Evidence requirements for the authorization and reimbursement of high-risk medical devices in the USA, Europe, Australia and Canada

An analysis of seven high-risk medical devices

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List of abbreviations

AHRQ .....Agency for Healthcare Research and Quality
AHA .....American Heart Association
ARTG.....Australian Register of Therapeutic Goods
AMD .....Age-related macular degeneration
ARGMD.....Australian Regulatory Guidelines for Medical Devices
CE.....Conformité Européenne
CDRH.....Center for Devices and Radiological Health
CMS .....Medicare and Medicaid Services
COPD.....Constructive obstructive pulmonary disease
CVZ.....College voor Zorgverzekeringen
DRG .....Diagnosis Related Group
EBM .....Einheitlicher Bemessungsstab
EC.....European Commission
EVB .....Endobronchial valves
EU .....European Union
FDA.....Federal Drug Administration
G-BA.....Federal Joint Committee (Gemeinsamer Bundesausschuss)
GHTF.....Global Harmonization Task Force
HDE .....Humanitarian Device Exemption
HTA .....Health Technology Assessment
HAS.....Haute Autorité de Santé
IPPS .....Inpatient Prospective Payment System
IQWIG .....Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KCE.....Belgian Health Care Knowledge Center
LVRS.....Lung volume reduction surgery
LBI-HTA .....Ludwig Boltzmann Institut für Health Technology Assessment
MEDCAC .....Medicare Evidence Development and Coverage Advisory Committee
MR.....Mitral regurgitation
MSD .....Medizinischer Dienst des Spitzenverbandes Bund der Krankenkassen e.V.
MTAC .....Medical Technology Advisory Committee
NETT.....National Emphysema Treatment Trial
NB .....Notified Body
NICE.....National Institute for Health and Care Excellence
NOC .....Notice of Compliance
ODA .....Office Device Authorization
PFO .....Patent foramen ovale
PMA .....Premarket approval
PPS .....Prospective payment system
PVSS.....Paracor Ventricular Support System
RCT.....Randomized controlled trial
RIZIV/INAMI.....Rijksinstituut voor Ziekte- en Invalidteitsverzekering
SHA.....Strategic Health Authorities
SHI .....Statutory Health Insurance
SLR .....Systematic literature review
SSED.....Summary of safety and effectiveness data
TGA.....Therapeutic Goods Administration (Australia)
TPD.....Therapeutic Products Directory
WHO .....World Health Organization

Zusammenfassung

Hintergrund und Zielsetzung: In allen Gesundheitssystemen spielen Medizinprodukte (MPs) eine wichtige Rolle. Im letzten Jahrzehnt hat sich die öffentliche Aufmerksamkeit verstärkt auf unsichere und unwirksame Hochrisiko-MPs gerichtet. Die Folge ist eine zunehmende öffentliche Diskussion darüber, dass der Zulassungsprozess für Medizinprodukte kein Garant für qualitativ hochwertige und sichere Gesundheitsversorgung mit MPs ist.

Hintergrund und Zielsetzung:

Dieser Forschungsbericht liefert zu einem eine Übersicht zu den Zulassungsverfahren insb. für MPs mit hohen Risiken in vier ausgewählten Regionen (USA, Kanada, Australien, Europa). Zum anderen werden die Anforderungen an klinische Evidenz und die öffentlich zugänglichen Informationen zum Zeitpunkt der Zulassung und zum Zeitpunkt der Bewertung vor einer Refundierung für sieben ausgewählte Hochrisiko-MPs analysiert.

Übersicht über Zulassungsverfahren und Anforderungen an die klinische Evidenz bei Zulassung und Refundierungsbewertung

Methode: Eine Literatursuche in PubMed, ergänzt durch Internet-Recherchen ist die Grundlage für die Übersicht über die vier Zulassungssysteme und deren Anforderungen an klinische Evidenz, insb. für Hochrisikoprodukte. Exemplarisch wurden sieben Medizinprodukte aus unterschiedlichen medizinischen Fachgebieten und Indikationsbereichen ausgewählt. Öffentlich zugängliche Informationen (offizielle Berichte der Zulassungsbehörden, Informationen der Hersteller, Ergebnisse der Literaturrecherche und Auswertung des Registers für klinische Studien) zum Zeitpunkt der Zulassung und zum Zeitpunkt der Refundierungsbewertung wurden gesucht und ausgewertet. Zuletzt wurde der „Level of Evidenz“ in einer Evidenzpyramide zusammengefasst.

Literatursuche in PubMed und www

7 MPs ausgewählt

klinische Evidenz analysiert durch öffentliche Berichte, Literatursuche und Register

Ergebnisse: Alle sieben ausgewählten Medizinprodukte haben in Europa eine Marktzulassung durch einen „Notified Body” (Benannte Stelle), nur vier in Australien durch die „TGA/Therapeutic Goods Administration“, je eines durch die US-Amerikanische „FDA/Food and Drug Administration“ und die Kanadische „TPD/Therapeutics Products Directorate“. Im Vergleich ist die Anzahl in Europa hoch, zumal vier weitere Medizinprodukte auch durch die FDA geprüft, aber zurückgewiesen oder nicht für eine breite Anwendung zugelassen wurden.

7 MPs Zulassung in EU, 4 in Australien, 1 in USA und 1 in Kanada

In nahezu allen Beispielen wurde die Europäische Zulassung zwischen zwei und fünf Jahren vor der Antragstellung/Zulassung anderswo gewährt. Trotzdem die klinische Evidenz, die zur Europäischen Zulassung führte, nicht bekannt ist (aufgrund des dezentralen und intransparenten Zulassungssystems), ist diese – naturgemäß, weil früher – auf einem niedrigeren Evidenzniveau. Im Gegensatz dazu wird keines der sieben Medizinprodukte – aufgrund des Mangels an Nachweisen von PatientInnennutzen – von einem HTA-Institut für eine generelle Refundierung empfohlen. Wenn doch, so lediglich im Forschungskontext.

in EU niedriges Evidenzlevel

keines der 7 zugelassenen Produkte empfohlen für Refundierung

Diskussion und Fazit: Die Ergebnisse unterstützen die Forderung einer Veränderung des Europäischen Medizinprodukte-Zulassungssystems, insb. für Hochrisikoprodukte zugunsten eines transparenten und evidenz-basierten Vorgehens. Bedingte Erstattung oder Erstattung unter der Bedingung von Generierung zusätzlicher Daten werden als Steuerungsinstrumente eingesetzt, um die große Kluft zwischen Medizinprodukten mit unsicherer Datenlage und den Erfordernissen für Refundierungsentscheidungen zu schließen.

Veränderung des EU-Zulassungsystems – transparenter und evidenzbasierter

Executive summary

background and objectives: description of medical device authorization systems in USA, Canada, Australia and Europe

Background and objectives: Medical devices play an important role in healthcare systems. In the last decade, public awareness has been raised because of unsafe and ineffective high-risk devices entering markets. Consequently, evidence requirements for the market authorization process of medical devices may not be enough to ensure high-quality and safe provision of care.

This research first explores the authorization systems for high-risk medical devices in four selected regions (USA, Canada, Australia and Europe). Secondly, it analyzes the clinical evidence accessible at time of market approval and decision support (HTA) for reimbursement for seven selected high-risk medical devices.

analysis of clinical evidence requirements in approval and reimbursement

methods:

Methods: A literature review in PubMed, complimented with a worldwide web search, was conducted about the authorization systems and their evidence requirements, esp. for high-risk devices, in the four selected regions. After a selection of seven high-risk devices across a broad range of medical specialties and indications information about clinical evidence accessible at time of authorization, evidence used for authorization and for pre-reimbursement assessments was searched and extracted from official reports, manufacturers, a literature search for each device in PubMed, and a search in a clinical trial registry. All accessible evidence was summarized in an evidence pyramid to show the levels of available evidence at time of approval and at time of pre-reimbursement assessment.

selection of 7 exemplary high-risk devices

multi-step searches for clinical evidence available at time of approval and of pre-reimbursement HTA

all 7 devices approved in Europe, 4 in Australia 1 in USA and Canada

Results: All seven medical devices have been approved in the European Union through an appointed Notified Body, only four by the Australian TGA/Therapeutic Goods Administration, one each by the US-American FDA/Food and Drug Administration and by the Canadian TPD/Therapeutics Products Directorate. In comparison to the other three regulatory systems, the number of approved devices in Europe is high, esp. if additionally taken into consideration that four further devices were also assessed by the FDA, but either rejected or not approved for general use.

approval in Europe 2-5 years earlier based on lower clinical evidence

In almost all of the seven analyzed examples, the premarket approval in Europe was granted two to five years before authorization in other systems. The evidence used for CE marking is not known due to the highly decentralized authorization system and the lack of transparency. Since authorization in Europe is earlier, the clinical evidence is naturally less mature. In contrast, none of the seven medical devices has been recommended for reimbursement yet. The pre-reimbursement assessments most often state that current evidence is not enough to ensure patient benefit and safety. Some devices are recommended for "research only."

none of 7 devices is recommended for general use by HTA

Europe needs transparent, evidence-based device regulation system to close gap between approval and reimbursement

Discussion and conclusion: The results support a change in the European authorization system towards a transparent and evidence-based regulation process. Conditional coverage or coverage under evidence development is applied as instrument to close the gap between immature data and reimbursement requirements.

1 Introduction

Healthcare systems all around the world highly depend on the usage of medical devices in the diagnosis, prevention and treatment of diseases [1]. It has been recognized that by means of a significant contribution of medical device technology, patients nowadays enjoy longer lives of higher quality. Especially for treatments in the cardiovascular, orthopedic and oncological fields, new devices are offering better alternatives to existing care standards [2]. In general, it can be observed that the advances in medical technologies have enhanced patient health outcomes [3]. As a result, a common objective of healthcare systems is to ensure and improve the access, quality and usage of medical devices [4].

medical devices significantly contribute to beneficial patient health outcomes
safe access to high quality devices should be ensured

Medical devices can range from the simplest daily life supports such as sticking plasters, pregnancy tests and contact lenses to the most sophisticated and advanced actively implantable devices like pacemakers and hip replacements [5]. In the European Union Medical Devices Directive, medical devices are described as "Any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, 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" [6]. International definitions of medical devices may carry some variations, creating even more room for diversity and complexity in this sector [7].

international variation in definition of medical devices

This diversity poses major challenges to healthcare systems, especially relating to regulation and financial access to medical devices [8]. The primary aim of regulation is the safe, high-quality and effective patient access to medical devices and the market restriction for those products that are ineffective and unsafe. Problems related to medical devices, such as unsafe and risky characteristics, can have serious health consequences for the end-user.

variation in medical device sector poses challenges to healthcare systems

To be able to ensure this primary aim through regulation, medical devices have to undergo several assessment and evaluation procedures in their usual life-cycle [9]. First, an authorization process, in which an in-depth assessment of the device and its characteristics for market entry is performed. Secondly, the reimbursement evaluation of the responsible national health authorities in which the "value" based on the effectiveness of the device is identified.

life-cycle of medical devices – authorization and reimbursement assessment

1.1 Background: Problem statement

In comparison to the pharmaceutical approval and reimbursement process, less attention has been paid to the approval and reimbursement process for medical devices. As a clear international history of regulating the processes of pharmaceuticals exists, no clear international medical device regulations have been set [4]. This can be explained by the high diversity and complexity of products in the medical device sector. Currently, many healthcare systems are struggling with the implementation of appropriate medical device evaluation practices [10].

approval and reimbursement of medical devices is less regulated than for pharmaceuticals due to complexity and diversity

Two of the most important world markets for medical devices, the United States of America and the European Union, have gone through a remarkable medical device regulation history. Nowadays they approach the regulation of medical devices in a vastly different manner.

medical device regulation history in the USA

- In the United States of America, device regulation began as early as 1938, and the regulatory structure reflected the relative simplicity of the medical devices being marketed at that time. In 1976, this regulatory structure was no longer adequate to deal with the high variation of medical devices and the increasing sophistication of the newly developed devices. The American Congress reacted to the sporadic public health incidences associated to low patient safety through unsafe and risky device usage and established the Medical Device Amendments of 1976 [11]. The law has been updated twice since then.

medical device regulation history in Europe

- In the European Union, the medical device regulatory system is quite young, approximately 25 years behind the regulation from the United States of America. The European regulatory system for medical devices is embedded in the single market policy (EU Article 100/100a for the European single market) and three device-specific core directives. First, the council directive on active implantable medical devices (AIMD, 90/385/EEC), agreed upon in June 1990 [12]. This directive was the first to be in force in European Member States from the 1st of January 1993. Secondly, the council directive on medical devices (MDD, 93/42/EEC) that has been effective in all Member States from the 1st of January 1995 [6]. Thirdly, the European Parliament and the council directive of in vitro diagnostic devices (IVDD, 98/79/EC) [13]. This directive went in force on the 8th of December 1998 after a revision and consultation time of almost 8 years and amended sections within the AIMD and the MDD. On September 24, 2013, a revision of the European Medical Device Directive was implemented. The main changes included in the new directive are a clearer scope for the EU regulation, a stronger assessment of the Notified Bodies and clearer responsibilities, an extended EUDAMED database, updated classification rules and more coordination. The target for adoption is 2014.

evidence standards for the authorization and reimbursement have to be high for drugs and devices

international standards have not been defined and implemented yet

While innovation brings a great variety to the medical device sector on the one hand, it brings challenges regarding evidence standards for the authorization and reimbursement processes on the other hand [14]. Yet, regulatory processes such as authorization and reimbursement of medical devices require certain evidence standards to base decisions on. It has to be recognized that the study evidence on which a device approval decision is based certainly has to be of high quality. A gold standard for evidence that is set up in pharmaceutical assessments would consist of randomized, double-blinded studies with adequate controls, sufficient duration, and a long follow-up on preselected primary endpoints without bias [15]. Nonetheless, no adequate gold standards have been implemented in the medical device sector yet, and ethical drawbacks for randomized controlled trials may be present.

need for the implementation of new approaches for the authorization and reimbursement

Missing clear requirements for evidence to be submitted within the authorization and reimbursement processes, healthcare systems experience difficulties in their regulation of medical devices. In various regions, it can be observed that device approval systems have become incapable of assuring safety, effectiveness and performance standards [16]. There is a clear need for the implementation of new approaches in the medical device sector.

1.2 Aim and objective

aims: insight into four authorization systems evidence at time of approval and reimbursement

This report aims to provide insight into the authorization process and its associated evidence requirements for high-risk medical devices in the USA, Europe, Australia and Canada. Further, this research aims at assessing the evidence for seven selected high-risk medical devices upon time of authorization approval and reimbursement decisions.

2 objectives:

This research has two main objectives:

authorization process in the four regions

- First, to explore and explain the authorization systems for medical devices in four selected regions, namely the USA, Canada, Australia and Europe: The main characteristics of regulatory bodies, medical device classification approaches, authorization procedures and the associated evidence requirements for each of the regions are described. Differences and similarities of the four systems are summarized and compared.

evidence available at time of approval and reimbursement decision

- Secondly, to investigate the evidence that is available for the seven high-risk medical devices at the time of authorization approval and reimbursement decision. All information is summarized and presented in an evidence pyramid.

1.3 Scope of project and limitations

The scope of this research is limited in a number of ways.

only inclusion of high-risk medical devices

- First, the research aims to only explore the evidence requirements for authorization and reimbursement for high-risk medical devices. This entails that only medical devices from the Class III device category will be included in the research [6].

four selected regions

- The research focuses on the regulatory frameworks of the four selected regions: the USA, Europe, Australia and Canada. Information provided is therefore only applicable within in these selected regions.

data collection limited to accredited regulatory bodies

- Furthermore, the authorization process will only be examined within accredited regulatory bodies. Consequently, the FDA (USA), Notified Bodies (Europe), the TGA (Australia) and Health Canada (Canada) are included. Documents referring to the evidence used within an authorization decision will only be used when issued by these regulatory bodies.

inclusion of only publicly available information

- Only information that has been publicly accessible can be included in this research. That means that the information collection is limited to open homepages of regulatory bodies, databases and published literature.

restricted selection of reimbursement agencies

- Additionally, national institutes or authorities (many countries have more than one) that are relevant for the reimbursement decision will be chosen on the basis of available information about the devices in question. These institutes are by no means representative of all regulatory reimbursement bodies, but have been chosen to serve as examples. In Europe, the situation will be represented only by a selection of six countries and their relevant reimbursement authorities; therefore, generalizability to all European Member States is limited.

seven high-risk devices for exemplary presentation

- Moreover, the research is limited to the assessment of seven devices selected on the representation of all major indications that are dependent on high-risk medical devices. It is understood that these devices can only serve as examples and that generalizability may be restricted.

