Health Technology Assessments on Medical Devices in Europe

Final Report

Ludwig Boltzmann Institut
Health Technology Assessment

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List of abbreviations

AETSA ..... Andalusian HTA Agency
AGENAS ..... National Agency for regional health services
AIMDD ..... Active Implantable Medical Device Directive
AOTMIT ..... Agency for Health Technology Assessment and Tariff System
AQuAS ..... Agency for Health Quality and Assessment of Catalonia
ASSR ..... Regione Emilia Romagna, Regional Agency for Health and Social Care
AVALIA-T ..... Galician Agency for HTA
CA ..... Competent Authority
CE ..... Conformité Européenne
CEDIT ..... Comité d'Evaluation et de Diffusion des Innovations Technologiques
CRT ..... Cardiac resynchronization therapy
DES ..... Drug-eluting stent
EMA ..... European Medicines Agency
EU ..... European Union
EUnetHTA ..... European Network for Health Technology Assessment
HAS ..... French National Authority for Health (Haute Autorité de Santé)
HIFU ..... High intensity focused ultrasound
HIS ..... Healthcare Improvement Scotland
HTA ..... Health Technology Assessment
IMRT ..... Intensity-modulated radiation therapy
IORT ..... Intraoperative radiation therapy
IVDD ..... In-vitro Diagnostic Medical Device Directive
KCE ..... Belgian Health Care Knowledge Centre
LBI-HTA ..... Ludwig Boltzmann Institute for Health Technology Assessment
MA ..... Meta-Analysis
MDD ..... Medical Device Directive
NB ..... Notified Body
NICE ..... National Institute for Health and Care Excellence
NIHR ..... National Institute for Health Research
NOKC ..... The Norwegian Institute of Public Health
OSTEBA ..... Basque Office for Health Technology Assessment – Ministry for Health
RCT ..... Randomized Clinical Trial
REA ..... Relative Effectiveness Assessment
SBU ..... Swedish Agency for Health Technology Assessment and Assessment of Social Services
SME ..... Small and Medium-sized Enterprises
SNS ..... Sacral nerve stimulation
TAVI ..... Transcatheter aortic valve implantation
UDI ..... Unique Identification Number
WHO ..... World Health Organization

Abstract

Background and objectives

In recent years, the European collaboration in health technology assessments (HTAs), not only on pharma products but also on (high-risk) medical devices and procedures has become a major issue of consideration due to weak market authorization and efficacy/safety concerns. This research sought to explore and synthesize the critical points and challenges in the assessment of medical devices in Europe discussed in publications and to analyze a number a selected European HTA reports regarding their timing in relation to market authorization (CE-mark), levels of evidence considered in the assessments and overlaps in topics.

HTA on high-risk medical devices:

research questions:
critical points discussed
timing + evidence used in HTAs

Methods

A literature review of publications searched in Medline via PubMed supplemented by a grey literature search was conducted to identify the critical points and challenges in the assessment of medical devices in Europe. Then the ADVANCE HTA database (developed in the EU-FP7 project) was used to select a cohort group of HTA reports on high-risk medical devices conducted in 2014: Ten devices and their respective reports were selected for further investigation. Finally, a search in several databases was conducted to find additional HTA reports on the selected technologies in earlier or later years.

literature review

HTA reports analyses of 10 selected medical devices

Results

The issues discussed in the recent literature can be summarized in five major critical points in the assessment of medical devices: 1. Missing of robust evidence at time of assessment; 2. Methodologic challenges; 3. Need for harmonization of HTA-requirements; 4. Variable impact on decisions; 5. Timing of HTA in life-cycle of medical devices.

5 major critical points are discussed in literature

The analyses of HTA reports on 10 selected high-risk medical devices t revealed the amount of the redundancies in European HTA production: the number of reports per technology ranged between 5 and 22 reports over a time-span of 10-12 years; ranging between 1-6 reports of the same technology within the same year, sometimes even within the same country (language).

high redundancy of HTA of medical devices:
up to 22 reports of same tech over time-span of 12 years

Discussion and conclusion

The results strongly support the assumption that the resources of HTA institutes can be used more efficiently. In contrast to pharma products entering the health care systems at almost the same time, medical devices and accordingly their pre-reimbursement assessments show a broader time-span (up to 12 years) in Europe. The knowledge gained contributes to the conclusion that there is a need not only to collaborate across borders within the same year but also to build on each other´s assessments of the same technologies over years by using the same format, method, language.

collaboration:
not only within the same HTA at 1 point in time, but building on each other by using:
same language
same method
same format

1 Introduction

healthcare systems struggle with efficient use of limited resources

All over the world healthcare systems struggle with the increasing pressure of using their given resources in the most efficient way.[1] The healthcare systems are not able to satisfy the health related demands of the population, particularly in the light of progressive aging and awareness of new and emerging health technologies.[2] New health technologies are often seen as a key driver for the increased health expenditures.

HTA as instrument to inform health policy

Health Technology Assessment (HTA) is one approach that has been widely adopted to support the introduction and appropriate use of new and emerging health technologies and procedures.[3] Health technology itself is a very broad term and refers to medical devices, procedures, pharmaceuticals and the responsible organizational and support systems which provide health care.[4] HTA aims to provide coverage bodies and policy makers with information regarding the clinical and economic value of the new technologies.[5,6] Hence, HTA can be considered as a „bridge between the world of research and the world of decision-making, particularly policy-making"[7].

study objective: focus on HTA for medical devices

This study focuses on HTA for medical devices. In recent years, medical devices have become more and more instrumental in health care. It has been acknowledged that patients nowadays enjoy longer lives of higher quality thanks to the contribution of medical device technologies.[8] Especially with regard to surgeries, medical devices made new innovative methods feasible by the use of imaging tools, implants or innovative instruments.[9]

definition of medical devices by the European Union (EU) Directive

The definition by the European Union (EU) Directive 2007/47/EC (amendment of the Council Directive 93/42/EEC on medical devices) describes medical devices as „any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, together with any accessories, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

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1 Iglesias, "Does Assessing the Value for Money of Therapeutic Medical Devices Require a Flexible Approach?"

2 Battista and Hodge, "The Evolving Paradigm of Health Technology Assessment."

3 Banta, "The Development of Health Technology Assessment."

4 International Journal of Technology Assessment in Health Care, "Health Technology Assessment."

5 International Journal of Technology Assessment in Health Care, "Health Technology Assessment."

6 Iglesias, "Does Assessing the Value for Money of Therapeutic Medical Devices Require a Flexible Approach?"

7 Battista and Hodge, "The Evolving Paradigm of Health Technology Assessment."

8 Kramer, Xu, and Kesselheim, "How Does Medical Device Regulation Perform in the United States and the European Union?"

9 Sauerland et al., "Approaches to Assessing the Benefits and Harms of Medical Devices for Application in Surgery."

diagnosis, prevention, monitoring, treatment

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for any injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception

medical devices:

very broad and heterogeneous group of products

classification of risk classes

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means"[10]. Therefore, medical devices are regarded as a very broad and heterogeneous group of products, which ranges from bandages and stethoscopes to active implantable pacemakers and hip prostheses.[11] Additionally, medical devices differ in form of their use from patients to medical professionals and their application for therapeutic or diagnostic purposes.[12] The regulatory framework, as well as the definition of medical devices and classification of risk classes, varies from country to country and sometimes even within economic regions.[13]

estimate: about 150 new high-risk medical devices each year

in 2010 around 1.5 million different medical devices

The market of medical devices, including diagnostic products, is one of the fastest growing in healthcare. Compared to pharmaceuticals, medical devices have nearly twice as many patent applications (over 10.000) filed in Europe in 2012.[14] Furthermore, experts estimate that about 150 new high-risk medical devices enter the market every year.[15] The total number of medical and in vitro diagnostic devices on the market in Europe is over 500.000.[16] 25.000 enterprises, most of them being small and medium-sized (SMEs) produce medical devices in Europe, generating nearly 100 billion Euro annual sales in the European market.[17]

increasing health care expenditures: collaboration between European HTA institutes

In consideration of the increasing health care expenditures of European health care systems, the scarce human and financial resources, and the influence of the medical device industry in Europe, this research looks into the challenges of conducting HTAs on medical devices to support efforts towards intensified collaboration between HTA institutes on a European level.

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10 "The European Parliament and the Council of the European Union. Directive 2007/46/EC of the European European Parliament and of the Council of 5 September 2007."

11 Schnell-Inderst et al., "Health Technology Assessment of Medical Devices."

12 Taylor and Iglesias, "Assessing the Clinical and Cost-Effectiveness of Medical Devices and Drugs."

13 Santos and Tavares, "Additional Peculiarities of Medical Devices That Should Be Considered in Their Development Process."

14 Craig et al., "A Review of the Economic Tools for Assessing New Medical Devices."

15 Sauerland et al., "Approaches to Assessing the Benefits and Harms of Medical Devices for Application in Surgery."

16 World Health Organization, "World Health Organization – Medical Devices."

17 European Council. Council of the European Union, "European Council. Council of the European Union – Modernising EU Rules for Medical Devices – Consilium."

1.1 Aim and objective of the report

This report aims to provide an overview of the challenges discussed in the recent literature on the assessment of medical devices in Europe. Furthermore, this research analyses the timing of the assessments and the level of evidence used by different HTA institutes. This may improve the collaboration on a European level and help to use resources more efficiently.

2 aims:

overview of challenges of HTA of medical devices discussed in literature

comparison of HTAs of 10 medical devices: timing, evidence

This research has two main objectives:

- Firstly, to explore and explain the medical devices landscape from regulation to coverage and the resulting critical points and challenges in the assessment of medical devices.
- Secondly, to analyze the timing and level of evidence of HTA reports by evaluating ten different high-risk technologies assessed by different HTA institutes.

2 Theoretical Background

This chapter provides an overview of the regulation of medical devices considering the pre-market evaluation as well as the assessment of medical devices, an approach given by the EUnetHTA, the unique characteristics of medical devices as well as the differentiation to pharmaceuticals, and finally the results of the new EU directive for medical device regulation in Europe.

overview of

regulation
unique characteristics
of medical devices

2.1 Pre-Market Approval of Medical Devices

The European Union published three directives for the classification of medical devices to achieve a consistent regulatory framework through Europe: Council Directive 93/42/EEC on medical devices (MDD), Council Directive 90/385/EEC on active implantable medical devices (AIMDD) and Council Directive 98/79/EC on in vitro diagnostic medical devices (IVDD).[18] These three directives came into effect in the 1990s and regulate safety and marketing of medical devices in Europe and were incorporated into the national laws at the Member State level, which harmonizes the requirements needed.[19, 20]

European Union 1990s:

three directives
as regulatory
framework

On June 15th, 2016 the Councils Committee confirmed the agreement with the European Parliament on a new medical device regulation for medical devices and in vitro medical devices. The aim of these new guidelines is to modernize the current legislations, including safety measures and allowing patient access to new innovations in a timely manner. In order to ensure safety of medical devices, regulations to get marketing approval are strengthened and combined with post-marketing surveillance.[21] The special focus of this new regulation lies on:

2016: new medical
device regulation

rules for placing devices
on the market and
surveillance:
strengthened

- Pre-market conformity assessment and the associated requirements,
- Post-market control and supervision,
- The possibility to trace medical devices and in vitro medical devices throughout the lifecycle.[22]

pre-market
conformity assessment
post-market control and
supervision

[18] "European Parliament and Council of the European Union. Council Directive 90/385/EEC of 20 June 1990 on the Approximation of the Laws of Member States Relating to Active Implantable Medical Devices."; "European Parliament and Council of the European Union. Council Directive 93/42/EEC of 14 June 1993 Concerning Medical Devices."; "European Parliament and Council of the European Union. Council Directive 98/79/EC of 27 October 1998 on in Vitro Diagnostic Medical Devices."

[19] French-Mowat and Burnett, "How Are Medical Devices Regulated in the European Union?"

[20] Tarricone et al., "Generating Appropriate Clinical Data for Value Assessment of Medical Devices."

[21] European Council. Council of the European Union, "European Council. Council of the European Union – Medical Devices: Council Confirms Deal with EP – Consilium."

[22] European Council. Council of the European Union, "European Council. Council of the European Union – Modernising EU Rules for Medical Devices – Consilium."

regulation on:

The draft regulations change in detail:

risk levels

- Risk Levels

  The in vitro medical devices were classified in four risk categories, to be in line with the categorization of the medical devices classified in the Medical Device Directive (MDD).

  The risk level is determined by:

  - „The obligations placed on manufacturers and other economic operators
  - The requirements for clinical investigations and clinical evidence
  - The requirements for market surveillance by national authorities“[23]

product conformity

- Product conformity

  The manufacturer of the medical device has to appoint a qualified person, who is in charge of ensuring that all requirements were successfully applied.

traceability

- Traceability

  Manufacturers and importers are required to equip their devices with a Unique Device Identification (UDI). Further, manufacturers, importers and products have to be registered in the European Union in a central database. This shall help to track the devices from supply chain to the end-user. In addition, manufacturers are also required to report serious incidents and corrective actions on an EU portal.

Notified Bodies

- Notified Bodies

  Notified Bodies (NB) are allowed to carry out unannounced factory inspections and to conduct physical or laboratory tests on the devices. The designation through the Member States still persists. However, the attendant decision would be subject to a joint assessment on which experts from the designating country, other countries, and the European Commission work and decide together.

Medical Device Coordination Group

- Medical Device Coordination Group

  A medical device coordination group consisting of national representatives will be installed to have a second look at the assessments of the Notified Bodies on high-risk medical devices before they receive the CE-mark and enter the European market.[24]

CE-mark: Conformité Européenne

Before a medical device can be put on the market in Europe, it has to receive the CE-mark (Conformité Européenne), which allows it to circulate freely throughout the European market.[25] Moreover, the CE-mark can be seen as a declaration by the manufacturer that the medical device meets all requirements of the relevant legislation.[26] The aim is to illustrate safety and performance, however, a proof of efficacy is not relevant.[27]

safety and performance, not efficacy – so far

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[23] Ibid.

[24] Ibid.

[25] Tarricone et al., “Generating Appropriate Clinical Data for Value Assessment of Medical Devices.”

[26] French-Mowat and Burnett, “How Are Medical Devices Regulated in the European Union?”

[27] voor de Gezondheidszorg, “The Pre-Market Clinical Evaluation of Innovative High-Risk Medical Devices.”

each Member State: Competent Authority (CA) that accredits Notified Bodies (NB)

While broad and consistent legislation for the regulation of medical devices exists, the implementation remains the responsibility of the Member States.[28] Each Member State government nominates a Competent Authority (CA), to monitor and ensure compliance with the requirements given by the MDD.[29] These Competent Authorities accredit the so-called Notified Bodies (NB), which are commonly for-profit organizations. NBs are responsible for performing the conformity assessment of medical devices.[30]

NB perform conformity assessments

four risk classes (1, 2a, 2b, 3)

The assessed medical device has to be classified by one of the four risk classes (1, 2a, 2b, 3). The classification depends on the characteristics of the device, such as duration of use and contact, active versus non-active devices and invasiveness or non-invasiveness of the device.[31] For most devices of low risk (class 1, e.g. bandages, plasters) the manufacturer is allowed to assign the CE-mark without the involvement of a NB, a so-called self-certification, and register this product with a national Competent Authority.[32] The other risk classes have to be reviewed by one of the Notified Bodies and include an assessment of the device's design and manufacturing quality system of the manufacturer as well as a review of clinical investigation studies.[33] The manufacturer is free to choose which Notified Body in Europe is responsible for the evaluation and issuing a certificate of conformity.[34]

manufacturer is free to choose NB in Europe

regulatory framework for medical devices

A classic regulatory framework consists of the following parts:

- Regulatory guidelines,
- Governmental approved regulatory authority,
- Conformity assessment bodies,
- Classification scheme concerning potential risk to the user,
- Quality management system,
- System for evaluating the clinical safety and performance of the device,
- System to allow market entrance,
- Surveillance system for the device in the market.[35]

Table 2.1-1 gives an overview about the pre-market evaluation in Europe, the risk classes as well as the general and essential requirements.

[28] Campillo-Artero, "A Full-Fledged Overhaul Is Needed for a Risk and Value-Based Regulation of Medical Devices in Europe."

[29] French-Mowat and Burnett, "How Are Medical Devices Regulated in the European Union?"

[30] Hulstaert et al., "Pre-Market Clinical Evaluations of Innovative High-Risk Medical Devices in Europe."

[31] "European Parliament and Council of the European Union. Council Directive 93/42/EEC of 14 June 1993 Concerning Medical Devices."

[32] Ibid.

[33] Parvizi and Woods, "Regulation of Medicines and Medical Devices."

[34] Campillo-Artero, "A Full-Fledged Overhaul Is Needed for a Risk and Value-Based Regulation of Medical Devices in Europe."

[35] Santos et al., "Medical Device Specificities."

Table 2.1-1: Summary of the authorization system in Europe (adapted from[36])

Regulatory body	Decentralized system – Notified Bodies across Europe			
Classification	Risk class approach – Class 1, Class 2a, Class 2b and Class 3			
Procedure	Class 1	Class 2a	Class 2b	Class 3
	General requirements	General requirements	General requirements	General requirements
	Self-certification	Essential requirements	Essential requirements	Essential requirements
		Conformity assessment by NB	Conformity assessment by NB	Conformity assessment by NB
Evidence requirements	General requirements		Essential requirements	
	❁ Safety ❁ Performance ❁ Risk-ratio		❁ Safety ❁ Performance ❁ Risk-ratio ❁ Packaging ❁ Information on side effects ❁ Chemical, physical and biological properties ❁ Infection and microbial contamination ❁ Construction and environmental properties ❁ Information about measuring function ❁ Information about protection against radiation ❁ Labeling and information leaflet	

[36] Krüger and Wild, "Evidence Requirements for the Authorization and Reimbursement of High-Risk Medical Devices in the USA, Europe, Australia and Canada."

2.2 Health Technology Assessment for Medical Devices

HTA to support healthcare decisions

Health Technology Assessment (HTA) is a broadly used and accepted way to support healthcare decisions and to manage the appropriate use of new and emerging health technologies in most of the healthcare systems in the world.[37, 38] The expansion of HTA reflects the concerns over the unsustainable growth of health care systems. HTA can potentially mediate between policy and research domains by giving a „problem-oriented systematic overview of research".[39]

expansion of HTA reflects concerns over unsustainable growth of health care systems

HTA = policy research

As a form of policy research, HTA has to examine short- and long-term consequences of health technologies in a systematic way and support policy-makers in making evidence-based decisions.[40, 41] Additionally, by using HTA, coverage bodies ensure that their decisions on coverage and reimbursement of new technologies are based on the best evidence available, considering the medical, social, ethical and economic implications of the health technology.[42, 43] The term health technology can be applied very broadly and includes medical devices, procedures, and pharmaceuticals, as well as the organizational systems that administer health care.[44] Started 1987 in Sweden, today's number of HTA institutes has grown up to over 90 institutes in Europe.[45]

for decisions on coverage and reimbursement of new technologies

around 90 institutes in Europe

European network for Health Technology Assessment (EUnetHTA)

The European network for Health Technology Assessment (EUnetHTA), which is a network of governmental organizations and other contributors to HTA in Europe, defines HTA as a „multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve the best value".[46] The intention of EUnetHTA is to collaborate in joint assessments and therefore to avoid duplication in the production of HTAs.

collaboration and avoidance of duplication

37 Drummond et al., "Key Principles for the Improved Conduct of Health Technology Assessments for Resource Allocation Decisions."

38 Banta, "The Development of Health Technology Assessment."

39 Velasco Garrido, World Health Organization, and European Observatory on Health Systems and Policies, Health Technology Assessment and Health Policy-Making in Europe: Current Status, Challenges, and Potential.

40 International Journal of Technology Assessment in Health Care, "Health Technology Assessment."

41 Velasco Garrido, World Health Organization, and European Observatory on Health Systems and Policies, Health Technology Assessment and Health Policy-Making in Europe: Current Status, Challenges, and Potential.

42 Martelli et al., "A Systematic Review of the Level of Evidence in Economic Evaluations of Medical Devices."

43 Hutton, Trueman, and Henshall, "Coverage with Evidence Development."

44 International Journal of Technology Assessment in Health Care, "Health Technology Assessment."

45 "Iqwig.de – In the HTA Network."

46 "EUnetHTA | Health Technology Assessment (HTA)."

life-cycle of a health technology

HTA at different stages

Figure 2.2-1 by the World Health Organization (WHO) shows the life-cycle of a health technology and the different approaches of HTA in the product´s life-cycle. HTAs intention is to improve the uptake of new cost-effective technologies, to avoid the uptake of technologies that can harm humans or are of doubtful value for health systems, and to slow down the uptake of technologies which seem promising but currently have uncertainties.[47]

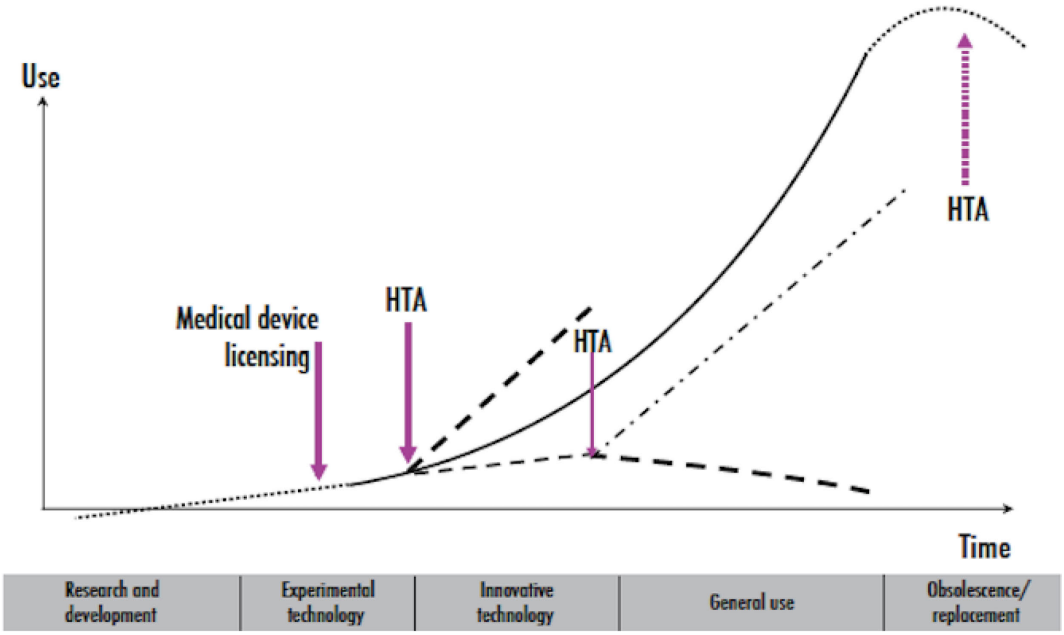

Figure 2.2-1: The natural life-cycle of a medical device (adapted from[48])

market approval for all medical devices, HTA only for some

While HTA is in general reserved for complex problems, the regulatory process concerns all medical devices and pharmaceuticals to some degree.[49] Table 2.2-1 gives an overview about the main differences between HTA and regulation.

