1st, 2011.

Date	September 17th 2019	
Database	PubMed (MEDLINE - 1966 to present; PubMed Central (PMC), and Bookshelf) <1966 to September 17, 2019>	
Search strategy		
1	CE Mark	473
2	"CE marking"	88
3	conformité européenne	67
4	conformity europeenne	2
5	"European conformity"	22
6	European conformity	324
7	"notified body"	55
8	"notified bodies"	28
9	"conformity assessment"	82
10	"competent authority"	179
11	"competent authorities"	383
12	licencing	107
13	unlicenced	7
14	licenced	294
15	"licensing"	8256
16	unlicensed	1462
17	"licensed"	18656
18	"European Medicines Agency"	3056
19	("Food and Drugs Administration")	142
20	"Therapeutic Goods Administration"	242

21	"Health Canada"	4544
22	Medsafe	26
23	Swissmedic	90
24	"EMA"	8559
25	"FDA"	51839
26	(united states food and drug administration[MeSH Terms])	28504
27	"market approval"	316
28	"pre market approval"	61
29	"premarket approval"	282
30	"regulatory approval"	2350
31	"marketing approval"	652
32	"marketing approvals"	28
33	"marketing authorisation"	442
34	"marketing authorization"	976
35	"market authorisation"	61
36	"market authorization"	210
37	"marketing authorisations"	92
38	"marketing authorizations"	88
39	"market authorisations"	22
40	"market authorizations"	9
41	dossier[Title/Abstract]	660
42	dossiers[Title/Abstract]	359
43	market[Title/Abstract]	65159
44	marketing[Title/Abstract]	25433
45	regulation[Title/Abstract]	805705
46	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 45	994627

47	("Prostheses and Implants"[Mesh])	498122
48	"medical devices"[Title/Abstract]	10389
49	"medical device"[Title/Abstract]	5076
50	47 or 48 or 49	510469
51	"Equipment and Supplies"[Mesh]	1404031
52	"Self-Help Devices"[Mesh]	11070
53	"Surgical Instruments"[Mesh]	23847
54	"device"	262866
55	"devices"	277108
56	"aid"	164850
57	"aids"	247381
58	"equipment"	312631
59	armamentarium	10449
60	"appliance"	12696
61	"appliances"	22073
62	"instrument"	115843
63	"instruments"	115136
64	"apparatus"	124798
65	"good"	767353
66	"goods"	6970
67	"implement"	65635
68	"implements"	5020
69	"material"	536721
70	"materials"	947486
71	"machine"	81894
72	"machines"	20219
73	51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72	4245742

74	"Diagnosis"[Mesh]	8264209
75	"Rehabilitation"[Mesh]	291508
76	"Secondary Prevention"[Mesh]	19391
77	"Therapeutics"[Mesh]	4413477
78	"diagnosis"	3442255
79	"diagnoses"	125212
80	"diagnosed"	532419
81	"diagnostic"	1872951
82	"diagnostics"	88141
83	"therapy"	4968857
84	"therapies"	293580
85	"treatment"	4626050
86	"treatments"	435514
87	"therapeutic"	2949045
88	"therapeutics"	146852
89	prevention	1678804
90	preventative	15326
91	monitoring	641629
92	screening	4586878
93	rehabilitation	596484
94	rehabilitative	599807
95	"alleviation"	10747
96	"alleviate"	34181
97	"alleviates"	10788
98	"diagnosis" [Subheading]	3415605
99	"diagnostic imaging" [Subheading]	1128120
100	"therapy" [Subheading]	6800473
101	"rehabilitation" [Subheading]	192243

102	74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101	16882897
103	73 and 102	2792956
104	50 or (73 and 102)	2889930
105	European[Title/Abstract]	189846
106	Europe[Title/Abstract]	111364
107	Europe's[Title/Abstract]	1038
108	"European Union"[Mesh]	15583
109	"Europe"[Mesh:NoExp]	100262
110	105 or 106 or 107 or 108 or 109	316158
111	evidence[Title/Abstract]	1650280
112	known[Title/Abstract]	1280423
113	knowns[Title/Abstract]	220
114	unknown[Title/Abstract]	451994
115	unknowns[Title/Abstract]	2217
116	knowledge[Title/Abstract]	650303
117	uncertain[Title/Abstract]	71843
118	uncertainty[Title/Abstract]	68775
119	uncertainties[Title/Abstract]	23470
120	claim[Title/Abstract]	24961
121	claims[Title/Abstract]	46634
122	claimed[Title/Abstract]	19015
123	"Evidence-Based Practice"[Mesh]	85318
124	111 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123	3873595
125	110 and 124 and 46	5073
126	110 and 124 and 46 and 104	774
127	reimbursement	41698

128	reimbursable	405
129	reimburse	690
130	reimbursed	3103
131	reimbursements	1741
132	coverage	119472
133	payer	8477
134	payers	6999
135	purchase	11612
136	purchaser	682
137	purchases	2513
138	purchasers	2031
139	procure	1233
140	procures	85
141	procured	3115
142	procurement	23995
143	finance	10027
144	finances	762526
145	financed	2845
146	financing	764692
147	payment	27342
148	payments	10801
149	"Reimbursement Mechanisms"[Mesh:NoExp]	12684
150	("Accounts Payable and Receivable"[Mesh])	1624
151	"Group Purchasing"[Mesh]	1054
152	"Purchasing, Hospital"[Mesh]	5804
153	"Economics"[Mesh]	583804
154	"economics" [Subheading]	410564

155	127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154	915633
156	155 and 124 and 110	5519
157	155 and 124 and 110 and 104	846
158	(110 and 124 and 46 and 104) or (155 and 124 and 110 and 104)	1473
159	Filters: Publication date from 2011/06/01	895