2 Methods

The data collection for this research is divided into three main parts: first, the search for information on the authorization; second, the reimbursement processes and their associated evidence requirements; third, the search for accessible information at the time of authorization approval and reimbursement decision of the high-risk medical devices.

methods: data collection on authorization systems, reimbursement system and accessible evidence

2.1 Selection of regions

This research focuses on four selected regions, namely the United States of America, Europe, Australia and Canada. The four regions represent the Western industrialized world and can be considered as major impact countries for the medical device sector. Moreover, healthcare systems within these regions are highly dependent on medical devices.

inclusion of USA, Europe, Australia and Canada

2.2 Selection of high-risk medical devices

The high-risk medical devices included in this research had to meet some inclusion criteria: They were chosen out of a broad range of medical specialties and indications that depend on the use of devices. Further, only high-risk medical devices, the highest risk classification, were selected, since the most stringent evidence requirements for the authorization process and reimbursement decisions are required in this class. Based on these criteria, seven high-risk medical devices were chosen (Table 2.2-1).

seven high-risk medical devices selected

Table 2.2-1: Seven exemplary high-risk medical devices

Medical Device	Manufacturer	Medical Specialty
Zephyr® Endobronchial Valve	PulmonX	Pulmonology
Paracor Ventricular Support System (PVSS)	Paracor Medical Inc.	Cardiology
Annular repair device Barricaid®	Intrinsic Therapeutics, Inc.	Orthopedics
Rheofilter ER-4000	Asahi Kasei Medical Co.	Ophthalmology
BSD-2000 Microwave Hyperthermia System	BSD Medical	Oncology
Amplatzer™ PFO Occluder	St. Jude Medical	Cardiology
MitraClip®	Abbott	Cardiology

2.3 Authorization

data collection based on two sources

The data collection for the authorization part is based on a literature search and on official reports from the relevant national regulatory bodies (except Notified Bodies, due to intransparency).

literature search in PubMed, www

The literature search first focused on the national authorization processes and their characteristics. The search was conducted in an academic database through PubMed, as well as in the worldwide web in an iterative way. 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 (See Appendix 1). The main inclusion and exclusion criteria for the data selection are presented in Table 2.3-1. All literature selected in the first screening underwent a second, more thorough examination.

inclusion and exclusion criteria

keywords for literature search

Keywords used during the search were *High-risk medical device** AND *methodology** AND *"clinical evaluation"** AND *class III devices** AND *market authorization** AND *Europe** AND *United States of America** AND *Australia** AND *Canada** AND *TGA** AND *Health Canada** AND *FDA** AND *evidence requirements** AND *guidance for medical devices** AND *assessment methods**

Table 2.3-1: Inclusion and exclusion criteria for the authorization data collection

Inclusion criteria	Exclusion criteria
✿ In English or German language ✿ Relevant for the four selected regions ✿ Focus on evidence requirements ✿ Comparison analysis of authorization processes ✿ Publications about the selected s even devices ✿ High-risk medical devices ✿ Publications available from 2000 until July 2013	✿ Very broad general narrative descriptions ✿ Publications about low-tech devices ✿ Clinical trial summaries of specific medical devices (only inclusion with focus on one of the seven selected devices) ✿ Publications about in-vitro diagnostics, medical device software, nanotechnology, off-label use, combination products and biotechnical engineering ✿ Descriptions about export and import of medical devices ✿ Supplement articles to already existing devices

2.4 Reimbursement

data collection based on literature search and reports

The data collection for the reimbursement section consisted of a literature search and of public reports from relevant reimbursement institutions.

literature search: PubMed and www

The literature search concentrated on the reimbursement practices and evidence requirements in the four selected regions. The search was conducted in an academic database through PubMed, as well as in the worldwide web in an iterative way. All search outcomes were documented and underwent a selection process. Predefined inclusion and exclusion criteria guided the literature selection process within the systematic literature review. All relevant steps are documented in a PRISMA-tree (See Appendix 2). The inclusion and exclusion criteria are presented in Table 2.4-1.

keywords for the literature review

Keywords used during the search were *High-risk medical device** AND *"clinical evaluation"** AND *class III devices** AND *reimbursement** AND *Europe** AND *The Netherlands** AND *Germany** AND *England** AND *Austria** AND *France** AND *Belgium** AND *United States of America** AND *Australia** AND *Canada** AND *TGA** AND *Health Canada** AND *evidence requirements** AND *guidance for medical devices** AND *assessment methods** AND *evaluation methods** AND *HTA assessment**

Table 2.4-1: Inclusion and exclusion criteria for the reimbursement data collection

Inclusion criteria	Exclusion criteria
✿ In English or German language ✿ Relevant for the four selected regions ✿ Focus on the national reimbursement practices ✿ Publications available from 2000 until October 2013	✿ Very broad general narrative descriptions ✿ Special reimbursement reports of pharmaceuticals or other technologies ✿ Supplement articles to reimbursement decisions

public reports from reimbursement agencies or HTA institutes

The second part of the data collection was based on public reports from reimbursement agencies or HTA institutes from the four selected regions. Information about evidence requirements and assessment methods used for the reimbursement decision were searched for. All data available in German and English were included in this research.

selection of reimbursement agencies or HTA institutes

The reimbursement agencies or HTA institutes selected for this research are listed in Table 2.4-2.

Table 2.4-2: Reimbursement agencies and HTA institutes

United States of America	✿ Centers for Medicare and Medicare Services (CMS) ✿ Aetna ✿ Blue Cross and Blue Shield (BSBC) ✿ United Healthcare ✿ Kaiser Permanente ✿ Agency for Healthcare Research & Quality (AHRQ)
Europe	✿ The Netherlands – College voor zorverzekeringen (CVZ) ✿ Germany – MDS, Federal Joint Committee (G-BA), Institute for Quality and Efficiency in Healthcare (IQWIG) ✿ England – National Institute for Health and Care Excellence (NICE) ✿ Austria – Ludwig Boltzmann Institute for HTA (LBI)
Australia	✿ Medical Services Advisory Committee (MSAC)
Canada	✿ Canadian Association of Healthcare Reimbursement (CAHR)

2.5 Accessible clincial evidence for seven high-risk medical devices

literature search on 7 medical devices

A literature search on the seven exemplary medical devices was performed. An academic database (PubMed) was searched. The keywords used during the search were the product name of the seven selected devices and the associated indication.

contact to the accredited national authorization bodies

In addition, the regulatory bodies responsible for the authorization procedure in the four selected regions were contacted, and information about the evidence used for the authorization decision of the seven medical devices was requested. The bodies that were contacted are the FDA in the United States of America, Health Canada in Canada and the TGA in Australia. A standardized e-mail was sent to the relevant departments within the regulatory bodies.

request to manufacturer for information about evidence submitted

Furthermore, the manufacturers of the seven devices selected for this research were approached with the request to provide information about the evidence submitted to the regulatory bodies in the four regions during the authorization process. A standardized e-mail was sent to the manufacturers.

clinical trial registry

The clinical trial registry clinicaltrial.gov was scanned using the product name of the seven devices and the associated indication as keywords.

guidance reports on reimbursement for seven medical devices

Further, public reports from reimbursement agencies or HTA institutes from the four selected regions (Table 2.4-2) on the seven exemplary devices were searched for. Only the exemplary medical devices approved through the authorization process in the regions were further assessed for reimbursement decisions. The reimbursement agencies were selected based on the existence of publicly available assessment reports in English or German.

All gathered information was summarized in a comprehensive and systematic way, and is presented within a separate section for each of the seven medical devices.

2.6 Research questions

research questions

The research project especially focuses on the evidence requirements used for the authorization process and the reimbursement decisions in the four selected regions. The main, guiding research questions have been organized within the two main focus points: the authorization and reimbursement processes. Moreover, research questions focusing on the comparison of both processes and overlapping evidence requirements have been formulated:

authorization and reimbursement

Authorization:

- How do the premarket authorization processes for high-risk medical devices in the four selected regions work and what evidence is required?

what evidence is required?

- What are the major similarities or differences of the authorization processes for high-risk medical devices in the four selected regions?

similarities and differences?

- What evidence is available for the seven selected high-risk medical devices? What is the scientific basis for the premarket authorization?

availability of evidence?

Reimbursement:

- How do the reimbursement processes for high-risk medical devices in the four selected regions work and what evidence is required?
- What are the major similarities or differences of the reimbursement processes for high-risk medical devices in the four selected regions?
- What evidence is available for the seven selected high-risk medical devices regarding the process for the reimbursement decision?

Comparison:

- Which policy improvements are proposed for the premarket authorization and the reimbursement decision in the four selected regions?

policy improvements

- How can the evidence requirements be more harmonized between the two processes of authorization and reimbursement?

3 Authorization

medical device regulation for authorization is very multifaceted

The regulations for the authorization process of medical devices are multifaceted. Manufacturers seeking to place a new medical device on the market generally have to provide evidence about the characteristics of the device based on its potential risk. These risk-appropriate regulatory frameworks are of utmost importance for the regulation and control of the massive number of heterogeneous products in the medical device sector. One of the primary aims of these regulations is to ensure timely patient access to safe and effective technology [17].

chapter overview

This chapter starts by introducing the current challenges within the authorization of medical devices. Subsequently, four different authorization systems from the United States of America, Europe, Australia and Canada and the associated evidence requirements for high-risk medical devices are described.

3.1 Challenges in the authorization process of high-risk medical devices

1.5 million different medical device products

According to the World Health Organization, 1.5 million different medical devices currently exist around the world [5]. The sector covers a wide range of products and is consequently struggling with the appropriate authorization systems to regulate and control the device markets. This struggle has been clearly highlighted through the scandals of unsafe and dangerous devices being marketed, especially in the European single market [18].

struggle to find appropriate regulation

criticism: lack of transparency in approval processes, no clear evidence standards

Authorization systems have been criticized for lacking transparency in their processes and for not stating clear evidence requirements for the assessment of clinical and patient benefit [19]. In response to the on-going debate and criticism, the medical device sector has provided the public with the major challenges of effective regulation and control.

approval decisions under uncertainty due to study designs

- First, the evidence generation for medical devices is assumed to be more complex than for pharmaceuticals. In particular, to perform a randomized clinical trial with high-risk medical devices using placebos as comparators is (often) impossible due to ethical research standards [4]. Therefore, other study designs such as (retrospective or prospective) case series are the only available evidence for the approval process.

mostly SMEs: lack of resources and experience in clinical research

- Secondly, the medical devices sector is overwhelmed by small- to medium-sized enterprises (SMEs) compared to the pharmaceutical sector, where only large, experienced enterprises are present. In general, SMEs neither have the resources nor the experience to perform large clinical trials for their products [20].

regulatory framework and authorities are less experienced

- Thirdly, authorities are asked to handle a great amount of products varying in characteristic and performance. In comparison to the pharmaceutical sector, the medical device sector and its regulatory frameworks are approximately 25 years younger [21].

3.2 USA: FDA/Food and Drug Administration

overview USA

The following section presents the authorization system in the United States of America. First, the regulatory body responsible for the authorization is introduced. Secondly, the current classification system for medical devices is presented and the authorization is explained in more detail. Finally, evidence requirements requested by the FDA are summarized.

3.2.1 Regulatory body

FDA centralized regulatory authority

CDRH main department for premarket applications of medical devices

The authorization process for medical devices in the United States of America is primarily the responsibility of the Food and Drug Administration (FDA). The FDA is a centralized body that is not only responsible for medical devices, but in general for the protection of the public health of American citizens [22]. That includes the supervision and assessment of all products associated with human health. In the medical device sector, the FDA regulates the manufacturer's application for market entry of a new device. A manufacturer must receive FDA permission before its device can be legally marketed in the United States. A subdivision of the FDA, the Center for Devices and Radiological Health (CDRH), is the main reviewing body for submitted premarket applications [23].

3.2.2 Classification

3 risk classes for medical devices based on risk

In the American system, every medical device has to be classified into its appropriate risk class before submission of any evidence to the FDA. The manufacturer itself has to identify the risk class of the device based on the potential risk the device carries for its user. In general, there are three different risk classes a device could be classified to. Device classification determines the kind of application a manufacturer must submit to the FDA [24].

low

- Class I is the low-risk class of devices. These devices present minimal potential harm to the user and their design is often less complex than designs from higher risk class devices. Examples of devices from this risk class are examination gloves, sterile instruments and bandages [25].

moderate

- Class II devices represent moderate risk devices. Examples of devices classified to this risk class are infusion pumps, surgical drapes and powered wheelchairs [24].

high

- The highest risk class is Class III, as these devices pose the potentially highest risk to the user. Most Class III devices have the characteristics to support or sustain human life and are therefore the devices that present the highest potential risk of illness or injury to users [24].

guidance documents by FDA for manufacturer to classify the device

The FDA provides guidance documents for manufacturers to classify their device in a certain risk class. After identification to a certain risk class, the authorization procedure and the requested evidence requirements can be identified, being less stringent for Class I devices ranging up to very stringent for Class III devices [22]. In some cases, special provisions allow reclassification to another risk class if the FDA or the manufacturer disagrees with the potential risk the device carries.

3.2.3 Procedure

registration with the agency is obligatory for every device

Regardless of its risk class, every medical device evaluated by the FDA has to be registered within the agency and has to pass the so-called general controls. These general controls are regulated under the Federal Food, Drug & Cosmetic (FD&C) Act of January 5, 2010. The basic characteristics of the device are evaluated by the controls and its further consideration within the authorization procedure is assessed. The main five elements included in the general controls are: the compliance with the registration establishments, the device listing within the agency, good manufacturing practices (GMP), adequate labeling and the submission of a premarket application [26].

device has to undergo general controls

different authorization pathways
class I – registration and general controls
class II – registration, general controls and special controls

After the initial general controls, medical devices may take different authorization pathways, based on their risk classification. Class I devices may enter the market based on an existing registration within the FDA and the assessment through the general controls [26]. The authorization pathway for Class II devices demands, in addition to the general controls, further special controls. These special controls are often shaped specifically to the device in question [27].

Class III devices have the most complex and stringent authorization. There are two options to obtain market entry for Class III devices.

class III – 510(k) notification application for substantial equivalence

First, the manufacturer may submit a 510(k) notification application, assessing the substantial equivalence to another, already legally marketed device (predicate device). This requires that substantial equivalence can be determined by comparing the performance characteristics, same intended use and technological characteristics of the new device to the predicate device [28]. The safety and effectiveness of the new device may be ensured through substantial equivalence. After the submission of the 510(k) premarket notification, FDA has the right to review the application within 90 days. The manufacturer may not proceed to market the device within these 90 days, but only when the FDA declares the device substantially equivalent [29].

class III – PMA/premarket approval for the assessment of safety and effectiveness of the device

If the Class III device is not substantially equivalent to any already legally marketed device, it has to apply for a premarket approval (PMA), the second possible authorization pathway for high-risk devices. A PMA is the FDA's most complex and stringent process for medical device authorization, aiming at novel and high-risk devices. Within the process, the FDA assesses the safety and effectiveness of the device based on studies submitted by the manufacturer. The FDA requests that the application contains sufficient valid scientific evidence to be able to evaluate the safety and effectiveness of the device within its intended use [30].

CDRH: 4-step process assessment of completeness

The PMA is reviewed by a subdivision of the FDA, the CDRH, and entails four steps [23].

- First, the FDA conducts a limited scientific review to conclude whether the application is complete and contains all required information necessary for further review. Within 45 days, the applicant receives a notification of completeness of the application by the agency.

in-depth scientific review by FDA staff

- Secondly, qualified FDA personnel will start an in-depth scientific and regulatory review and a quality system review. During this review the FDA is entitled to contact the applicant and request more information that is needed to complete the assessment. Within 100 days, a meeting can be arranged between the FDA and the applicant to discuss the status of the PMA process.

external panel review with public meeting of advisory committee

- Subsequently, an external panel review will take place; the PMA is revealed to an external advisory committee for review and recommendations. In a public meeting, the advisory committee is asked to discuss the PMA and later submit a final decision document, including the recommendation of the committee and the basis for such a recommendation, to the FDA.

decision by the FDA publication of SSED

- The final and fourth step of the PMA process involves the final deliberation, documentation, and the notification to the manufacturer of the decision by the FDA on the device. After a device receives approval, the FDA publishes the approval order, labeling guidelines, and a summary of safety and effectiveness data (SSED) on its homepage.