Table 2.2-1: Regulation/Approval vs. Reimbursement (adapted from[50])

Characteristics	Health Technology Regulation	Health Technology Assessment
Perspective	Safety and efficacy	Efficacy, effectiveness, and appropriateness
Requirement	Mandatory	Recommendation in complex technologies
Role	Prevent harm	Maximize clinical and cost effectiveness

EUnetHTA: collaboration in standardized HTA

The following subchapter provides information about a methodological approach developed by the EUnetHTA, to assess medical devices in a standardized manner that facilitates collaboration between HTA-agencies across Europe.

47 World Health Organization, Health Technology Assessment of Medical Devices.

48 Ibid.

49 Ibid.

50 Ibid.

2.2.1 The HTA CoreModel®

common set of methodological approaches and principles

HTA agencies around the world share a common set of methodological approaches and principles. However, the structure of HTA reports differs considerably across the agencies because of different national standards, specific work processes, and context. This hinders information sharing among HTA agencies.[51] As a possible solution, the task force Work Package 4 of the EUnetHTA, consisting of twenty-four organizations from seventeen countries and led by the Finnish Office for Health Technology Assessment, developed a multidisciplinary common core of Health Technology Assessment evidence, the HTA Core Model®.[52, 53]

EUnetHTA developed HTA Core Model®

HTA Core Model® consists of

ontology

methodological guidance

reporting structure

The Core Model® consists of three different parts with specific purposes:

- The *Ontology* is a standardized set of HTA questions that allow users to define their specific research questions within a hierarchical structure.
- The *Methodological guidance* assists and supports in answering the research questions.
- The *Reporting structure* is a common structure for presenting findings in a standardized 'question-answer pair' format.[54]

sharing HTA results in a common and structured format

The main aim of the HTA Core Model® was to enable collaboration between international HTA agencies in producing HTA information, to share the results in a common and structured format, as well as to avoid redundant work in case of similar projects. Besides, the model represents a wide range of different perspectives.[55]

content: 9 different domains

The HTA Core Model® consists of nine different domains to assess the dimensions of value, as defined in the EUR-ASSESS project: Health problem and current use of the technology (implementation level); Description and technical characteristics of technology; Safety; Clinical effectiveness; Costs, economic evaluation; Ethical analysis; Organizational aspects; Social aspects; and Legal aspects.[56]

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51 Kristensen et al., "Practical Tools and Methods for Health Technology Assessment in Europe."

52 Ibid.

53 Kristensen et al., "European Network for Health Technology Assessment, EUnetHTA."

54 "EUnetHTA | HTA Core Model®."

55 Kristensen et al., "Practical Tools and Methods for Health Technology Assessment in Europe."

56 Liberati, Sheldon, and Banta, "EUR-ASSESS Project Subgroup Report on Methodology. Methodological Guidance for the Conduct of Health Technology Assessment."

Table 2.2-2: Domains of the HTA Core Model®

Domains	Relative effectiveness assessment (REA)	Comprehensive/ Full HTA Report
Health problem and current use of technology (implementation level)		
Description and technical characteristics		
Safety		
Clinical effectiveness		
Costs and economic evaluation		
Ethical analysis		
Organizational aspects		
Patient and social aspects		
Legal aspects		

relative effectiveness assessment (REA) and full HTA report

A domain, in this context, is a wide framework, representing a perspective from which to view the use, consequences and implications of any technology.[57] Depending on the scope of the assessment, a relative effectiveness assessment (REA) includes the first four domains, a comprehensive/full HTA report includes all of the nine domains (Table 2.2-2).[58]

assessment elements: potential questions

HTA Core Model®: enable transnational HTA collaborations

The HTA Core Model® consists of 133 assessment elements for medical and surgical interventions as well as 153 elements for diagnostic.[57, 59] While the objective of the HTA Core Model lies on enabling collaboration on the international level, the envisioned goal is to create a platform that enables transnational HTA collaborations between different stakeholders to create a common pool of structured HTA information.[60]

2.2.2 Unique characteristics of Medical Devices

HTAs of medical devices ev. more difficult

Compared to pharmaceuticals, medical devices have some unique characteristics that might render the assessment more difficult.

characteristics:

short lifespan

device-operator interaction

economic and organizational implications, etc.

These characteristics are:

- Incremental innovation/short lifespan of a device,
- Learning curve of the device-user (device-operator interaction),
- Wider economic and organizational implications,
- Pricing strategy and procurement policies,
- Heterogeneity of medical devices and class effect,
- Difficulties in performing experimental studies (e.g. RCTs).[61, 62]

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57 Lampe et al., "The HTA Core Model."

58 "EUnetHTA | HTA Core Model®."

59 Pasternack et al., "Testing the HTA Core Model."

60 Kristensen et al., "Practical Tools and Methods for Health Technology Assessment in Europe."

61 Drummond, Griffin, and Tarricone, "Economic Evaluation for Devices and Drugs – same or Different?"

incremental (stepwise) technological innovation – permanent modifications

Firstly, in the lifetime of a medical device an incremental (stepwise) technological innovation takes place. Medical devices evolve very rapidly, sometimes within18 to 24 months, and product modifications in delivery systems or reduction of their size are common.[63] As a result, patients' benefit might steadily increase over time, but these product modifications can also have negative implications on efficacy and other endpoints such as costs.[64, 65] This means HTA institutes may face evidence of an older version of a medical device once the assessment takes place, with a newer version already on the market.[66, 67] Additionally, the short lifespan of medical devices, sometimes shorter than the length of clinical tests, makes it hard to obtain clear and useful clinical evidence at one point in time.[68] The analyses of clinical studies with different versions of medical devices are difficult and retroactively subgrouping cannot be recommended.[69]

clinical evidence often of older version

learning curve depends on the device-operator interaction

device efficacy depends also on handling

Secondly, the learning curve for the use of a medical device depends on the device-operator interaction. While drugs are a so-called „embodied technology", meaning as long as given in the right dose the efficacy relates only to the drug itself, the device efficacy depends not only on the device itself but rather how it is used by the operator (e.g. surgeon or medical professional). Errors and adverse outcomes are more likely to occur during the learning curve of the operators, which can distort the outcome result of clinical trials. After a period of training, the clinician's experience increases, fewer errors occur and the medical device performance improves.[70]

economic and organizational implications: reorganization of workflow, maintenance costs ...

Thirdly, the wider economic and organizational implications of the introduction of medical devices are different in comparison to pharmaceuticals. For instance, there might be a need for training of device operators or physicians. Alternatively, processes in a hospital must be reorganized to shelter or support the new technology.[71] Furthermore, the initial and annual (running) costs of a medical device must be considered.[72]

iterative developments affect pricing and procurement

Fourthly, the price for medical devices constantly changes, resulting from iterative improvements of the devices (incremental innovation), market entry of new products or different ways of procurement in different health systems.

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62 Taylor and Iglesias, "Assessing the Clinical and Cost-Effectiveness of Medical Devices and Drugs."

63 Facey, "HTAi Policy Forum 2015 Background Paper: Improving the Effectiveness and Efficiency of Evidence Production for HTA in the Light of Current Trends in Drug and Device Development, Health System Funding, Regulation and HTA. Edmonton: Health Technology Assessment International; 2015."

64 Taylor and Iglesias, "Assessing the Clinical and Cost-Effectiveness of Medical Devices and Drugs."

65 Sorenson et al., "Applying Health Economics for Policy Decision Making."

66 Mowatt et al., "When and How to Assess Fast-Changing Technologies: A Comparative Study of Medical Applications of Four Generic Technologies."

67 Sorenson et al., "Applying Health Economics for Policy Decision Making."

68 Craig et al., "A Review of the Economic Tools for Assessing New Medical Devices."

69 Parquin and Audry, "Clinical Evaluation of Medical Devices."

70 Taylor and Iglesias, "Assessing the Clinical and Cost-Effectiveness of Medical Devices and Drugs."

71 Ibid.

72 Ferrusi et al., "Health Technology Assessment from a Canadian Device Industry Perspective."

This is dissimilar to pharmaceuticals, where, once the price for the drug is negotiated, it is more likely to stay close to that initial price until the patent expires.[73]

heterogeneity of medical devices

Fifthly, the heterogeneity of medical devices makes them difficult to compare. This heterogeneity gets evident when looking at the various applications as either diagnostic and therapeutic medical devices. While showing the results of a therapeutic device is straightforward, the results of diagnostic devices are difficult to separate from the improved patient outcome. Furthermore, some of the devices are implantable and need a long-term follow-up. Additionally, the diagnostic devices sometimes have multiple applications, which challenges the assessment of the total value and health impact of a device, as a weighted average value needs to be calculated.[74, 75, 76]

therapeutic device easier to assess than diagnostic devices
short- and long-term follow-up
equivalence more difficult

good clinical evidence: RCTs sometimes more difficult

Sixthly, the implementation of experimental studies like randomized clinical trials (RCTs) is sometimes more difficult. Some of the aforementioned characteristics make it complicated to accomplish a randomized clinical trial. For example, the learning curve of the device operators makes it difficult in an RCT to compare a traditional surgical procedure with a new procedure involving a device. Further blinding, randomization and the use of sham procedures for the trials are difficult to apply, and in some cases unethical. Additionally, RCTs are often of small sample size because the target population is rather small and it is difficult to obtain the patient consent when the RCT involves invasive surgical procedures.[77, 78]

blinding, sham procedures
small sample sizes
patient consent

2.2.3 Differentiation to pharmaceuticals

medical devices and pharmaceuticals are essentially different

Medical devices and pharmaceuticals are both meant to improve quality of life and are crucial for prevention, diagnosis, and treatment of patients. Yet, they are essentially different in their mode of action. While drugs achieve their intended action on the human body or in interaction with biochemical pathways in the body (pharmacological, immunological or metabolic means), medical devices have many different functionalities and modes of action, such as heat, mechanical or radiation. Consequently, most of the medical devices need an intermediary, the professional for the interaction with patients, while drugs interact directly with or in the patient. Another major difference compared to pharmaceuticals is that medical devices are used for therapeutically as well as for diagnostic purposes.[79, 80]

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73 Drummond, Griffin, and Tarricone, "Economic Evaluation for Devices and Drugs – same or Different?"

74 Martelli et al., "A Systematic Review of the Level of Evidence in Economic Evaluations of Medical Devices."

75 Drummond, Griffin, and Tarricone, "Economic Evaluation for Devices and Drugs – same or Different?"

76 Craig et al., "A Review of the Economic Tools for Assessing New Medical Devices."

77 Martelli et al., "A Systematic Review of the Level of Evidence in Economic Evaluations of Medical Devices."

78 Drummond, Griffin, and Tarricone, "Economic Evaluation for Devices and Drugs – same or Different?"

79 Taylor and Iglesias, "Assessing the Clinical and Cost-Effectiveness of Medical Devices and Drugs."

80 Santos et al., "Medical Device Specificities."

The life-cycle of medical devices and pharmaceuticals varies in different sectors. While the development of a drug takes around a decade to complete, the development of a medical device is generally shorter. Figure 2.2-2 shows a typical product life cycle of medical devices and pharmaceuticals. Compared to pharmaceuticals life cycle, medical devices have faster cycle times because of the incremental improvements, which bring essential information and evidence for further device versions.[81]

life-cycle: drugs around a decade to develop medical devices: much shorter and faster turn-over

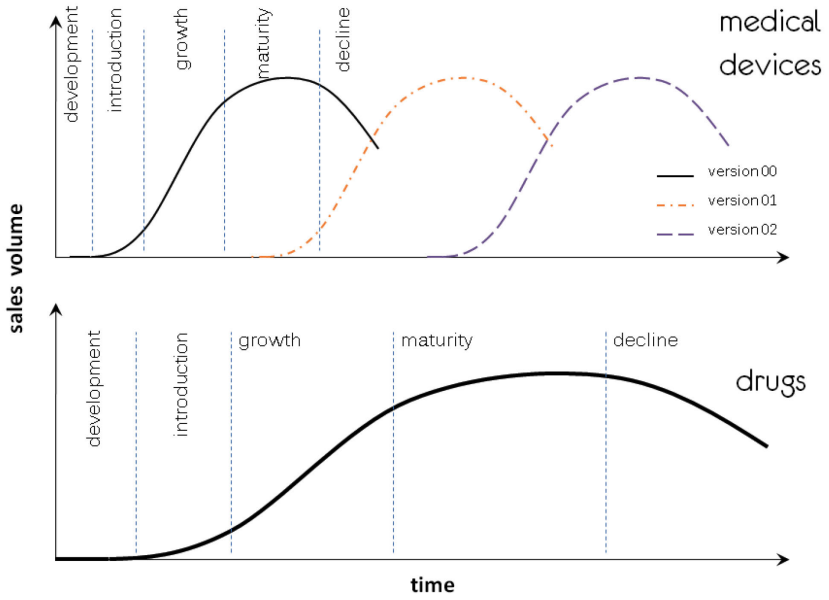

Figure 2.2-2: Life-cycle of medical devices and pharmaceuticals (adapted from[82])

Another disparity between medical devices and pharmaceuticals is the industrial development environment. While the majority (95%) of medical device industry consists of small- and medium-sized enterprises (SMEs), the pharmaceutical industry subsists on a few large companies.[83] This circumstance relates directly to the implementation of RCTs, because the performance of RCTs is very time-consuming and costly, attributes which SMEs cannot handle easily. Consequently, less RCTs are conducted or have short follow-ups.[84]

medical devices: small- and medium-sized enterprises (SMEs)

drugs: large companies

Finally, medical devices and pharmaceuticals differ in their pre-market evaluation process. While the medical device process is decentralized and handled by the competent authorities and their designated Notified Bodies, pharmaceuticals licensing and market access is centralized and granted by the European Medicines Agency (EMA). The EMA usually only accepts RCTs for new pharmaceuticals, whereas RCTs for medical devices are not feasible in some cases.[85, 86]

pre-market evaluation

medical devices: decentralized drugs: centralized

[81] Ibid.

[82] Ibid.

[83] "MedTech Europe.The European Medical Technology Industry in Figures 2015."

[84] Craig et al., "A Review of the Economic Tools for Assessing New Medical Devices."

[85] Taylor and Iglesias, "Assessing the Clinical and Cost-Effectiveness of Medical Devices and Drugs."

[86] Tsoi et al., "Harmonization of Reimbursement and Regulatory Approval Processes."

3 Methods

The data collection for this research is divided into two main parts: the first part collected and analyzed information on Health Technology Assessment (HTA) for medical devices in Europe and the critical points discussed in the literature compared to pharmaceuticals. The second part focused on accessible information to discover similarities between European Health Technology Assessment institutes in the context of the assessment of medical devices, and the used evidence compared to the year of the CE-mark.

2 data collections:

for literature review

for analysis of European HTAs of medical devices

3.1 Research questions

This research project aims at contributing to the efforts towards a stronger collaboration of European HTA institutes. The research questions are focusing on the critical points and challenges in the assessment of medical devices and procedures as well as the comparison of different HTA institutes and their reports regarding the used evidence and timing:

- Which critical points in the assessment of medical devices and procedures were discussed in the recent literature?
- Which high-risk medical devices have been assessed in Europe at a specific time by using varying evidential information?
- Is there a possibility to group (cluster) HTA institutes according to timing (time between CE-mark and early or late HTAs)?

RQ on

critical points in HTAs of medical devices

HTAs of high-risk medical devices in Europe

timing and evidence used in HTAs of medical devices in Europe

3.2 Literature Review

A systematic literature search was conducted in Medline via PubMed. The literature search was supplemented by hand searches („informed electronic browsing") in search engines (e.g. google) and screening of the references cited in the documents previously identified (i.e. cross-referencing). All search outcomes were documented and underwent a selection process. Predefined inclusion and exclusion criteria guided the literature selection process. All relevant steps are documented in a PRISMA-tree. The main inclusion and exclusion criteria are represented in Table 3.2-1.

searches in Medline

documented in PRISMA

The following keywords were used during the literature search:

keywords used in search

*Health Technology Assessment** AND *HTA** AND *Technology Assessment, biomedical [MeSH Terms]* AND *equipment and supplies [MeSH Terms]* AND *medical devices** AND *medical instruments** AND *Europe** AND *EU** AND *European Union** AND *Regulation** AND *Characteristics** AND *Reimbursement** AND *Classification** AND *Harmonization** AND *Policy-making** AND *Impact** AND *Influence** AND *Timing** AND *Challenges**

Table 3.2-1: Inclusion and exclusion criteria for literature review

Inclusion criteria	Exclusion criteria
❁ In English and German language ❁ European HTA agencies only ❁ Articles about medical devices, procedures, and technologies ❁ Critical points of European HTA ❁ Publications available from 2010 until August 2016 ❁ Full articles with abstracts	❁ Only abstracts ❁ HTA agencies outside of Europe ❁ Articles mainly about pharmaceuticals ❁ Other languages

The PRISMA-tree (see Figure 3.2-1) shows the documentation of the relevant steps to identify the literature used in the review.

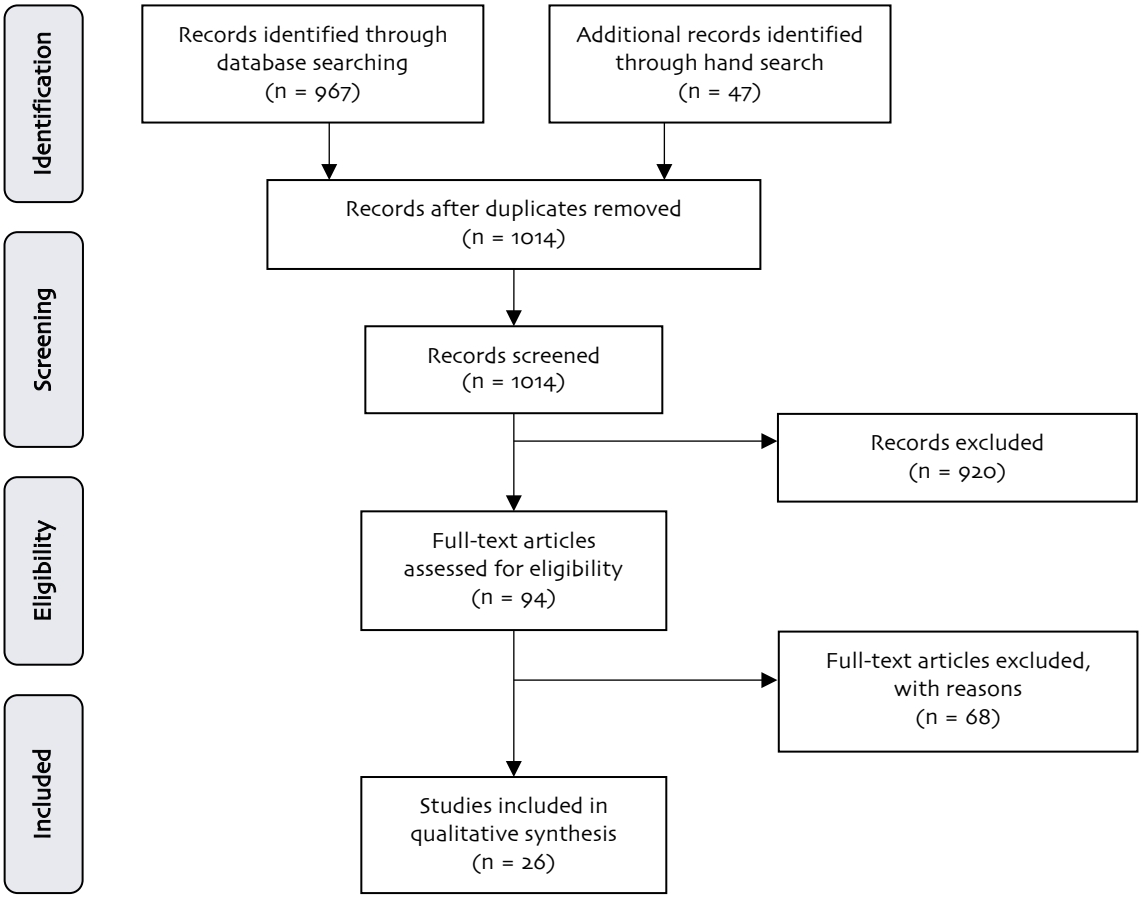

Figure 3.2-1: PRISMA-tree for the documentation of the literature search

3.3 Analysis of European HTAs on selected medical devices

The data collection for this section is (partially) based on a database developed in the EU-FP7 (2007-2013 under grant agreement No. 305983) project ADVANCE_HTA (Advancing and strengthening the methodological tools and policies relating to the application and implementation of Health Technology Assessment). The database consists of all HTA reports conducted from 2004 till 2015 by European HTA institutes and are classified by their taxonomic position.

data collection (partially) based on ADVANCE_HTA Db

all HTAs on medical devices 2004-2015

As a first step, a cohort group of all HTA reports conducted in 2014 was selected from the database. Then, the inclusion criteria for further processing of the 2014 cohort group was defined: all class 2b, 3 (high-risk) or active implantable medical devices (class 4) by the ADVANCE_HTA taxonomic position. To identify the risk class of each of the data records, a matrix developed by the EU-FP7 project ADVANCE_HTA was used (Table 3.3-1).

further selection: cohort group of 2014 HTA reports, then only high-risk-devices

Table 3.3-1: Matrix of taxonomic position and risk classes (adapted from[87])

Classification criteria of EU-Directives according to risk aspects		Classification according to the relevance of product & service and reimbursement characteristics (includes OECD Classification of Health Care Functions) + HTA logic					
		Diagnostic Technologies			Therapeutic Technologies		
		Assistive technology devices (directly used by patients) A1	Artificial body parts (implanted by medical procedure) B1	Medical devices for the assistance of medical professionals C1	Assistive technology devices (directly used by patients) A2	Artificial body parts (implanted by medical procedure) B2	Medical devices for the assistance of medical professionals C2
93/42/ EEC	1	Thermometer		Stethoscope	Walking frame		Spatula
	2a	Pulse oximeter		Ultrasound	Hearing aid	Dental crown	Tracheal tube
	2b			X-ray, PET-CT	Insulin pen; Corrective lenses	Dental implant; Bone prosthesis	Laser RT-Unit
	3			Neuro-endoscope	Condoms with spermicide	Cardiac stents; Artificial joints	Angioplasty balloon catheter
90/385/ EEC	4		ICD: heart monitor unit			ICD: defibrillator unit	
98/79/ EC	5	Glucose strip; pregnancy test		ABO/Rh (D) blood analyzer			

Based on the classification of this matrix, n = 87 HTA reports of high-risk medical devices in 2014 were identified (full list of the 87 reports in Appendix Table 8-1). Out of these 87 reports, ten topics (medical procedures or devices) were chosen for further processing.

87 European HTA reports of high-risk medical devices in 2014

[87] Fuchs et al., "Testing the Plausibility of a Taxonomy for Medical Devices in the Logic of HTA: Poster Presentation HTAi Oslo;2015."

for 10 (of 87) topics: search for HTAs in years before and after 2014 in CRD and Synergus

For the ten chosen topics from 2014, a further literature search was conducted to find HTA reports by other institutions in years before and after 2014. For this step, the University of York's Centre for Reviews and Dissemination (CRD-)HTA database, as well as the commercial Synergus database were analyzed. The inclusion and exclusion criteria for this search were represented in Table 3.3-2.