APPENDIX 9. ADAPTED SEARCH STRATEGY FOR DRUGS

20191217 PubMed Search strategy for:

Market Approval AND Europe AND Evidence AND Drugs

Search Strategy 20190916		
CONCEPT	Search String	# Results
Market approval	"competent authority" OR "competent authorities" OR licencing OR unlicenced OR licenced OR "licensing" OR unlicensed OR "licensed" OR "European Medicines Agency" OR "Food and Drug Administration" OR "Therapeutic Goods Administration" OR "Health Canada" OR Medsafe OR Swissmedic OR "EMA" OR "FDA" OR "United States Food and Drug Administration"[Mesh] OR "market approval" OR "regulatory approval" OR "marketing approval" OR "marketing approvals" OR "marketing authorisation" OR "marketing authorization" OR "market authorisation" OR "market authorization" OR "marketing authorisations" OR "marketing authorizations" OR "market authorisations" OR "market authorizations" OR dossier[Title/Abstract] OR	1031662 (17DEC2019)

	dossiers[Title/Abstract] OR market[Title/Abstract] OR marketing[Title/Abstract] OR regulation[Title/Abstract]	
AND		
Evidence Gaps	"Evidence-Based Practice"[Mesh] OR evidence[Title/Abstract] OR known[Title/Abstract] OR knowns[Title/Abstract] OR unknown[Title/Abstract] OR unknowns[Title/Abstract] OR knowledge[Title/Abstract] OR uncertain[Title/Abstract] OR uncertainty[Title/Abstract] OR uncertainties[Title/Abstract] OR claim[Title/Abstract] OR claims[Title/Abstract] OR claimed[Title/Abstract]	3938356
AND		
Europe	European[Title/Abstract] OR Europe[Title/Abstract] OR Europe's[Title/Abstract] OR "European Union"[Mesh] OR "Europe"[Mesh:NoExp]	321059
Combining Market Approval AND Evidence AND Europe		
5317		
AND		
Drug Terms		
Drugs	"Pharmaceutical Preparations"[Mesh] OR "pharmaceutic"[Title/Abstract] OR "pharmaceutical"[Title/Abstract] OR "pharmaceuticals"[Title/Abstract] OR	2252619

	"drug"[Title/Abstract] OR "drugs"[Title/Abstract] OR “medicinal product”[Title/Abstract] OR “medicinal products”[Title/Abstract]
Combining Market Approval AND Evidence AND Europe AND Drugs	
2197	

If also including Reimbursement		
CONCEPT	Search Terms	# Results
Reimbursement	reimbursement OR reimbursable OR reimburse OR reimbursed OR reimbursements OR coverage OR payer OR payers OR purchase OR purchaser OR purchases OR purchasers OR procure OR procures OR procured OR procurement OR finance OR finances OR financed OR financing OR payment OR payments OR "Reimbursement Mechanisms"[Mesh:NoExp] OR	930385

	"Accounts Payable and Receivable"[Mesh] OR "Group Purchasing"[Mesh] OR "Purchasing, Hospital"[Mesh] OR "Economics"[Mesh] OR "economics" [Subheading] OR “health technology assessment”[Title/Abstract] OR “HTA”[Title/Abstract]
Combining Market Approval AND Evidence AND Europe AND Drugs AND Reimbursement	
384	
Combining Market Approval AND Evidence AND Europe AND Drugs AND Reimbursement AND Past 10 years	
282 (17DEC2019)	

APPENDIX 10. UPDATE OF THE SEARCH STRATEGY

Appendix 10.1. Medline

Date	January 15, 2021	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to January 15, 2021>	
Search strategy		
1	CE Mark*.ab,ti,kf.	581
2	(conformit* adj2 europe*).ab,ti,kf.	173
3	"notified body".ab,ti,kf.	31
4	"notified bodies".ab,ti,kf.	37
5	"conformity assessment".ab,ti,kf.	95
6	"competent authority".ab,ti,kf.	265
7	"competent authorities".ab,ti,kf.	526
8	licen#ing.ab,ti,kf.	8635
9	unlicen#ed.ab,ti,kf.	1597
10	licen#ed.ab,ti,kf.	20143
11	"European Medicines Agency".ab,ti,kf.	3317
12	"Food and Drugs Administration".ab,ti,kf.	136
13	"Therapeutic Goods Administration".ab,ti,kf.	230
14	"Health Canada".ab,ti,kf.	1457
15	Medsafe.ab,ti,kf.	21
16	Swissmedic.ab,ti,kf.	59
17	"EMA".ab,ti,kf.	9285
18	"FDA".ab,ti,kf.	46519
19	"United States Food and Drug Administration"/	29952
20	((market or premarket or regulatory or marketing) adj2 (approval? or authori#ation?)).ab,ti,kf.	6813
21	dossier?.ab,ti,kf.	1589

22	market.ab,ti,kf.	74289
23	marketing.ab,ti,kf.	28078
24	regulation?.ab,ti,kf.	915245
25	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	1107197
26	exp "Evidence-Based Practice"/	89595
27	evidence.ab,ti,kf.	1824827
28	known.ab,ti,kf.	1407073
29	knowns.ab,ti,kf.	299
30	unknown?.ab,ti,kf.	507951
31	knowledge.ab,ti,kf.	739182
32	uncertain*.ab,ti,kf.	176977
33	claim.ab,ti,kf.	27491
34	claims.ab,ti,kf.	52981
35	claimed.ab,ti,kf.	20572
36	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	4292776
37	25 and 36	287165
38	Europ*.ab,ti,kf.	319265
39	Europe/	106946
40	38 or 39	356939
41	37 and 40	6476
42	exp "Prostheses and Implants"/	529125
43	medical device?.ab,ti,kf.	16235
44	42 or 43	543606
45	exp "Equipment and Supplies"/	1493610
46	exp "Self-Help Devices"/	11799
47	exp Surgical Instruments/	24728
48	device?.ab,ti,kf.	444144

49	aid.ab,ti,kf.	174155
50	aids.ab,ti,kf.	156576
51	equipment?.ab,ti,kf.	101701
52	armamentarium.ab,ti,kf.	11461
53	appliance?.ab,ti,kf.	18190
54	instrument?.ab,ti,kf.	205074
55	apparatus.ab,ti,kf.	93543
56	good?.ab,ti,kf.	844736
57	implement?.ab,ti,kf.	80213
58	material?.ab,ti,kf.	1236235
59	machine?.ab,ti,kf.	113191
60	45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59	4236145
61	exp Diagnosis/	8677851
62	exp Rehabilitation/	311994
63	exp Secondary Prevention/	20858
64	exp Therapeutics/	4674140
65	diagnos*.ab,ti,kf.	2612649
66	therapy.ab,ti,kf.	2001966
67	therapies.ab,ti,kf.	311138
68	treatment?.ab,ti,kf.	4685103
69	therapeutic?.ab,ti,kf.	1169001
70	prevention.ab,ti,kf.	594121
71	preventative.ab,ti,kf.	15392
72	monitoring.ab,ti,kf.	521790
73	screening.ab,ti,kf.	555822
74	rehabilitation.ab,ti,kf.	174130
75	rehabilitative.ab,ti,kf.	8536
76	alleviat*.ab,ti,kf.	105181

77	di.xs.	3626895
78	th.xs.	7187717
79	61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78	17706784
80	60 and 79	2769981
81	44 or 80	2876659
82	41 and 81	937
Comments		