3.2.4 Evidence requirements

different procedures require different level of evidence
general controls focus on the basic characteristics of the device

The FDA requests a minimum standard of evidence for the different risk-class-based authorization procedures. The general controls affect every medical device, regardless of its risk class, and require information related to adulteration; misbranding; device registration and listing; premarket notification; banned devices; notification, including repair, replacement, or refund; records and reports; restricted devices; and good manufacturing practices. The manufacturer is asked to independently submit this information within the appropriate format provided on the FDA homepage [26].

special controls are tailored to the device

Special controls for Class II devices often request evidence especially tailored to the device in question [27].

510(k) – evidence that the device is substantial equivalent in intended use and technological characteristics

Minimum evidence requested for the 510(k) procedure mainly focuses on the substantial equivalence. The device is only substantially equivalent if it has the same intended use and very similar technological characteristics as the predicate. In the case of minor changes to the technological characteristics of the new device, substantial equivalence can only be ensured for an evidence submission containing a detail description of the changes and an adequate explanation why safety is not jeopardized. It is not intended by the FDA that a claim of substantial equivalence anticipates that the devices are identical; it is rather that evidence about intended use, design, energy used, or delivered materials, chemical compositions, manufacturing processes, performance, safety, effectiveness, labeling, biocompatibility, standards and other characteristics are suggested to be equivalent [28].

introduction with information about the device

technical section including non-clinical laboratory studies

A PMA has certain additional administrative elements and evidence requirements [31]. Generally, PMA documents have to contain an introduction about the applicant, the device, alternative practices and procedures to the device and the marketing history. In addition to this information, a summary of all studies associated with the device should be included. The FDA obliges applicants to include a technical section in the PMA [32]. The technical sections can be subdivided into the non-clinical laboratory studies section and the clinical investigation section. Evidence required to be included in the non-clinical laboratory studies section are information on microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf life, and any further laboratory or animal tests [33].

clinical investigation studies

effectiveness, safety

In the clinical investigation section, information on the study protocols, safety and effectiveness data, adverse reactions and complications, device failure and replacements, patient information, patient complaints, tabulations of data from all individual subjects, results of statistical analyses, and any other information from the clinical investigations is required. The FDA has 180 days to review the PMA application and either grants or deny the market clearance. Once a Class III device has failed to meet the PMA requirements, it is considered adulterated and cannot be marketed [31].

Table 3.2-1: Summary of the authorization system characteristics in the USA

Regulatory Body	*Centralized system – Food and Drug Administration, Center for Devices and Radiological Health*			
Classification	*Risk class approach – Class I, Class II and Class III*			
Procedure	*Class I*		*Class II*	*Class III*
	General controls		*General controls*	*General controls*
			Special controls	*510(k) – Substantial equivalence*
				PMA – New technology
Evidence Requirements	*General Controls*	*Special Controls*	*510(k)*	*PMA*
	❁ *Registration* ❁ *Device listing* ❁ *GMP* ❁ *Labeling*	❁ *Specified for the device in question*	❁ *Intended use* ❁ *Design* ❁ *Energy used or delivered materials* ❁ *Chemical compositions* ❁ *Manufacturing process* ❁ *Performance* ❁ *Safety* ❁ *Effectiveness* ❁ *Labeling* ❁ *Biocompatibility* ❁ *Any changes in other haracteristics*	❁ *Introduction with alternatives, device history* ❁ *Summaries of all studies conducted* ❁ *Non-clinical laboratory studies:* ❁ *Microbiology* ❁ *Toxicology* ❁ *Immunology* ❁ *Biocompatibility* ❁ *Stress wear* ❁ *Shelf life* ❁ *Laboratory, animal test summaries* ❁ *Clinical investigation section:* ❁ *Study protocols* ❁ *Safety* ❁ *Effectiveness* ❁ *Adverse reactions and complications* ❁ *Device failure and replacements* ❁ *Patient information* ❁ *Patient complaints* ❁ *Data from all individual subjects* ❁ *Statistical analyses*

3.3 European Union: NB/Notified Bodies

3 EU directives that shape the regulatory framework for devices

In the European Union, the core regulatory framework of medical devices is based on three important directives [6, 12, 13]:

- the Directive for active implantable devices (AIMD, 90/385/EEC, 20th of June 1990),
- the Directive for medical devices (MDD, 93/42/EEC, 1st of January, 1995), and
- the Directive for in vitro diagnostic medical devices (IVDD, 98/79/EC).

medical device has to hold the Conformité Européene/CE marking

The aim of these directives is to ensure the protection of human health and safety within a well-functioning European Single Market. Every medical device, under a wide range of other products from different groups, has to carry the Conformité Européene (CE) marking before being able to legally enter the European market [34]. The regulatory framework established through the three directives aims at providing a dual purpose. On the one hand, it sets European-wide regulatory requirements for manufacturers of medical devices to access the EU market. On the other hand, it provides device users with a high level of confidence in the safety and performance of the marketed products. The directives must be recognized and implemented in each European Member State through an appointed competent authority [35].

revision of the three EU core directives for medical devices

Currently, the European Commission is revising the medical device directives. A press release and a summary with the major changes were published on September 26, 2012. A proposal for a regulation on medical devices, aiming at replacing the Directive 90/385/EEC regarding active implantable medical devices and Directive 93/42/EEC regarding medical devices was published. Further, a proposal to replace the existing Directive 98/79/EC regarding in-vitro diagnostic medical devices was submitted. The aim of these proposals is to ensure that products are safe and can be freely and fairly traded throughout Europe. The European Commission has listed a number of points that have been improved in the published proposals [36]:

proposal published in September 2012 with several improvement points and adapted in September 2013

- Wider, clearer scope for EU legislation – extended to include, e.g., implants for aesthetic purposes; clarification provided with regards to genetic tests
- Stronger supervision of independent assessment bodies – conducted through national authorities
- More power for assessment bodies – insurance of thorough testing and regular checks on manufacturers
- Clearer rights and responsibilities for manufacturers, importers and distributors
- Extended database on medical devices for information exchange on a European level
- Better traceability of medical devices
- Stricter requirements for clinical evidence during the conformity assessment of medical devices
- Update on risk classification rules
- Better coordination within European authorities
- International guidelines to be incorporated into EU law.

The European Commission states that patients, healthcare professionals and manufacturers will benefit from the proposed changes. Currently, the published proposals are in the revision period. 2014 is targeted as the adoption year and the changes should then be implemented in national practices between 2015 and 2019 [37].

patients, healthcare professionals and manufacturers benefit from changes

As an answer to the published proposals, a petition was written by a group of European healthcare experts, clearly stating that major improvements can be recognized in the proposals, but that further changes have to be adapted to ensure a high-quality and safe patient access. The petition has three main reasons for disagreement with the proposals and presents solutions [38]:

petition regarding EU proposal in medical devices: 3 major disagreements

- Decentralized regulatory system and the independence of the regulator → Centralized approval for high- and medium-risk devices conducted by a new public body similar to the EMA
- Lack of requirements for evidence of clinical and patient benefit → Proper scientific assessments of clinical and patient benefits and harms in short-term and long-term results from well-designed clinical studies
- Lack of transparency in the authorization process and the results → Publication of all information on the process and basis for approvals of medical devices

The European Medical Device Directive was updated and implemented with the requested changes on September 24, 2013. It is intended that the new regulation will be adopted by 2014 throughout Europe.

updated regulation implemented in September 2013

3.3.1 Regulatory body

Every European Member State has a so-called competent authority. This competent authority constitutes the regulatory and administrative head of the national Notified Bodies. The main responsibility of these Notified Bodies is to conduct the conformity assessment, the premarket evaluation for medical devices aiming to enter the European Single Market. If the products fulfill the essential requirements and consequently pass the conformity assessment, the notified body labels these products with a so-called CE marking [7].

every member state has a competent authority constituting the head of all Notified Bodies

Notified Bodies responsible for the conformity assessment

A Notified Body is a for-profit organization and not every European Member State is obliged to administer such a body. In some cases, a national medicine agency serves the role, whereas other Member States do not have any institution serving as a Notified Body installed [39]. These Notified Bodies are not only responsible for the evaluation of medical devices, but also for other products such as toys and construction material that are applying for the CE marking. Approximately 168 accredited Notified Bodies exist within Europe. The competent authority of each European Member State is entitled to affirm a Notified Body within the Member State for the performance of the conformity assessment as outlined within the EU directives [40].

Notified Body is a for-profit organization

The manufacturer may freely choose the Notified Body that conducts the conformity assessment for the device in question. In addition, manufacturers are entitled to work with several Notified Bodies for different medical devices and their separate conformity assessments. The European Commission provides guidance documents for the Notified Bodies with standard procedure summaries for the conformity assessment. It is crucial to recognize these standards and follow them to facilitate European-wide standardized assessments [34].

manufacturer may freely choose the Notified Body

3.3.2 Classification

4 different risk classifications in the EU

Medical devices are categorized into four different risk classes to determine the appropriate evidence level for the conformity assessment. Their classification is based on different criteria such as the intended use, the duration of contact with the patient, the degree of invasiveness and the part of the body affected by the use of the medical device. The existing risk classification is Class I, Class IIa, Class IIb and Class III [41].

low

- Class I devices represent the lowest potential risk to consumers, with devices being basic medical examination tools such as stethoscopes.

moderate

- The Class IIa category represents moderate potential risk devices, e.g., dental fillings.

moderate to high (not-active implantable)

- Class IIb and Class III devices are generally devices that have the characteristics to be placed within the body with a potential invasive surgery.

high (active implantable)

- Class III devices often carry the characteristic of being life sustaining and are therefore the high-risk devices.

risk classification concludes further regulatory assessment

The classification to a certain risk class by a Notified Body concludes the further regulatory assessment. For the low-risk devices, assessment starts with a self-certification of required evidence. A more thorough assessment is required for high-risk devices [42].

3.3.3 Procedure

every device has to fulfill the general requirements

The procedures for the conformity assessment and the rules for the affixing and use of the CE marking are codified in the three European Core Directives mentioned in chapter 3.3. All medical devices, regardless of their risk class, have to fulfill some general requirements [43]. In order to sign an EC declaration of conformity, the manufacturer must verify that the new device fulfills safety and performance requirements and that it is appropriately labeled, providing the user with all relevant information. The conformity assessment modules are divided into full quality assurance system, type of examinations and products or production quality assurances [44].

class I devices may enter the market based on the manufacturer's self-certification

If the general requirements are fulfilled, the risk class of the device in question determines the further regulatory pathway. Manufacturers of low-risk class devices, Class I devices, are entitled to verify through self-certification that the medical device conforms to the safety and performance standards set in the European directives. The device may therefore legally enter the market based on the manufacturer's self-assessment[45].

other risk classes have to undergo assessment by Notified Bodies

For moderate- and higher-risk devices, Class IIa, Class IIb and Class III, a Notified Body has to be appointed to perform the conformity assessment. Within the conformity assessment, the Notified Body verifies and assesses whether EU safety and performance standards are fulfilled. The NB focuses on the clinical evaluation that supports the clinical safety and performance of the device when used as intended by the manufacturer. Clinical investigation must be performed to confirm or refute the manufacturer's claims for the device [46].

EU standards for safety and performance are verified

essential requirements focus on technological characteristics of the device

Further, the essential requirements set out in the EU core directives are evaluated. The main focus of these essential requirements lays on the technological characteristics of the device. It is important to recognize that clinical efficacy is not taken into account during the conformity assessment [39].

Once a Notified Body has labeled a product with the CE marking, it does not need any additional approval or certification to enter the entire European Market. It may be that the device has to fulfill requirements of national regulatory frameworks and the manufacturer should be aware of these possible additional requirements [47].

CE marking applies to the entire European Market

3.3.4 Evidence requirements

A set of requirements from the Directive 93/42/EEC is outlined in Annex I. These requirements can be divided into two parts: general requirements and essential requirements [6].

The general requirements focus on the presentation of safety and performance studies. It is stated that the medical device should perform safely in its intended use and should not compromise human health in any situation [48].

general requirements for safety and performance

Further, the essential requirements focus on the design and construction, data concerning the chemical, physical, and biological properties, infection and microbial contamination, construction and environmental properties, labeling and information leaflet for users. In the case that a measuring function or radiation is implemented in the device, more information is requested on those properties. These data sets should be submitted to the Notified Body for the conformity assessment [49].

essential requirements focus on technological characteristics of the device

Notified Bodies may ask the manufacturer to submit data from published clinical investigations or other studies of similar devices, so-called equivalence data. Moreover, Notified Bodies are entitled to review the facilities of the manufacturer and evaluate the compliance with the essential quality requirements for good manufacturing [34].

submission of additional data

Table 3.3-1: Summary of authorization system characteristics in Europe

Regulatory body	Decentralized system – Notified Bodies across Europe			
Classification	Risk class approach – Class I, Class IIa and IIb and Class III			
Procedure	*Class I*	*Class IIa*	*Class IIb*	*Class III*
	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	

3.4 Australia: TGA/Therapeutic Goods Administration

3 core frameworks that serve as basis for medical device regulation

The core legal frameworks that serve as the basis of medical device regulation in Australia are the Therapeutic Goods Act (1989), the Therapeutic Goods Regulations (1990), and the Therapeutic Goods Regulations (2002). These legislative frameworks adopt the philosophies of the Global Harmonization Task Force (GHTF), an international pilot project to achieve greater uniformity between national medical device regulatory systems [50]. One centralized body, the Therapeutic Goods Administration (TGA), holds the responsibility in the medical device sector. The main aim of the TGA is to apply scientific and clinical expertise to decision making while ensuring that the benefits to consumers outweigh any risks associated with the use of medical devices [51].

TGA centralized responsible body

ARGMD provide information about the Australian system

The TGA has developed the so-called Australian Regulatory Guidelines for Medical Devices (ARGMD) to provide guidance to the manufacturers and sponsors (persons with the legal obligation of the authorization application) of medical devices. Further, the ARGMD should help to ensure that all medical device applications to the TGA meet the necessary regulatory requirements and conform with the clarity and transparency standards, so that market entry is not delayed [50].

3.4.1 Regulatory body

TGA holds responsibility for the authorization of devices

In Australia, the Therapeutic Goods Administration holds the responsibility for the authorization of medical devices. It is accountable for the regulation of medicines and therapeutic goods. The TGA is part of the Australian Government Department of Health and Ageing. It is a centralized body and has developed the Australian Regulatory Guidelines for Medical Devices to outline the various phases within the lifecycles of medical devices [52].

ODA is the main premarket application reviewing body

Within the TGA, the Office of Devices Authorization (ODA) is the main reviewing body for premarket applications. The agency is based upon scientific expertise in close collaboration with healthcare professionals and industry [52].

3.4.2 Classification

4 risk classes and 7 categories

The TGA classifies medical devices into four risk classes with seven risk categories. The approach is based on the potential risk the device poses to the consumer and on the device characteristics [50].

low

- The lowest risk class is Class I, and includes devices such as examination gloves. Within the Class I, a distinction is made between general Class I devices, Class I sterile devices and Class I measuring devices. Class I sterile devices have certain characteristics that have to be maintained in a sterile setting, and Class I measuring devices include a measuring function in their device technology.

moderate

- The second main risk classification includes Class II devices: A distinction based on the potential risk the medical device poses to the consumer into Class IIa and Class IIb has to be made within this class. All Class II devices carry a moderate risk character.

- The third main risk classification is devices from Class III. High-risk devices are included in this class. — high
- The last risk class is active implantable devices (AIMD), which carry the highest potential risk to the user, as they often support or sustain life. — very high (active implantable)

3.4.3 Procedure

Before any medical device may be supplied on the Australian market, the TGA needs to administer the Therapeutic Goods Act and the associated legislation through an assessment of the device. As Australia is governed by a Commonwealth (Federal) government and six State and two Territory governments, the TGA provides a uniform national standard for the authorization of medical devices, which may have additional legislative characteristics within the separate State or Territory legislations [51].

TGA provides a uniform national standard for the authorization of devices

The Office of Devices Authorization, a subdivision within the TGA, reviews the pre-market authorization application of medical devices. The assessment level of medical devices performed by the ODA depends on the potential risk the device presents to patients. The manufacturer has to send an application to the TGA for inclusion into the Australian Register of Therapeutic Goods (ARTG). The ARTG is a register of therapeutic goods accepted for supply and use in Australia. It is important to recognize that only an Australian sponsor, who carries the legal responsibility of the medical device, can apply to be included into the ARTG [52].