Table 3.3-2: Inclusion and exclusion criteria for further HTA report search

Inclusion criteria	Exclusion criteria
❁ All languages of the European HTA agencies ❁ HTA reports and rapid assessments	❁ Agencies outside of Europe ❁ Just abstracts
❁ clinical evidence used is clearly described	❁ clinical evidence used is unclear

for 10 selected topics 109 additional HTA reports were identified

for each 10 topics 4 HTA reports chosen for detailed analysis

only reports with a clear presentation of evidence used

In this search, 109 different HTA reports regarding the ten topics selected were identified in CRD and Synergus. Out of the 109 reports a comprehensive pool of four reports per topic (medical procedure or device) were chosen for detailed data collection. The 109 reports were scanned and four reports were chosen for each topic for further analysis. A pre-defined in-/exclusion criterion for the selection of the four HTA reports was the clear presentation of the clinical evidence used. These reports underwent a second, more thorough examination. The second examination focused on the evidence used in the process of conducting the HTA reports. In a final step, the year of CE-mark of the medical devices was searched in literature and in in the worldwide web.

4 Results

4.1 Literature Review: Critical Points in Assessing Medical Devices in Europe

Critical arguments in the assessment of medical devices are brought into the public discussion from several perspectives (from different stakeholders and their points of view).

arguments from several stakeholder perspectives:

These key stakeholders are:

- Patients,
- Health Management,
- The Health Professionals,
- Industry,
- Payers and Insurances,
- Regulators and Government.[88, 89]

health management, payers

health professionals

industry

In the recent literature, several different critical points in assessing medical devices are discussed. Those points can be attributed to some of the stakeholders mentioned above. Figure 4.1-1 provides an overview of the different themes that cause challenges in the assessment of medical devices.

5 critical points that cause challenges in assessing medical devices

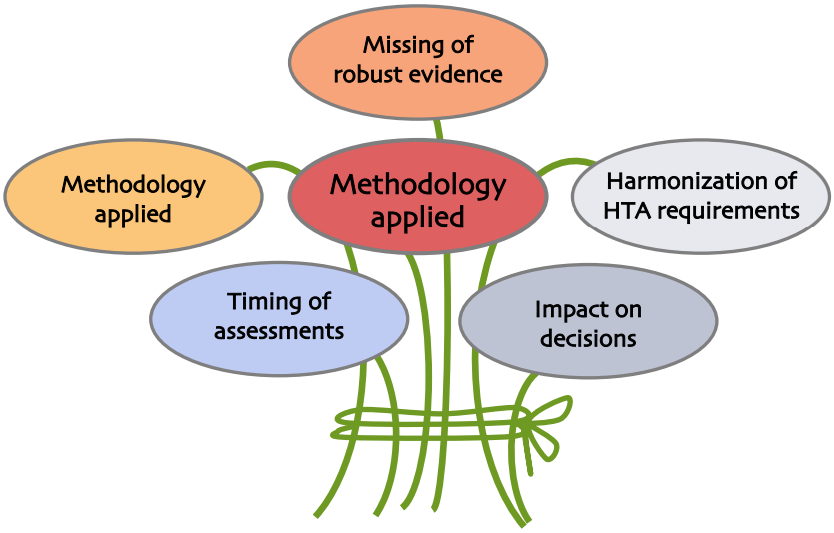

Figure 4.1-1: Critical points in assessing medical devices in Europe

In the following, each subchapter captures one of the critical points shown above and explains the circumstances why and how those points are challenging.

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88 Velasco Garrido, World Health Organization, and European Observatory on Health Systems and Policies, Health Technology Assessment and Health Policy-Making in Europe.

89 Henshall et al., "Interactions between Health Technology Assessment, Coverage, and Regulatory Processes."

4.1.1 Critical Point: Missing of robust evidence

at time of product launch:

HTA institutes are frequently confronted with the missing of high-level clinical evidence, while they should assess new innovative medical devices on the best evidence available.[90] When HTA institutes assess the value of health technologies, the existence of relevant and robust clinical data regarding efficacy, safety and effectiveness is of high importance. While for pharmaceuticals much of the clinical data available is generated to demonstrate efficacy and safety to the regulator, clinical data for medical devices is very limited, especially at the time of product launch. This is a result of the different regulatory frameworks in the various jurisdictions and is a consequence of the eventual difficulty in conducting relevant clinical trials.[91, 92]

clinical data for medical devices is very limited

reasons: early product launch and eventual difficulty for RCTs

regulatory requirements: safety and performance data

In addition, the regulatory process of medical devices generally targets product safety and function. However, the required evidence depends on the medical devices risk-level to which the patients are exposed. Despite these rules for evidence requirements, for many products trials to create clinical evidence are not required or the trials were conducted by the manufacturer.[93] This leads to the huge variation between the evidence requirements for market authorization and reimbursement (HTA).[94]

liberal regulatory framework in Europe is perceived differently by diverse stakeholder groups

One of the views on the European medical device regulatory system is that it is „opaque and patchy" – as expressed in a debate in the US Congress. The medical device industry perceives Europe as more favorable than most of the other economic regions like the United States or Australia.[95] The liberal regulatory framework in Europe has supported the growth of the medical device industry.[96] Despite the better conditions for the device industry, most of the HTA-institutes assume that it is not better for patients. Although there are agreed European standards like the MDD or AIMDD, concerns were raised that these standards are not applied or fully performed. This leads to the assumption that some of the organizations, designated to control market entry in Europe, are not rigorous enough in auditing safety or performance of the devices.[97] Coverage bodies are aware that most of the evidence generated by the manufacturers meets the regulatory requirements, but is not sufficient to satisfy the evidence requirements of HTA.[98]

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90 Hulstaert et al., "Pre-Market Clinical Evaluations of Innovative High-Risk Medical Devices in Europe."

91 Tarricone et al., "Generating Appropriate Clinical Data for Value Assessment of Medical Devices."

92 Santos and Tavares, "Additional Peculiarities of Medical Devices That Should Be Considered in Their Development Process."

93 Henshall et al., "Interactions between Health Technology Assessment, Coverage, and Regulatory Processes."

94 Krüger et al., "Divergent Evidence Requirements for Authorization and Reimbursement of High-Risk Medical Devices – The European Situation."

95 Cohen and Billingsley, "Europeans Are Left to Their Own Devices."

96 Sauerland et al., "Approaches to Assessing the Benefits and Harms of Medical Devices for Application in Surgery."

97 Cohen and Billingsley, "Europeans Are Left to Their Own Devices."

98 Frønsdal et al., "Interaction Initiatives between Regulatory, Health Technology Assessment and Coverage Bodies, and Industry."

early approvals in Europe show risks of post-marketing safety alerts

approvals on the basis of case-series

The results of a recently conducted cohort study support this hypothesis, because the devices studies were approved first in the EU and showed a higher risk of post-marketing safety alerts as well as recalls.[99, 100] These results are supported by another study that investigated seven medical devices authorized in four economic regions (Europe, United States, Canada, Australia). The results show that only in Europe all seven devices were approved, while three were approved in Australia, and only one in Canada and the United States.[101] Furthermore, considering the time of CE-marking of those seven devices in comparison to the time needed to develop robust clinical evidence (e.g. RCTs), the CE-mark is granted several years before robust clinical data is available.[102] This supports the statement that many devices received the CE-mark on the evidence base of case series with around 50 cases.[103]

4.1.2 Critical Point: Methodology applied

HTA methodology mostly developed for pharmaceuticals

In the last decade, a great variety of new and highly developed medical devices has emerged.[104] These devices bring therapeutic and diagnostic advantages, but they also shed light on emerging methodological challenges regarding their assessment. Since most of the methodological guidelines have been developed to suite the assessment of pharmaceuticals, these methods are difficult to apply for medical devices.[105]

users' training and skills etc. often not considered in common methods

methods to capture incremental innovation

In the context of ill-fitted methodology, some of the major methodological challenges for the assessment of medical devices are related to their unique characteristics and were mentioned afore, such as the potentially high learning curve (device-user interaction) or incremental and dynamic innovation.[106] Medical devices are often associated with a learning curve because the users' training and skills can have an important impact on the devices' performance, which is hard to include and measure in the assessment with the current methodological tools. Further, the learning curve influences the cost-effectiveness of the medical devices.[107, 108] The rapid pace of the advancement of medical devices leads to more incremental innovation, rather than new breakthrough technologies. This step-by-step innovation poses specific methodological hurdles for the assessing medical devices.[109]

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99 Hwang et al., "Comparison of Rates of Safety Issues and Reporting of Trial Outcomes for Medical Devices Approved in the European Union and United States."

100 Campillo-Artero, "A Full-Fledged Overhaul Is Needed for a Risk and Value-Based Regulation of Medical Devices in Europe."

101 Krüger et al., "Divergent Evidence Requirements for Authorization and Reimbursement of High-Risk Medical Devices – The European Situation."

102 ibid

103 Sauerland et al., "Approaches to Assessing the Benefits and Harms of Medical Devices for Application in Surgery."

104 Dhruva and Redberg, "Medical Device Regulation."

105 Iglesias, "Does Assessing the Value for Money of Therapeutic Medical Devices Require a Flexible Approach?"

106 Schnell-Inderst et al., "Health Technology Assessment of Medical Devices."

107 Tarricone et al., "Generating Appropriate Clinical Data for Value Assessment of Medical Devices."

108 Iglesias, "Does Assessing the Value for Money of Therapeutic Medical Devices Require a Flexible Approach?"

109 Schnell-Inderst et al., "Health Technology Assessment of Medical Devices."

methods to evaluate the contribution of diagnostics to patients´ outcomes

Moreover, the differentiation between therapeutic and diagnostic devices comprises challenges for the methodology. The value of improved diagnosis through the new device cannot be separated from the overall treatment success.[110] Furthermore, some indirect and broader aspects of assessing the impact of the device on productivity or the caregivers quality of life are mentioned in the literature as methodological challenges.[111, 112] In addition, the assessment of the long-term outcome of diagnostic devices contains challenges for the methodology, because the result of a diagnostic device can improve diagnosis, but this outcome is difficult to measure.[113, 114]

4.1.3 Critical Point: Harmonization of HTA requirements

European coordination: drug approval and coverage requirements well defined

In contrast to the pharmaceutical sector, the HTA processes and regulations around medical devices are less harmonized within the EU. The coordination between national pharmaceutical regulators and the centralized European Medicines Agency (EMA) as well as the evidence requirements for coverage in benefit catalogues is well defined and established.

European coordination: medical device approval and coverage requirement less well developed

In contrast, the medical device regulators have some similarities in their information requirements, but their international coordination is less developed compared to pharmaceuticals.[115] The harmonization of requirements for Health Technology Assessment is even less developed. This harmonization covers three different areas:

„(i) harmonization of approaches and processes;

(ii) harmonization of methods and evidence requirements;

(iii) harmonization of decisions"[116].

harmonization of HTA-requirements:

Many new developments have been made in order to harmonize the methods for HTA assessments on medical devices; less focus was set on harmonized approaches and decision making. This can partially be attributed to politics since coverage and reimbursement decisions are subject to individual countries decision making.[117]

huge difference between the quality of evidence used

A review on the basis of 21 economic evaluation suggested that there is a wide variety of methods used as well as a huge difference between the quality of evidence used to perform analyses.[118] Some of the technologies are assessed multiple times by different institutes which has a strong influence on

110 Drummond, Griffin, and Tarricone, "Economic Evaluation for Devices and Drugs – same or Different?"

111 Sorenson et al., "Applying Health Economics for Policy Decision Making."

112 Drummond, Griffin, and Tarricone, "Economic Evaluation for Devices and Drug – same or Different?"

113 Craig et al., "A Review of the Economic Tools for Assessing New Medical Devices."

114 Hutton, Trueman, and Henshall, "Coverage with Evidence Development."

115 Henshall et al., "Interactions between Health Technology Assessment, Coverage, and Regulatory Processes."

116 Trueman et al., "The Feasibility of Harmonizing Health Technology Assessments across Jurisdictions."

117 Ibid.

118 Martelli et al., "A Systematic Review of the Level of Evidence in Economic Evaluations of Medical Devices."

the institute's human and financial resources.[119, 120] Therefore, a better communication and coordination could reduce discrepancies regarding the evidence requirements and consequently improve the efficiency of the review process.[121]

prerequisite for collaboration

A further example of a lack of harmonization is the definition of medical devices itself. Even though there is a Council directive outlined by the European Parliament which defines medical devices, numerous additional definitions of medical devices exist and vary from country to country as well as their classification of risk-classes.[122, 123, 124]

definitions of medical devices vary between countries

4.1.4 Critical Point: Impact on decisions

The impact of Health Technology Assessment on decision making depends on the legally binding requirements of the jurisdiction. Some of the institutes´ recommendations are binding for the reimbursement agency, while other institutes' reports only have a supporting or advising function.[125] A study conducted by the Austrian LBI-HTA concerning the impact of HTA reports on reimbursement of new hospital interventions found, that the majority of their reports have been used in decision processes regarding reimbursement/investment or disinvestment, although the LBI-HTA only has an advisory function.[126]

legally binding or advisory function of HTA on medical devices

mostly not binding

Another study, which surveyed 16 HTA institutes of 14 European countries, confirmed these results, suggesting that many institutions consider their assessments to have an impact on the decision and policy-making process.[125] The Swedish HTA institute SBU conducted a study concerning the effect of their Health Technology Assessment reports on policy-making and clinical practice. Therefore, 26 conducted reports between 2006 and 2010 were analyzed and the level of impact scored (low, moderate, high). The results showed that the HTA reports influence comprehensive decisions and on national guidelines.[127]

examples from Sweden and Austria:

HTAs of medical devices are influential

Nonetheless, the monitoring of HTA impact is difficult because most assessments produced by the institutes are not binding for the decision-making process. Moreover, the impact relies on the level (e.g. national, regional) to which the HTA report was formulated for.[125]

amount of impact dependent on political decision process

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119 Mathes et al., "Methods of International Health Technology Assessment Agencies for Economic Evaluations-a Comparative Analysis."

120 Nachtnebel et al., "HTA goes Europe."

121 Henshall et al., "Interactions between Health Technology Assessment, Coverage, and Regulatory Processes."

122 Santos et al., "Medical Device Specificities."

123 Santos and Tavares, "Additional Peculiarities of Medical Devices That Should Be Considered in Their Development Process."

124 Iglesias, "Does Assessing the Value for Money of Therapeutic Medical Devices Require a Flexible Approach?"

125 Fuchs et al., "HTA of Medical Devices: Challenges and Future Impulses from a European Perspective – Forthcoming."

126 Zechmeister and Schumacher, "The Impact of Health Technology Assessment Reports on Decision Making in Austria."

127 Rosén and Werkö, "Does Health Technology Assessment Affect Policy-Making and Clinical Practice in Sweden?"

4.1.5 Critical Point: Timing of assessments

lack of publicly available approval decisions = absence of clear market entry at one point in time

The timing for conducting an assessment is crucial, due to the lack of clearly defined and publicly available market authorization decisions valid throughout Europe, the absence of a clear point of market entry, as well as the existence of robust clinical data. For the coverage bodies, assessments are relevant and should be available at the time when the reimbursement and coverage decisions take place.

timing of HTA: before diffusion

Therefore, the timing of the assessment is key. If the assessment happens at a late stage of the medical device life cycle, the decision for or against reimbursement might already be obsolete, since a decision has to be made close to the device's introduction to the market. If the assessment is conducted too early, it is likely that there is not enough robust clinical evidence available to make a clear decision without uncertainty.[128, 129]

4.2 Analysis: Comparison of European HTAs on same Technologies

comparison with regard to proximity to CE-mark and clinical evidence used in assessments

This chapter will give an overview on and insights into the differences between European HTAs of selected medical devices in consideration of the timing of the assessment and the clinical evidence used. The following information was essential for the comparison:

- Year of obtaining the CE-mark of the technology
- Year of conducting the HTA report
- The clinical evidence used for performing the assessment

10 technologies selected based on frequency of HTAs in Europe

Therefore, ten different technologies and procedures were chosen based on their frequency of assessment in Europe and for each of them, four reports were selected for further analysis. The mentioned HTA reports were found through multiple searches in databases and search engines. Moreover, the date of CE-mark was searched on the manufactures website as well as the worldwide web for announcements regarding the CE-mark.

structure of following chapters

In the following sections, the results for the ten technologies and procedures are presented: first, the indication and procedure of the medical device is explained, secondly, the ten high-risk devices and their respective assessments are presented

4.2.1 Implantable cardiac resynchronization therapy and defibrillator (CRT: CRT-D/CRT-P)

indication and procedure

Several cardiac diseases such as myocardial infarction or heart valve disorders weaken the heart and negatively impact the ability to pump blood to the rest of the body. The resulting state is called a heart failure. Usually, heart failure

[128] Schnell-Inderst et al., "Health Technology Assessment of Medical Devices."

[129] Tarricone et al., "Generating Appropriate Clinical Data for Value Assessment of Medical Devices."

develops stepwise, depending on the severity of the underlying cardiac disease. A healthy heart has a well-coordinated pumping cycle that can be damaged by heart failure, causing an unsynchronized contraction of the ventricles. The cardiac resynchronization therapy and defibrillator is a method aiming to synchronize the action of the heart in order to improve the heart's ability to pump. Currently, pacemaker stimulation of the right atrium and ventricle for treating a slow pulse rate (bradycardia) is the common and well-established therapy. For the cardiac resynchronization therapy, an additional electrode over the left ventricle is placed, to synchronize the contraction of both ventricles.[130]

all HTA reports and evidence used in HTAs

11 reports 2003-2015

Between 2003 and 2015, nine HTA institutes assessed CRT technology in 11 HTA reports. Of those 11, four were selected for an analysis of the evidence used, displayed in Table 4.2-1. In addition a short form (a, b, c, d) is assigned in order to locate the respective report in the evidence pyramid presented in the appendix (see Figure 8-1). The first CRT technology received the CE-mark in 2001. The manufacturer of this technology was the Guidant Corporation with the heart failure therapy system CONTAK™ RENEWAL™ cardiac resynchronization therapy defibrillator (CRT-D).[131] The CRT technology is comprising a multitude of different devices (CRT-P, CRT-D) from different manufacturers and generations of devices.

Table 4.2-1: Summary of HTA institutes that conducted reports on CRT-D/CRT-P

Institute	Country	Year of report	Short form
SBU	Sweden	2003	*a*
HIS	Scotland	2005	
KCE	Belgium	2007	
NIHR	England	2007	
AETSA	Spain	2009	*b*
UETS	Spain	2010	
KCE	Belgium	2011	
AGENAS	Italy	2014	*c*
NIHR	England	2014	
NICE	England	2014	
Swiss Medical Board	Switzerland	2015	*d*

detailed analysis of 4 HTAs:
2003: 7 RCTs
2009: SR + 17 RCTs + CPG
2014: 8 SR + 34 CT
2015: 9 MA + 5 RCTs

The first HTA in 2003 (SBU), 2 years after the receipt of the CE-mark, was based on seven RCTs. The HTA conducted in 2009 (AETSA) is already based on systematic reviews, 17 RCTs and seven clinical practice guideline. The HTA conducted in 2014 (AGENAS) used the evidence of eight systematic reviews and meta-analysis, and additional 34 primary comparative studies. The latest HTA in 2015 by the Swiss Medical Board, is based on nine meta-analyses and five randomized clinical trials (see Table 4.2-2 below and Figure 8-1 in Appendix).

minimum level of evidence: RCTs

The minimum level of evidence used in the four analyzed HTAs is comparative trials and randomized clinical trials, revealing a high level of clinical evidence at time of HTAs. The first assessment after CE-mark (2001) was conducted 2 years after (2003) the market approval.

[130] SBU, "Cardiac Resynchronization Therapy (CRT) in Chronic Heart Failure."
[131] "Boston Scientific | Guidant Announces CE-Mark Approval of CRT-D."

Table 4.2-2: Summary of information of 4 HTA reports on CRT-D/CRT-P

Technology	HTA title	Institute	Year of report	Year of CE-mark	Evidence	Link
Implantable cardiac resynchronization therapy and defibrillator (CRT-P, CRT-D)	Pacemaker för synkronisering av hjärtkamrarnas rytm (CRT) vid kronisk hjärtsvikt	SBU	2003	2001	7 RCTs	http://bit.ly/2bOEb2h
	Standards for health technologies appropriateness: Cardiac resynchronization therapy	AETSA	2009		7 systematic reviews/ meta-analysis 17 randomized clinical studies 7 clinical practice guidelines	http://bit.ly/29KrisN
	Implantable cardiac resynchronization therapy and defibrillator (CRT-D) in patient with heart failure	AGENAS	2014		8 systematic reviews/ meta-analysis 34 primary comparative studies	http://bit.ly/29Jzc48
	Le stimulateur cardiaque de resynchronisation dans le traitement de l'insuffisance cardiaque	Swiss Medical Board	2015		9 meta-analysis 5 RCTs	http://bit.ly/29AJ4fx

4.2.2 MitraClip®

indication and procedure

Mitral regurgitation is described as the state in which a backward flow of blood from the left ventricle to the left atrium during the contraction phase of the cardiac cycle (systole) takes place. The underlying reason is the dysfunction of the mitral valve to close entirely. Usually, the mitral valve opens to fill the ventricle with blood from the atrium and closes automatically due to the pressure in the ventricle, while the blood is pushed out to the aorta. Because of the insufficient closure of the valve, blood streams back to the atrium and the pressure in the left atrium increases. Over time, this can lead to a growth of the left atrium. In severe cases of mitral regurgitation, the blood accumulates back into the lung. Additionally, the performance of the left ventricle is weakened. If left untreated, severe mitral regurgitation can result in a heart failure and potentially lead to death. The implantation of the MitraClip® onto the valve leaflets forms two smaller orifices allowing improved valve closure and reduced leakiness.[132, 133] The MitraClip® procedure is performed through a venous access, avoiding open-heart surgery and cardiopulmonary bypass.

all HTA reports and evidence used in HTAs

9 reports: 2010-2016

Between 2010 and 2016 the MitraClip® procedure was assessed by seven HTA-institutes in nine reports. Of those nine reports, four were selected for an analysis of the evidence used. The results are displayed in Table 4.2-3. In addition a short form (a, b, c, d) is assigned in order to locate the respective report in the evidence pyramid presented in the appendix (see Figure 8-2).

[132] "HIS | MitraClip® Transcatheter Mitral Valve Repair System | Evidence Note."

[133] Janatzek, Thomas, and Mad, "Percutaneous Repair of Mitral Regurgitation with the MitraClip."

The MitraClip® is developed and produced by Abbott and received the CE-mark first in 2008.[134]

Table 4.2-3: Summary of HTA institutes that conducted reports on MitraClip®

Institute	Country	Year of report	Short form
LBI-HTA	Austria	2010	*a*
LBI-HTA	Austria	2012	
Stockholm County Council HTA Center	Sweden	2012	*b*
CEDIT	France	2012	
AOTMIT	Poland	2013	
OSTEBA	Spain	2014	*c*
HAS	France	2015	*d*
LBI-HTA	Austria	2015	
HIS	Scotland	2016	

detailed analysis of 4 HTAs:

2010: 1 case-series
2012: 1 RCT + 10 case-series
2014: SR + 2 RCTs + 9 case-series
2015: 1 RCT + 9 case-series

The first HTA was conducted in 2010 (LBI-HTA), 2 years after receiving the CE-mark, and is based on one prospective, uncontrolled before-after study. An update in 2012 included one RCT and ten prospective, uncontrolled studies. Another HTA in 2012 (Stockholm County Council HTA-Center) based their decision on one prospective multicenter single arm study, one randomized multicenter study and ten observational studies. The third selected HTA in 2014 (OSTEBA) was based on one systematic review, two RCTs, and nine case series. The latest selected HTA was conducted in 2015 (HAS) and used one prospective multicenter randomized study and nine non-comparative cohort studies (see Table 4.2-4 below and Figure 8-2 in Appendix).

minimum: prospective case-series

The minimum level of evidence used in the analyzed HTAs ranges from observational studies to uncontrolled trials, revealing a mid-level of clinical evidence at time of HTAs. The first assessment after CE-mark (2008) was conducted 2 years after (2010) the market approval.