Appendix 10.2. Embase

Date	**29 Jan 2021**	
Database	Embase.com	
Search strategy		
#1	(ce NEAR/1 mark*):ab,ti	1526
#2	(conformit* NEAR/2 europe*):ab,ti	200
#3	'notified body':ab,ti	54
#4	'notified bodies':ab,ti	62
#5	'conformity assessment':ab,ti	125
#6	'competent authority':ab,ti	434
#7	'competent authorities':ab,ti	864
#8	licen?ing:ab,ti	10971
#9	unlicen?ed:ab,ti	2297
#10	licen?ed:ab,ti	28143
#11	'european medicines agency':ab,ti	5558
#12	'food and drugs administration':ab,ti	179
#13	'therapeutic goods administration':ab,ti	366
#14	'health canada':ab,ti	2239
#15	medsafe:ab,ti	32

#16	swissmedic:ab,ti	137
#17	'ema':ab,ti	15751
#18	'fda':ab,ti	83230
#19	'food and drug administration'/exp	90972
#20	((market OR premarket OR regulatory OR marketing) NEAR/2 (approval? OR authori?ation?)):ab,ti	1027
#21	dossier?:ab,ti	908
#22	market:ab,ti	100141
#23	marketing:ab,ti	37413
#24	regulation?:ab,ti	62351
#25	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	374176
#26	'evidence based practice'/exp	1387856
#27	evidence:ab,ti	2233392
#28	known:ab,ti	1851564
#29	knowns:ab,ti	351
#30	unknown?:ab,ti	3100
#31	knowledge:ab,ti	926624
#32	uncertain*:ab,ti	226620
#33	claim:ab,ti	37922
#34	claims:ab,ti	77561
#35	claimed:ab,ti	26752
#36	#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35	5895064
#37	#25 AND #36	90076
#38	europ*:ab,ti	522386
#39	'europe'/exp	1699355
#40	#38 OR #39	2040454
#41	#37 AND #40	15023
#42	'prostheses and orthoses'/exp	391656

#43	(medical NEAR/1 device?):ab,ti	16535
#44	#42 OR #43	407112
#45	'devices'/exp	4163855
#46	'self help device'/exp	1606
#47	'surgical equipment'/exp	424087
#48	device?:ab,ti	270924
#49	aid:ab,ti	224440
#50	aids:ab,ti	176776
#51	equipment?:ab,ti	3776
#52	armamentarium:ab,ti	15040
#53	appliance?:ab,ti	10415
#54	instrument?:ab,ti	123791
#55	apparatus:ab,ti	100773
#56	good?:ab,ti	9949
#57	implement?:ab,ti	6487
#58	material?:ab,ti	1045439
#59	machine?:ab,ti	29963
#60	#45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59	5499222
#61	'diagnosis'/de	1381649
#62	'rehabilitation'/exp	421063
#63	'secondary prevention'/de	29445
#64	'therapy'/exp	9127981
#65	diagnos*:ab,ti	3747760
#66	therapy:ab,ti	2759238
#67	therapies:ab,ti	465955
#68	treatment?:ab,ti	681614
#69	therapeutic?:ab,ti	114574

#70	prevention:ab,ti	745212
#71	preventative:ab,ti	21913
#72	monitoring:ab,ti	714508
#73	screening:ab,ti	769408
#74	rehabilitation:ab,ti	239865
#75	rehabilitative:ab,ti	12062
#76	alleviat*:ab,ti	130949
#77	#61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76	14220345
#78	#60 AND #77	2511328
#79	#44 OR #78	2759398
#80	#41 AND #79	2082
#81	#80 NOT [medline]/lim	1306
#82	#81 NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it)	227
Comments		

Appendix 10.3. Cochrane

Date	29/01/2021 20:26:12	
Database	Cochrane@Wiley.com	
Search strategy		
#1	(CE NEAR/1 Mark*):ab,ti	292
#2	(conformit* NEAR/2 europe*):ab,ti	40
#3	"notified body":ab,ti	7
#4	"notified bodies":ab,ti	2
#5	"conformity assessment":ab,ti	5
#6	"competent authority":ab,ti	44
#7	"competent authorities":ab,ti	37
#8	licen?ing:ab,ti	427
#9	unlicen?ed:ab,ti	77
#10	licen?ed:ab,ti	3328
#11	"European Medicines Agency":ab,ti	475
#12	"Food and Drugs Administration":ab,ti	12
#13	"Therapeutic Goods Administration":ab,ti	36
#14	"Health Canada":ab,ti	244
#15	Medsafe:ab,ti	1
#16	Swissmedic:ab,ti	24
#17	"EMA":ab,ti	906
#18	"FDA":ab,ti	7757
#19	[mh ^"United States Food and Drug Administration"]	220
#20	((market or premarket or regulatory or marketing) NEAR/2 (approval? or authori?ation?)):ab,ti	525
#21	dossier?:ab,ti	220
#22	market:ab,ti	2826
#23	marketing:ab,ti	1900

#24	regulation?:ab,ti	16103
#25	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	33394
#26	[mh "Evidence-Based Practice"]	1227
#27	evidence:ab,ti	122763
#28	known:ab,ti	57903
#29	knowns:ab,ti	7
#30	unknown?:ab,ti	25273
#31	knowledge:ab,ti	35470
#32	uncertain*:ab,ti	12507
#33	claim:ab,ti	1241
#34	claims:ab,ti	2233
#35	claimed:ab,ti	1415
#36	#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35	230163
#37	#25 and #36	8371
#38	Europ*:ab,ti	33452
#39	[mh ^"Europe"]	2394
#40	#38 or #39	34589
#41	#37 and #40	562
#42	[mh "Prostheses and Implants"]	17318
#43	(medical NEAR/1 device?):ab,ti	1384
#44	#42 or #43	18690
#45	[mh "Equipment and Supplies"]	48579
#46	[mh "Self-Help Devices"]	403
#47	[mh "Surgical Instruments"]	749
#48	device?:ab,ti	46684
#49	aid:ab,ti	9762
#50	aids:ab,ti	8493

#51	equipment?:ab,ti	6247
#52	armamentarium:ab,ti	488
#53	appliance?:ab,ti	2623
#54	instrument?:ab,ti	16084
#55	apparatus:ab,ti	1660
#56	good?:ab,ti	53142
#57	implement?:ab,ti	6844
#58	material?:ab,ti	76463
#59	machine?:ab,ti	6141
#60	#45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59	244030
#61	[mh "Diagnosis"]	333380
#62	[mh "Rehabilitation"]	35803
#63	[mh "Secondary Prevention"]	3175
#64	[mh "Therapeutics"]	306063
#65	diagnos*:ab,ti	147820
#66	therapy:ab,ti	313425
#67	therapies:ab,ti	29456
#68	treatment?:ab,ti	700090
#69	therapeutic?:ab,ti	91150
#70	prevention:ab,ti	80333
#71	preventative:ab,ti	1476
#72	monitoring:ab,ti	48559
#73	screening:ab,ti	52258
#74	rehabilitation:ab,ti	33489
#75	rehabilitative:ab,ti	1478
#76	alleviat*:ab,ti	10443
#77	[mh /DI]	52173