ODA, reviews all premarket applications

medical device has to be included in ARTG to legally enter the market

There are two main processes for medical devices to be included in the ARTG: a process for Class I devices and a process for all devices other than Class I. It is important to outline that Class I sterile and Class I measuring devices fall under other devices than the Class I category [50].

2 pathways for inclusion in ARTG

Manufacturers of Class I general devices are asked to apply a conformity assessment to their device and prepare an Australian Declaration of Conformity. Yet, these documents do not have to be submitted to the TGA. The manufacturer is asked to apply for the inclusion into the ARTG, but only the application form is needed. Successful applications will result in an "automatic" inclusion into the ARTG. However, after inclusion into the ARTG, the manufacturers may have to provide the evidence to the TGA upon request [50].

procedure for class I devices: application form only for inclusion into the ARTG

For all other devices than Class I devices, the evidence has to be submitted to the TGA before the application for inclusion into the ARTG. Two main things have to be submitted and approved before lodging an application: first, the conformity assessment evidence and, secondly, the evidence of compliance of the device with the so-called essential requirements. The key elements of these principles are quality, safety, and performance. After these documents have been accepted, the manufacturer may apply for inclusion into the ARTG [50].

procedure for all other devices: submission of conformity assessment and evidence compliance

3.4.4 Evidence requirements

The TGA bases the required evidence on the risk class of the device in question. Manufacturers of Class I devices do not have to submit any evidence at the moment of application. After inclusion into the ARTG, the TGA may request a conformity declaration.

required evidence is based on risk classification

All other devices have to submit evidence of conformity assessment and compliance with the essential principles before applying for the inclusion into the ARTG.

information requested by the TGA within conformity assessment

Within the conformity assessment, the TGA request information about the general details of the device, the application scope, whether it is a new device, a device like one that already exists, or a recertification, the manufacturer's details, including facility, and whether the device has already been marketed in other countries and received certification. Further, a critical supplier's form has to be filled in, and more details about the device are requested. All these evidence documents have to be submitted via an online form on the TGA homepage [50].

essential requirements can be divided into general principles and design and construction principles

The essential principles can be divided into general principles and the design and construction principles of the device. The general principles include evidence about the intended use, the safety principles, especially long-term safety, the transport and storage, as well as the risk ratio. The design and construction principles contain evidence about chemical, physical and biological properties, infection and microbial contamination, construction and environmental properties, measuring function or radiation, information supplied by the manufacturer and all relevant clinical evidence [52].

Table 3.4-1: Summary of authorization system characteristics in Australia

Regulatory body	Centralized body – Therapeutic Goods Administration, Office of Device Authorization						
Classification	Risk and characteristic approach – Class I, Class I sterile, Class I measuring, Class IIa, Class IIb, Class III and AIMD						
Procedure	*Class I*	*Class I Sterile*	*Class I Measuring*	*Class IIa*	*Class IIb*	*Class III*	*AIMD*
	Application for inclusion into the ARTG	Conformity assessment	Conformity assessment	Conformity assessment	Conformity assessment	Conformity assessment	Conformity assessment
		Essential principles	Essential principles	Essential principles	Essential principles	Essential principles	Essential principles
		Application for inclusion into the ARTG	Application for inclusion into the ARTG	Application for inclusion into the ARTG	Application for inclusion into the ARTG	Application for inclusion into the ARTG	Application for inclusion into the ARTG
Evidence requirements	Conformity Assessment			Essential requirements			

	✿ General details
	✿ Application scope
	✿ Manufacturer details
	  ✿ Facility details
	  ✿ Other certifications
	✿ Critical supplier's details
	✿ Device details
				✿ General principles
				  ✿ Intended use
				  ✿ Safety principles (long-term safety)
				  ✿ Transport and storage
				  ✿ Risk ratio
				✿ Design and construction principles
				  ✿ Chemical, physical and biological properties
				  ✿ Infection and microbial contamination
				  ✿ Construction and environmental properties
				  ✿ Measuring function or radiation
				  ✿ Information supplied by manufacturer
				  ✿ Clinical evidence			

3.5 Canada: Health Canada and the TPD/Therapeutic Produtcs Directorate

centralized body is Health Canada

Health Canada is the regulatory agency responsible in all matters related to maintaining and improving the health of Canadian citizens. The agency has the task of testing, approving, regulating and monitoring all health-related activities within Canada. In the medical devices sector, Health Canada is the enforcing body of the existing medical device regulations. Medical device regulations are based on risk management philosophy. The highest priority of the agency is to ensure the patient safety and effectiveness of medical care administered within the Canadian healthcare system [53].

3.5.1 Regulatory body

TPD subdivision within Health Canada responsible for monitoring and evaluation

The Medical Devices Bureau of the Therapeutic Products Directorate (TPD) is a department of Health Canada, the national agency responsible for the monitoring and evaluation of diagnostic and therapeutic medical devices. Besides medical devices, this federal authority regulates pharmaceuticals as well. The TPD is one of the seven operational directorates of the Health Products and Food Branch division of Health Canada. A device license listing within the authorization process can only be granted by the TPD [54].

3.5.2 Classification

4 different risk classes for medical devices

In the Canadian medical device sector, products are grouped into four distinct risk classes. Every device has to be categorized before being able to enter the market. The approach assesses the potential risk the device carries for its user and determines the appropriate risk class. The approach is very similar to the European classification [55].

- Class I devices are the low-risk devices, e.g., thermometer, laboratory culture media and some surgical instruments. — low
- Class II and Class III are the moderate-risk devices like contact lenses. — moderate (2 classes)
- The last risk class, Class IV, includes the devices with the highest potential risk for the consumer, e.g., pacemakers. — high

Based on the classification into the appropriate risk class, the TPD may request different evidence within the premarket authorization process.

3.5.3 Procedure

TPD main reviewing body of the premarket applications

The TPD is the main reviewing body of medical devices. The agency aims to ensure the safety, effectiveness and quality of medical devices that are marketed in Canada. This is realized by the TPD through a process of premarket approval, post-approval surveillance and quality systems in manufacturing processes.

all devices need a Notice of Compliance of Health Canada

Class I devices need an Establishment License

all other devices are obliged to hold a Medical Device License before marketing

In order to obtain a license from the TPD, the manufacturer must first be accredited with a Notice of Compliance (NOC) by Health Canada. Devices that fall into Class I have to apply through the TPD for a so-called Establishment License. That means that the TPD is aware of the establishments that are manufacturing and selling medical devices. To obtain an Establishment License, no clinical evidence is required. The devices that fall into risk Class II, Class III and Class IV are obliged to obtain a Medical Device License before being able to enter into the market. To obtain that License, the manufacturer has to submit a Medical Device License Application; the amount of information being submitted varies depending on the risk class of the device. Requested evidence mainly focuses on safety and effectiveness in Class II devices, additional information on labeling and packaging in Class III, while the highest evidence standards for Class IV require additional information on quality and risk management assessments [55].

3 device groups undergo administrative review which determines acceptability into validation process

The three device groups all undergo an administrative review, which determines whether the device is acceptable for the application validation process. If recognized as acceptable, Class II devices undergo the application validity assessment and the license is either issued or rejected based on the presented information. In the case of Class III and IV devices, the application validity assessment is followed by a technical review, either determining the issuing or rejection of the license. Generally, the TPD completes the approval procedure within 75 to 90 days, and announces whether the Device License is issued or rejected. Throughout the whole procedure, information exchange and additional evidence requirements from the manufacturers are communicated [55].

3.5.4 Evidence requirements

evidence focuses on safety, efficacy/effectiveness and quality

The evidence requested by the TPD within the review of the application varies between the different medical device risk classes. In general, all evidence requirements focus on the key elements of safety, efficacy/effectiveness and quality [54].

class I devices

Class I devices are not subject to any regulatory review with associated evidence requirements. However, manufacturers are required to confirm that the product facilities have standards installed for the documentation of procedures for the distribution, the handling of complaints and the product recalls.

class II devices

The evidence requirements for Class II devices focus mainly on safety and effectiveness standards the device ought to fulfill. That includes that a senior official of the manufacturer has to attest through technical documentation that the device meets those standards [55].

class III devices

Class III devices undergo a more complex and in-depth review. Manufacturers are requested to submit summaries of all studies that have been conducted to assess the safety and effectiveness of the device in question. Moreover, information about labeling, packing and production are requested. To obtain

market approval for a Class III device, the manufacturer must include a quality of management certificate that ensures that certain standards are satisfied.

class IV devices

Class IV devices have the most complex and thorough approval process and the highest evidence requirements. In addition to the evidence requirements from Class I – Class III, information about a risk assessment, the quality plan and the manufacturing process are requested in Class IV [55].

Table 3.5-1: Summary of authorization system characteristics in Canada

Regulatory body	Centralized body – Health Canada with the Therapeutic Products Directorate			
Classification	Risk class approach – Class I, Class II, Class III and Class IV			
Procedure	*Class I*	*Class II*	*Class III*	*Class IV*
	Establishment License	Medical Device License Application	Medical Device License Application	Medical Device License Application
Evidence requirements	Establishment License		Medical Device License	
	❁ General details ❁ Documentation for distribution ❁ Mechanisms of complaints and product recalls		❁ General details ❁ Safety standards ❁ Effectiveness ❁ Summaries of all studies ❁ Labeling ❁ Packaging ❁ Production ❁ Quality management certificate ❁ Risk assessment ❁ Manufacturing process	

3.6 Summary of premarket approval characterictics – Similarities and differences

regulatory basis for authorization is different

Within the four selected regions, different approaches have been set as the regulatory basis for the authorization process of high-risk medical devices. In order to provide an overview, the processes explained above are summarized in Table 3.6-1.

every system has authorization instrument installed that serves as market entry label

Every system has an authorization instrument installed that serves as a market entry label. In the European Union, products have to carry the CE marking, whereas in the United States of America products have to hold the certification of the FDA. In Australia, an inclusion in the ARTG listing and the receiving of a number enables the manufacturer to legally market the product. In the Canadian system, the product receives a license after a successful premarket application submission.

evidence requirements vary the most between EU and USA

The standards of approval vary, whereas the largest difference can be observed in the comparison between Europe and the other three analyzed systems. In the USA, Australia and Canada, similarities can be observed in the requirements for clinical evidence of safety and effectiveness as a standard for approval. On the contrary, the European system focuses on safety and performance alone and takes neither efficacy nor effectiveness into account. This might change in the near future, but how it will go is not known yet.

highest evidence standard are RCTs

The evidence required does appear – at first sight – quite similar throughout the description of all systems. Yet, it has been recognized that the quality and depth of the minimum evidence basis for the approval of a device differs. The FDA, considered as the most stringent authorization body among the four, always aims for the highest evidence level – randomized controlled trials. In Europe, Notified Bodies seem to accept devices and grant the CE marking requesting little clinical evidence. Yet, limited information is available due to a lack of transparency within the approval process.

centralized body in USA, Canada and Australia decentralized in EU

The approval is granted in the USA, Australia and Canada by one centralized body. This body generally assesses the device and reviews the submitted application. In contrast, Notified Bodies all over Europe are accredited to assess the conformity of the device. The system is highly decentralized and manufacturers may freely choose the Notified Body for the assessment.

information on marketed devices publicly available: USA, Canada, and Australia

no information from NBs in EU

The approval decision in the USA, Australia and Canada is publicly available on the homepages of the relevant regulatory authorities. Yet, only the approval for PMA or 510(k) clearance (USA), the ARTG number (Australia), or the Device License (Canada) can be accessed. Evidence that has been submitted as the basis for the decision is rarely available. The EU has the least transparent system with decentralized NBs, no information access point (website) with data on if, where and when a medical device has received market approval (CE marking).

Table 3.6-1: Evidence requirements in the four selected authorization systems

	Europe	USA	Australia	Canada
Approval granted by	Notified Bodies, for-profit organizations	Central regulatory authority – FDA	Central regulatory agency – TGA	Central regulatory agency – Health Canada
Authorization instrument	CE Marking (Compliance Label)	Premarket Authorization (PMA) or Marketing Clearance (510k)	ARTG inclusion with number	Device license listing
Standard for approval	❁ Safety ❁ Technical performance	*PMA:* ❁ Safety ❁ Effectiveness *510(k):* ❁ "substantial equivalence"	❁ Risk ratio ❁ Safety/long-term safety ❁ Effectiveness ❁ Benefits to patients	❁ Safety ❁ Effectiveness
Evidence required	❁ Laboratory testing ❁ Literature reviews ❁ Small clinical trials	❁ Clinical trials → generally randomized and controlled	❁ Risk analysis ❁ Literature searches ❁ Clinical trials ❁ Expert opinion	❁ Summary of all studies ❁ Bibliography of all published reports
Transparency of approval decision	No public information	Approval and evidence is publicly available	ARTG listing publicly available	Device license listing publicly available

4 Clinical evidence for seven selected medical devices – Authorization

This chapter introduces the evidence available at the time of authorization and approval for the seven medical devices selected for the purpose of this research. The four regulatory bodies in charge of the authorization processes for medical devices in the European Union, the USA, Australia and Canada were contacted about the evidence submitted within the premarket application for each of the seven devices. Further, the respective manufacturers were informed about the research and asked to present the relevant evidence documents for the devices that were submitted to the authorization institutions. In addition, a literature search for each of the devices was performed and the international clinical trial database (clinialtrial.gov) was scanned for more information on clinical trials conducted for the device. The results for each medical device are provided in the following.

evidence from regulatory bodies, manufacturers, literature search and clinical trial database for the 7 devices

Table 4-1: Authorization status of the seven exemplary medical devices

Medical Device	CE marking	FDA application	Inclusion in ARTG	License by TPD	Manufacturer
Zephyr® Endobronchial Valve	Yes (2003)	Rejection (2008)	No application submission; similar device (2011) by Olympus Australia	No application submission	PulmonX – Interventional Pulmonology
Paracor Ventricular Support System (PVSS)	Yes (2000)	Rejection (2000)	No application submission	No application submission	Paracor Medical Inc.
Annular repair device Barricaid®	Yes (2009)	No application submission	Yes (2011)	No application submission	Intrinsic Therapeutics, Inc.
Rheofilter ER-4000	Yes (1998)	No application submission	No application submission	Rejection (Yes from 2002 – 2005)	Asahi Kasei Medical Co., LTD.
BSD-2000 Microwave Hyperthermia System	Yes	Rejection (Only under HDE since 2011)	No application submission	No application submission	BSD Medical Inc.
Amplatzer™ PFO Occluder	Yes	Rejection (Only under HDE until 2006)	Yes (2006)	Yes (2001)	St. Jude Medical
MitraClip®	Yes (2008)	Yes (2013)	Yes (2010)	No application submission	Abbott

4.1 Zephyr® Endobronchial Valve

Zephyr currently on the market in Europe only

The following section provides information on the Zephyr® Endobronchial Valve. The device is produced by the company PulmonX. It is currently on the market in Europe only.

4.1.1 Indication

device designed for the treatment of emphysema: a chronic disease of the lungs

The Zephyr® Endobronchial Valve is a device designed for the treatment of Emphysema, a chronic disease of the lungs. Emphysema is a disabling, irreversible and progressive disease that decreases the tolerance to active exercise and impairs the quality of life. The disease has the characteristic that it is poorly responsive to medical interventions. Through structural changes induced into the lung system, the regular airflow is hindered. Emphysema results into a decrease in lung elastic recoil that subsequently increases the expiratory airflow resistance. Consequently, the exchange of the life-supporting gases in the alveoli is impaired. The lungs are suffering from a dynamic hyperinflation. This hyperinflation progresses rapidly. Complications associated with emphysema are breathlessness, low tolerance to physical activity, decreased chest wall and muscle function mechanics, prolonged respiratory failure and increased mortality. Emphysema is categorized within the class of chronic obstructive pulmonary diseases (COPD). The Zephyr® Endobronchial Valve aims at controlling the airflow through pointed placement of several valves into the diseased airways of a particular lung loop [56].

4.1.2 Mechanic procedure

Zephyr is an implantable, silicone valve

The valve is a sterile, single-use system consisting of three parts: the Zephyr EBV valve, the Zephyr ELS loader system and the Zephyr EDC delivery catheter. The valve is an implantable, one-way, silicone valve. It entails a self-expanding stent structure that inflates in the diseased lung lobe. Once implanted, the valve intends to prevent airflow into the hyper-inflated regions of the lung while still allowing airflow out of them. The valve is implanted through a delivery catheter that includes a loader system for the compressed valve at its distal end. The delivery catheter is passed through a bronchoscope to place the valve in the bronchial loop [57].