[134] "Abbott | Clinical Experience With MitraClip Therapy."

Table 4.2-4: Summary of information in 4 HTA reports on MitraClip®

Technology	HTA title	Institute	Year of report	Year of CE-mark	Evidence	Link
MitraClip®	Perkutane Mitral-klappenintervention mittels MitraClip bei Mitralklappen-insuffizienz	LBI-HTA	2010 2012	2008	2010 1 prospective, uncontrolled before-after study 2012 1 RCT 10 prospective, uncontrolled studies	http://bit.ly/29Ub4Nh http://bit.ly/29AUrqy
	MitraClip®	Stockholm County Council HTA Center	2012		1 prospective, multicenter single arm study 1 randomized multicenter study 10 observational studies (2 multicenter; 5 prospective)	http://bit.ly/29LNzU9
	Using MitraClip® to repair mitral valve regurgitation	OSTEBA	2014		1 systematic review 2 RCTs 9 uncontrolled trials	http://bit.ly/29A2ynp
	Evaluation d'un clip de réparation mitrale bord à bord et de son acte d'implantation	HAS	2015		1 prospective, multicenter, randomized study 9 non-comparative cohort studies	http://bit.ly/1Q1h5CN

4.2.3 Intensity-modulated radiation therapy (IMRT)

indication and procedure

The intensity-modulated radiation therapy is a sophisticated technology of high-precision radiotherapy. Via computer-controlled linear accelerators, the radiation doses are transported to a malignant tumor or specific areas within the tumor. IMRT is able to transport the radiation dose more precisely to the three-dimensional (3-D) shape of the tumor by regulating the intensity of the radiation beam in multiple small volumes. In addition, IMRT allows also the use of higher doses of radiation within the tumor, while minimizing the dose to the surrounding normal tissue. The treatment is planned with 3-D computed tomography (CT) or magnetic resonance images (MRI) of the patient as well as computerized dose calculations to determine which dose fits best. Currently, the IMRT is used to treat prostate, head and neck, lung and breast cancer.[135]

all HTA reports and evidence used

11 reports: 2003-2015

The IMRT technology was assessed in 11 HTA reports by eight institutes between 2003 and 2015. For a further analysis of the evidence used, four reports were selected (blue-colored rows). The results of this analysis are presented in Table 4.2-5. In addition a short form (a, b, c, d) is assigned in order to locate the respective report in the evidence pyramid presented in the appendix (see Figure 8-3).The IMRT technology was first introduced on the European market by the NOMOS Corporation under the name Peacock® system, unfortunately, the year of CE-mark is not accessible or has not been published.[136] The IMRT technology is comprising a multitude of different devices from different manufactures, generations of devices and scope of application.

[135] "Radiology Info | Intensity-Modulated Radiation Therapy (IMRT)."

[136] "PR Newswire | IMRT Receives CE-Mark."

Table 4.2-5: Summary of HTA institutes that conducted reports on IMRT

Institute	Country	Year of report	Short form
NIHR	England	2003	
AVALIA-T	Spain	2005	*a*
HAS	France	2006	
KCE	Belgium	2007	*b*
NIHR	England	2010	*c*
AETSA	Spain	2010	
ASSR	Italy	2010	
KCE	Belgium	2013	
OSTEBA	Spain	2014	*d*
OSTEBA	Spain	2014	
HAS	France	2015	

detailed analysis of 4 HTA reports

The first selected HTA on IMRT in 2005 (AVALIA-T) was based on two different indications: on prostate cancer based on evidence from one retrospective study and two retrospective case series and on head and neck cancer based on evidence from one retrospective case series. The HTA by the Belgian KCE (2007) includes three different indications ranging from head and neck cancer to prostate cancer and breast cancer. For head and neck cancer one RCT, six retrospective comparisons, and two prospective studies were included, while for prostate cancer six retrospective comparisons were used. The indication breast cancer was based on one RCT and one retrospective comparison. The NIHR (2010) conducted their report only on prostate cancer with the evidence used in four systematic reviews and eight comparative studies of which five were retrospective patient records and three were prospective comparisons. The HTA from the Spanish OSTEBA (2014) conducted their report on prostate (six studies), head and neck (five studies), breast (3 studies) and lung cancer (2 studies). All the studies included were observational prospective studies (see Table 4.2-6 below and Figure 8-3 in Appendix).

2005 (2 indications): retrospective case-series
2007 (3 indications): 1 RCT + retrospective + prospective comparisons
2010 (1 indication): 4 SR + 8 retrospective + prospective comparisons
2014 (4 indications): prospective case-series

minimum: retrospective case series

The minimum level of evidence used in the analyzed HTAs was retrospective case series and retrospective comparisons (low level of evidence). Since the year of CE-mark is not known, no information can be provided on the proximity of the first assessment to market approval.

Table 4.2-6: Summary of information in 4 HTAs on IMRT

Technology	HTA title	Institute	Year of report	Year of CE-mark	Evidence	Link
Intensity-modulated radiation therapy (IMRT)	Radioterapia de intensidad modulada	AVALIA-T	2005	-	*Prostate cancer* 1 retrospective study (review of medical records) 2 retrospective case series *Head/Neck cancer* 1 retrospective case series	http://bit.ly/29MCCRL
	Intensity-modulated radiotherapy (IMRT)	KCE	2007		*Head/Neck cancer* 1 RCT 6 retrospective comparisons 2 prospective studies *Prostate cancer* *6 retrospective comparisons* *Breast cancer* 1 RCT 1 retrospective comparison	http://bit.ly/29Bcjwk
	Intensity-modulated radiotherapy for the treatment of prostate cancer	NIHR	2010		*Prostate cancer* 4 systematic reviews 8 comparative studies (5 retrospective patient records; 3 prospective comparisons)	http://bit.ly/29O79i9
	An evaluation of intensity-modulated radiotherapy (IMRT)	OSTEBA	2014		*Prostate cancer* 6 studies *Head/neck cancer* 5 studies *Breast* *3 studies* *Lung cancer* 2 studies studies = observational prospective studies	http://bit.ly/29MCzFO

4.2.4 High intensity focused ultrasound (HIFU)

indication and procedure

The high intensity focused ultrasound technology is a cancer treatment, which works with high-frequency sound waves. These bundled sound waves deliver a strong beam to a specific part of defined tissue and heat it up between 90 and 100 degrees Celsius for a maximum of three seconds. This leads to the death of tumor cells. HIFU can be used for single tumors and parts of large tumors, however, HIFU cannot be used for tumors that have spread throughout the patient's body. The advantage of this type of treatment is the less frequent occurrence of side effects, compared to the side effects of other cancer treatments. The HIFU treatment can be used for prostate, kidney, liver, pancreatic and bladder cancer.[137] [138]

[137] "High-Intensity Focused Ultrasound, HIFU – Clinic for Prostate Therapy Heidelberg."

[138] UK Cancer Research, "High Intensity Focused Ultrasound (HIFU)."

Table 4.2-7: Summary of institutes which conducted reports on HIFU

Institute	Country	Year of report	Short form
NIHR	England	2003	
NICE	England	2005	*a*
UETS	Spain	2007	
IQWIG	Germany	2009	
HAS	France	2010	
LBI-HTA	Austria	2010	*b*
AQuAS	Spain	2010	
G-BA	Germany	2010	
AGENAS	Italy	2011	*c*
AETSA	Spain	2013	
ZIN	Netherlands	2013	
AOTMIT	Poland	2014	*d*

all HTA reports
evidence used in HTAs

12 reports 2003-2014

Between 2003 and 2014 twelve HTA reports by twelve different institutes were conducted on the HIFU technology. Of those twelve, four reports were selected for an analysis of evidence used. The results are presented in Table 4.2-7. In addition a short form (a, b, c, d) is assigned in order to locate the respective report in the evidence pyramid presented in the appendix (see Figure 8-4). The first HIFU device was CE-marked in 1999/2000 by the manufacturer EDAP TMS and is called Ablatherm® HIFU.[139] HIFU can be used for the treatment of several cancer types, but the selected reports are exclusively focused on prostate cancer.

detailed analysis
of 4 HTAs:

2005: 4 SR of
8 case-series
2010: 20 case-series
2011: 2 SR of
23 case-series
2014: 15SR + 5CT +
10 case-series

The first selected HTA in 2005 (NICE), 5 years after the CE- mark, was based on one systematic review, which included 8 case series studies. The second selected HTA by the LBI-HTA (2010) included 20 prospective, uncontrolled case series to make a decision. One year later in 2011, the Italian AGENAS conducted a HTA based on two systematic reviews, 23 observational case series (not randomized or comparative) and three HTA reports by other institutes. The latest selected HTA by the Polish institute AOTMIT (2014) based their decision on 15 systematic reviews, five clinical trials and ten case-series. Most studies included were observational prospective case-series (see Table 4.2-8 below and Figure 8-4 in Appendix).

minimum:
retrospective case-series

The minimum level of evidence used in the analyzed HTAs was uncontrolled and observational retrospective case series, revealing a rather low level of clinical evidence at time of HTAs.

[139] EDAP TMS, "High Intensity Focused Ultrasound (HIFU)."

Table 4.2-8: Summary of information of 4 HTA reports on HIFU

Technology	HTA title	Institute	Year of report	Year of CE-mark	Evidence	Link
High intensity focused ultrasound (HIFU)	High intensity focused ultrasound for prostate cancer	NICE	2005	1999/ 2000	1 systematic review (including 8 case series studies)	http://bit.ly/29JB5O7
	Hochintensiver fokussierter Ultraschall (HIFU) zur Behandlung des Prostatakarzinoms	LBI-HTA	2010		20 prospective, uncontrolled case series	http://bit.ly/29O7u4C
	Trattamento del carcinoma della prostata mediante termoablazione con HIFU	AGENAS	2011		2 systematic reviews 23 observational case series (not randomized or comparative) 3 HTAs	http://bit.ly/2a4KGNr

4.2.5 Lumbar total disc replacement

indication and procedure

The human spine includes 33 vertebrae grouped according to their location: 7 cervical (numbered C1-C7), 12 thoracic (T1-T12), 5 lumbar (L1-L5), 5 sacral (S1-S5) and four coccygeal vertebrae. While the last two groups, sacral and coccygeal, are fixed, the other three groups are so-called moveable. Between C2 to S1, an intervertebral disc separates the vertebrae. These discs are flexible and responsible for absorbing shock and ensure the spine movement and stability. The most affected parts of the spine are the cervical and the lumbar spine. When the lumbar spine is affected by degenerative disc disease (DDD), the most common symptom is lower back pain. As a treatment, first conservative and without any improvement a discectomy is recommended. A possible alternative is a total disc replacement, in which the natural disc is replaced by a non-rigid artificial disc prosthesis without fastening the vertebrae together, as it is made in a discectomy.[140]

Table 4.2-9: Summary of institutes which conducted reports on lumbar total disc replacement

Institute	Country	Year of report	Short form
HAS	France	2007	*a*
NICE	England	2009	
LBI-HTA	Austria	2010	*b*
Metodrådet i Sydöstra Sjukvårdsregionen	Sweden	2013	
AETSA	Spain	2014	*c*
KCE	Belgium	2015	*d*
Swiss Medical Board	Switzerland	2015	
AGENAS	Italy	2016	

all HTA reports and evidence used in HTAs

8 reports 2007 - 2016

Between 2007 and 2016 eight HTA institutes assessed the lumbar total disc replacement procedure. Of those eight, four reports were selected for an analysis of evidence used. The results are displayed in Table 4.2-9. In addition a short form (a, b, c, d) is assigned in order to locate the respective report in the evidence pyramid presented in the appendix (see Figure 8-5).

[140] "KCE | Cervical and Lumbar Total Disc Replacements | HTA Report."

The artificial disc, which is the base for the procedure of a lumbar total disc replacement, received the CE-mark in 1987 or was at least marketed in Europe at this time. The CHARITÉ Artificial disc by DePuy Spine is the first disc to be reported about on the European market.[141] [142]

detailed analysis of 4 HTAs:

2007: 1 SR + 2RCT + 7 case-series
2010: 12SR + 11 RCT
2014: 7 RCT
2015: 1 SR of 7 RCT + 4 RCT

The first selected HTA in 2007 (HAS), 20 years after the CE-mark, was based on one systematic review, two randomized comparative prospective studies, seven prospective case-series, one retrospective case-series, seven case reports and three HTAs. The next HTA by LBI-HTA (2010) was based on twelve systematic reviews, eleven RCTs, one prospective cohort study and one non-comparative registry. The HTA conducted in 2014 (AETSA) included the evidence of seven randomized clinical trials, of which three were multicenter trials. The final selected HTA in 2015 (KCE) based their decision on one Cochrane review (including seven RCTs) and four additional RCTs. The weakest used evidence in the analyzed HTAs were case reports and case series (see Table 4.2-10 below and Figure 8-5 in Appendix).

minimum: case-series, but mostly RCTs

The minimum level of evidence used in the analyzed HTAs was retrospective/prospective case-series, but mostly systematic reviews and RCTs were used, displaying a high level of evidence.

Table 4.2-10: Summary of information of 4 HTA reports on lumbar total disc replacement

Technology	HTA title	Institute	Year of report	Year of CE-mark	Evidence	Link
Lumbar total disc replacement	Remplacement du disque intervertébral lombaire par prothèse	HAS	2007	1987	1 systematic review 2 randomized comparative prospective studies 7 prospective case series 1 retrospective case series 7 case reports 3 HTAs	http://bit.ly/29BPxa8
	Bandscheiben-prothesen	LBI-HTA	2010		12 systematic reviews 11 RCTs 1 prospective cohort study 1 non-comparative registry	http://bit.ly/29MdZbv
	Lumbar total disc replacement effectiveness and safety in chronic low back pain	AETSA	2014		7 randomized clinical trials (3 multi center)	http://bit.ly/29LO4ow
	Cervical and lumbar total disc replacements	KCE	2015		1 Cochrane review (including 7 RCTs) 4 RCTs	http://bit.ly/29tGA4l

141 The Medical Advisory Secretariat Ontario, "Artificial Discs for Lumbar and Cervical Degenerative Disc Disease –Update."

142 Geisler, "The CHARITE Artificial Disc."

4.2.6 Intraoperative radiation therapy (IORT)

indication and procedure

Intraoperative radiotherapy is a technology that delivers a (high) dose of radiation therapy to the tumor bed during the surgery. The radiation does as little damage as possible to the surrounding tissue. This technology can reduce radiation treatment times or provide an added radiation boost. Because of fewer treatment sessions compared to standard radiation therapy and less exposure to healthy tissue, the therapy may reduce the side effects. The IORT differs to the standard radiation treatment in the range of irradiation. The standard treatment treats a whole area, while the IORT treats only the tissue surrounding the tumor. Currently, the IORT is used to treat breast and colorectal cancer.[143]

Table 4.2-11: Summary of institutes which conducted reports on IORT

Institute	Country	Year of report	Short form
LBI-HTA	Austria	2009	*a*
KCE	Belgium	2013	
AVALIA-T	Spain	2013	*b*
AVALIA-T	Spain	2014	*c*
HAS	France	2016	*d*

all HTA reports and evidence used in HTAs

5 reports: 2009-2015

The IORT technology was assessed between 2009 and 2015 by four institutes through five HTA reports. Of those five, four (blue-colored rows) were selected for an analysis of evidence used. The results are displayed in Table 4.2-11. In addition a short form (a, b, c, d) is assigned in order to locate the respective report in the evidence pyramid presented in the appendix (see Figure 8-6). The IORT was assessed by the AVALIA-T at two different points of time, considering in the first report breast cancer and in the second colorectal cancer. The first device CE-marked for that procedure was the INTRABEAM® System by Carl Zeiss Meditec in 1999.[144] The IORT technology is comprising a multitude of different devices and different device generations, which can influence the available evidence.

detailed analysis of 4 HTAs:

2009: 3 CTs + 13 case-series
2013: 1 MA + SR + 1 RCT + case-series
2014: 2SR + 3RCT + case-series
2016: 3 SR + 2RCT + 2 CT + case-series

The first selected HTA in 2009 (LBI-HTA) – 10 years after CE-mark was based on one RCT, three non-randomized comparative studies, and 13 prospective uncontrolled studies. The following HTA in 2013 (AVALIA-T) concerning the treatment of breast cancer, was based on one meta-analysis, one systematic review, one RCT, nine comparative case series and 32 case series. The second HTA by AVALIA-T (2014) concerning colorectal cancer, includes two systematic reviews, three RCTs, one multi-national pooled analysis of case series and 17 case series. The final HTA by the French HAS in 2016 was based on two RCTs, two non-randomized controlled trials, two studies of unknown type, seven comparative retrospective studies, 15 uncontrolled prospective case-series and three HTA reports.

[143] "Cancer Treatment Centers of America (CTCA) | Intraoperative Radiation Therapy (IORT)."

[144] Market Wired, "Carl Zeiss Meditec | INTRABEAM Intraoperative Radiotherapy System."

The minimum level of evidence used in the selected and analyzed HTAs were uncontrolled trials and case series (see Table 4.2-12 below and Figure 8-6 in Appendix).

minimum: retrospective case-series

Table 4.2-12: Summary of information of 4 HTA reports on IORT

Technology	HTA title	Institute	Year of report	Year of CE-mark	Evidence	Link
Intraoperative radiation therapy (IORT)	Intraoperative Radiotherapie bei frühem Brustkrebs	LBI-HTA	2009	1999	1 RCT 3 non-randomized comparative studies 13 prospective uncontrolled studies	http://bit.ly/29BPZFn
	Intraoperative radiation therapy in the treatment of breast	AVALIA-T	2013		1 meta-analysis 1 systematic review 1 RCT 9 comparative case series 32 case series	http://bit.ly/1myxMpY
	Intraoperative radiation therapy in the treatment of colorectal cancer	AVALIA-T	2014		2 systematic reviews 3 RCTs 1 multi-national pooled analysis of case series 17 case series	http://bit.ly/29DQQ9z
	Evaluation de la radiothérapie peropératoire dans le cancer du sein	HAS	2016		2 RCTs 2 non-randomized controlled trials 2 other types of study 7 comparative retrospective studies 15 uncontrolled prospective case series 3 HTAs	http://bit.ly/29KMInU

4.2.7 Sacral nerve stimulation (SNS)

indication and procedure

Sacral nerve stimulation is used as therapy for several indications. Here, the focus was on HTA assessments of sacral nerve stimulation for the treatment of fecal incontinence. Fecal incontinence occurs when a person is not able to control his/her bowel and cannot keep the feces in the rectum. This could result from a spinal injury, a dysfunction of the anal sphincter due to sphincter damage or a neurological disorder. For patients with a weak but intact sphincter, it is possible to adapt bowel and sphincter behavior by using the surrounding nerves and muscles. This procedure involves the stimulation of one of the sacral nerves by use of an electric current transmitted by an electrode through the associated sacral foramen. After a test trial phase of 2-3 weeks with a temporary percutaneous peripheral nerve electrode, an implantable pulse generator can be implanted if the benefit of the procedure is considered significant.[145]

HTA reports and evidence used in HTAs

8 reports 2004-2016

Between 2004 and 2016, eight HTA reports by seven institutes were conducted to assess the sacral nerve stimulation procedure. Of those eight reports, four were selected for an analysis of evidence used. The results are presented in Table 4.2-13. In addition a short form (a, b, c, d) is assigned in order to lo-

[145] "NICE | Sacral Nerve Stimulation for Faecal Incontinence."

cate the respective report in the evidence pyramid presented in the appendix (see Figure 8-7). The first system used for this procedure, the InterStim® System by Medtronic, Inc., was CE-marked in 1994.[146]

Table 4.2-13: Summary of institutes that conducted reports on SNS

Institute	Country	Year of report	Short form
NICE	England	2004	*a*
Region Västra Götaland, HTA-Centrum	Sweden	2009	*b*
LBI-HTA	Austria	2011	*c*
HAS	France	2013	
AQuAs	Spain	2014	*d*
VASPVT	Lithuania	2014	
ZIN	Netherlands	2014	
NICE	England	2016	

detailed analysis of 4 HTAs:

2004: RCT + CT + 6 case-series
2009: 2 RCT
2011: MA + 5 SR + RCT
2014: MA + SR of RCT + 2 RCT + case-series

The first report conducted in 2004 (NICE), 10 years after receiving the CE-mark, was based on one unpublished prospective multicenter non-randomized trial, six case series and one double-blind crossover study; the HTA in 2009 (The HTA Center of the Stockholm Country Council/Gotland) already included two RCTs. The HTA by the LBI-HTA in 2011 included one meta-analysis, five systematic reviews, and one RCT. The final selected HTA by the Spanish AQuAS (2014) was based on one meta-analysis of different study designs, one systematic review of RCTs, three studies with different study designs, two RCTs, one quasi-experimental study and nine case series (see Table 4.2-14 below and Figure 8-7 in Appendix).

minimum: case-series

The initial level of evidence used in the HTAs was low-level case series but increased to high-level evidence studies such as RCTs, systematic reviews, and meta-analysis.

Table 4.2-14: Summary of information of 4 HTA reports on SNS

Technology	HTA title	Institute	Year of report	Year of CE-mark	Evidence	Link
Sacral nerve stimulation (SNS)	Sacral nerve stimulation for the treatment of faecal incontinence	NICE	2004	1994	1 unpublished prospective multicenter non-randomized trial 6 case series 1 double-blind crossover study	http://bit.ly/29MEiuy
	Sakralnervstimulering (SNS) vid fekal inkontinens	The HTA Center of the Stockholm County Council/ Gotland	2009		2 RCTs	http://bit.ly/29xAHoS
	Sakralnervstimulation bei fäkaler Inkontinenz. Rapid Assessment	LBI-HTA	2011		1 meta-analysis 5 systematic review 1 RCT	http://bit.ly/2a8Hnc4

[146] FDA, "InterStim | Summary of Safety and Effectiveness Data of Medtronic InterStim(R) System."