#78	[mh /TH]	93077
#79	#61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78	1154939
#80	#60 and #79	188195
#81	#44 or #80	190644
#82	#41 and #81	164
Comments		

APPENDIX 11. UPDATE FROM JANUARY 2021 TO SEPTEMBER 2021

Appendix 11.1. Medline

Date	August 17, 2021	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to August 17, 2021>	
Search strategy		
1	reimburs*.ab,ti,kf.	29258
2	coverage.ab,ti,kf.	132542
3	payer?.ab,ti,kf.	16562
4	purchase?.ab,ti,kf.	23787
5	purchaser?.ab,ti,kf.	2726
6	procure*.ab,ti,kf.	15165
7	financ*.ab,ti,kf.	120234
8	payment?.ab,ti,kf.	30783
9	Reimbursement Mechanisms/	13212
10	exp "Accounts Payable and Receivable"/	1630
11	exp Group Purchasing/	1065
12	exp Purchasing, Hospital/	5826
13	exp economics/	625003
14	ec.fs.	436750
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	991436
16	exp "Evidence-Based Practice"/	91260
17	evidence.ab,ti,kf.	1895705
18	known.ab,ti,kf.	1457070
19	knowns.ab,ti,kf.	329
20	unknown?.ab,ti,kf.	528809
21	knowledge.ab,ti,kf.	777668

22	uncertain*.ab,ti,kf.	185836
23	claim.ab,ti,kf.	28435
24	claims.ab,ti,kf.	55434
25	claimed.ab,ti,kf.	21194
26	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	4462747
27	15 and 26	159159
28	Europ*.ab,ti,kf.	332390
29	Europe/	111367
30	28 or 29	370520
31	27 and 30	6189
32	exp "Prostheses and Implants"/	546497
33	medical device?.ab,ti,kf.	17170
34	32 or 33	561771
35	exp "Equipment and Supplies"/	1540739
36	exp "Self-Help Devices"/	12182
37	exp Surgical Instruments/	25210
38	device?.ab,ti,kf.	465755
39	aid.ab,ti,kf.	181529
40	aids.ab,ti,kf.	159473
41	equipment?.ab,ti,kf.	106712
42	armamentarium.ab,ti,kf.	11874
43	appliance?.ab,ti,kf.	18668
44	instrument?.ab,ti,kf.	212501
45	apparatus.ab,ti,kf.	94828
46	good?.ab,ti,kf.	879693
47	implement?.ab,ti,kf.	85620
48	material?.ab,ti,kf.	1297062
49	machine?.ab,ti,kf.	125522

50	35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49	4405167
51	exp Diagnosis/	8922316
52	exp Rehabilitation/	324196
53	exp Secondary Prevention/	21533
54	exp Therapeutics/	4806717
55	diagnos*.ab,ti,kf.	2713580
56	therapy.ab,ti,kf.	2068022
57	therapies.ab,ti,kf.	328008
58	treatment?.ab,ti,kf.	4856031
59	therapeutic?.ab,ti,kf.	1221686
60	prevention.ab,ti,kf.	617913
61	preventative.ab,ti,kf.	16387
62	monitoring.ab,ti,kf.	545275
63	screening.ab,ti,kf.	581018
64	rehabilitation.ab,ti,kf.	181841
65	rehabilitative.ab,ti,kf.	8899
66	alleviat*.ab,ti,kf.	114544
67	di.xs.	3773405
68	th.xs.	7437911
69	51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68	18242007
70	50 and 69	2883019
71	34 or 70	2993105
72	31 and 71	955
73	CE Mark*.ab,ti,kf.	623
74	(conformit* adj2 europe*).ab,ti,kf.	183
75	"notified body".ab,ti,kf.	31
76	"notified bodies".ab,ti,kf.	40
77	"conformity assessment".ab,ti,kf.	104

78	"competent authority".ab,ti,kf.	287
79	"competent authorities".ab,ti,kf.	575
80	licen#ing.ab,ti,kf.	8916
81	unlicen#ed.ab,ti,kf.	1642
82	licen#ed.ab,ti,kf.	20940
83	"European Medicines Agency".ab,ti,kf.	3543
84	"Food and Drugs Administration".ab,ti,kf.	144
85	"Therapeutic Goods Administration".ab,ti,kf.	245
86	"Health Canada".ab,ti,kf.	1530
87	Medsafe.ab,ti,kf.	21
88	Swissmedic.ab,ti,kf.	64
89	"EMA".ab,ti,kf.	9948
90	"FDA".ab,ti,kf.	49368
91	"United States Food and Drug Administration"/	30713
92	((market or premarket or regulatory or marketing) adj2 (approval? or authori#ation?)).ab,ti,kf.	7223
93	dossier?.ab,ti,kf.	1952
94	market.ab,ti,kf.	78191
95	marketing.ab,ti,kf.	29139
96	regulation?.ab,ti,kf.	943313
97	73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96	1144812
98	97 and 26	298278
99	98 and 30	6839
100	99 and 71	987
101	("European Public Assessment Reports" or EPARS).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	93
102	72 or 100 or 101	1847
103	limit 102 to yr="2019-2021"	408

Comments

Appendix 11.2. Embase

Date	24 Aug 2021	
Database	Embase.com	
Search strategy		
#1	(ce NEAR/1 mark*):ab,ti	1613
#2	(conformit* NEAR/2 europe*):ab,ti	208
#3	'notified body':ab,ti	56
#4	'notified bodies':ab,ti	66
#5	'conformity assessment':ab,ti	134
#6	'competent authority':ab,ti	463
#7	'competent authorities':ab,ti	910
#8	licen?ing:ab,ti	11463
#9	unlicen?ed:ab,ti	2371
#10	licen?ed:ab,ti	29708
#11	'european medicines agency':ab,ti	5953
#12	'food and drugs administration':ab,ti	194
#13	'therapeutic goods administration':ab,ti	398
#14	'health canada':ab,ti	2338
#15	medsafe:ab,ti	32
#16	swissmedic:ab,ti	143
#17	'ema':ab,ti	16747
#18	'fda':ab,ti	89368
#19	'food and drug administration'/exp	93284
#20	((market OR premarket OR regulatory OR marketing) NEAR/2 (approval$ OR authori?ation$)):ab,ti	11851
#21	dossier$:ab,ti	1952