4.1.3 Accessible evidence

2003 CE marking, rejection FDA 2008

The device obtained CE marking in 2003. A very similar device is on the market in Australia, but no specific information about the Zephyr valve is accessible. In the USA, the device was rejected for approval in 2008; no application for a device license listing was found in Canada. All accessible evidence is summarized in Table 4.1-1.

Table 4.1-1: Available evidence for market approval of Zephyr® Endobronchial Valve (extracted 26.03.2013)

Studies by year	Level of evidence	*FDA*	*ARTG*	*TPD (no application submitted)*	Notified Bodies	Literature Search	Clinical trials
Herth et al., 2012	Open label, randomized, multicenter trial (VENT Europe)	-	NA	/	NA	√	-
Sciurba et al., 2010	Open label, randomized, multicenter trial (VENT reporting)	√	NA	/	NA	√	√
Lee et al., 2010	Case series	-	NA	/	NA	√	-
Herth, 2008	Safety and Efficacy study	-	NA	/	NA		√°
Strange et al., 2007	Study design: Open label, prospective, randomized, multi-center trial (VENT)	√	NA	/	NA	√	√
Wan et al., 2006	Retrospective analysis from prospective multicenter registry	-	NA	/	NA	√	-
Hopkinson et al., 2005	Case series	-	NA	/	NA	√	-
Leroy and Marquette, 2004	Announcement of planning of the VENT trial	-	NA	/	NA	√	-

*Explanation: * Not completed ° Status unknown ^ Terminated/Suspended, cursive – not authorized, underlined – authorized*

FDA

In the United States of America, the FDA evaluated the evidence available for the Zephyr® Endobronchial Valve in a panel discussion of the Anaesthesiology and Respiratory Therapy Devices committee in 2008. The panel voted 11:2 that the premarket approval application of the Zephyr® Endobronchial Valve was found "not approvable."

FDA denied the premarket application of the Zephyr in 2008

The FDA documents used during the panel discussion provide five clinical studies [58].

five clinical studies have been used as evidence basis for the FDA rejection

- The VENT (Endobronchial Valve for Emphysema PalliatioN Trial) is an open-label, randomized, multicenter trial comparing the Zephyr EBV system to optimal medical management controls. Strange et al. published the results of the trial in 2007.
- The Zephyr EBV Europe was conducted between June 2004 and January 2006; 171 subjects were enrolled and randomized (2:1), with 111 EBV-treated subjects and 60 control subjects). The demographic profile and the results can be seen as consistent with those observed in the VENT.
- A compassionate and emergency use study mostly for air leaks with a total of 65 subjects.
- A study with the first generation version of the device EBV – "Over-the-wire (OTW)" with a total of 62 subjects was conducted.
- A feasibility trial of the Zephyr EBV and the EBV-OTW with the inclusion of 113 subjects was conducted.

Notified Bodies

no evidence available – device marketed

The Notified Body which has been assessing the endobronchial valve is unknown. No information about the body or about the assessment and included evidence was found.

TGA

similar device marketed in Australia with different manufacturer

The TGA has installed a tool to search manually through the ARTG to identify whether a medical device has been granted market authorization in Australia. Using this search tool, it has been recognized that an endobronchial valve with very similar characteristics to the Zephyr® Endobronchial Valve was assessed and included into the ARTG in 2011. The manufacturer of the device is Spiration Inc., a US firm and the sponsor is Olympus Australia Pty Ltd. A public summary from the ARTG regarding this device is accessible. Yet, the summary only describes the device briefly and states the inclusion of the device into the ARTG; no evidence that was used during the premarket assessment can be found [59].

no information about the valve

From this information it cannot be extracted whether the Zephyr® Endobronchial Valve has been rejected or approved and included in the ARTG in Australia.

TPD

no application submission of the device available

The TPD has installed a search tool only for the devices that are currently on the market in Canada, but not for devices that have been assessed or whose market authorization has been rejected. Therefore, no information about an application or evidence submitted to the TPD within the authorization procedure is publicly available.

Literature search

1 RCT and several case series

A literature search in PubMed was conducted using the keywords Zephyr®, OR Endobronchial Valve AND emphysema. 40 hits were listed in the search. With a limitation to clinical trials, seven of these articles focused on the valve and one on the Chartis™ treatment plan.

planning of VENT (2004)

- In 2004, Leroy and Marquette announced the planning of the VENT trial [60].

case series (2005)

- In 2005, Hopkinson et al. published a case series including 19 patients [61].

case series (2006)

- In 2006, Wan et al. presented a retrospective analysis from a prospective multicenter registry. Included in the study were 98 patients [62].

Study design VENT (2007)

- In 2007, Strange et al. provided the study design of the VENT (Endobronchial Valve for Emphysema Palliation Trial), a randomized controlled trial planning to include 270 patients [63].

case series (2010)

- In 2010, Lee et al. reported about a case series including 8 patients [64].

VENT reporting (2010)

- In the same year, 2010, Sciurba et al. reported about the VENT. 321 patients were enrolled, with 220 to receive the valve and 101 to receive standard medical care. The trial was funded by PulmonX [65].

Vent Europe reporting (2012)

- In 2012, Herth et al. reported about the VENT European cohort results, as well as about a randomized controlled trial including 171 patients [66].

Clinical trial database

The database was searched with the keywords Zephyr® OR Endobronchial Valve OR emphysema. The database registered several trials conducted on the device.

- The VENT trial was received by the registry in August 2005 and has successfully been completed and published.

VENT trial (2005)

- A clinical trial about sequential endoscopic lung volume reduction started in 2008 and was sponsored by the University of Heidelberg. The status of this trial is currently unknown and the estimated study completion date was December 2011.

safety and efficacy study (2008)

- A trial investigating the long-term effects of endobronchial valves in Emphysema (LIVE) was registered with clinicatrial.gov in April 2012. The study is sponsored by the manufacturer PulmonX Inc. It is currently recruiting participants. The estimated study completion date is April 2019.

LIVE – long-term effects of endobronchial valves in emphysema (2012)

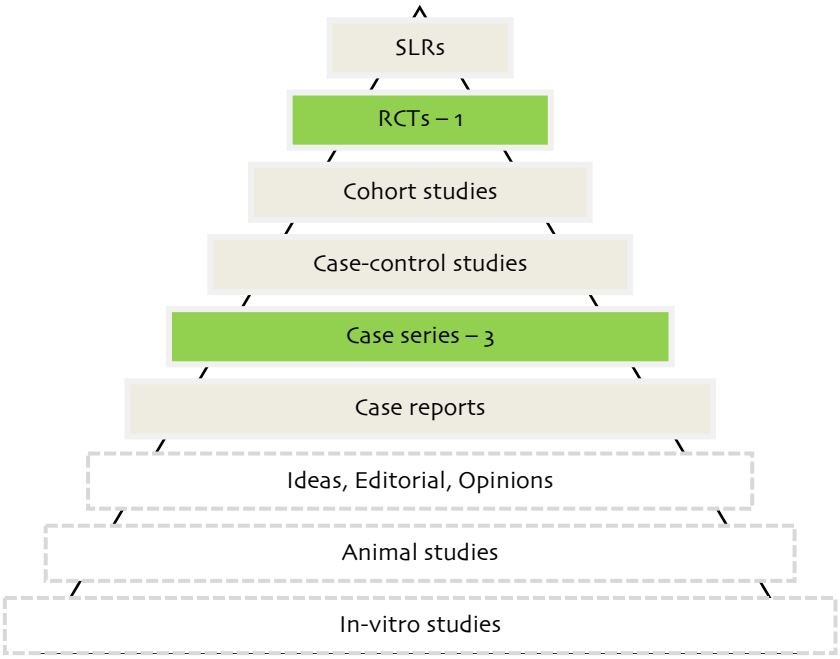

Figure 4.1-1: Evidence pyramid for Zephyr® Endobronchial Valve

At the time of the approval for the CE marking for the Zephyr® Endo-bronchial Valve in 2003, no randomized controlled trial or another clinical study was available.

no clinical evidence available at time of CE marking

All the clinical evidence found for the valve is summarized in Table 4.1-1. Further, the evidence is presented in an evidence pyramid (Figure 4.1-1) It can be recognized that the level of evidence available for the valve is one randomized controlled trial and three case series.

1 RCT (2010) and 3 case studies (2005; 2006; 2010)

The rejection of the application for premarket approval from the FDA for the device in 2008 was based on one randomized controlled trial and four other clinical studies. Information about application for market entry in Canada and Australia has not been found.

rejection by FDA based on 1 RCT, 4 clinical studies

4.2 Paracor Ventricular Support System (PVSS)

PVSS only on the European market

The following chapter provides information about the PVSS. The device was produced by Paracor Medical Inc. and can only be marketed in Europe.

4.2.1 Indication

PVSS designed to halt or reverse congestive heart failure

The PVSS is designed for patients with congestive heart failure to halt or reverse the disease process of dilated cardiomyopathy. Heart failure is a progressive, chronic condition in which the heart muscle is unable to pump enough oxygen-rich blood through the body. The disease is associated with a high level of disability, morbidity and mortality. In early stages of heart failure, the heart tries to compensate with enlarging, developing more muscle mass and pumping faster. Yet, at a certain time point the heart and body reach an exhaustion phase and the patient experiences fatigue and breathing problems, among other symptoms. Due to the compensation mechanism of the body, many patients are not aware of the progressive heart failure until years after their heart function begins to decline [67].

4.2.2 Mechanic procedure

PVSS is a prosthetic elastic mesh out of nitinol and silicone, implanted through a delivery system

The Paracor Ventricular Support System is a prosthetic elastic mesh made of nitinol and silicone that can only be used in combination with a delivery system, a long stick in combination with an introducer being used to reach the ventricles. The mesh is loaded onto the delivery system and implanted over the epicardial surface of the right and left ventricles. It is intended to reduce wall stress by the application of low levels of epicardial pressure and consequently treat the progression of cardiomyopathy. The surgical procedure is described as minimally invasive. The PVSS should support the heart muscle and its functions. As the homepage and the e-mail contact of the producer Paracor Medical Inc. is not active, no more detailed information about the mechanic procedure of the PVSS is available [68].

4.2.3 Accessible evidence

PVSS can only be legally marketed in Europe. The device was labeled with the CE marking in 2000. In the same year, the FDA rejected the application for premarket approval. No information about a submission of premarket approval application in Australia and Canada was found.

CE marking and FDA rejection both in 2000

Table 4.2-1: Available evidence for the Paracor Ventricular Support System (extracted 28.03.2013)

Studies by year	Level of evidence	*FDA*	*ARTG (no application submitted)*	*TPD (no application submitted)*	Notified Bodies	Literature Search	Clinical trials
Abraham et al., 2012 (HeartNet)	Randomized controlled trial – Rationale and design	NA	/	/	NA	√	-
Constanzo et al., 2012	Prospective, randomized, controlled multicenter trial – Interim analysis	NA	/	/	NA	√	√^
Klodell et al., 2007	Case series	NA	/	/	NA	√	-
Paracor Medical Inc., 2005	Feasibility study	NA	/	/	NA	-	√

*Explanation: * Not completed ° Status unknown ^ Terminated/Suspended, cursive – not authorized, underlined – authorized*

FDA

The FDA rejected the market authorization application for the PVSS in 2000. However, no information was released on what basis the application was rejected.

rejection of premarket application in 2000

Notified Bodies

In 2000, the PVSS entered the European market. No information is available about the Notified Body that conducted the conformity assessment and the evidence submitted.

no information available

TGA

The PVSS is not on the market in Australia. The ARTG was scanned and no listing for Paracor Medical Inc. with/or the PVSS was recognized. Further, no information about the submission of a premarket approval application can be found.

no premarket approval application

TPD

Paracor Medical Inc. has no market authorization for the Canadian market. Searching within the TPD database has released no information. No information about the submission of a premarket approval application is available.

no premarket approval application

Literature search

3 studies

A literature search with the keywords Paracor AND congestive heart failure was conducted. With the limitation to only clinical trials, three hits were presented.

case series (2007)

- In 2007, a report was published by Klodell et al. about a case series including 21 patients. This case series focused on the HeartNet device [69].

PEERLESS-HF trial – rationale and design (2012)

- In 2012, Abraham et al. reported about the rationale and the design of a multicenter, randomized controlled trial (PEERLESS-HF) for the HeartNet device. The planned enrolment was 27 patients [70].

PEERLESS-HF trial – enrollment stop (2012)

- In the same year, 2012, Costanzo et al. presented a prospective evaluation of the PEERLESS-HF trial and reported that enrollment was stopped based on interim results [71].

Clinical trial database

The clinical database was searched with Paracor OR ventricular support system. Two registered studies were found.

feasibility study (2005)

- In 2005, an early feasibility study was registered by Paracor Medical Inc. The study enrolled 39 patients and first results were received in 2011.

PEERLESS-HF trial (2006) – Early termination

- The PEERLESS-HF trial was registered within the database in 2006, but was then terminated.

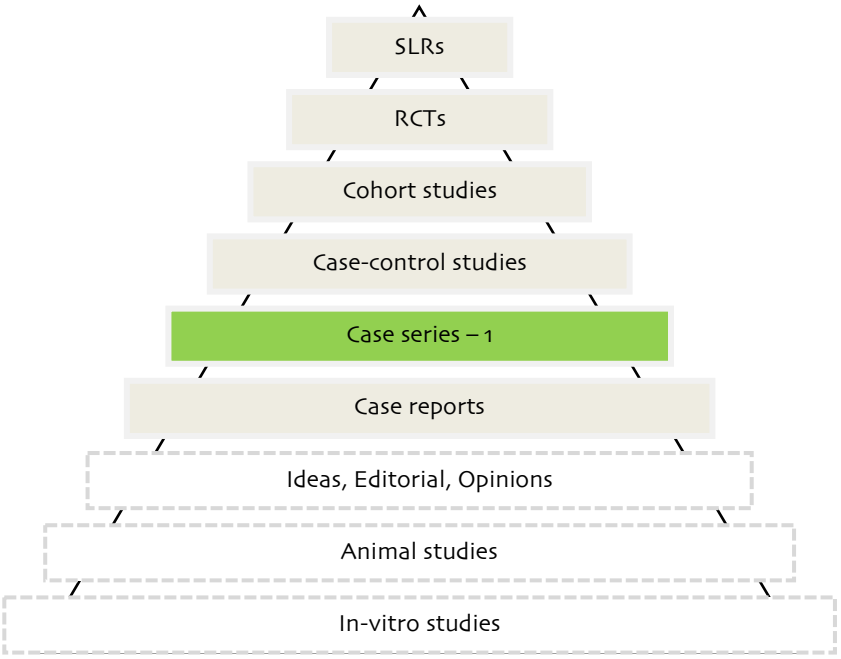

Figure 4.2-1: Evidence pyramid for Paracor Ventricular Support System

All evidence is summarized in Table 4.2-1. Furthermore, the evidence is presented in an evidence pyramid. At the time of CE marking approval and FDA rejection, no randomized controlled trial or clinical studies were available.

no clinical evidence at CE marking approval and FDA rejection

A case series was performed seven years later. In addition, Paracor Medical Inc. developed the HeartNet device, which bears very similar characters to the PVSS. A randomized clinical trial was started for the HeartNet device, but soon suspended based on an interim analysis.

7 years later – 1 case series for HeartNet

4.3 Annular Repair Device Barricaid®

The following chapter provides information about Barricaid®. The manufacturer of Barricaid® is Intrinsic Therapeutics.

on the market in Europe and Australia

4.3.1 Indication

The human spine consists of five lumbar discs, each of which is comprised of the annulus (outer ring) and the nucleus (central space) in its lower section. These discs help to balance out the external loads, gravity and physical activity placed on the spine. A spinal disc herniation occurs when the annulus partially of fully tears apart and portions of the nucleus bulge out. Symptoms are generally local pain and leg pain. In about 10% of patients suffering from spinal disc herniation, a surgical discectomy procedure is advised. The procedure aims at relieving the pain caused from the bulging nucleus material and therefore takes the pressure off a certain nerve root. The success rates have been very high, yet major adverse events have been recognized following a discectomy. One major challenge is the hole, called a "defect" that a discectomy procedure leaves in the annulus wall. The risk of reherniation, i.e., the nucleus bulges out through the already existing defect, is consequently very high. The Barricaid® annular repair device was designed to target the adverse effects, especially to close the defects in the annulus wall subsequent to the discectomy procedure and reduce reherniation rates [72].

spinal herniation occurs when the annulus partially or fully tears apart

the device aims at closing the defects after discectomy and preventing reherniation

4.3.2 Mechanic procedure

The Barricaid® annular repair device is supposed to treat larger defects of the annulus wall by creating a barrier for the remaining nucleus within the annulus wall. The device is placed within the inner surface of the disc annulus and serves as a barrier/closure to stop more nuclei to leave the inner space. It is believed that through the implant of the Barricaid®, the damaged disc can be preserved. The device is formed from a flexible mesh that is made up of multiple layers of counter-angulated fibers. The layers are designed to mimic the structure of the healthy annulus wall. The layers are sewn together and secured to a strong titanium bone anchor. Through that anchor the mesh is connected to one of the surrounding vertebral bones [73].

flexible mesh with multiple layers of counter-angulated fibers

4.3.3 Accessible evidence

The Barricaid® has been on the market in Europe since 2009 and in Australia since 2011.