4.2.8 Robot-assisted surgery system

Indication and procedure

Robotic surgery, computer-assisted surgery, and robotically-assisted surgery are terms for technological developments that use robotic systems to support surgical procedures. Instead of directly moving the instruments, the surgeon uses one of two tools to control the instruments: a direct telemanipulator or computer control. The surgeon controls the robotic arms via computer gadgetry and gets an inside view through a vision system, which delivers a 3-dimensional live picture. The robot, da Vinci®, can be used for cardiac, colorectal, general, gynecologic, head and neck, thoracic and urologic surgeries.[147, 148]

Table 4.2-15: Summary of institutes, which conducted reports on robot-assisted surgery systems

Institute	Country	Year of report	Short form
AETSA	Spain	2007	
AETSA	Spain	2007	
AETSA	Spain	2007	
AETSA	Spain	2007	
ASSR	Italy	2008	*a*
KCE	Belgium	2009	*b*
UETS	Spain	2011	
NIHR	England	2012	
CEDIT	France	2014	*c*
LBI-HTA	Austria	2015	*d*
HAS	France	2015	

all HTA reports and evidence used in HTAs

11 reports: 2007-2015

Between 2007 and 2015, eight HTA institutes assessed the robot-assisted surgery system technology in eleven reports. Of those eleven reports, four were selected For further analysis of evidence used. The results are presented in Table 4.2-15. In addition a short form (a, b, c, d) is assigned in order to locate the respective report in the evidence pyramid presented in the appendix (see Figure 8-8). The first robot-assisted surgery system that received the CE-mark in 1999 was the da Vinci® surgical system by Intuitive Surgical, Inc.[149]

detailed analysis of 4 HTAs:

2008: 8 SR + 5 case-series
2009: 18 SR + CT + case-series
2014: SR
2015: 2 SR + 8 RCT + 14 CT

9 years after the CE-mark was granted, the first HTA selected for this study was conducted in 2008 (ASSR) and based on eight systematic reviews, five case series and four HTA reports by other institutes. The HTA in 2009 (KCE) was based on 18 HTAs, rapid assessments, systematic reviews or horizon scans and additional comparative studies and observational case series. In 2014, the French institute CEDIT conducted an HTA that included one systematic review. The fourth selected report, conducted in 2015 (LBI-HTA, was based on two systematic reviews, eight RCTs, 14 non-randomized controlled trials and two HTA reports (see Table 4.2-16 below and Figure 8-8 in Appendix).

147 "LBI – HTA – Robotic-Assisted Surgery: A Systematic Review of Effectiveness and Safety for Elected Indications and Accumulating Costs."

148 "Da Vinci Surgery | Minimally Invasive Robotic Surgery with the Da Vinci Surgical System."

149 "Intuitive Surgical, Inc. | Da Vinci Surgical System."

minimum: case-series

The weakest level of evidence were case-series and comparative trials, however, the majority of reports used systematic reviews and RCTs, resulting in an overall high level of clinical evidence.

Table 4.2-16: Summary of information of 4 HTA reports on robot-assisted surgery systems

Technology	HTA title	Institute	Year of report	Year of CE-mark	Evidence	Link
Robot-assisted surgery system	La chirurgia robotica: il robot da Vinci	ASSR	2008	1999	8 systematic reviews 5 case series 4 HTAs	http://bit.ly/29F7vc4
	Robot-assisted surgery: health technology assessment	KCE	2009		18 HTAs, rapid assessments, systematic reviews or horizon scans comparative studies observational case series	http://bit.ly/29GiMsC
	Robotique chirurgicale en pédiatrie	CEDIT	2014		1 systematic review	http://bit.ly/29uJf9k
	Roboter-assistierte Chirurgie	LBI-HTA	2015		2 systematic reviews 8 RCTs 14 non-randomized controlled trials 2 HTAs	http://bit.ly/29Bd9cj

4.2.9 Drug-eluting stents for peripheral artery diseases (DES)

indication and procedure

A stent is a small mesh tube used for the treatment of artery diseases. It is inserted into an artery to keep the artery lumen open. In order to place a stent patients undergo the procedure of a percutaneous coronary intervention (PCI), also known as a coronary angioplasty. The PCI renews the blood flow of blocked or narrow arteries and the stent helps to support the inner wall of the artery. One side effect of the procedure is the possibility of restenosis, inflammation, and fibrosis. In order to avoid this, drug-eluting stents are coated with a drug, to reduce inflammation and/or cell proliferation by releasing small therapeutic concentrations of the anti-inflammatory messenger molecules in the surrounding tissue.[150, 151]

Table 4.2-17: Summary of institutes which conducted reports on DES

Institute	Country	Year of report	Short form
DIMDI	Germany	2005	
UETS	Spain	2006	
KCE	Belgium	2007	*a*
NICE	England	2008	*b*
HAS	France	2009	
UETS	Spain	2013	
UETS	Spain	2013	

[150] "National Heart, Lung, and Blood Institute | What Is a Stent?"

[151] "NICE | Drug-Eluting Stents for the Treatment of Coronary Artery Disease."

Institute	Country	Year of report	Short form
LBI-HTA	Austria	2014	*c*
SBU	Sweden	2014	
ASSR	Italy	2014	
IQWIG	Germany	2015	
Region Västra Götaland, HTA-Centrum	Sweden	2015	*d*

Between 2005 and 2015, twelve reports from ten HTA institutes assessed the drug-eluting stent technology. Four reports were selected for further processing and to analyze the level of evidence used. The results are shown in Table 4.2-17. In addition a short form (a, b, c, d) is assigned in order to locate the respective report in the evidence pyramid presented in the appendix (see Figure 8-9). The first drug-eluting stent Cypher™ was CE-marked in 2002. The manufacturer Cordis Corporation used the drug Sirolimus to coat the stents.[152]

all HTA reports and evidence used in HTAs

12 reports 2005-2015

The first HTA selected for this study was conducted in 2007 (KCE), 5 years after CE-mark, and was based on 29 meta-analyses, which consisted of 43 RCTs. In 2008, NICE conducted an HTA (NICE) including one meta-analysis, which was based on 17 RCTs. In 2014, (LBI-HTA) the HTA by an Austrian institute was based on ten RCTs, five clinical controlled trials, and five case series. The fourth selected HTA by the Swedish HTA Center of the Stockholm County Council/Gotland (2015) was based on eleven systematic reviews or meta-analysis, 17 RCTs, four cohort studies and 13 case series (see Table 4.2-18 below and Figure 8-9 in Appendix).

detailed analysis of 4 HTAs:

2007: 29 MA of 43 RCT
2008: 1MA of 17 RCT
2014: 10 RCT + 5 CT + 5 case-series
2015: 11 SR + 17 RCT + case-series

The minimum level of evidence used in the analyzed HTAs were case series and cohort studies, however, the most evidence used were meta-analysis and systematic reviews, revealing a high level of clinical evidence at time of HTAs.

minimum: case-series, but mostly RCTs

Table 4.2-18: Summary of information of 4 HTA reports on DES

Technology	HTA title	Institute	Year of report	Year of CE-mark	Evidence	Link
Drug-eluting stents for peripheral artery diseases	Drug-eluting stents in Belgium: Health Technology Assessment	KCE	2007	2002	29 meta-analyses (consisting out of 43 RCTs)	http://bit.ly/29UaXRN
	Drug-eluting stents for the treatment of coronary artery disease	NICE	2008		1 meta-analysis (consisting out of 17 RCTs)	http://bit.ly/29SPngJ
	Medikamenten-freisetzende Stents bei peripherer arterieller Verschlusskrankheit	LBI-HTA	2014		10 RCTs 5 Clinical controlled trials 5 case series	http://bit.ly/29SPbOC
	Drug eluting balloons and stents for symptomatic peripheral arterial disease	The HTA Center of the Stockholm County Council/ Gotland	2015		11 systematic reviews/meta-analysis 17 RCTs 4 cohort studies 13 case series	http://bit.ly/29LNaRC

[152] "Johnson & Johnson | Cordis' CYPHER (TM) Sirolimus-Eluting Stent."

4.2.10 Transcatheter aortic valve implantation (TAVI)

indication and procedure

Aortic stenosis is the narrowing of the aortic opening causing a restriction of the blood flow from the left ventricle of the heart to the aorta. As a result, the chronic compressive overload of the left ventricle leads to a left ventricle hypertrophy. Without treatment, this can cause cardiac insufficiency. A valve replacement usually requires open-heart surgery. Transcatheter aortic valve implantation (TAVI) is a minimal invasive treatment technique, and thus indicated for patients whose conditions do not allow open-heart surgery. The procedure involves the implantation of an artificial valve onto the damaged valve without stopping the heart. Two options to implant the valve are possible: either transluminal, through a large artery such as the femoral or subclavian artery or via a mini-thoracotomy with apical puncture of the left ventricle, called the transapical approach.[153, 154]

Table 4.2-19: Summary of institutes, which conducted reports on TAVI

Institute	Country	Year of report	Short form
FinOHTA	Finland	2008	
KCE	Belgium	2008	*a*
LBI-HTA	Austria	2008	*b*
HAS	France	2008	
AGENAS	Italy	2009	
LBI-HTA	Austria	2009	
LBI-HTA	Austria	2010	
LBI-HTA	Austria	2011	
HIS	Scotland	2011	*c*
HIS	Scotland	2011	
KCE	Belgium	2011	
ASSR	Italy	2012	
NICE	England	2012	*d*
HAS	France	2013	
AVALIA-T	Spain	2013	
NIHR	England	2013	
HIS	Scotland	2014	
HIS	Scotland	2014	
ZIN	Netherlands	2014	
OSTEBA	Spain	2014	
ASSR	Italy	2014	
AVALIA-T	Spain	2014	

153 "NICE | Transcatheter Aortic Valve Implantation for Aortic Stenosis."

154 "KCE | Transcatheter Aortic Valve Implantation (TAVI): A Health Technology Assessment Update | HTA-Report."

all HTA reports and evidence used in HTAs

Between 2008 and 2014, twelve HTA institutes assessed TAVI through 22 reports. Because of the importance of this advanced technology, several reports or updates were conducted. Of those 22 reports, four were selected for the analysis of the evidence level. The results are presented in Table 4.2-19. In addition a short form (a, b, c, d) is assigned in order to locate the respective report in the evidence pyramid presented in the appendix (see Figure 8-10). Two manufacturers received the CE-mark for this technology in 2007 named Edwards Lifesciences with the balloon-expandable Edwards SAPIEN transcatheter heart valve and the self-expanding Medtronic CoreValve produced by Medtronic.[155]

22 reports: 2008-2014

detailed analysis of 4 HTAs:

2008: 5 SR + 12 case-series + 13 case-reports
2008: 10 case-series
2011: 8SR + 1RCT
2012: 1SR + 2RCT + case-series

The first conducted HTA selected for this study in 2008 (KCE), 1 year after the CE-mark, was based on 12 case series, 13 single case reports, and five HTA reports. The update in 2011 included one RCT. The other HTA in 2008 (LBI-HTA) was based on ten uncontrolled interventional studies. Updates were conducted in 2009 and 2010 and the evidence used was based on four uncontrolled before-after studies (2009) and five uncontrolled before-after studies, respectively, and additionally four HTAs in 2010. The 2011 update included one RCT, nine uncontrolled studies, six registry studies and 18 background studies. The report in 2011 (HIS) was based on three systematic reviews, one RCT and five HTA reports by other institutes. The update in 2014 included one RCT. The final selected HTA in 2012 (NICE) was conducted on the base of one systematic review, two RCTs, one non-randomized comparative study and six case series (see Table 4.2-20 below and Figure 8-10 in Appendix).

minimum: case reports

The weakest evidence used in the analyzed HTAs were case reports and case series, revealing a low level of clinical evidence at time of HTAs. However, later HTA reports (2011) were based on RCTs and systematic reviews, which reflect a high level of clinical evidence.

[155] Phang, Tay, and Hon, "Transcatheter Aortic Valve Implantation-2014 Update."

Table 4.2-20: Summary of information of 4 HTA reports on TAVI

Technology	HTA title	Institute	Year of report	Year of CE-mark	Evidence	Link
Transcatheter Aortic Valve Implantation (TAVI)	Percutaneous heart valve implantation in congenital and degenerative valve disease Transcatheter Aortic Valve Implantation (TAVI)	KCE	2008 2011	2007	*2008* 12 case series 13 single case reports 5 HTAs *2011* 1 RCT	http://bit.ly/29xyiDL http://bit.ly/29ATCKD
	Minimal-invasiver perkutaner Aorten-klappenersatz (2008/2009/2010) Minimal-invasiver perkutaner Aorten-klappenersatz/TAVI (2011)	LBI-HTA	2008 2009 2010 2011		*2008/2009/2010* 10 uncontrolled interventional studies + 4 uncontrolled before-after studies + 5 uncontrolled before-after studies 4 HTAs *2011* 1 RCT 9 uncontrolled studies 6 registry studies 18 background studies	http://bit.ly/29LMXxP http://bit.ly/29JzsQr http://bit.ly/29KrhVJ http://bit.ly/29ESJ6f
	Transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic stenosis in adults Note 33/38 Transcatheter aortic valve implantation (TAVI for severe symptomatic aortic stenosis in adults at high surgical risk/in adults who are not eligible for surgery Note 51/52	HIS	2011 2014			
					2011 3 systematic reviews 1 RCT 5 HTAs *2014* 1 RCT	http://bit.ly/29LMw6O http://bit.ly/29Jyvb2 http://bit.ly/29ATJpt http://bit.ly/29Kq40A
	Transcatheter aortic valve implantation for aortic stenosis	NICE	2012		1 systematic review 2 RCTs 1 non-randomized comparative study 6 case series	http://bit.ly/29A1pwd

5 Discussion

This research had two main objectives:

- to identify the critical points in the assessment of medical devices discussed in the recent literature.
- to analyze the timing of the HTA reports of European HTA institutes in relation to the year of CE-mark and the level of evidence used in the HTAs.

2 research objectives:

- identify critical issues discussed

- characteristics of European HTA on medical devices

5.1 Summary: Literature Review

A systematic literature review analyzing published literature from 2010 until 2016 brought insights into the critical points of the assessment of medical devices. Table 5.1-1 gives an overview of the results found and the conclusions made.

critical issues discussed in recent publications

Table 5.1-1: Critical points in the assessment of medical devices and procedures discussed in publications

Missing of robust evidence	• Weak clinical evidence is required for receiving the CE-mark, not suitable to meet the evidence-requirements of European HTA institutes to support reimbursement decisions.
Methodology applied	• No specific methods for the different kinds of high-risk medical devices (diagnostic and therapeutic) exist. • The Influence of specific aspects of medical devices such as the learning curve of operators and the incremental innovation is not reflected in HTA methodology.
Harmonization of HTA requirements	• Different requirements, if any, exist for the minimal evidence used in the HTA reports. • The harmonization of requirements might be a driver for reducing redundancy of assessing the same technology or procedure multiple times.
Impact on decisions	• The impact of the HTAs of medical devices on decision-making in different institutions is not well known.
Timing of assessment	• Due to lack of a clearly defined market entry of medical devices, difficulties in conducting the assessment at the right time in the products life cycle exist.

The presented critical points and challenges in the assessment of medical devices differ from issues discussed on pharmaceuticals. Each of the critical points can be related to the unique characteristics of medical devices and their market authorization. Additionally, some of these points are interrelated such as the harmonization and methodology in HTA of medical devices.

issues discussed differ from pharma related to market authorization and methodology

The critical points vary in their importance or influence on the assessment of medical devices. The challenge of receiving robust clinical data is the most discussed critical point in recent publications: several severe (late) adverse events (e.g. with breast implants or metal-on-metal hip implants) have led to a dispute about the submitted clinical evidence in the regulatory approval process and the need for post-marketing surveillance. Therefore, the new EU directive aims at modernizing the current legislations for the regulation of medical devices by strengthening the rules for placing medical devices on the market as well as the post-market surveillance.

vary in importance or influence

most important: robust evidence for approval post-market surveillance data for safety

pharma: advanced methods available not so for medical devices

Several studies and reviews criticize the considerably large differences between the methodological standards for pharmaceuticals and medical devices, in the sense that pharmaceutical methodology is further developed than it is for medical devices. In contrast to pharmaceuticals, the discussion on evidence requirements for medical device assessments is relatively new and needs time to develop extensive and specific methods suiting their unique characteristics.

5.2 Summary: Redundancies

high redundancy

Multiple HTA reports on the same technology or procedure are conducted either within the same year or over several years. A data analysis of all – in 2014 – identified HTA reports on medical devices risk-class 2b and 3 (see Table 8-1 in Appendix) and of ten selected technologies and procedures (see Table 8-2 in Appendix) revealed the amount of the redundancies:

for 10 selected technologies

Figure 5.2-1 and Figure 5.2-2 present the reports that were conducted over time. The number of reports per technology or procedure range between five for IORT and 22 for TAVI:

range 5-22 HTAs

1-6 for same tech p.a.

- 5 HTA-reports on IORT (2013: 2 times)
- 8 HTA-reports on lumbar total disc replacement (2015: 2 times)
- 8 HTA-reports on SNS (2014: 3 times)
- 9 HTA-reports on Mitraclip® (2012: 3 times)
- 11 HTA-reports on IMRT (2010: 3 times)
- 11 HTA-reports on CRT-P, CRT-D (2014: 4 times)
- 11 HTA-reports on robot-assisted surgery (2007: 4 times)
- 12 HTA-reports on DES (2014: 3 times)
- 12 HTA-reports on HIFU (2010: 4 times)
- 22 HTA-reports on TAVI (2008: 4 times; 2011: 4 times; 2014: 6 times)

The lowest number of reports conducted in a year for a technology is one report, while the highest number is six reports in one and the same year.

huge potential for collaboration

It is obvious that there is a huge potential for collaboration: be it building on each other´s HTA in successive years or collaborating within the same year. These data show the importance of European collaboration in HTA. As discussed in recent publications the redundancy of HTA-reports leads to waste in human and financial resources.[156]

[156] Mathes et al., "Methods of International Health Technology Assessment Agencies for Economic Evaluations-a Comparative Analysis."

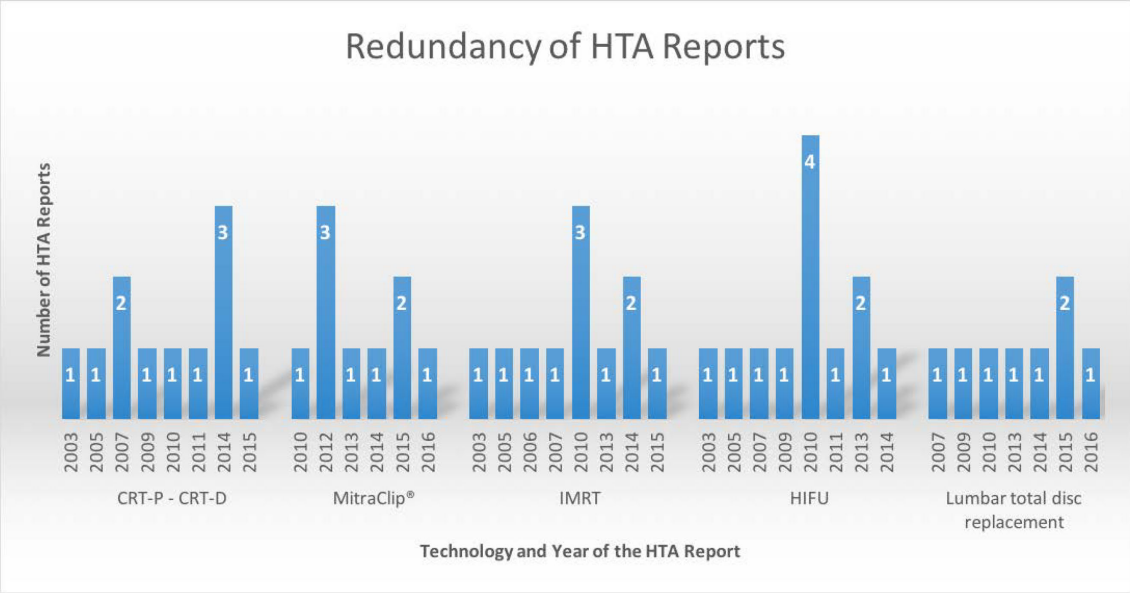

Figure 5.2-1: Comparison of reports conducted on the same technology (1-5)

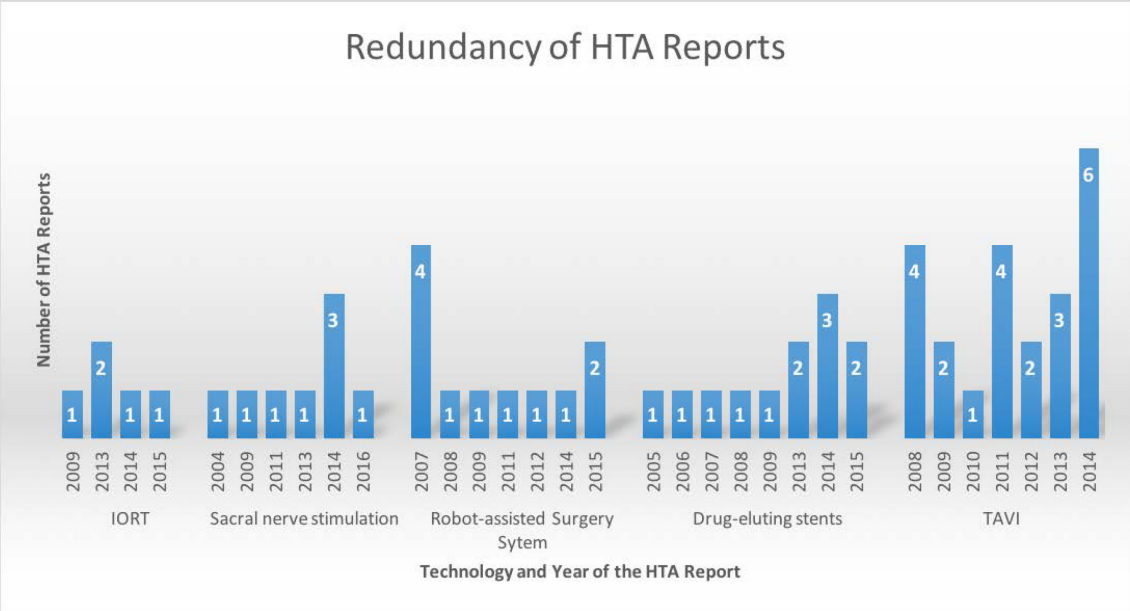

Figure 5.2-2: Comparison of reports conducted on the same technology (6-10)

Not only methodology but language seems to be the major barrier for collaboration: In the European Union currently 24 different official languages are spoken.[157] The reports used for this research were conducted in seven different languages (English, French, Spanish, Italian, German, Polish and Swedish). Therefore, an increasing harmonization in the use of a common language should be considered.

EU:
24 official languages
reports analyzed:
7 languages

[157] "EUROPA – EU Administration – Staff, Languages and Location."

5.3 Summary: Level of Evidence used

clinical evidence is – naturally – evolving over time

As seen in Table 5.3-1, there is a – natural – trend regarding the evidence used: the best available evidence is being used at time (year) of assessment (see also evidence pyramids in Appendix Figures 8-1 to 8-10). In general, the first reports (early assessment) are based on rather low clinical evidence (case reports and retrospective case-series), while the latter reports are conducted on somewhat stronger clinical evidence (prospective case-series, non-randomized comparative trials, and randomized clinical trials), sometimes for one indication only, but also for several indications. The use of systematic reviews (SR) in the evidence pyramid is somewhat misleading, since SR can be based on RCTs, but also on less robust study designs (case-series).

later assessments: better evidence

no trend for „lower limit" identified

In the selected 10 technologies and four analyzed HTA-reports no trend could be identified concerning *not* using very low clinical evidence (case reports or retrospective case-series) at all for assessing technologies. This study did not analyses, however, if the HTA-requirements became more rigorous in recent years.