#22	market:ab,ti	104873
#23	marketing:ab,ti	38879
#24	regulation$:ab,ti	1138993
#25	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	1460911
#26	'evidence based practice'/exp	1476984
#27	evidence:ab,ti	2328104
#28	known:ab,ti	1923541
#29	knowns:ab,ti	389
#30	unknown$:ab,ti	731078
#31	knowledge:ab,ti	976128
#32	uncertain*:ab,ti	238776
#33	claim:ab,ti	39469
#34	claims:ab,ti	81973
#35	claimed:ab,ti	27661
#36	#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35	6690397
#37	#25 AND #36	405566
#38	europ*:ab,ti	541327
#39	'europe'/exp	1744892
#40	#38 OR #39	2097659
#41	#37 AND #40	23641
#42	'prostheses and orthoses'/exp	404052
#43	(medical NEAR/1 device$):ab,ti	23593
#44	#42 OR #43	426184
#45	'devices'/exp	4400275
#46	'self help device'/exp	1933
#47	'surgical equipment'/exp	456049
#48	device$:ab,ti	582653

#49	aid:ab,ti	234448
#50	aids:ab,ti	180743
#51	equipment$:ab,ti	134372
#52	armamentarium:ab,ti	15602
#53	appliance$:ab,ti	19028
#54	instrument$:ab,ti	269873
#55	apparatus:ab,ti	102356
#56	good$:ab,ti	1208474
#57	implement$:ab,ti	111862
#58	material$:ab,ti	1806130
#59	machine$:ab,ti	151280
#60	#45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59	7516098
#61	'diagnosis'/de	1393728
#62	'rehabilitation'/exp	438564
#63	'secondary prevention'/de	30750
#64	'therapy'/exp	9460769
#65	diagnos*:ab,ti	3912923
#66	therapy:ab,ti	2870418
#67	therapies:ab,ti	495116
#68	treatment$:ab,ti	6785995
#69	therapeutic$:ab,ti	1637812
#70	prevention:ab,ti	777055
#71	preventative:ab,ti	23252
#72	monitoring:ab,ti	747199
#73	screening:ab,ti	806012
#74	rehabilitation:ab,ti	249621
#75	rehabilitative:ab,ti	12510

#76	alleviat*:ab,ti	142056
#77	#61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76	17184575
#78	#60 AND #77	3982255
#79	#44 OR #78	4202310
#80	#41 AND #79	4398
#81	reimburs*:ab,ti	45544
#82	coverage:ab,ti	170442
#83	payer$:ab,ti	29093
#84	purchase$:ab,ti	33637
#85	purchaser$:ab,ti	3095
#86	procure*:ab,ti	22703
#87	financ*:ab,ti	160535
#88	payment$:ab,ti	38529
#89	'reimbursement'/de	60080
#90	'accounting'/exp	80411
#91	'hospital purchasing'/exp	7300
#92	'economics'/exp	247681
#93	#81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92	743259
#94	#93 AND #36	159298
#95	#94 AND #40	22947
#96	#95 AND #79	4710
#97	'european public assessment reports':ab,ti OR epars:ab,ti	189
#98	#80 OR #96 OR #97	8661
#99	#98 NOT [medline]/lim	5066
#100	#99 AND [2019-2021]/py	1024
#101	#100 NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it)	198
Comments		

Appendix 11.3. Cochrane

Date	24/08/2021 10:20:27	
Database	Cochrane@Wiley.com	
Search strategy		
#1	reimburs*:ab,ti	1586
#2	coverage:ab,ti	6058
#3	payer?:ab,ti	1439
#4	purchase?:ab,ti	1736
#5	purchaser?:ab,ti	68
#6	procure*:ab,ti	775
#7	financ*:ab,ti	7540
#8	payment?:ab,ti	1256
#9	[mh ^"Reimbursement Mechanisms"]	52
#10	[mh "Accounts Payable and Receivable"]	0
#11	[mh "Group Purchasing"]	1
#12	[mh "Purchasing, Hospital"]	4
#13	[mh "economics"]	13015
#14	[mh /EC]	11818
#15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	32521
#16	[mh "Evidence-Based Practice"]	1268
#17	evidence:ab,ti	130353
#18	known:ab,ti	61404
#19	knowns:ab,ti	10
#20	unknown?:ab,ti	26929
#21	knowledge:ab,ti	38090
#22	uncertain*:ab,ti	13343
#23	claim:ab,ti	1318

#24	claims:ab,ti	2425
#25	claimed:ab,ti	1468
#26	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	244501
#27	#15 and #26	9899
#28	Europ*:ab,ti	34880
#29	[mh "Europe"]	30125
#30	#28 or #29	62841
#31	#27 and #30	1529
#32	[mh "Prostheses and Implants"]	17860
#33	medical device?:ab,ti	12731
#34	#32 or #33	30166
#35	[mh "Equipment and Supplies"]	50358
#36	[mh "Self-Help Devices"]	415
#37	[mh "Surgical Instruments"]	773
#38	device?:ab,ti	49966
#39	aid:ab,ti	10416
#40	aids:ab,ti	8833
#41	equipment?:ab,ti	6728
#42	armamentarium:ab,ti	518
#43	appliance?:ab,ti	2771
#44	instrument?:ab,ti	17075
#45	apparatus:ab,ti	1714
#46	good?:ab,ti	56042
#47	implement?:ab,ti	7416
#48	material?:ab,ti	81686
#49	machine?:ab,ti	6804
#50	#35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49	258629

#51	[mh "Diagnosis"]	344216
#52	[mh "Rehabilitation"]	37859
#53	[mh "Secondary Prevention"]	3260
#54	[mh "Therapeutics"]	314844
#55	diagnos*:ab,ti	157231
#56	therapy:ab,ti	327557
#57	therapies:ab,ti	31298
#58	treatment?:ab,ti	731941
#59	therapeutic?:ab,ti	95903
#60	prevention:ab,ti	84098
#61	preventative:ab,ti	1564
#62	monitoring:ab,ti	51367
#63	screening:ab,ti	55886
#64	rehabilitation:ab,ti	35671
#65	rehabilitative:ab,ti	1569
#66	alleviat*:ab,ti	11189
#67	[mh /DI]	54142
#68	[mh /TH]	97315
#69	#51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68	1205951
#70	#50 and #69	198901
#71	#34 or #70	203920
#72	#31 and #71	359
#73	CE Mark*:ab,ti	1151
#74	(conformit* NEAR/2 europe*):ab,ti	43
#75	"notified body":ab,ti	8
#76	"notified bodies":ab,ti	2
#77	"conformity assessment":ab,ti	5