Table 4.3-1: Available evidence for annular repair device Barricaid® (extracted 04.04.2013)

Studies by year	Level of evidence	*FDA (no application submitted)*	ARTG	*TPD (no application submitted)*	Notified Bodies	Literature Search	Clinical trials
Lequin et al., 2012	Prospective case series	/	NA	/	-	√	√*
Intrinsic Therapeutics, 2011	Randomized study	/	NA	/	-	-	√*
Chiang et al., 2011	Technical feasibility study	/	NA	/	-	√	-
Intrinsic Therapeutics, 2009 (received by manufacturer)	Benchtop testing/ Biomechanical comparison	/	NA	/	√	-	-
Gorensek et al., 2004	Abstract report for a prospective, multi-center, controlled clinical study	/	NA	/	-	√	-

*Explanation: * Not completed ° Status unknown ^ Terminated/Suspended, cursive – not authorized, underlined – authorized*

FDA

no premarket approval application has been submitted

The Barricaid® is currently not on the market in the United States of America and a premarket approval application has not yet been submitted. The manufacturer, Intrinsic Therapeutics Inc. has stated that the application for the market authorization will be submitted in the near future.

Notified Bodies

CE certificate made available by manufacturer

no evidence available

The manufacturer has released the information about the Notified Body responsible for the conformity assessment of the device. In 2009, the device was assessed by the TÜV Rheinland Product Safety GmbH, in Cologne. The certificate serves as an approval with the EC Directive 93/42/EEC Annex II, Article 3 – Full Quality Assurance System, Medical devices, and entitles Intrinsic Therapeutics Inc. to market the Barricaid® legally in Europe. The certificate expired in August 2013 and the manufacturer has to ensure its renewal. However, the certificate does not offer any insight into the evidence used as a basis for the approval decision.

TGA

CE marking basis for ARTG inclusion

The device was listed in the ARTG, as stated by the manufacturer. Yet, the TGA was not able (willing?) to release any further information about the evidence used as a basis for the decision to include the Barricaid® into the ARTG. The manufacturer has stated that it is believed that the ARTG inclusion was based on the obtained CE marking.

TPD

The TPD has not yet reviewed any evidence of the Barricaid® annular repair device, as the manufacturer has not yet applied for the premarket approval. It has been stated by the contact to Intrinsic Therapeutics that the application will be submitted in connection with the application for the FDA.

no premarket approval application was submitted

Literature search

The literature search used the keywords Barricaid® OR lumbar discectomy OR reherniation. The limitation was set to clinical trials. In the literature search three relevant academic articles were found.

3 articles were found

- Gorensek et al. published an abstract report about a prospective, multicenter, controlled clinical study in 2004. This study included 15 patients with an implanted Barricaid® device [74].
- In 2011, a technical feasibility study was presented by Chiang et al. The techniques were only assessed in animal models [72].
- In 2012, an article by Lequin et al. was published describing one-year clinical and radiographic results from a non-randomized, partly uncontrolled study being nested in a prospective, multicenter trial. The study included 45 patients [75].

abstract: prospective, multicenter, controlled clinical study (2004)

technical feasibility study (2011)

non-randomized, partly uncontrolled study (2012)

Clinical trial database

The clinical trial database was searched with the keywords Barricaid® OR lumbar discectomy. Two trials have been registered within the database.

2 trials registered

- A randomized study registered by Intrinsic Therapeutic in 2011, is currently recruiting patients. Estimated enrolment is 500 patients and study completion in 2016.
- A multicenter EU post-marketing surveillance study published by Lequin et al. (described above) was registered in 2012.

randomized study (2011) – on-going

Lequin et al. (2012)

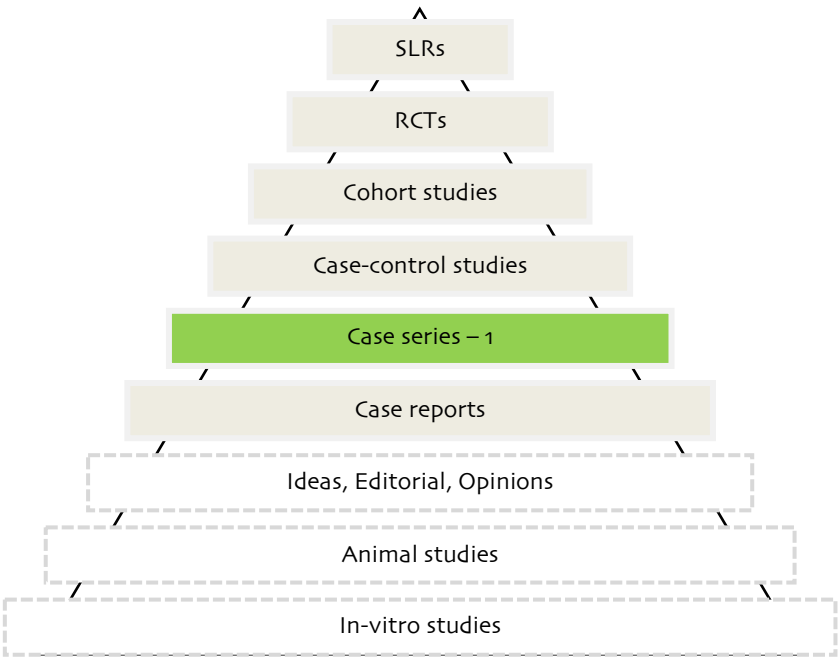

Figure 4.3-1: Evidence pyramid for the annular repair device Barricaid®

evidence available at time of CE marking and ARTG inclusion

All the evidence available for the Barricaid® device has been summarized in Table 4.3-1. At the time of CE marking approval in 2009, only an abstract from a planned RCT and benchmark testing/biomechanical comparison was available. At the time of inclusion into the ARTG in 2011, the abstract, the benchmark testing and a technical feasibility study were available.

highest level of evidence – case series

The highest level of evidence presented in the evidence pyramid for the device is currently one case series.

4.4 Rheofilter ER-4000

only on the market in Europe

The following chapter summarizes the evidence of the Rheofilter ER-4000. Produced by Asahi Kasei Medical Co., the device can only be legally marketed in Europe.

4.4.1 Indication

the device targets at dry age-related macular degeneration causing irreversible vision loss and blindness

The Rheofilter ER-4000 is a procedure targeted at dry age-related macular degeneration (AMD). AMD is the leading cause of irreversible vision loss and blindness in patients older than 65 years in Western industrialized societies. The indication is a deterioration of the macula, a light-sensitive tissue lining the back of the eye in the central part of the retina. During the progression of the disease, the macula is compromised. This compression leads to a disruption of both structure and vision function. There are several forms of AMD and dry AMD is the most common form, amounting up to 85-90% of all diseased cases. Patients may experience symptoms such as blurriness, dark areas, and distortion in their central vision ability. The disease might finalize in total loss of central vision. The aetiology of the disease is not yet fully understood, but it is believed that genetic factors play a major role in the pathology next to risk factors such as age, gender and smoking [76].

4.4.2 Mechanic procedure

extracorporeal double filtration system for selective plasma therapy

The Rheofilter ER-4000 is part of an extracorporeal double filtration system. It is used in combination with a plasma separator for selective extracorporeal plasma therapy, e.g., Rheopheresis. The therapy involves the removal and replacement of blood and blood plasma. Blood is extracted from the body and separated into a plasma and blood pump. A plasma component separator is installed in the plasma pump, aiming at removing harmful and disease-causing substances while leaving all valuable substances to be returned to the patient. There are several therapeutic approaches for various indications, whereas the blood extraction and filtration system can be adapted to the special needs of patients [77].

4.4.3 Accessible evidence

The Rheofilter ER-4000 is currently only on the market in the European Union, receiving its CE marking in 1998. It had been approved in the Canadian system from 2002 until 2005, but was then removed from the device license listing.

currently on market in Europe, was removed from the listing in Canada

Table 4.4-1: Available evidence for the Rheofilter ER-4000 (extracted 15.04.2013)

Studies by year	Level of evidence	*FDA (no application submitted)*	*ARTG (no application submitted)*	*TPD*	Notified Bodies	Literature Search	Clinical trials
Wild et al., 2009	Systematic literature review	/	/	NA	NA	√	-
Klingel et al., 2009	Analysis of Registry – Safety and Efficacy study	/	/	NA	NA	√	-
Koss et al., 2009	Prospective, randomized, controlled clinical study	/	/	NA	NA	√	-
Choudry, OccuLogix Inc., 2007	Multicenter, randomized, sham controlled trial	/	/	NA	NA	-	√^
Kubista, Ludwig Boltzmann Institute, 2007	Prospective case study	/	/	NA	NA	-	√*
Pulido et al., 2006	Multicenter, randomized clinical trial	/	/	NA	NA	√	-
Choudry, Occu-Logix Inc., 2006	Long-term efficacy study	/	/	NA	NA	-	√°
Pulido et al., 2005	Literature review	/	/	NA	NA	√	-
Siegel, OccuLogix Inc., 2004	Randomized, double-blind clinical trial	/	/	NA	NA	-	√°
Koch, Apheresis Research Institute, 2003	Prospective, randomized, controlled clinical study	/	/	NA	NA	-	√
Klingel et al., 2003	Literature review	/	/	NA	NA	√	-
Brunner et al., 2000	Randomized controlled trial	/	/	NA	NA	√	-

*Explanation: * Not completed ° Status unknown ^ Terminated/Suspended, cursive – not authorized, underlined – authorized*

FDA

The FDA homepage was scanned without any relevant results; no information about an application for premarket approval submission is available from the FDA.

no premarket approval application submitted

Notified Bodies

No publicly available information regarding the evidence used for the conformity assessment from the Notified Body can be found.

no information available

TGA

no premarket approval application submitted

The ARTG was searched for the product and/or the manufacturer. No information about the submission of a premarket approval application or an assessment of the device could be extracted in any search combination.

TPD

search for the manufacturer showed the inclusion of the Plasmaflo-Op in 1999

The Medical Device Active License Listing (MDALL) established by Health Canada was searched with the product name and the manufacturer. No information could be found using the product name; however, using the manufacturer's name resulted in some hits. On November 21, 1999 the Plasmaflo-Op 05W, which is a part of the complete Rheopheresis therapy, was included in the active device license listing of products marketed in Canada. No further evidence that led to the inclusion into the MDALL could be extracted [78].

Literature search

7 articles were found

A literature search was conducted using the keywords Rheopheresis OR Rheofilter ER-4000. With the limitation to clinical trials only, seven results were identified.

RCT (2000)
literature review (2003)

- In 2000, a randomized controlled trial including 43 patients in Germany was performed by Brunner et al. The study was sponsored by Ashai Kasei Medical, the manufacturer of the product in combination with the Diamed Medzintechnik GmbH.

literature review (2005)

- A literature review was published in 2003 by Klingel et al. [79].
- A literature review from Pulido et al. was made available in 2005.

RCT (2006)
systematic literature review (2009)

- In 2006, Pulido et al. published data about a multicenter, randomized clinical study sponsored by OccuLogix, Inc. A total of 216 patients were recruited for this study [80].
- In 2009, Wild et al. conducted a systematic literature review about the Rheopheresis therapy for AMD [81].

RheoNet registry for safety and efficacy (2009)

- In 2009, Klingel et al. evaluated the RheoNet registry for the safety and efficacy of the Rheopheresis treatment. The registry was established counting 7722 Rheopheresis treatments of 1110 patients, from which 833 were diagnosed with AMD [82].

RCT (2009)

- Koss et al. (2009) performed a prospective, randomized, controlled clinical study including 52 patients [83].

Clinical trial database

5 trials registered

The clinical trial database was searched with the keyword Rheopheresis. Five relevant results were included in this research.

prospective, randomized controlled study (2003)

- In 2003, a study was registered by the Apheresis Research Institute. The study design was a prospective, randomized, controlled study.

RCT (2004)
long-term efficacy study (2006)

- A study sponsored by OccuLogix was registered in 2004. Study design was a randomized, double blind clinical trial.
- In 2006, OccuLogix introduced a long-term efficacy study.

multicenter, sham RCT (2007)

- In 2007, OccuLogix registered a multicenter, randomized, sham controlled study.

prospective case study (2007)

- In the same year, a prospective case study was registered by the Ludwig Boltzmann Institute for retinology.

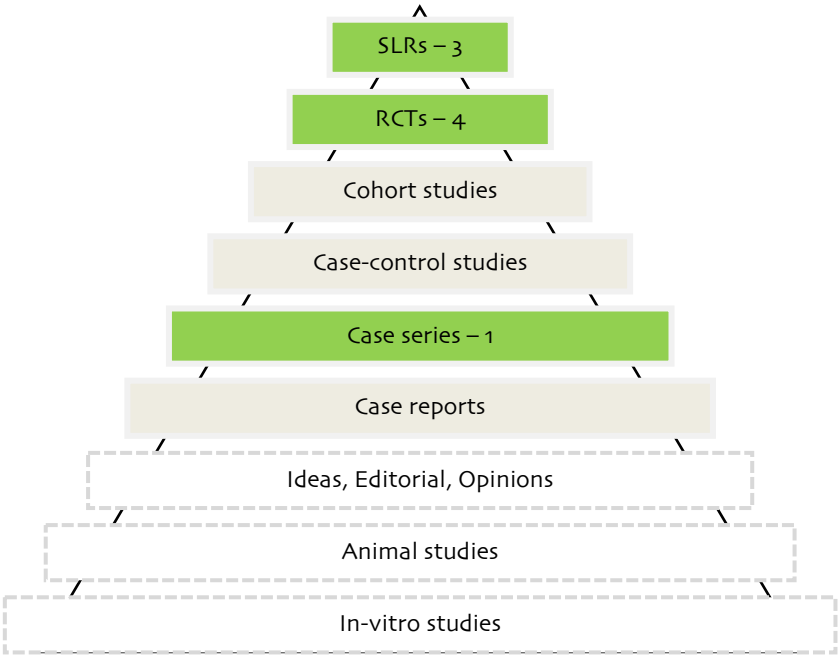

Figure 4.4-1: Evidence Pyramid for Rheofilter ER-4000

CE marking 1998 approval no clinical evidence available

All the evidence accessible for the Rheofilter ER-4000 is summarized in Table 4.4-1. At the time of CE marking approval in 1998, no randomized controlled trial or other clinical studies were available. The device was included in the medical device licence listing in Canada from 2002-2005. At the time of approval in 2002, one randomized controlled trial was available.

highest level of evidence, SLRs are available

The evidence available for the device has been presented in an evidence pyramid. Three systematic literature reviews make up the highest level of evidence. Further, four completed controlled studies and one completed case series are available.

4.5 BSD-2000 Microwave Hyperthermia System

device currently on the market in Europe and USA under HDE

The following chapter summarizes the evidence for the BSD-2000 Microwave Hyperthermia System. The device is produced by BSD Medical and is on the market in Europe and the United States of America under a humanitarian device exception (HDE/Humanitarian Device Exemption).

4.5.1 Indication

hyperthermia system used in conjunction with radiation therapy for cancer patients

The BSD-2000 Microwave Hyperthermia System is used in conjunction with radiation therapy for the treatment of cancer patients who are ineligible for chemotherapy. The device provides deep regional therapeutic hyperthermia to attack tumors by applying radiofrequency energy. It is assumed that the effectiveness of radiation therapy is increased while using the BSD-2000 in conjunction [84].

4.5.2 Mechanic procedure

heating is targeted to the tumor region by a power source and multiple antennae surrounding the patient's body

The BSD-2000 delivers energy to a patient by using a power source and an array of multiple antennae that surround the patient's body. The BSD-2000 was designed to provide an optimized heating zone targeted to the tumor region by utilizing the adjustment of frequency, phase, and amplitude from multiple power sources. The energy can be focused electronically to the tumor region, thus providing dynamic control of the heating delivered to the tumor region. During a treatment, the cancerous tumor is heated to 40°C and 45°C. Hyperthermia damages cells in solid tumors, without damaging normal tissues, because higher temperatures selectively damage cells that are hypoxic and have low pH, a condition of tumor cells and not a condition of normal cells [85].