Table 5.3-1: Summary of findings in the comparison of HTA institutes

Device or procedure	Institute	Report year	Level of used evidence	Year of CE-mark
Implantable cardiac resynchronization therapy and defibrillator (CRT-D/CRT-P)	SBU	2003	Level 3	2001
	AETSA	2009	Level 1	
	AGENAS	2014	Level 1	
	Swiss Medical Board	2015	Level 1	
MitraClip®	LBI-HTA	2010	Level 4	2008
	Stockholm County Council HTA-Center OSTEBA	2012	Level 3	
	HAS	2014	Level 2	
		2015	Level 3	
Intensity-modulated radiation therapy (IMRT)	AVALIA-T	2005	Level 7	-
	KCE	2007	Level 3	
	NIHR	2010	Level 2	
	OSTEBA	2014	Level 5	
High intensity focused ultrasound (HIFU)	NICE	2005	Level 7	1999/2000
	LBI-HTA	2010	Level 7	
	AGENAS	2011	Level 5	
	AOTMIT	2014	Level 2	
Lumbar total disc replacement	HAS	2007	Level 2	1987
	LBI-HTA	2010	Level 2	
	AETSA	2014	Level 3	
	KCE	2015	Level 2	
Intraoperative radiation therapy (IORT)	LBI-HTA	2009	Level 3	1999
	AVALIA-T	2013	Level 1	
	AVALIA-T	2014	Level 2	
	HAS	2016	Level 3	
Sacral nerve stimulation (SNS) for fecal incontinence	NICE	2004	Level 4	1994
	HTA Center of Stockholm/Gotland	2009	Level 3	
	LBI-HTA	2011	Level 1	
	AQuAs	2014	Level 1	

Device or procedure	Institute	Report year	Level of used evidence	Year of CE-mark
Robot-assisted surgery systems	ASSR	2008	Level 2	1999
	KCE	2009	Level 2	
	CEDIT	2014	Level 2	
	LBI-HTA	2015	Level 2	
Drug-eluting stents (DES) for peripheral artery disease (PAD)	KCE	2007	Level 1	2002
	NICE	2008	Level 1	
	LBI-HTA	2014	Level 3	
	HTA Center of Stockholm/Gotland	2015	Level 1	
Transcatheter aortic valve implantation (TAVI)	KCE	2008	Level 7	2007
	LBI-HTA	2008	Level 4	
	HIS	2011	Level 3	
	NICE	2012	Level 2	

5.4 Summary: Timing and Clusters of Institutes

clustering for timing of 109 assessments of 10 technologies and 14 countries

For a comprehensive grouping of HTA-institutes based on timing of their assessments to potentially distinguish between early and late assessors not only the four selected and analyzed HTA reports, but all HTA reports for the ten technologies were used for the clustering analysis. The data are displayed in Figure 5.4-1. The institutes were summarized to their country of origin (n = 14), because of the high number of different institutes (n = 27) in order to reduce complexity. The bubbles mark each of the reports (n = 109).

most reports on medical devices:

Spain, England, Austria, France, Belgium, Italy

The countries with the most published reports are Spain (25), England (14), Austria and France (13), Belgium (10) and Italy (9), some of them are updates of earlier reports. For the clustering of the institutes, we intended to build groups of HTA-institutes according to their timing in relation to the other European assessments. E.g. for three technology-assessments (IMRT, HIFU, SNS) England was the first assessor in Europe, but for other technologies (total disc replacement, TAVI, robot-assisted surgery) it was later.

The data can also be presented taking a different perspective: Figure 5.4-2 shows which of the 10 selected technologies was assessed at which point in time in relation (proximity) to the market authorization (CE-mark) from which countries.

Table 5.4-1 presents the countries and agencies that were engaged in assessing the 10 selected technologies.

no cluster of early/late assessors identifiable

To summarize the clustering exercise: there is no clear picture that allows concluding on early or late assessors (Figure 5.4-1). Nevertheless, it shows that some countries (and agencies) have assessed almost all selected technologies (Figure 5.4-2 and Table 5.4-1) and some of them have assessed the technologies even several times along the evolvement of evidence and along the lifecycle, updating earlier assessments. Additional there is considerably in-country redundancy (esp. in Spain).

countries and agencies: candidates for collaborating

These countries and agencies (Table 5.4-1) might be the candidates for collaborating in future European joint assessments.

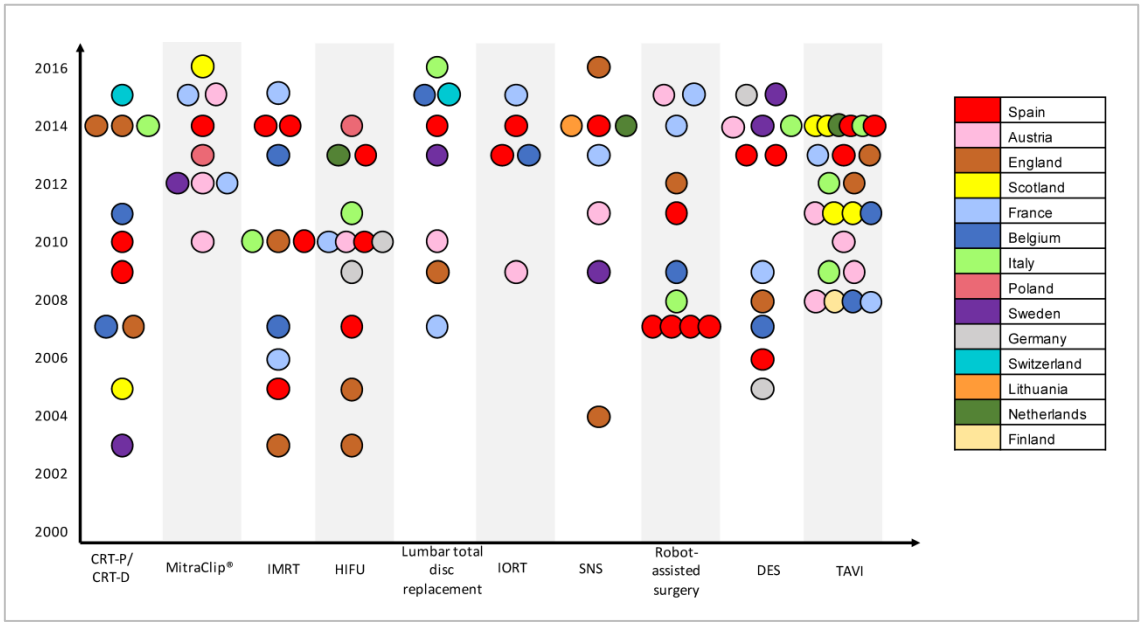

Figure 5.4-1: HTA reports performed for the ten interventions

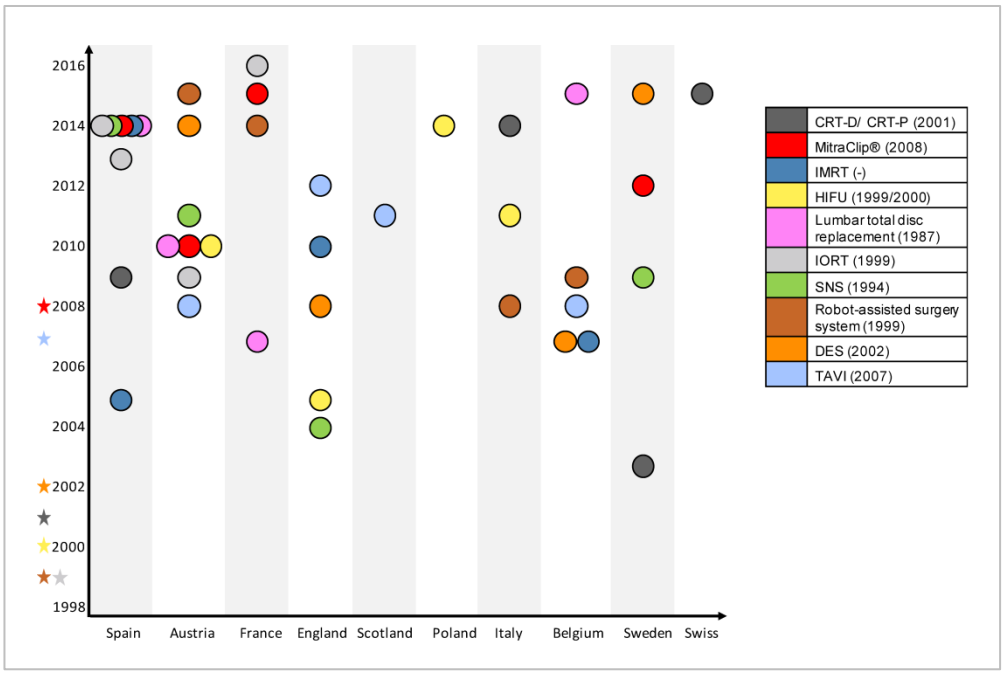

Figure 5.4-2: Distribution of CE-mark to the used HTA reports

Table 5.4-1: 10 selected technologies: Countries and HTA agencies that conducted assessments

Country	Agencies	Technologies
Spain	AETSA: UETS OSTEBA AVALIA-T AQuAS	CRT, IMRT, HIFU, disc replacement, robot surgery CRT, HIFU, robot surgery, DES Mitraclip, IMRT, TAVI IMRT, IORT, TAVI HIFU, SNS
Austria	LBI-HTA	Mitraclip, HIFU, disc replacement, IORT, SNS, robot surgery, DES, TAVI
France	CEDIT HAS	Mitraclip, robot surgery Mitraclip, IMRT, HIFU, disc, IORT, SNS, robot surgery, DES, TAVI
England	NIHR NICE	CRT, IMRT, HIFU, robot surgery, TAVI CRT, HIFU, disc replacement, SNS, DES, TAVI
Italy	AGENAS ASSR	CRT, HIFU, disc replacement, TAVI IMRT, robot surgery, DES, TAVI
Belgium	KCE	CRT, IMRT, disc replacement, IORT, robot surgery, DES, TAVI)
Sweden	SBU St. County Council Metodrådet i Sydöstra Sjukvårdsregionen Västra Götalandsregionen	CRT, DES Mitraclip disc replacement SNS, DES
Switzerland	Swiss Medical Board	CRT, disc replacement disc
Scotland	HIS	CRT, Mitra, TAVI
Poland	AOTMIT	Mitraclip, HIFU
Germany	IQWIG DIMDI	HIFU, DES DES
Netherlands	ZIN	HIFU, SNS, TAVI
Lithuania	VASPVT	SNS
Finland	FinOHTA	TAVI

5.5 Limitations of this research

This study has several limitations that have to be recognized. Only literature from 2010 until 2016 was reviewed to obtain the recently discussed critical points.

only literature from 2010 till 2016

For the data analysis, only European HTA institutes, agencies ad units were included, due to the shared regulatory framework. Other jurisdictions like United States, Canada or Australia were excluded.

only European HTA report included

The focus was limited to high-risk medical devices (risk-class 2b and 3 and active implantable devices) because these are the ones attracting most interest from the European HTA institutes. Of these high-risk devices, the 10 most frequently assessed technologies were selected for further investigation and limited to detailed analysis of four 4 reports only. The 10 different technologies chosen for this study represent only a small percentage of all devices on the European market.

only high-risk medical devices limited scope for analysis

Any generalization must be considered in the context of these limitations.

cautious generalization

Additionally, the HTA reports had to have a clear statement of the evidence used. The information on the year of the market authorization (CE-mark) is based on company announcements, investor reports and news articles on marketed products only. Hence, it is probable that some of the identified CE-mark dates vary, due to lack of official published sources.

only publicly accessible information used

Additionally, only publicly accessible information was included.

6 Conclusion

This research project aimed at contributing to the efforts of increasing European collaboration on HTA of medical devices.

It can be concluded that

- even if it cannot be foreseen in detail if and how the new regulation of medical devices in Europe will change the clinical evidence required at time of market authorization (CE-marking),
- the collaboration between European HTA-institutions is occurring more frequently, supported by the European Commission and facilitated within the structures of EUnetHTA Joint Action 3 and the various tools developed to support such collaborations.
- Within this collaboration, a harmonization of methodologies (guidelines), of formats (Core Model® and manufacturer submission template) and even of language (English as working language) is evolving.
- The data analysis of timing of the diverse assessments of medical devices showed clearly that only some assessments of similar products are conducted within the same year, but most often within a time-range of several (even more than 10) years.
- The analysis of the HTA reports indicates that there is room for improvement regarding the collaboration of HTA institutes in Europe, since many reports were redundant or overlapping. One possible way to use resources more efficiently could be clustering of HTA institutes with similar work profiles.

contribution of this research:

systematic data analysis

of redundancies of HTA products

and

of clusters of European HTA agencies with a similar profile

collaboration!

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8 Appendix

Table 8-1: All HTA reports (high risk medical devices risk class 2b, 3 and active implantable) conducted in 2014 (n = 87)

Institute	Taxonomic position	Technology(ies)	Full title of report
AAZ	27	Triclosan-coated sutures	Impact of triclosan-coated sutures on surgical site infection
AETSA	9	Digital tomosynthesis	Digital tomosynthesis in breast cancer
AETSA	26	Interspinous decompression devices	Effectiveness and safety of interspinous devices.
AETSA	29	Lumbar total disc replacement	Lumbar total disc replacement effectiveness and safety in chronic low back pain.
Agenas	27	Ultrasonic devices	Rapid HTA report: Ultrasonic energy devices for surgery
Agenas	14, 32	ICD	Rapid HTA report. Implantable cardiac resynchronization therapy and defibrillator (CRT-D) in patient with heart failure
AOTMiT	27	HIFU	Leczenie raka stercza skupioną wiązką ultradźwiękową
ASSR	4, 25, 25, 4	Sensor Augmented Pump (SAP); Continuous subcutaneous insulin infusion (CSII); Continous blood monitoring systems devices (CGMS)	Dispositivi medici innovativi nella gestione del diabete
AVALIA-T	26	Repair mesh	Mallas transvaginales en la reparación del prolapso de órganos pélvicos
AVALIA-T	27	IORT	Radioterapia intraoperatoria en el tratamiento del cáncer colorrectal
AVALIA-T	27	Photopheresis	Fotoaféresis para pacientes con enfermedad de injerto contra huésped resistente a esteroides.
AVALIA-T	27	Brachytherapy	Braquiterapia de alta tasa en el tratamiento de tumores de lengua móvil
AVALIA-T	27	Ablation (Pancratic and hepatic cancer)	Efectividad y seguridad de la electroporación irreversible en el tratamiento de los cánceres de páncreas e hígado
AVALIA-T	30	Stents retrievers	Seguridad y eficacia de la trombectomía mecánica mediante stents retrievers en el tratamiento del ictus isquémico agudo
CAHIAQ (AQuAs)	27	Proton therapy	La protonterapia en el tratamiento del cáncer
CAHIAQ (AQuAs)	32	Sacral nerve stimulation (SNS)	La estimulación deraíces sacras para el tratamiento dela incontinencia fecal: revisión de la eficacia y análisis de coste-efectividad
CEDIT	27	DaVinci Robotic Surgery	Intérêt de la robotique chirurgicale da Vinci en pédiatrie
CVZ (ZiN)	26	Duodenal-Jejunal bypass (EndoBarrier)	Duodenal-Jejunal bypass (EndoBarrier) voor de behandeling van obesitas met of zonder Diabetes Mellitus type II
CVZ (ZiN)	27	sleeve gastrectomy	Standpunt Bariatrische Chirurgie• sleeve bij gastrectomie• bij DM2 én BMI tussen 30 en 35
CVZ (ZiN)	27	Extracorporeal Shock Wave Therapy	Extracorporeal Shock Wave Therapy bij Achillespees Tendinopathie
CVZ (ZiN)	29	Transcatheter aortic valve implantation (TAVI)	Transcatheter aortic valve implantation (TAVI)
CVZ (ZiN)	30	Trans-Arterial chemoembolisatie (TACE)	Transarteriële Chemoembolisatie (TACE) bij Neuroendocriene Levermetastasen (NELM)
CVZ (ZiN)	30	Trans-Arterial chemoembolisatie (TACE) and/or laser-induced thermotherapy (LITT)	Transarteriële chemoembolisatie (TACE) en/of laser geïnduceerde thermotherapie (LITT) bij colorectale levermetastasen

Institute	Taxonomic position	Technology(ies)	Full title of report
CVZ (ZiN)	30	Trans-arterial chemo-embolization (TACE)	Transarteriële chemo-embolisatie (TACE) bij levermetastasen van pancreascarcinoom
CVZ (ZiN)	30	Minimally invasive lumbar interbody fusion	Standpunt Minimaal invasieve lumbale interbody fusie
CVZ (ZiN)	32	Sacral neurostimulation	Sacrale neurostimulatie bij kinderen en volwassenen met therapieresistente functionele obstipatie
FinOHTA	30	Sutureless aortic valve replacement	Sutureless valve replacement for aortic valve stenosis
HAS	9	EBUS-TBNA	Endobronchial ultrasound-guided transbronchial needle aspiration
HAS	29	Shoulder joint implant	Assessment of shoulder joint implants
HAS	29	Hip implants	Hip implants
HAS	30	Ultrasound guidance for PNB	Ultrasound guidance for peripheral nerve blockade
HAS	32	Spinal cord stimulation (neurostimulators)	Assessment of spinal cord stimulation
HVB	27	Radiofrequency ablation	Radiofrequenzablation bei benignen und malignen Veränderungen der Schilddrüse. Update
IQWiG	29	Stents	Stents zur Behandlung intrakranieller arterieller Stenosen
KCE	27	Machine perfusion	Machine perfusion in kidneys from decreased donoers- a rapid assessment
KCE	26, 27	intraocular lenses; laser refractive surgery	Correction of refractive errors of the eye in adults- part 2: Laser surgery and intraocular lenses)
LBI	26	endobronchial valve implantation	Endobronchiale Ventilimplantation bei Lungenemphysem. Systematischer Review – 3. Update 2014. Decision Support Dokument Nr. 20/Update 2014
LBI	27	Stereotactic Radio Frequency Ablation	Stereotaktische Radiofrequenztherapie/SRFA bei Leberzellkarzinom und Lebermetastasen. Systematischer Review
LBI	27	Cytoreduction surgery (CRS) combined with intraoperative, intra-peritoneal, hyperthermic chemotherapy (HIPEC/HIIC/IPCH/IPHC)	Zytoreduktive Chirurgie und hypertherme intraperitoneale Chemotherapie bei Peritonealkarzinose. Systematischer Review
LBI	29	drug-eluting stent	Medikamentenfreisetzende Stents bei peripherer arterieller Verschlusskrankheit. Systematischer Review
LBI	30	Percutaneous (transcatheter transseptal) Left Atrial Appendage Occlusion/Obliteration/Exclusion (different devices p10)	Perkutaner Verschluss des linken Vorhofohres zur Thrombembolieprophylaxe bei PatientInnen mit Vorhofflimmern. Systematischer Review. 1. Update 2014
NICE	29	Protheses	Total hip replacement and resurfacing arthroplasty for endstage arthritis of the hip (review of technology appraisal guidance 2 and 44) (TA304)
NICE	29	MAGEC (spinal implants (growing rods) and an External Remote Controller)	The MAGEC system for spinal lengthening in children with scoliosis (MTG18)
NICE	30	ReCell Spray-On Skin system	The ReCell Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury NICE medical technology guidance [MTG21]
NICE	32	implantable defibrillator	Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (review of TA95 and TA120) (TA314)
NICE	12	Optical Coherence Tomography (using catheter)	Optical coherence tomography to guide percutaneous coronary intervention (IPG481)
NICE	26	Jaw Replacement	Total prosthetic replacement of the temporomandibular joint (IPG500)

Institute	Taxonomic position	Technology(ies)	Full title of report
NICE	26	Magnetic Bead Band	Insertion of a magnetic bead band for faecal incontinence (IPG483)
NICE	27	Radiofrequency Ablation	Endoscopic radiofrequency ablation for squamous dysplasia of the oesophagus (IPG497)
NICE	27	Radiofrequency Ablation	Endoscopic radiofrequency ablation for Barrett's oesophagus with low-grade dysplasia or no dysplasia (IPG496)
NICE	27	Laser Surgery	Transoral carbon dioxide laser surgery for primary treatment of oropharyngeal malignancy (IPG484)
NICE	27	Prostatic urethral lift implants	Insertion of prostatic urethral lift implants to treat lower urinary tract symptoms secondary to benign prostatic hyperplasia NICE interventional procedure guidance [IPG475]
NICE	27	Chemosaturation	Chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic liver cancer (IPG488)
NICE	27	Radiofrequency Turbinoplasty	Radiofrequency tissue reduction for turbinate hypertrophy (IPG495)
NICE	27	Radiofrequency Ablation	Radiofrequency ablation of the soft palate for snoring (IPG476)
NICE	27	Athroscopic radiofrequency chondroplasty	Arthroscopic radiofrequency chondroplasty for discrete chondral defects of the knee (IPG493)
NICE	29	Gastroelectrical Stimulation	Gastroelectrical stimulation for gastroparesis (IPG489)
NICE	29	Transcatheter Aortic Valce Replacement	Transcatheter valve-in-valve implantation for aortic bioprosthetic valve dysfunction (IPG504)
NICE	29	Stent	Bioresorbable stent implantation for treating coronary artery disease (IPG492)
NICE	29	Collagen Plug	Insertion of a collagen plug to close an abdominal wall enterocutaneous fistula (IPG507)
NICE	30	Extracorporeal Membrane Oxygenation	Extracorporeal membrane oxygenation (ECMO) for acute heart failure in adults (IPG482)
NICE	30	Insertion of an annular disc implant	Insertion of an annular disc implant at lumbar discectomy NICE interventional procedure guidance [IPG506]
NICE	32	Adjustable Pulmonary Artery Banding	Telemetric adjustable pulmonary artery banding for pulmonary hypertension in infants with congenital heart defects (IPG505)
NICE	32	Battery-Powered Drainage System	Subcutaneous implantation of a battery-powered catheter drainage system for managing refractory and recurrent ascites (IPG479)
NIHR	30	Fenestrated and branched endovascular aneurysm repair	The use of fenestrated and branched endovascular aneurysm repair for juxtarenal and thoracoabdominal aneurysms: a systematic review and cost-effectiveness analysis
NIHR	30	Percutaneous vertebroplasty (PVP) vs. Percutaneous balloon kyphoplasty (BKP)	Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for the treatment of osteoporotic vertebral fractures: a systematic review and cost-effectiveness analysis
NIHR	30	percutaneous transluminal balloon angioplasty	Enhancements to angioplasty for peripheral arterial occlusive disease: systematic review, cost-effectiveness assessment and expected value of information analysis