#78	"competent authority":ab,ti	49
#79	"competent authorities":ab,ti	44
#80	licen?ing:ab,ti	441
#81	unlicen?ed:ab,ti	79
#82	licen?ed:ab,ti	3542
#83	"European Medicines Agency":ab,ti	504
#84	"Food and Drugs Administration":ab,ti	12
#85	"Therapeutic Goods Administration":ab,ti	37
#86	"Health Canada":ab,ti	254
#87	Medsafe:ab,ti	1
#88	Swissmedic:ab,ti	28
#89	"EMA":ab,ti	1005
#90	"FDA":ab,ti	8334
#91	[mh ^"United States Food and Drug Administration"]	230
#92	((market or premarket or regulatory or marketing) NEAR/2 (approval? or authori?ation?)):ab,ti	556
#93	dossier?:ab,ti	230
#94	market:ab,ti	3075
#95	marketing:ab,ti	2023
#96	regulation?:ab,ti	17149
#97	#73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96	36422
#98	#97 and #26	9241
#99	#98 and #30	750
#100	#99 and #71	209
#101	("European Public Assessment Reports" or EPARS):ab,ti,kw	7
#102	#72 or #100 or #101	535
#103	#102 with Cochrane Library publication date Between Jan 2019 and Dec 2021	221
Comments		

APPENDIX 12. LAST UPDATES

Appendix 12.1. Cochrane Library

Database:	Cochrane Library	
Search Name:	(Market Entry OR Reimbursement) AND Evidence AND Europe AND (Medicines OR Devices) Date limited June 2011-Dec 2021	
Date Run:	30/09/2021	
Comment:	Combined search 20210930	
ID	**Search**	**Hits**
#1	(CE Mark):ti,ab,kw (Word variations have been searched)	399
#2	(CE Marking):ti,ab,kw	27
#3	(conformit√© europ√©enne):ti,ab,kw	25
#4	(conformity europeenne):ti,ab,kw	5
#5	(European conformity):ti,ab,kw	32
#6	(European conformity):ti,ab,kw	32
#7	(notified body):ti,ab,kw	100
#8	(notified bodies):ti,ab,kw	8
#9	(conformity assessment):ti,ab,kw	113
#10	(competent authority):ti,ab,kw	59
#11	(competent authorities):ti,ab,kw	51
#12	(licencing):ti,ab,kw	523
#13	(unlicenced):ti,ab,kw	0
#14	(licenced):ti,ab,kw	3594
#15	(licensing):ti,ab,kw	523
#16	(unlicensed):ti,ab,kw	84

#17	(licensed):ti,ab,kw	3594
#18	(European Medicines Agency):ti,ab,kw	568
#19	(Food and Drugs Administration):ti,ab,kw	1241
#20	(Therapeutic Goods Administration):ti,ab,kw	47
#21	(Health Canada):ti,ab,kw	3904
#22	(Medsafe):ti,ab,kw	1
#23	(Swissmedic):ti,ab,kw	31
#24	(EMA):ti,ab,kw	1033
#25	(FDA):ti,ab,kw	8543
#26	MeSH descriptor: [United States Food and Drug Administration] this term only	233
#27	(market approval):ti,ab,kw	168
#28	(pre market approval):ti,ab,kw	34
#29	(premarket approval):ti,ab,kw	43
#30	(regulatory approval):ti,ab,kw	749
#31	(marketing approval):ti,ab,kw	252
#32	(marketing approvals):ti,ab,kw	15
#33	(marketing authorisation):ti,ab,kw	310
#34	(marketing authorization):ti,ab,kw	310
#35	(market authorisation):ti,ab,kw	57
#36	(market authorization):ti,ab,kw	57
#37	(marketing authorisations):ti,ab,kw	19
#38	(marketing authorizations):ti,ab,kw	19
#39	(market authorisations):ti,ab,kw	4
#40	(market authorizations):ti,ab,kw	4

#41	(dossier):ti,ab,kw	81
#42	(dossiers):ti,ab,kw	158
#43	(market):ti,ab,kw	3164
#44	(marketing):ti,ab,kw	2473
#45	(regulation):ti,ab,kw	23870
#46	[or #1-#45]	47939
#47	(reimbursement):ti,ab,kw	1525
#48	(reimbursable):ti,ab,kw	37
#49	(reimburse):ti,ab,kw	53
#50	(reimbursed):ti,ab,kw	350
#51	(reimbursements):ti,ab,kw	107
#52	(coverage):ti,ab,kw	6230
#53	(payer):ti,ab,kw	1093
#54	(payers):ti,ab,kw	494
#55	(purchase):ti,ab,kw	1004
#56	(purchaser):ti,ab,kw	14
#57	(purchases):ti,ab,kw	359
#58	(purchasers):ti,ab,kw	57
#59	(procure):ti,ab,kw	338
#60	(procures):ti,ab,kw	246
#61	(procured):ti,ab,kw	284
#62	(procurement):ti,ab,kw	471
#63	(finance):ti,ab,kw	306
#64	(finances):ti,ab,kw	259

#65	(financed):ti,ab,kw	150
#66	(financing):ti,ab,kw	448
#67	(payment):ti,ab,kw	942
#68	(payments):ti,ab,kw	526
#69	MeSH descriptor: [Reimbursement Mechanisms] this term only	52
#70	MeSH descriptor: [Accounts Payable and Receivable] explode all trees	0
#71	MeSH descriptor: [Group Purchasing] explode all trees	1
#72	MeSH descriptor: [Purchasing, Hospital] explode all trees	4
#73	MeSH descriptor: [Economics] explode all trees	13145
#74	MeSH descriptor: [Resource Allocation] explode all trees	75
#75	[or #47-#74]	25303
#76	(evidence):ti,ab,kw	134174
#77	(known):ti,ab,kw	62224
#78	(knowns):ti,ab,kw	10
#79	(unknown):ti,ab,kw	27388
#80	(unknowns):ti,ab,kw	47
#81	(knowledge):ti,ab,kw	42505
#82	(uncertain):ti,ab,kw	8233
#83	(uncertainty):ti,ab,kw	5396
#84	(uncertainties):ti,ab,kw	725
#85	(claim):ti,ab,kw	1383
#86	(claims):ti,ab,kw	2473
#87	(claimed):ti,ab,kw	1477
#88	MeSH descriptor: [Evidence-Based Practice] explode all trees	1281