4.5.3 Accessible evidence

The device has received the CE marking, but no information is available about the year in which it was received. The FDA allowed the device in 2011 under a HDE/humanitarian device exemption. The following section presents the accessible evidence for the device.

Table 4.5-1: Available evidence for the BSD-2000 Microwave Hyperthermia System (extracted on 16.04.013)

Studies by year	Level of evidence	FDA (HDE)	*ARTG (no application submitted)*	*TPD (no application submitted)*	Notified Bodies	Literature Search	Clinical trials
BSD Medical Corporation, 2011	Registry study – Benefit and safety	√	/	/	NA	-	-
Duke Medical Center, 2008	Case series	-	/	/	NA	-	√
Sreenivasa et al., 2006	Case series	-	/	/	NA	√	-
Jones et al., 2006	Case series	-	/	/	NA	√	-
Hildebrandt et al., 2004	Case series	-	/	/	NA	√	-
Wust et al., 2004	Case series	-	/	/	NA	√	-
Rau et al., 1998/2000	Case series	-	/	/	NA	√	-
Daniel den Hoed Cancer Centre, 1996	Prospective randomized trial	√	/	/	NA	-	-
Wust el al. 1995	Phantom study	-	/	/	NA	√	-
Sapozink et al., 1990	Case series	-	/	/	NA	√	-

*Explanation: * Not completed ° Status unknown ^ Terminated/Suspended, cursive – not authorized, underlined – authorized*

FDA

the device was approved under a humanitarian device exemption in 2011 by the FDA
RCT (1996)

The BSD-2000 was approved under a humanitarian device exemption (HDE) in 2011 by the FDA. The FDA stated clearly that the device can only be administered to cervical carcinoma patients in conjunction with radiation therapy. Those patients have to be ineligible for chemotherapy. The FDA based the HDE approval decision on the following evidence [86]:

- Phase III prospective, randomized study. The study duration was from May 1990 to September 1996. A total of 65 patients were included in the study.
- BSD Medical Cooperation, the manufacturer of the device, initiated a registry study in 2011 to provide additional evidence of the probable benefit and the safety of the use of hyperthermia delivered through the hyperthermia system in conjunction with radiation therapy for advanced cervical carcinoma.

registry study was initiated by the manufacturer (2011)

Notified Bodies

no information available

No information about the Notified Body that assessed the BSD-2000 device could be found.

TGA

no premarket approval application submitted

The device may not be legally marketed in Australia, as no ARTG listing exits. The ARTG listing was scanned under the device name BSD-2000 Hyperthermia System OR hyperthermia. Just searching with the keyword hyperthermia, a variety of different products from different manufacturers could be found. For the BSD-2000 device, no information about an application for premarket submission or evidence submitted could be found.

TPD

no premarket approval application submitted

The device listing of Health Canada was searched and no entry for the BSD-2000 Hyperthermia System was found. Further, no information about the submission of a premarket approval application could be extracted. However, as in the ARTG of Australia, scanning the listing with only the keyword of hyperthermia detected some hits. As in Australia, where various companies have legally marketed a hyperthermia system, in Canada only Belmont Instrument Cooperation is listed within the device licenses. However, BSD Medical Cooperation was contacted and no collaboration between the two companies exists.

Literature search

7 articles were found

The literature search was conducted using the keywords BSD-2000 AND hyperthermia system. With the limitation to clinical trials, seven hits were presented.

- In 1990, a case series including 26 patients was published by Sapozink et al. [87].

case series (1990)

- In 1995, Wust et al. reported about a quality control using an animal phantom model [88].

phantom study (1995)

- In 1998 and 2000, Rau et al. published two articles about a case series including 37 patients applying the BSD-2000 device [89, 90].

case series (1998, 2000)

case series (2004)

- In 2004, a case series including 33 patients, in which the BSD-2000 was applied with a modification to a multi-antenna, was published by Wust et al. [91].

case series (2004)

- In 2004, a case series including 28 patients to test the toxicity and the feasibility of the hyperthermic chemotherapy approach was published by Hildebrandt et al. [92].

case series (2006)

- In 2006, a case series including 41 patients was published by Jones et al. [93].

case series (2006)

- In 2006, Sreenivasa et al. reported about a case series including 32 patients [94].

Clinical trial database

1 trial registered

The database was searched with the keyword BSD-2000 hyperthermia system. One clinical trial was registered.

case series (2008)

- The Duke Medical Center reported about a pilot study including 15 patients concerning the efficacy and safety of hyperthermia in bladder cancer treatment in 2008.

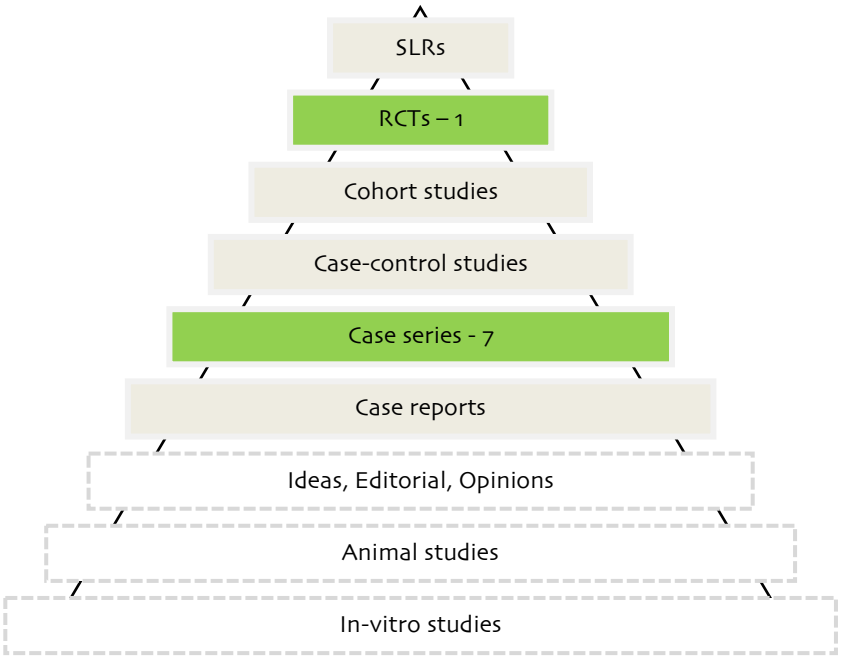

Figure 4.5-1: Evidence pyramid for BSD-2000 Microwave Hyperthermia System

FDA approval HDE – 1 RCT, 7 case series

All the evidence available for the BSD-2000 device is summarized in Table 4.5-1. As the time of CE marking approval is not known, the evidence available at approval cannot be assessed. For the approval as an HDE by the FDA in 2011, one RCT and seven case series were available.

highest evidence 1 RCT

The evidence presented in the evidence pyramid concludes that the highest evidence available is one RCT. A further seven case studies and one on-going registry study were found.

4.6 Amplatzer™ PFO Occluder

The following chapter focuses on the Amplatzer™ PFO Occluder. The device is manufactured by St. Jude Medical and is currently on the market in Europe, Australia and Canada. In the United States it was approved under the HDE until 2006.

on the market in Europe, Australia, Canada

4.6.1 Indication

The Amplatzer™ PFO Occluder is a patent foramen ovale (PFO) closure device designed for a minimally invasive transcatheter procedure. A patent foramen ovale is a tunnel-lie opening between the two upper chambers of the heart. This opening is formed during the development of the heart in-utero and it generally closes naturally after birth. Yet, in nearly 25% of the general population the opening does not close completely. The disease has been related to paradoxical embolism, orthostatic desaturation, or pulmonary hypertension. It has been investigated whether the administration of a PFO Occluder may reduce the side effects of the disease [95].

designed to treat patent foramen ovale, a tunnel-lie opening between the two upper chambers of the heart

4.6.2 Mechanic procedure

The Occluder is a double-disc device comprised of nitinol mesh and poly-ester fabric. It is designed to close all types of PFOs with an easy-to-perform deployment system. The device is inserted to close the PFO; an optimal fit is achieved through a flexible, narrow waist to keep the disc well-opposed to the septal walls. The device is inserted through a catheter placed in a vein in the groin. The PFO is a permanent implant that stays in the heart after the procedure [96].

double disc comprised of a nitinol mesh and polyester fabric

4.6.3 Accessible evidence

The following section presents the evidence that is publicly available about the device. Although the device obtained the CE marking, no information can be found as to in which year. In Australia, the device was approved in 2006 and in Canada in 2001. In the Unites States of America, the device was approved under HDE until 2006.

CE marking, ARTG inclusion (2006), device license listing (2001) and HDE in USA until 2006

Table 4.6-1: Available evidence for the Amplatzer™ PFO Occluder (extracted on 24.07.2013)

Studies by year	Level of evidence	*FDA (no HDE since 2006)*	ARTG	TPD	Notified Bodies	Literature Search	Clinical trials
Kwong, Lam and Yu, 2013	Systematic literature review	/	NA	NA	NA	√	-
Duk-Woo Park Research Foundation, 2012	Randomized clinical trial	/	NA	NA	NA	-	√*
Stern et al., 2012	Case series	/	NA	NA	NA	√	-
Khattab et al., 2011	Randomized controlled trial	/	NA	NA	NA	√	-

Studies by year	Level of evidence	*FDA (no HDE since 2006)*	ARTG	TPD	Notified Bodies	Literature Search	Clinical trials
Fischer et al., 2011	Cohort study	/	NA	NA	NA	√	-
Michaels, 2010	Case-control study	/	NA	NA	NA	-	√^
Taaffe et al., 2008	Randomized controlled trial	/	NA	NA	NA	√	-
Silvestry et al., 2008	Cohort study	/	NA	NA	NA	√	-
AGA Medical Cooperation, 2007	Prospective, randomized clinical trial	/	NA	NA	NA	-	√*
AGA Medical Cooperation, 2007	Randomized clinical trial	/	NA	NA	NA	-	√*
AGA Medical Cooperation, 2007	Expanded Access – registry study	/	NA	NA	NA	-	√*
AGA Medical Cooperation, 2006	Randomized clinical trial	/	NA	NA	NA	-	√*
AGA Medical Cooperation, 2005	Randomized clinical trial	/	NA	NA	NA	√	√°
Salomé et al., 2004	Case series	/	NA	NA	NA	√	-
Schwerzmann et al., 2004	Case-control study	/	NA	NA	NA	√	-
Hong et al., 2003	Multicenter clinical trial (intermediate results)	/	NA	NA	NA	√	-
Chan et al., 1999	Case series	/	NA	NA	NA	√	-

*Explanation: * Not completed ° Status unknown ^ Terminated/Suspended, cursive – not authorized, underlined – authorized*

FDA

approved under humanitarian device exemption in 2006
FDA has withdrawn HDE as patient number exceeded 4000 per year

The FDA approved the device under the HDE until October, 2006. The decision to withdraw the HDE approval was based on the increasing patient numbers treated with the PFO Occluder. Under the HDE, the patient number per year in the USA may not exceed 4000 patients. However, in 2006 the FDA's review concluded that the patient population significantly exceeded 4000 patients per year. Therefore, the HDE was withdrawn and the FDA stated that the device should be subject to the general premarket approval application. Up to 2013, the device has not been granted market approval through a general authorization pathway [97].

Notified Bodies

no information available

No information was found about the year the CE marking was obtained, the Notified Body that granted the CE marking or the evidence submitted.

TGA

in the ARTG since 2006 – no further information about evidence submitted

The Amplatzer™ PFO Occluder was found in the ARTG listing; it was approved in the year 2006. Only the public summary of the ARTG listing can be found, but no evidence that has been submitted to support the inclusion decision [98].

TPD

The device can be found in the Canadian Device Listing and it was approved in 2001. However, the manufacturer of the device is not St. Jude Medical, but AGA Medical Corporation. Further research revealed that the two companies work in collaboration. The Device Listing does not include any evidence that was assessed during the reviewing process and the approval decision [99].

included in listing but from AGA Medical Cooperation since 2001

Literature search

A literature search was conducted with the keywords PFO Occluder AND Amplatzer. The search showed ten hits.

10 articles were found

- In 1999, Chan et al. published a prospective, multicenter case study including 100 patients [100]. — case series (1999)
- In 2003, Hong et al. published intermediate-term results of a US multicenter clinical trial. 50 patients were included in this study [101]. — Intermediate results CT (2003)
- Schwerzmann et al. published an article about a case-control study in 2004. The study included 100 patients [95]. — case-control study (2004)
- In 2004, Salomé et al. reported a case series including 27 patients [102]. — case series (2004)
- In 2008, a randomized study comparing three PFO Occluder devices (Amplatzer, CardioSEAL-STARflex and Helex) was published by Taaffe et al. The study included 660 patients [103]. — RCT (2008)
- In 2008, a long-term follow-up cohort study with 19 cases was reported by Silvestry et al. [104]. — cohort study (2008)
- In 2011, a randomized clinical trial with the enrolment of 414 patients was published by Khattab et al. [105]. — RCT (2011)
- In 2011, Fischer et al. published a report about a prospective cohort study including 114 patients [106]. — cohort study (2011)
- In 2012, a case series was published by Stern et al. The study included 25 patients in total [107]. — case series (2012)
- In 2013, a systematic literature review, including a meta-analysis, was published by Kwong, Lam and Yu [108]. — SLR (2013)

Clinical trial database

The clinical trial database was searched with the keywords PFO Occluder AND Amplatzer. Seven registered clinical studies were presented.

7 clinical studies registered

- In 2005, the AGA Medical Cooperation initiated a randomized clinical trial to assess the safety and effectiveness of the Amplatzer™ PFO Occluder. — RCT (2005)
- In 2006, a randomized clinical trial was sponsored by AGA Medical Cooperation to assess the safety and effectiveness of the device in association with incidence of headache reduction in subjects with migraines using the PFO Amplatzer™ Occluder. — RCT (2006)
- In 2007, AGA Medical Cooperation registered a randomized clinical trial to evaluate the recurrence of stroke in patients, comparing the PFO closure device to the established current standard of care treatment. — RCT (2007)
- In the same year, AGA Medical Cooperation started an expanded access study – a registry study. — expanded access study (2007)

prospective RCT (2007)

- The PRIMA PFO Migraine Trial, a prospective randomized clinical trial sponsored by the AGA Medical Cooperation, was registered in 2007.

case-control study (2010)

- In 2010, the University of Utah started a case-control study.

RCT (2012)

- In 2012, the Duk-Woo Park Cardiovascular Research Foundation from Korea registered a randomized clinical trial within the database.

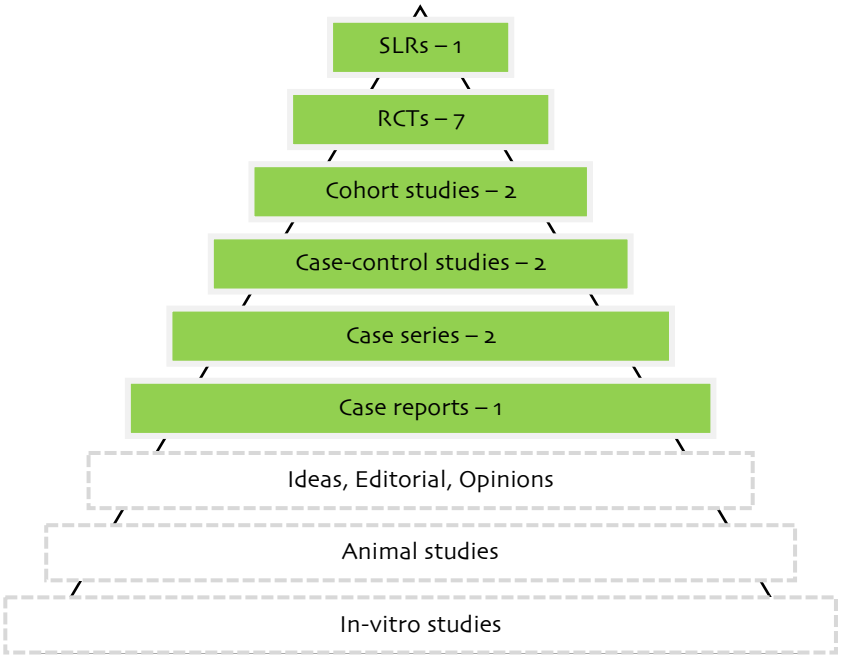

Figure 4.6-1: Evidence pyramid for Amplatzer™ PFO Occluder

CE marking no year known, device listing Canada: 1 case series, ARTG inclusion: 1 case series, one case-control and 1 RCT

All the evidence for the Amplatzer™ PFO Occluder has been summarized in Table 4-7. No information was found about the year in which the CE marking was obtained. Therefore, the evidence available at approval cannot be assessed. In 2001, when the device received a license in Canada, one case series was available. In 2006, when the FDA withdrew the HDE for the device and the device was included in ARTG listing, one case series, one case-control and one randomized controlled trial were available.

highest level of evidence: 1 SLR

All the evidence was put into an evidence pyramid and it can be observed that the highest level of evidence, a systematic literature, has been available since 2013. Further, eight randomized controlled trials, two cohort studies, two case-control studies, three case series and one case report have been conducted over the last years.