Institute	Taxonomic position	Technology(ies)	Full title of report
NIHR	6, 9	magnetic resonance diffusion-weighted brain imaging vs. computed tomography (CT) brain scanning	An assessment of the cost-effectiveness of magnetic resonance, including diffusion-weighted imaging, in patients with transient ischaemic attack and minor stroke: a systematic review, meta-analysis and economic evaluation
OSTEBA	27	IMRT	An evaluation of intensity-modulated radiotherapy (IMRT)
OSTEBA	27	IMRT	New IMRT techniques for moving targets. An analysis of their safety and efficacy.
OSTEBA	29	MitraClip®	MitraClip® para la reparación del reflujo de la válvula mitral
OSTEBA	29	Bioresorbable peripheral stents	Stents periféricos biorreabsorbibles.
OSTEBA	29	Percutaneous aortic valve replacement using prosthetic valve versus the standard surgical treatment	Análisis coste-efectividad del recambio valvular aórtico mediante prótesis valvular percutánea frente al tratamiento quirúrgico habitual.
OSTEBA	30	Cryoablation with Arctic Front catheter	Crio-ablación en la fibrilación auricular con catéter Arctic-Front.
OSTEBA	32	Magnetic resonance compatible pacemaker	Marcapasos Compatible con Resonancia Magnética.
OSTEBA	32	Subcutaneous defibrillator	Desfibrilador subcutáneo.
Regione Veneto	27	Renal denervation system	DENERVAZIONE RENALE
Regione Veneto	29	Sutureless aortic valves (Perceval S Tm, 3f Enable® (Modello 6000), Edwards INTUITY Elite Valve System)	PROTESI VALVOLARE AORTICA A RILASCIO CHIRUGICO VELOCE: RIVALUTAZIONE
Regione Veneto	30	Transcatheter ablation	TRATTAMENTO NON FARMACOLOGICO DELLA FIBRILLAZIONE ATRIALE: ABLAZIONE TRANSCATETERE E ABLAZIONE CHIRURGICA
SBU	27	Low Level Laser Therapy	Laser treatment of neck pain
SBU	29	drug-eluting stents	Drug-eluting stents in coronary arteries
SBU	6, 9	MRI; PET/CT; doppler ultrasound; applications of ultrasound techniques such as elastog raphy; HistoScanning®	Diagnostic Imaging in Suspected Prostate Cancer
SHTG/HIS	27	renal denervation (RDN)	Evidence note 54: What is the clinical effectiveness, cost effectiveness and safety of treatment with renal denervation (RDN) for patients with resistant hypertension (RH), and what model of treatment centres should be adopted? Advice Statement 004/14: Renal denervation for patients with resistant hypertension
SHTG/HIS	29	TAVI	Transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic stenosis in adults who are not eligible for surgery: Evidence note 51. Advice Statement 001/14 Is Transcatheter aortic valve implantation (TAVI) clinically and cost effective for severe symptomatic aortic stenosis in adults who are not eligible for surgery?
SHTG/HIS	29	TAVI	Transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic stenosis in adults at high surgical risk: Evidence note 52. Advice Statement 002/14. Is Transcatheter aortic valve implantation (TAVI) clinically and cost effective for severe symptomatic aortic stenosis in adults at high surgical risk?
UETS	27	Brachytherapy and external beam radiation	Efectividad comparada del tratamiento conservador del cáncer de mama con braquiterapia y radioterapia externa
UETS	30	hip resurfacing and traditional total hip arthroplasty	Eficacia y seguridad de la prótesis de cadera de superficie frente a la artroplastia convencional

Table 8-2: All HTA reports on 10 selected technologies (n = 109)

Technology	HTA title	Institute	Year	Link-shortened
Transcatheter Aortic Valve Implantation (TAVI)	Transcatheter aortic valve replacement for severe aortic valve stenosis	FinOHTA	2008	http://bit.ly/29LMqfd
	Minimal-invasiver perkutaner Aortenklappenersatz	LBI-HTA	2008	http://bit.ly/29LMXxP
	Percutaneous heart valve implantation in congential and degenerative valve disease. A rapid Health Technology Assessment	KCE	2008	http://bit.ly/29xyiDL
	Évaluation des bioprothèses valvulaires aortiques implantées par voie rétrograde transfémorale et transapicale	HAS	2008	http://bit.ly/29A85VT
	TransApical Transcatheter Aortic Valve Implantation (TA-TAVI)	AGENAS	2009	http://bit.ly/29MBD4l
	Minimal-invasiver perkutaner Aortenklappenersatz	LBI-HTA	Update 2009	http://bit.ly/29JzsQr
	Minimal-invasiver perkutaner Aortenklappenersatz	LBI-HTA	Update 2010	http://bit.ly/29KrhVJ
	Minimal-invasiver perkutaner Aortenklappenersatz/TAVI	LBI-HTA	Update 2011	http://bit.ly/29ESJ6f
	Transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic stenosis in adults	HIS	2011	http://bit.ly/29LMw6O
	Transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic stenosis in adults	HIS	2011	http://bit.ly/29Jyvb2
	Transcatheter Aortic Valve Implantation (TAVI): a Health Technology Assessment Update	KCE	2011	http://bit.ly/29ATCKD
	The cost of innovation in treating aortic stenosis: transcatheter aortic valve implantation	ASSR	2012	http://bit.ly/29AIsqi
	Transcatheter aortic valve implantation for aortic stenosis	NICE	2012	http://bit.ly/29A1pwd
	JenaVALVE TAVI System	HAS	2013	http://bit.ly/29KqKmU
	Efficacy and safety of percutaneous and transapical aortic valve implantation in the treatment of severe aortic stenosis. Systematic review	AVALIA-T	2013	http://bit.ly/29AUF15
	Cost-effectiveness of Transcatheter Aortic Valve Implantation (TAVI) for Aortic Stenosis in patients who cannot undergo surgery	NIHR	2013	http://bit.ly/29JhrlP
	Transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic stenosis in adults at high surgical risk	HIS	2014	http://bit.ly/29Kq4oA
	Transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic stenosis in adults who are not eligible for surgery	HIS	2014	http://bit.ly/29ATJpt
	Evaluatie indicatieprotocol TAVI	ZIN	2014	http://bit.ly/2a4Ijdp
	Cost-effectiveness of percutaneous aortic valve replacement using prosthetic valve versus the standard surgical treatment	OSTEBA	2014	http://bit.ly/29F4oRt
	Effect of severe left ventricular systolic dysfunction on hospital outcome after transcatheter aortic valve implantation or surgical aortic valve replacement: results from a propensity-matched population of the Italian OBSERVANT multicenter study	ASSR	2014	http://bit.ly/29O6s8I
	Development of appropriateness criteria for transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic stenosis	AVALIA-T	2014	http://bit.ly/29AU6jy

Technology	HTA title	Institute	Year	Link-shortened
Implantable cardiac resynchronization therapy and defibrillator (CRT-D/CRT-P)	Cardiac Resynchronization Therapy (CRT) in Chronic Heart Failure	SBU	2003	http://bit.ly/2bOEb2h
	The use of cardiac resynchronization therapy (CRT) for heart failure	HIS	2005	http://bit.ly/29Jzbgv
	The Implantable Cardioverter Defibrillator: a Health Technology Assessment	KCE	2007	http://bit.ly/29N5Y3d
	The clinical effectiveness and cost-effectiveness of cardiac resynchronization (biventricular pacing) for heart failure: systematic review and economic model	NIHR	2007	http://bit.ly/29A8kzX
	Standards for health technologies appropriateness: Cardiac resynchronization therapy	AETSA	2009	http://bit.ly/29KrisN
	Cardiac Resynchronisation Therapy. Economic evaluation	UETS	2010	http://bit.ly/29F4XKX
	Cardiac Resynchronisation Therapy	KCE	2011	http://bit.ly/29uW50I
	Implantable cardiac resynchronization therapy and defibrillator (CRT-D) in patient with heart failure	AGENAS	2014	http://bit.ly/29Jzc48
	Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronization therapy for the treatment of heart failure: systematic review and economic evaluation	NIHR	2014	http://bit.ly/29Jz98x
	Implantable cardioverter defibrillators and cardiac resynchronization therapy for arrhythmias and heart failure	NICE	2014	http://bit.ly/29SP3OQ
	Le stimulateur cardiaque de resynchronisation dans le traitement de l'insuffisance cardiaque	Swiss Medical Board	2015	http://bit.ly/29AJ4fx
Drug-eluting stents (DES) for Peripheral Artery Disease (PAD)	Senkung der Restenoserate durch Einsatz beschichteter Stents bei koronarer Herzkrankheit	DIMDI	2005	http://bit.ly/29sSDi7
	Economic Evaluation of Drug Eluting Stents for high risk indications	UETS	2006	http://bit.ly/29xyXoz
	Drug-eluting stents in Belgium: Health Technology Assessment	KCE	2007	http://bit.ly/29UaXRN
	Drug-eluting stents for the treatment of coronary artery disease	NICE	2008	http://bit.ly/29SPngJ
	Évaluation des endoprothèses coronaires à libération de principe actif	HAS	2009	http://bit.ly/29sSlb2
	Cost effectiveness of different types of coronary stents which are used in patients with acute coronary syndrome (ACS)	UETS	2013	http://bit.ly/29xznv8
	Economic evaluation of drug eluting stents in the treatment of ischemic heart disease (update)	UETS	2013	http://bit.ly/2a4JJ7D
	Medikamenten-freisetzende Stents bei peripherer arterieller Verschlusskrankheit	LBI-HTA	2014	http://bit.ly/29SPbOC
	Drug-eluting stents in coronary arteries	SBU	2014	http://bit.ly/29AU9w1
	New-generation drug-eluting stents reduce stent thrombosis and myocardial infarction: a propensity-score-adjusted analysis from the multicenter REAL registry (REgistro Regionale Angioplastiche dell'Emilia-Romagna)	ASSR	2014	http://bit.ly/29AIWwC
	Antikörperbeschichtete, medikamentenfreisetzende Stents zur Behandlung von Koronargefäßstenosen	IQWIG	2015	http://bit.ly/1SZJroA

Technology	HTA title	Institute	Year	Link-shortened
	Drug eluting balloons and stents for symptomatic peripheral arterial disease	The Regional Health Technology Assessment Centre (HTA-centrum)	2015	http://bit.ly/29LNaRC
MitraClip®	Perkutane Mitralklappenintervention mittels MitraClip bei Mitralklappeninsuffizienz	LBI-HTA	2010	http://bit.ly/29Ub4Nh
	Perkutane Mitralklappenintervention mittels MitraClip bei Mitralklappeninsuffizienz. 1. Update 2012	LBI-HTA	2012	http://bit.ly/29AUrqy
	MitraClip®	The HTA Center of the Stockholm County Council/ Gotland	2012	http://bit.ly/29LNzU9
	Mitraclip® – clip de réparation mitrale	CEDIT	2012	http://bit.ly/29LMKLj
	przezcewnikowa nieoperacyjna naprawa zastawki mitralnej (MitraClip) u chorych wysokiego ryzyka	AOTMit	2013	http://bit.ly/29MHcPX
	Using MitraClip® to repair mitral valve regurgitation	OSTEBA	2014	http://bit.ly/29A2ynp
	Evaluation d'un clip de réparation mitrale bord à bord et de son acte d'implantation	HAS	2015	http://bit.ly/1Q1h5CN
	Perkutane Mitralklappenreparatur bei chronischer Mitralklappeninsuffizienz (MitraClip®, Carillon®, NeoChord DS1000). Deutsche Kurzfassung zum gleichnamigen EUnetHTA Bericht	LBI-HTA	2015	http://bit.ly/29vHglg
	What is the effectiveness, safety and cost-effectiveness of the MitraClip® transcatheter mitral valve repair system in patients with moderate to severe or servere mitral regurgitation who are at high surgical risk or are non-surgical candidates?	HIS	2016	http://bit.ly/29A2S5J
Intensity-modulated radiation therapy (IMRT)	Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review	NIHR	2003	http://bit.ly/29xzx5K
	Radioterapia de intensidad modulada	AVALIA-T	2005	http://bit.ly/29MCCRL
	Radiothérapie extracrânienne en conditions stéréotaxiques	HAS	2006	http://bit.ly/29ESU19
	Intensity-modulated radiotherapy (IMRT)	KCE	2007	http://bit.ly/29Bcjwk
	Intensity-modulated radiotherapy for the treatment of prostate cancer: a systematic review and economic evaluation	NIHR	2010	http://bit.ly/29O79i9
	A study on efficacy, effectivity and efficiency of Intensity Modulated Radiotherapy (IMRT). Utility for treatment of breast and central nervous system neoplasms and sarcomas of bones and soft tissue.	AETSA	2010	http://bit.ly/29AJjau
	Innovative radiation treatment in cancer: IGRT/IMRT	ASSR	2010	http://bit.ly/29LNf81
	Innovative radiotherapy techniques: a mulitcentre time-driven activity-based costing study	KCE	2013	http://bit.ly/29DQrnB
	An evaluation of intensity-modulated radiotherapy (IMRT)	OSTEBA	2014	http://bit.ly/29MCzFO
	New IMRT techniques for moving targets. An analysis of their safety and ef cacy.	OSTEBA	2014	http://bit.ly/29DPTy7
	Radiothérapie conformationnelle avec modulation d'intensité dans le cancer du canal anal	HAS	2015	http://bit.ly/29AV83e

Technology	HTA title	Institute	Year	Link-shortened
High intensity focused ultrasound (HIFU)	Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer	NIHR	2003	http://bit.ly/29xzx5K
	High-intensity focused ultrasound for prostate cancer	NICE	2005	http://bit.ly/29JB5O7
	Efficacy, safety of high intensity focused ultrasound (HIFU-ExAblate)	UETS	2007	http://bit.ly/29JARGK
	Nichtmedikamentoese lokale Verfahren zur Behandlung des benignen Prostatasyndroms	IQWIG	2009	http://bit.ly/29F7nJw
	Destruction par ultrasons focalisés de haute intensité par voie rectale d'un adénocarcinome localisé de la prostate	HAS	2010	http://bit.ly/29MCTnL
	Hochintensiver Fokussierter Ultraschall (HIFU) zur Behandlung des Prostatakarzinoms	LBI-HTA	2010	http://bit.ly/29O7u4C
	Ultrasonido focalizado de alta intensidad (HIFU) extracorporeo en tumores solidos [Extracorporeal High-Intensity Focused Ultrasound (HIFU) in solid tumours]	CAHIAQ (AQuAs)	2010	
	Nichtmedikamentoese lokale Verfahren zur Behandlung des benignen Prostatasyndroms	G-BA	2010	http://bit.ly/29xAgnj
	HTA Report: Trattamento del carcinoma della prostata mediante termoablazione con HIFU	AGENAS	2011	http://bit.ly/2a4KGNr
	New treatments in organ-confined cancer vs. prostatectomy. Systematic review. Ablation with cryotherapy, HIFU and laser therapy.	AETSA	2013	http://bit.ly/29Ks35b
	High-intensity focused ultrasound (HIFU) bij prostaatcarcinoom	ZIN	2013	http://bit.ly/29xA6fD
	Leczenie raka stercza skupioną wiązką ultradźwiękową (HIFU)	AOTMiT	2014	http://bit.ly/29BcuI7
Lumbar total disc replacement	Remplacement du disque intervertébral lombaire par prothèse	HAS	2007	http://bit.ly/29BPxa8
	Prosthetic intervertebral disc replacement in the lumbar spine	NICE	2009	http://bit.ly/29JBoIL
	Bandscheibenprothesen	LBI-HTA	2010	http://bit.ly/29MdZbv
	Sökning i databaser för vetenskaplig evidens: Diskproteskirurgi i ländryggen	Metodrådet i Sydöstra Sjukvårdsregionen	2013	http://bit.ly/29MDBBL
	Lumbar total disc replacement effectiveness and safety in chronic low back pain	AETSA	2014	http://bit.ly/29LO4ow
	Cervical and Lumbar total disc replacements	KCE	2015	http://bit.ly/29tGA4l
	Operative versus konservative Behandlung von Diskushernien	Swiss Medical Board	2015	http://bit.ly/29LOoxH
	[Protesizzazione del disco intervertebrale cervicale e lombare] – HTA report adaptation di „Cervical and lumbar total disc replacements" Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE). 2015. KCE Reports 254. D/2015/10.273/94.	AGENAS	2016	nichtauffindbar
Intraoperative radiation therapy (IORT)	Intraoperative Radiotherapie bei fruehem Brustkrebs	LBI-HTA	2009	http://bit.ly/29BPZFn
	Innovative radiotherapy techniques: a multicenter time-driven activity-based costing study	KCE	2013	http://bit.ly/29DQrnB
	Intraoperative radiation therapy in the treatment of breast cancer	AVALIA-T	2013	http://bit.ly/1myxMpY
	Intraoperative radiation therapy in the treatment of colorectal cancer	AVALIA-T	2014	http://bit.ly/29DQQ9z
	Evaluation de la radiothérapie peropératoire dans le cancer du sein	HAS	2015	http://bit.ly/29KMInU

Technology	HTA title	Institute	Year	Link-shortened
Sacral nerve stimulation (SNS) for the treatment of fecal incontinence	Sacral nerv stimulation for faecal incontince	NICE	2004	http://bit.ly/29MEiuy
	Sakralnervstimulering (SNS) vid fekal inkontinens	Västra Götalands-regionen, Sahlgrenska Uni-versitetssjukhuset	2009	http://bit.ly/29xAHoS
	Sakralnervstimulation bei faekaler Inkontinenz	LBI-HTA	2011	http://bit.ly/2a8Hnc4
	INTERSTIM (I ET II)	HAS	2013	http://bit.ly/29yUSM7
	Sacral nerve stimulation for the treatment of fecal in- continence: an effectiveness review and cost-effective- ness analysis	CAHIAQ (AQuAs)	2014	http://bit.ly/29KsY5s
	Management of incontinence:sacral nerve stimulation vs. electrical stimulation	VASPVT	2014	
	Standpunt Sacrale neurostimulatie bij kinderen en volwassenen met therapieresistente functionele obstipatie	ZIN	2014	http://bit.ly/29SQGvV
	Secca System for faecal incontinence	NICE	2016	http://bit.ly/29uJD7L
Robot-assisted surgery system	Robot-assisted surgery using da Vinci® robot telemanipulation in prostatectomy	AETSA	2007	http://bit.ly/29uJAZF
	Robotic surgery by means of the da Vinci® robotic telemanipulation system in cardiovascular surgery	AETSA	2007	http://bit.ly/29ETQCQ
	Robotic surgery by means of the da Vinci® robotic telemanipulation system in general and digestive surgery	AETSA	2007	http://bit.ly/29yULQI
	Robotic surgery using the da Vinci® robotic telemanipulation system in hysterectomy	AETSA	2007	http://bit.ly/29Me1Qk
	La chirurgia robotica: il robot da vinci	ASSR	2008	http://bit.ly/29F7vc4
	Robot-assisted surgery: health technology assessment	KCE	2009	http://bit.ly/29GiMsC
	Revision sistematica de las evaluaciones economicas de la cirurgia mediante equipo quirurgico da Vinci	UETS	2011	http://bit.ly/29uJrWb
	Systematic review and economic modelling of the relative benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localized prostate cancer	NIHR	2012	http://bit.ly/2a64TlG
	Robotique chirurgicale en pédiatrie	CEDIT	2014	http://bit.ly/29uJf9k
	Roboterassistierte Chirurgie: Eine systematische Uebersichtsarbeit zu Wirksamkeit und Sicherheit bei ausgewaehlten Indikationen und anfallenden Kosten	LBI-HTA	2015	http://bit.ly/29Bd9cj
	Évaluation des dimensions clinique et organisationnelle de la chirurgie robot-assistée dans le cadre d'une prostatectomie totale	HAS	2015	http://bit.ly/29O96eo

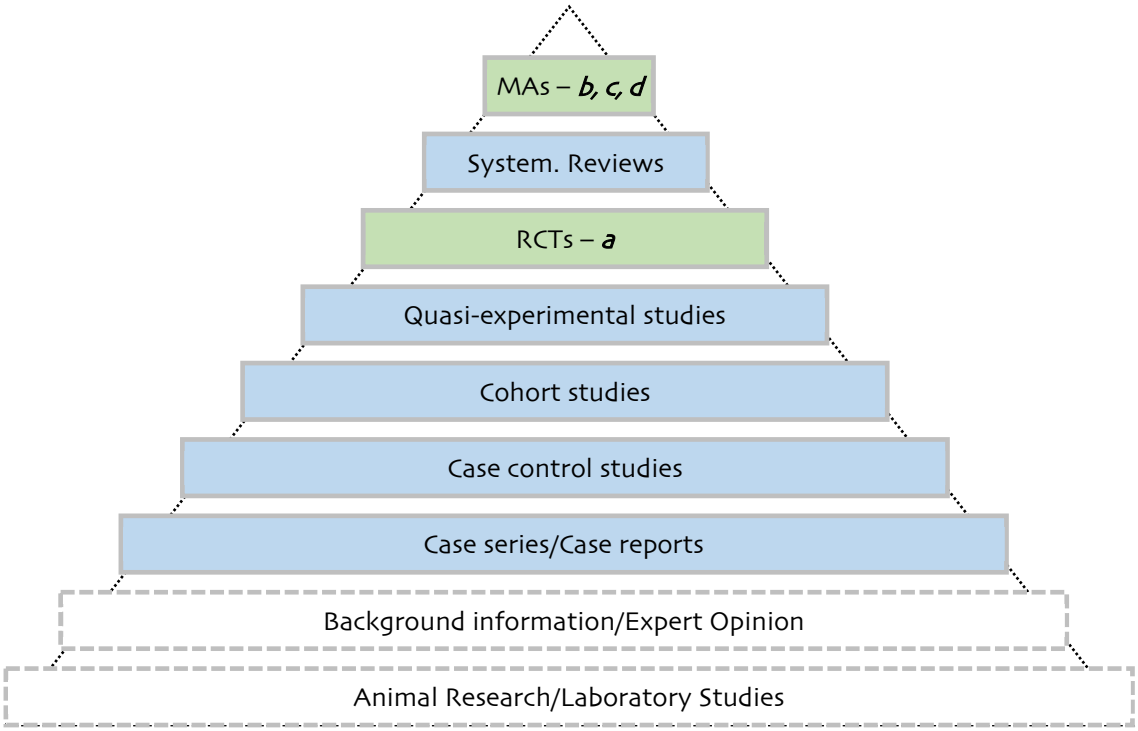

Figure 8-1: Evidence pyramid for implantable cardiac resynchronization therapy (CRT)
(green = used evidence, blue (and white) = not used evidence)

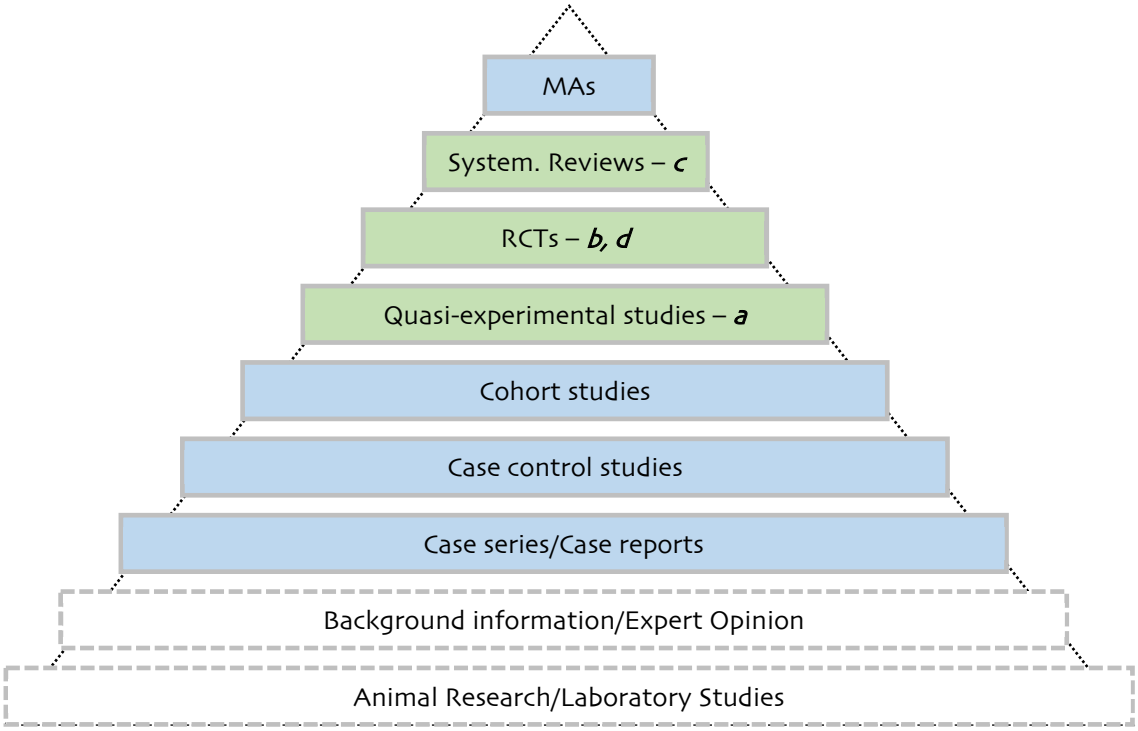

Figure 8-2: Evidence pyramid for MitraClip®
(green = used evidence, blue (and white) = not used evidence)