#89	[or #76-#88]	252829
#90	(European):ti,ab,kw	37209
#91	(Europe):ti,ab,kw	10565
#92	(Europe's):ti,ab,kw	10548
#93	MeSH descriptor: [European Union] explode all trees	61
#94	MeSH descriptor: [Europe] this term only	2502
#95	(EU):ti,ab,kw	3080
#96	(EU's):ti,ab,kw	3080
#97	[or #90-#96]	47761
#98	MeSH descriptor: [Pharmaceutical Preparations] explode all trees	74865
#99	(pharmaceutic):ti,ab,kw	210
#100	(pharmaceutical):ti,ab,kw	39014
#101	(pharmaceuticals):ti,ab,kw	3493
#102	(drug):ti,ab,kw	622268
#103	(drugs):ti,ab,kw	92799
#104	(medicinal product):ti,ab,kw	1165
#105	(medicinal products):ti,ab,kw	579
#106	(medicine):ti,ab,kw	55451
#107	(medicines):ti,ab,kw	6190
#108	(European Public Assessment Report*):ti,ab,kw	88
#109	(EPAR OR EPARs):ti,ab,kw	14
#110	[or #98-#109]	725810
#111	MeSH descriptor: [Prostheses and Implants] explode all trees	18031
#112	(medical devices):ti,ab,kw	3926

#113	(medical device):ti,ab,kw	9100
#114	[or #111-#113]	28601
#115	MeSH descriptor: [Equipment and Supplies] explode all trees	50914
#116	MeSH descriptor: [Self-Help Devices] explode all trees	420
#117	MeSH descriptor: [Surgical Instruments] explode all trees	778
#118	(device):ti,ab,kw	47770
#119	(devices):ti,ab,kw	23082
#120	(aid):ti,ab,kw	11006
#121	(aids):ti,ab,kw	10513
#122	(equipment):ti,ab,kw	17335
#123	(armamentarium):ti,ab,kw	525
#124	(appliance):ti,ab,kw	2083
#125	(appliances):ti,ab,kw	2032
#126	(instrument):ti,ab,kw	11617
#127	(instruments):ti,ab,kw	9113
#128	(apparatus):ti,ab,kw	2079
#129	(good):ti,ab,kw	56760
#130	(goods):ti,ab,kw	259
#131	(implement):ti,ab,kw	7375
#132	(implements):ti,ab,kw	209
#133	(material):ti,ab,kw	30501
#134	(materials):ti,ab,kw	59989
#135	(machine):ti,ab,kw	6515
#136	(machines):ti,ab,kw	1055

#137	189-#136	274489
#138	MeSH descriptor: [Diagnosis] explode all trees	347281
#139	MeSH descriptor: [Rehabilitation] explode all trees	38509
#140	MeSH descriptor: [Secondary Prevention] explode all trees	3272
#141	MeSH descriptor: [Therapeutics] explode all trees	317631
#142	(diagnosis):ti,ab,kw	157630
#143	(diagnoses):ti,ab,kw	157630
#144	(diagnosed):ti,ab,kw	61119
#145	(diagnostic):ti,ab,kw	71052
#146	(diagnostics):ti,ab,kw	2018
#147	(therapy):ti,ab,kw	729430
#148	(therapies):ti,ab,kw	32535
#149	(treatment):ti,ab,kw	807831
#150	(treatments):ti,ab,kw	86389
#151	(therapeutic):ti,ab,kw	298118
#152	(therapeutics):ti,ab,kw	2863
#153	(prevention):ti,ab,kw	188115
#154	(preventative):ti,ab,kw	1583
#155	(monitoring):ti,ab,kw	66356
#156	(screening):ti,ab,kw	60440
#157	(rehabilitation):ti,ab,kw	53729
#158	(rehabilitative):ti,ab,kw	1589
#159	(alleviation):ti,ab,kw	1807
#160	(alleviate):ti,ab,kw	5123

#161	(alleviates):ti,ab,kw	938
#162	(diagnosis).sh.	179995
#163	(diagnostic imaging).sh.	21944
#164	(therapy).sh.	753527
#165	(rehabilitation).sh.	88361
#166	[or #138-#165]	1328772
#167	#137 and #166	225210
#168	#114 or #167	228637
#169	#46 or #75	71720
#170	#110 or #168	857215
#171	#89 and #97 and #168 and #169	348
#172	#171 with Cochrane Library publication date Between Jun 2011 and Dec 2021	342

Appendix 12.2. Medline

Date	October 08, 2021	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to October 08, 2021>	
Search strategy		
1	ce mark.ab,ti,kf.	252
2	ce marking.ab,ti,kf.	110
3	conformite europeenne.ab,ti,kf.	96
4	conformity europeenne.ab,ti,kf.	0
5	european conformity.ab,ti,kf.	30
6	european conformity.ab,ti,kf.	30
7	notified body.ab,ti,kf.	31
8	notified bodies.ab,ti,kf.	43
9	conformity assessment.ab,ti,kf.	107
10	competent authority.ab,ti,kf.	293
11	competent authorities.ab,ti,kf.	593
12	licencing.ab,ti,kf.	136
13	unlicenced.ab,ti,kf.	8
14	licenced.ab,ti,kf.	397
15	licensing.ab,ti,kf.	8887
16	unlicensed.ab,ti,kf.	1646
17	licensed.ab,ti,kf.	20787
18	european medicines agency.ab,ti,kf.	3613
19	"food and drugs administration".ab,ti,kf.	146
20	therapeutic goods administration.ab,ti,kf.	250
21	health canada.ab,ti,kf.	1550
22	medsafe.ab,ti,kf.	21
23	swissmedic.ab,ti,kf.	66

24	ema.ab,ti,kf.	10079
25	fda.ab,ti,kf.	50151
26	"United States Food and Drug Administration"/	30906
27	market approval.ab,ti,kf.	383
28	pre market approval.ab,ti,kf.	66
29	premarket approval.ab,ti,kf.	316
30	regulatory approval.ab,ti,kf.	3048
31	marketing approval.ab,ti,kf.	717
32	marketing approvals.ab,ti,kf.	33
33	marketing authorisation.ab,ti,kf.	543
34	marketing authorization.ab,ti,kf.	1197
35	market authorisation.ab,ti,kf.	78
36	market authorization.ab,ti,kf.	260
37	marketing authorisations.ab,ti,kf.	106
38	marketing authorizations.ab,ti,kf.	118
39	market authorisations.ab,ti,kf.	1
40	market authorizations.ab,ti,kf.	12
41	dossier.ab,ti,kf.	839
42	dossiers.ab,ti,kf.	1248
43	market.ab,ti,kf.	79347
44	marketing.ab,ti,kf.	29422
45	regulation.ab,ti,kf.	908811
46	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45	1116503
47	reimbursement.ab,ti,kf.	24831
48	reimbursable.ab,ti,kf.	461
49	reimburse.ab,ti,kf.	763