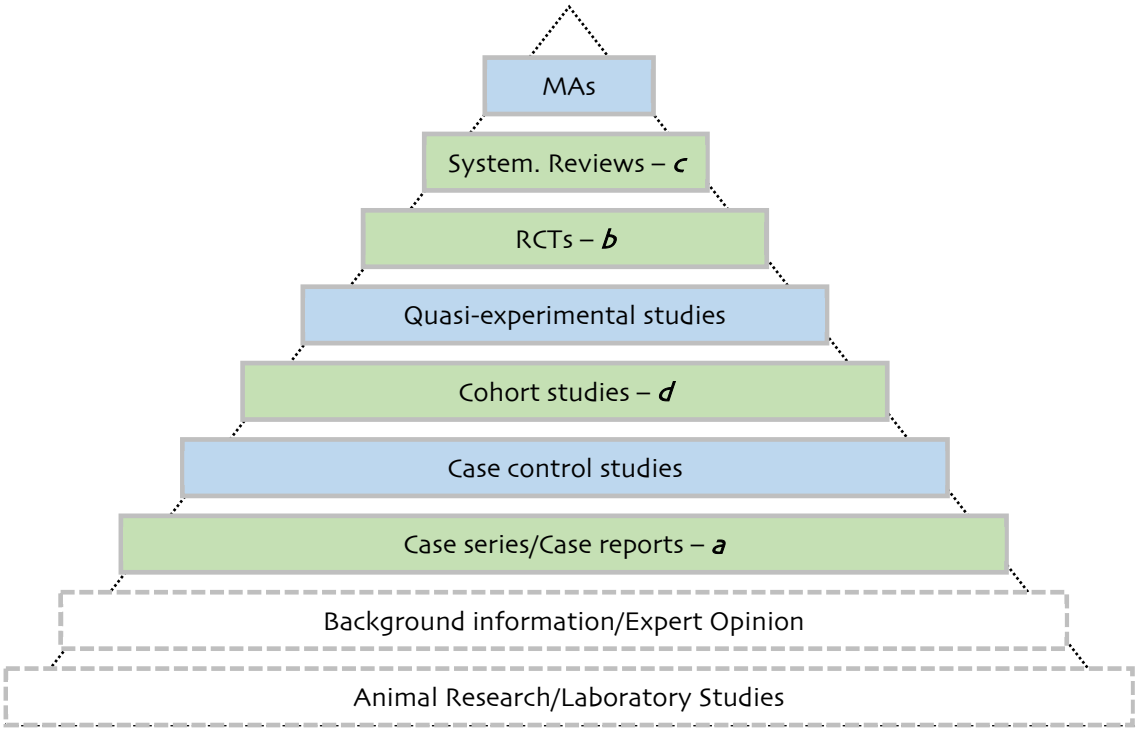

Figure 8-3: Evidence pyramid for Intensity-modulated radiation therapy (IMRT)
(green = used evidence, blue (and white) = not used evidence)

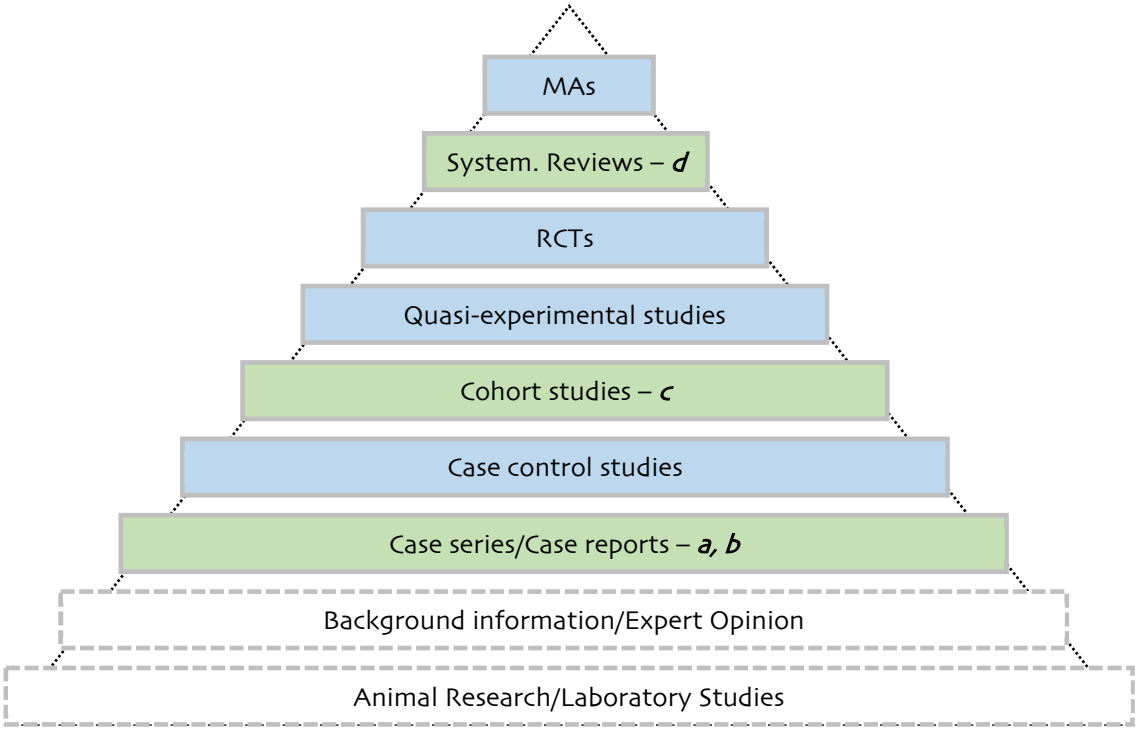

Figure 8-4: Evidence pyramid for high intensity focused ultrasound (HIFU)
(green = used evidence, blue (and white) = not used evidence)

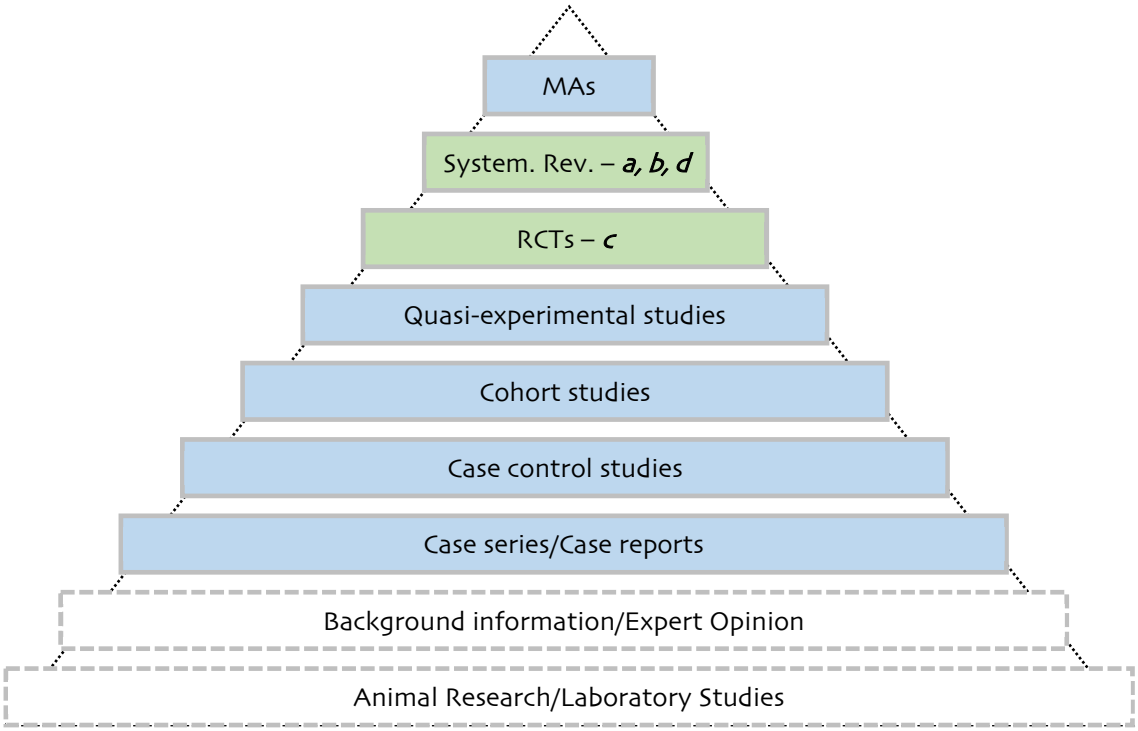

Figure 8-5: Evidence pyramid for lumbar total disc replacement
(green = used evidence, blue (and white) = not used evidence)

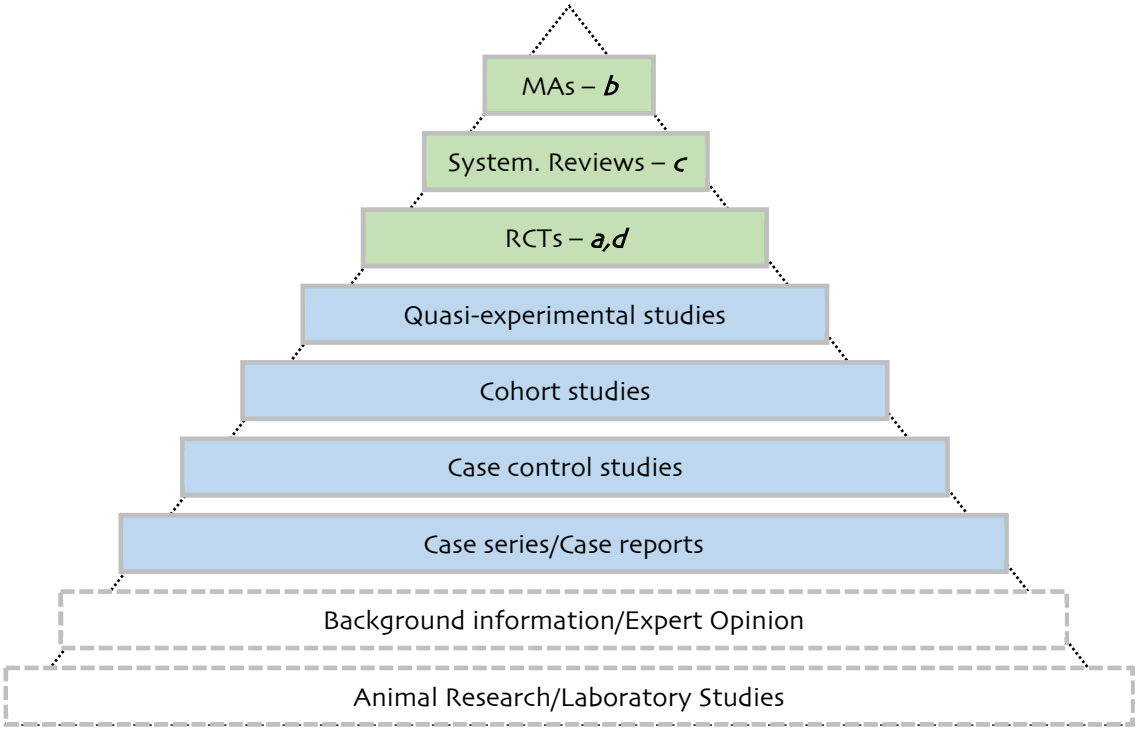

Figure 8-6: Evidence pyramid for intraoperative radiotherapy (IORT)
(green = used evidence, blue (and white) = not used evidence)

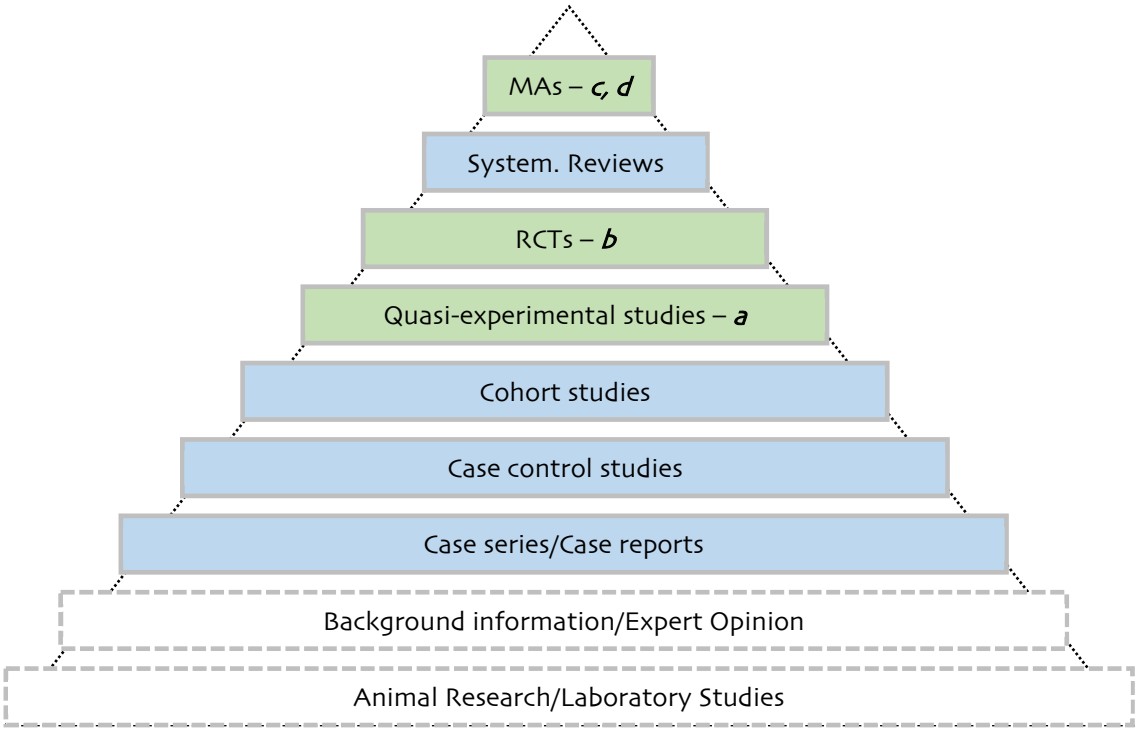

Figure 8-7: Evidence pyramid for sacral nerve stimulation (SNS)
(green = used evidence, blue (and white) = not used evidence)

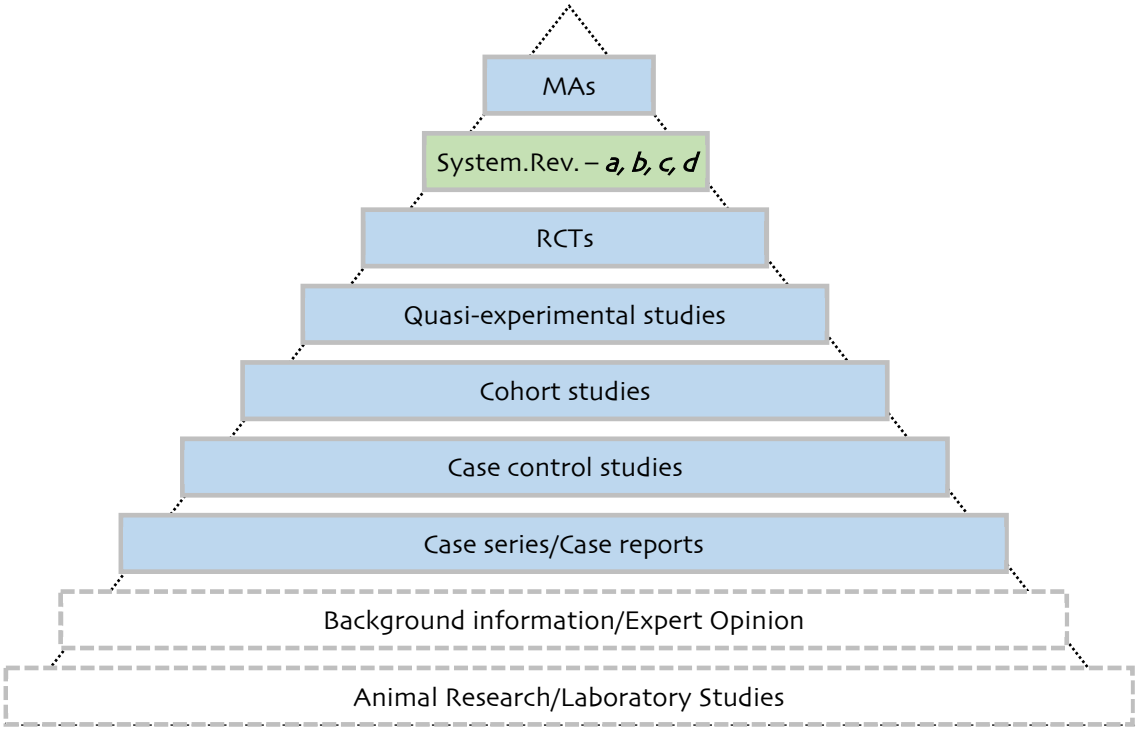

Figure 8-8: Evidence pyramid for robot-assisted surgery system
(green = used evidence, blue (and white) = not used evidence)

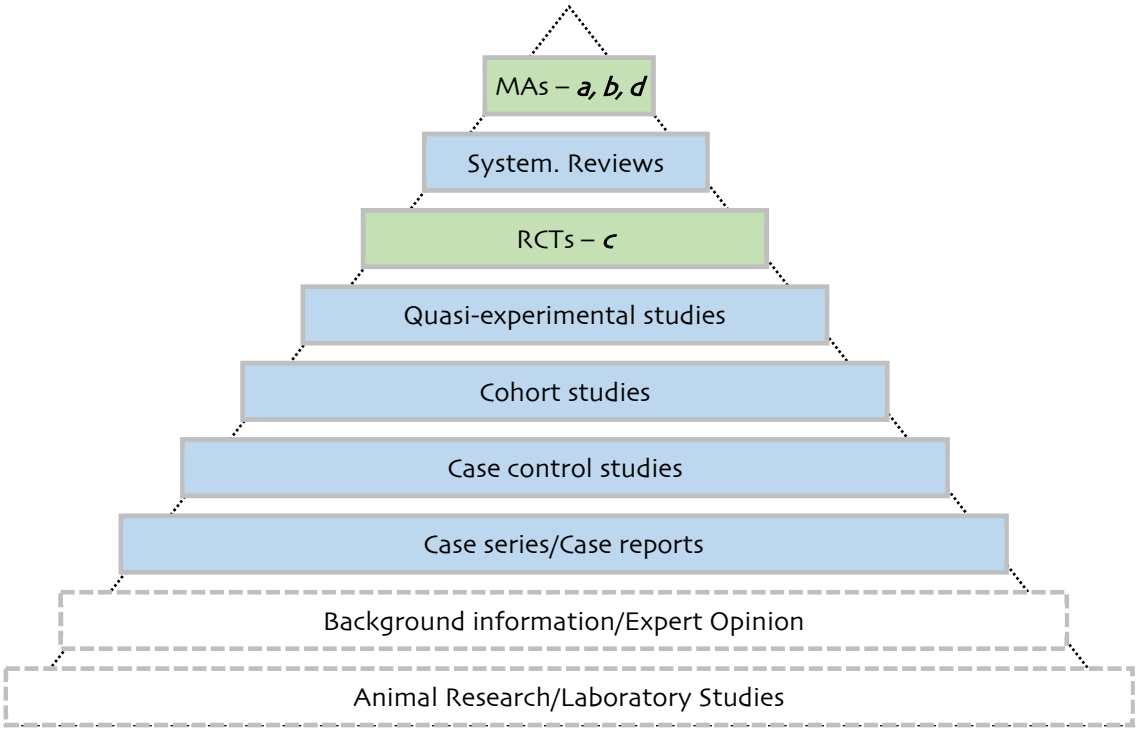

Figure 8-9: Evidence pyramid for drug-eluting stents (DES)
(green = used evidence, blue (and white) = not used evidence)

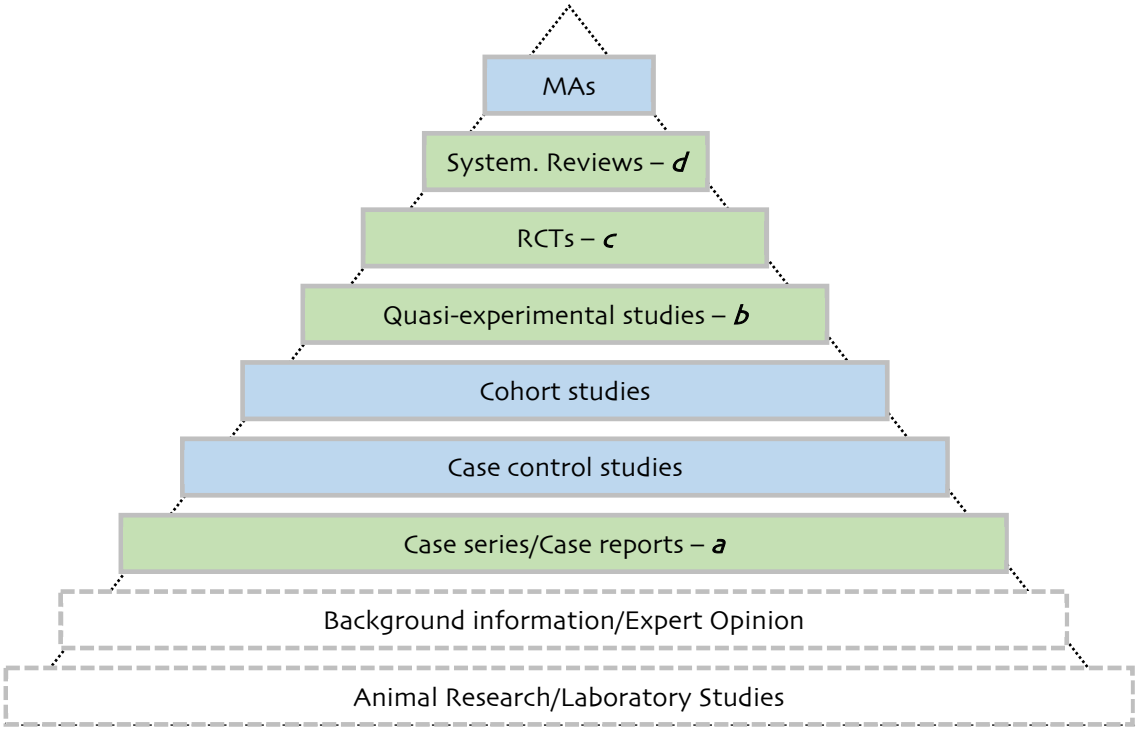

Figure 8-10: Evidence pyramid for Transcatheter Aortic Valve Implantation (TAVI)
(green = used evidence, blue (and white) = not used evidence)

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