50	reimbursed.ab,ti,kf.	3521
51	reimbursements.ab,ti,kf.	1998
52	coverage.ab,ti,kf.	134231
53	payer.ab,ti,kf.	9225
54	payers.ab,ti,kf.	8722
55	purchase.ab,ti,kf.	12683
56	purchaser.ab,ti,kf.	718
57	purchases.ab,ti,kf.	3174
58	purchasers.ab,ti,kf.	2179
59	procure.ab,ti,kf.	1233
60	procures.ab,ti,kf.	109
61	procured.ab,ti,kf.	3673
62	procurement.ab,ti,kf.	10985
63	finance.ab,ti,kf.	6193
64	finances.ab,ti,kf.	3847
65	financed.ab,ti,kf.	2880
66	financing.ab,ti,kf.	15508
67	payment.ab,ti,kf.	23032
68	payments.ab,ti,kf.	11675
69	Reimbursement Mechanisms/	13243
70	exp "Accounts Payable and Receivable"/	1630
71	exp Group Purchasing/	1066
72	exp Purchasing, Hospital/	5827
73	exp economics/	628776
74	ec.fs.	438217
75	47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74	936683
76	evidence.ab,ti,kf.	1915229

77	known.ab,ti,kf.	1470726
78	knowns.ab,ti,kf.	338
79	unknown.ab,ti,kf.	532289
80	unknowns.ab,ti,kf.	2818
81	knowledge.ab,ti,kf.	788222
82	uncertain.ab,ti,kf.	84777
83	uncertainty.ab,ti,kf.	85872
84	uncertainties.ab,ti,kf.	28895
85	claim.ab,ti,kf.	28714
86	claims.ab,ti,kf.	56170
87	claimed.ab,ti,kf.	21354
88	exp "Evidence-Based Practice"/	91705
89	76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88	4509386
90	european.ab,ti,kf.	224062
91	europe.ab,ti,kf.	129611
92	europe#s.ab,ti,kf.	430
93	exp European Union/	16876
94	exp Europe/	1491894
95	eu.ab,ti,kf.	33735
96	eu#s.ab,ti,kf.	216
97	90 or 91 or 92 or 93 or 94 or 95 or 96	1706975
98	exp Pharmaceutical Preparations/	903308
99	pharmaceutic.ab,ti,kf.	849
100	pharmaceutical.ab,ti,kf.	117206
101	pharmaceuticals.ab,ti,kf.	29838
102	drug.ab,ti,kf.	1294029
103	drugs.ab,ti,kf.	818181
104	medicinal product.ab,ti,kf.	1175

105	medicinal products.ab,ti,kf.	3741
106	medicine.ab,ti,kf.	560489
107	medicines.ab,ti,kf.	57906
108	european public assessment report*.ab,ti,kf.	116
109	epar*.ab,ti,kf.	230
110	98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109	3042433
111	exp "Prostheses and Implants"/	550637
112	medical devices.ab,ti,kf.	12950
113	medical device.ab,ti,kf.	6502
114	111 or 112 or 113	566156
115	exp "Equipment and Supplies"/	1551631
116	exp "Self-Help Devices"/	12310
117	exp Surgical Instruments/	25322
118	device.ab,ti,kf.	292189
119	devices.ab,ti,kf.	250343
120	aid.ab,ti,kf.	183484
121	aids.ab,ti,kf.	160247
122	equipment.ab,ti,kf.	106423
123	armamentarium.ab,ti,kf.	11979
124	appliance.ab,ti,kf.	10100
125	appliances.ab,ti,kf.	11369
126	instrument.ab,ti,kf.	128649
127	instruments.ab,ti,kf.	105929
128	apparatus.ab,ti,kf.	95196
129	good.ab,ti,kf.	881342
130	goods.ab,ti,kf.	8524
131	implement.ab,ti,kf.	81213
132	implements.ab,ti,kf.	6086

133	material.ab,ti,kf.	603295
134	materials.ab,ti,kf.	807364
135	machine.ab,ti,kf.	109975
136	machines.ab,ti,kf.	23033
137	115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136	4448198
138	exp Diagnosis/	8982167
139	exp Rehabilitation/	327229
140	exp Secondary Prevention/	21696
141	exp Therapeutics/	4842734
142	diagnosis.ab,ti,kf.	1698654
143	diagnoses.ab,ti,kf.	145749
144	diagnosed.ab,ti,kf.	633089
145	diagnostic.ab,ti,kf.	787249
146	diagnostics.ab,ti,kf.	75180
147	therapy.ab,ti,kf.	2086103
148	therapies.ab,ti,kf.	332777
149	treatment.ab,ti,kf.	4684093
150	treatments.ab,ti,kf.	522092
151	therapeutic.ab,ti,kf.	1173299
152	therapeutics.ab,ti,kf.	90017
153	prevention.ab,ti,kf.	624399
154	preventative.ab,ti,kf.	16674
155	monitoring.ab,ti,kf.	551768
156	screening.ab,ti,kf.	587874
157	rehabilitation.ab,ti,kf.	183840
158	rehabilitative.ab,ti,kf.	8996
159	alleviation.ab,ti,kf.	13441

160	alleviate.ab,ti,kf.	47135
161	alleviates.ab,ti,kf.	16637
162	di.xs.	3809909
163	su.fs.	2100044
164	th.xs.	7499730
165	rh.fs.	204906
166	138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165	18357837
167	137 and 166	2907354
168	114 or 167	3018253
169	46 or 75	2006153
170	110 or 168	5691673
171	89 and 97 and 168 and 169	4521
172	limit 171 to yr="2011-2021"	2950
Comments		

Appendix 12.3. Embase

Date	6 Oct 2021	
Database	Embase.com	
Search strategy		
#1	'ce mark':ti,ab,kw	600
#2	'ce marking':ti,ab,kw	229
#3	'conformitã© europã©enne':ti,ab,kw	0
#4	'conformity europeenne':ti,ab,kw	1
#5	'european conformity':ti,ab,kw	36
#6	'european conformity':ti,ab,kw	36
#7	'notified body':ti,ab,kw	73
#8	'notified bodies':ti,ab,kw	74
#9	'conformity assessment':ti,ab,kw	167
#10	'competent authority':ti,ab,kw	497
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#173	#172 AND ('animal experiment'/de OR 'animal model'/de OR 'clinical trial'/de OR 'controlled clinical trial'/de OR 'double blind procedure'/de OR 'randomized controlled trial'/de) AND ('animal tissue'/de OR 'controlled study'/de OR 'feasibility study'/de)	1203
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#175	#174 NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it)	3605
#176	#175 AND [2011-2021]/py	3568
#177	#176 NOT [medline]/lim	783
Comments		

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