4.7 MitraClip®

The following section gives information on the MitraClip®. The device is manufactured by the company Abbott and is currently on the market in Europe, the USA and Australia. The device has just recently been approved (March 2013) by the FDA.

on the market in Europe, USA and Australia

4.7.1 Indication

The MitraClip® is designed to perform a percutaneous mitral valve repair (MVR) for the treatment of mitral regurgitation (MR). MR is a mitral valve disease and is one of the leading cardiac valve pathologies in Western societies. MR occurs when the leaflets of the heart's mitral valve do not close properly and leak. During the heart's pumping phase, the leak in the mitral valve causes blood to flow into the left atrium and decreases the blood amount that is distributed to the body. To maintain regular blood flow and blood distribution into the body, the left ventricle has to increase the pumping activity. Eventually this over-activity can cause stroke, irregular heartbeat, progressive myocardial injury and congestive heart failure [109].

treatment of mitral regurgitation through a percutaneous mitral valve repair

4.7.2 Mechanic procedure

The MitraClip® aims at closing the leak in the mitral valve and ensuring normal heart functioning. The device consists of a percutaneously delivered MRI-compatible, cobalt-chromium implant with two arms and two grippers. The procedure is performed under general anesthesia and the device is delivered via a transfemoral venous route. Placement of the MitraClip® device is supposed to improve the patient condition through advancements in the coaptation in the mitral valve leaflet [110].

the implant is a percutaneously delivered MRI-compatible, cobalt chromium device

4.7.3 Accessible evidence

The subsequent section provides the publicly accessible evidence about the device. The device obtained the CE marking in 2008, the ARTG inclusion in 2010, and the FDA approval just recently in 2013.

CE marking (2008), ARTG inclusion (2010) and FDA approval (2013)

Table 4.7-1: Available evidence for the MitraClip®

Studies by year	Level of evidence	FDA	ARTG	*TPD (no application has been submitted)*	Notified Bodies	Literature Search	Clinical trials
Munkholm-Larsen et al., 2013	Systematic literature review	-	NA	/	NA	√	-
Evalve, 2013	Randomized clinical trial	-	NA	/	NA	-	√*
Biner et al., 2012	Case series	-	NA	/	NA	√	-
Baldus et al., 2012	Registry study	-	NA	/	NA	√	-
Alegria-Barrero et al., 2012	Review – State-of-the-Art	-	NA	/	NA	√	-

Studies by year	Level of evidence	FDA	ARTG	*TPD (no application has been submitted)*	Notified Bodies	Literature Search	Clinical trials
Evavle (Collaborator Abbott Vascular), 2012	Clinical Outcome Assessment	-	NA	/	NA	-	√*
Auricchio et al., 2011	Case series	-	NA	/	NA	√	-
Siegel et al., 2011	Case series	-	NA	/	NA	√	-
Conradi et al., 2011	Case series	-	NA	/	NA	√	-
Franzen et al., 2011	Case series	-	NA	/	NA	√	-
Evalve (Collaborator Abbott), 2011	Observational cohort study	-	NA	/	NA	-	√*
Rudolph et al., 2011	Case series	-	NA	/	NA	√	-
Evalve, 2011	Observational cohort study	-	NA	/	NA	-	√*
Deutsches Herzzentrum München, 2011	Randomized clinical trial	-	NA	/	NA	-	√*
Franzen et al., 2010	Case series	-	NA	/	NA	√	-
Mieghem et al., 2010	Review	-	NA	/	NA	√	-
Schaefer and Bertram, 2010	Review	-	NA	/	NA	√	-
Herrmann et al., 2006	Case series	-	NA	/	NA	√	-
REALISM, 2005	Prospective access registry	√	NA	/	NA	-	-
High Risk Registry (HRR), 2008	Registry study	√	NA	/	NA	-	-
EVEREST I, 2005	Feasibility study	√	NA	/	NA	√	√
EVEREST II, 2005	Randomized clinical trial	√	NA	/	NA	√	√*

*Explanation: * Not completed ° Status unknown ^ Terminated/Suspended, cursive – not authorized, underlined – authorized*

FDA

recently approved the device (March 2013) based on 4 studies

The FDA has just recently approved the premarket application of the MitraClip® device. In March 2013, a panel committee voted on the approval with eight out of nine votes in favor of the device. The evidence the FDA has based their decision on is subsequently summarized [111]:

EVEREST I, feasibility study (2005)

- The EVEREST I trial (2005), a feasibility study that involved 55 patients.

EVEREST II, randomized controlled trial (2005)

- The EVEREST II study (2005), a randomized controlled trial included 279 patients.

High Risk Registry (2008)

- The High Risk Registry (HRR) was an adjunctive, single-arm registry approved by the FDA for conjoined evaluation with the EVEREST II study data. The HRR enrolled 78 patients.

REALISM, prospective access registry – on-going (2013)

- The REALISM study (2013), currently on-going, aims at data collection of high-risk patients and the use of the MitraClip® device. The study was designed as a prospective access registry.

Notified Bodies

The MitraClip® device was approved for the European market in 2008. Information about the approval process and the evidence used as the basis for this approval decision are not publicly available.

no information accessible

TGA

The device may be legally marketed in Australia since 2010. In the ARTG listing, the device can be found and the public summary of the device is accessible. However, no evidence on which the decision was taken can be detected [112].

included in the ARTG since 2010

TPD

The device is not approved in Canada and no information can be found concerning a possible application or any evidence that has been submitted to the Canadian regulatory body.

no premarket approval application

Literature search

The literature search using MitraClip® OR mitral regurgitation as the search keyword resulted in fourteen hits.

14 publications

- In 2006, Herrmann et al. conducted a case series including 27 patients [113]. — case series (2006)
- Feldman et al. published data in 2009 about safety and mid-term durability assessed in a prospective, multicenter single-arm study. A total of 107 patients from the EVEREST I cohort were included in the study [114]. — EVEREST I, prospective, multicenter single-arm study (2009)
- In 2010, Schaefer and Bertram released a review about the treatment of MR with devices such as the MitraClip® [115]. — review (2010)
- In the same year, 2010, another review was published by Mieghem et al. [116]. — review (2010)
- Franzen et al. performed a case series with 51 patients in 2010 [117]. — case series (2010)
- In 2011, a case series by Rudolph et al. was published. 104 patients were included in the study [118]. — case series (2010)
- Franzen et al. performed a retro perspective analysis in 2011 [119]. — case series (2011)
- A case series with 51 patients was provided by Auricchio et al. in 2011 [120]. — case series (2011)
- Likewise in 2011, Conradi et al. published data about a case series including 215 patients [121]. — case series (2011)
- Siegel at al. evaluated 107 patients in a case series, published in 2011 [122]. — case series (2011)
- A case series from Biner et al. in 2012 assessed 107 patients and the acute procedural success (APS) after the MitraClip® therapy [123]. — case series (2012)
- A review of the state-of the art of edge-to-edge percutaneous repair of severe mitral regurgitation was published by Alegria-Barrero et al. in 2012 [124]. — review (2012)
- In 2012, Baldus et al. presented initial results from the German transcatheter mitral valve interventions registry study (TRAMI). The study enrolled 486 patients into a registry [125]. — registry study (2012)
- A systematic review was published by Munkholm-Larsen et al. in 2013 [126]. — SLR (2013)

Clinical trial database

Six studies were found in the clinical trial registry, seven of which were considered as relevant for this research.

EVEREST I and EVEREST II (2005)

- In overlap with the evidence the FDA has used for the approval decision, the EVEREST I feasibility study from 2005 and the EVEREST II randomized clinical trial from 2005 were registered within the database.

RCT (2011)

- A 2011 randomized clinical trial from the German Heart Centre Munich was found in the database.

observational cohort study (2011)

- In the same year, 2011, Evalve started the ACCESS-Europe study, an observational cohort study.

observational cohort study (2011)

- In 2011 as well, Evalve, in collaboration with Abbott, initiated another observational cohort study for the MitraClip® in Australia and New Zealand.

clinical outcome assessment (2012)

- Evalve and Abbott Vascular collaborated in starting a clinical outcome assessment of the MitraClip® therapy in high-risk surgical patients. The trial was first received in 2012. The recruitment phase is currently running.

RCT (2013)

- In 2013, Evalve has designed a randomized study for the MitraClip® device in heart failure patients with clinically significant functional mitral regurgitation. The trial has not started recruitment yet.

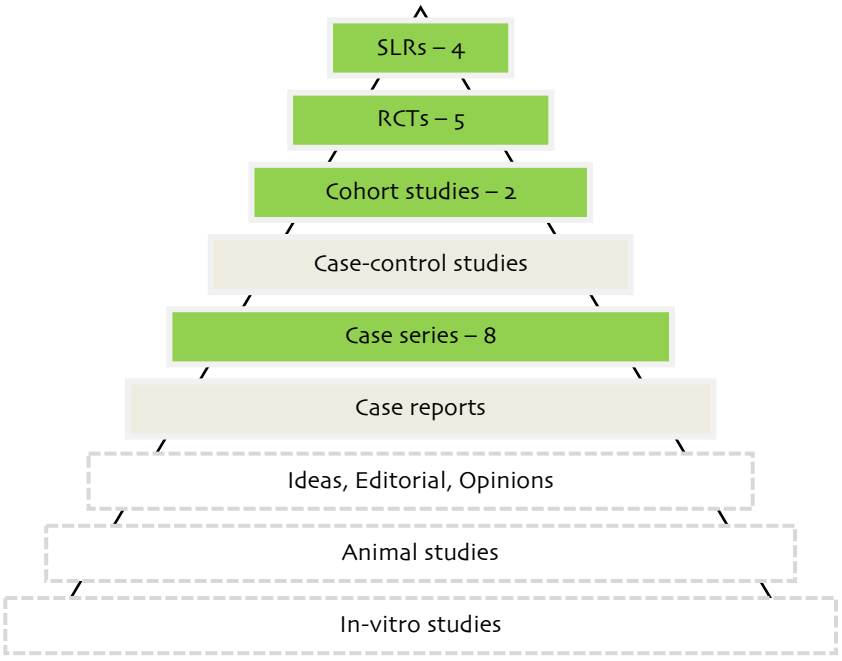

Figure 4.7-1: Evidence pyramid for MitraClip®

All the evidence for the MitraClip® device is summarized in Table 4.7-1. At the CE marking approval in 2008, one case series and one randomized controlled trial were available. In 2010, for the ARTG inclusion, two randomized controlled trials, three case series and one review were available. In 2013, when the FDA approved the device, five systematic literature reviews, five randomized controlled trials, two cohort studies and eight case series were available.

Summarizing the evidence for the MitraClip® in the evidence pyramid, it can be observed that the highest level of evidence available are the systematic literature reviews. Randomized controlled trials, cohort studies and case series are also available.

CE marking:
1 RCT, 1 case series,
ARTG inclusion: RCTs,
3 case series, 1 review,
FDA approval:
5 SLRs, 5 RCTs,
cohort and 8 case series

highest level of evidence available SLRs

5 Reimbursement

life-cycle of medical devices with authorization and reimbursement

All medical devices generally undergo a standard life-cycle with specified pathways. Within this life-cycle, the two most important assessments are the authorization evaluation and the reimbursement appraisal of the devices. As explained earlier, set regulations exist in different countries for the authorization evaluation of medical devices. Regulatory bodies are set in place, as the gateway medical devices have to pass in order to obtain the premarket approval. However, only being authorized does not implicitly entail the availability of the device on the market. Subsequently, national funding bodies, insurance programs or HTA institutions review medical devices a second time. Different national reimbursement frameworks for the assessments of evidence of the products in question exist [127].

major differences in national reimbursement frameworks

There is a great variety in the way these national reimbursement frameworks and their assessment methods are organized. Every system has specific characteristics, which place focus on different evidence requirements. National authorities responsible for taking such reimbursement decisions need high-quality and objective evidence from arduous clinical research to conduct liable assessments [128].

reimbursement guidance from relevant institutes will be provided

In this chapter, the reimbursement evaluation and/or the guidance provided by insurance programs, national funding bodies and national HTA-institutes for the seven medical devices is analyzed. Self-explaining only devices that have been granted market entry through the authorization process within the national evaluation are further considered in this research. As there is a great variety of national reimbursement and/or national health technology advising institutes, a selection of some institutions has been made in the four selected regions (Table 2.4-2).

evidence available through selected institutes analyzed

Evidence that was used in the reimbursement assessment of the selected institutes is summarized and analyzed in an evidence pyramid.

5.1 United States of America

public or private health insurance programs assess device for reimbursement

In the United States of America, the FDA is the gateway through which new drugs and medical devices must pass before they can legally be marketed. Yet, the access to the devices, which have been granted market authorization by the FDA, is implemented through health insurance programs. That means that following the FDA approval, the public or private health insurance programs will determine whether the approved products are “covered.” The coverage decision can either be a local coverage or a national coverage determination [129].

chapter overview

The following section briefly explains the USA healthcare system and its characteristics. Subsequently, the MitraClip®, the only device authorized by the FDA from the seven exemplary devices, and according documents are discussed.

5.1.1 The healthcare system in the United States of America

private or governmental health insurance programs in the US

The healthcare system in the United States of America is organized on the basis of healthcare insurance programs, either provided by the government or privately/by employers. There are several health insurance programs US citizens may choose from. What is unique in the system is the strong dominance of the private health insurance programs over the public ones [130].

private insurance associated with the workplace

The private insurance programs are often associated with the workplace. They are also called employer-sponsored insurances. Employers provide health insurance as part of the benefit package for employees.

CMS, Aetna, BCBS, Healthcare United and Kaiser Permanente selected for this research

The insurance programs offered by the government often focus on a certain population group, e.g., children or seniors. For the purpose of this research, five of the biggest public health insurance programs have been selected: the Medicare and Medicaid Services (CMS), Aetna, BlueCross and BlueShield Association (BCBS), Healthcare United and Kaiser Permanente.

AHRQ included in research

Further, the Agency for Healthcare Research and Quality (AHRQ) was chosen for this research. The agency is a national HTA institute frequently publishing reports about new medical interventions.

Guidance on the medical devices in the United States of America

The five insurance programs and the national health insurance institute were scanned for guidance reports or coverage decision documents. All available evidence regarding the coverage or reimbursement for the MitraClip® is summarized in Table 5.1-1.

Table 5.1-1: MitraClip® recommendations in the United States of America

Insurance program	Status
CMS	Application for coverage fiscal year 2014
Aetna	No information available
BCBS	No information available
Healthcare United	Coverage decision for transcatheter heart valve procedures – MitraClip® included
Kaiser Permanente	Guidance for cardiac rehabilitation – Recommendation mitral valve repair or replacement
AHRQ (HTA institute)	Horizon scanning report: MitraClip® device – expected high impact

CMS

NCDs or LCDs are evidence-based process

The CMS states that Medicare coverage is limited to items and services that are necessary and practical for the diagnosis or treatment of diseases. The national coverage decisions (NCDs) from Medicare are an evidence-based process with public participation. In the case of rejection for an NCD, Medicare has installed local coverage determination (LCD) possibilities. A Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) exists within the CMS [131].

MEDCAC advisory committee for Medicare coverage

The MEDCAC has the responsibility to give expert advice to Medicare for coverage decisions. During the decision process, the medical device is classified into different benefit categories. 55 benefit categories currently exist and

to be eligible for coverage under Medicare, the health service in question has to fit into these categories. In addition, it is stated that no payment will be made for health services that are not necessary or reasonable for the diagnosis or treatment of illness or injury [131].

CMS has coverage database

A coverage database is provided on the official CMS homepage, listing all products, pharmaceuticals and medical devices that have been allowed for coverage. Currently, only an application for coverage of MitraClip® is provided [132].

application for coverage in fiscal year 2014

This can be explained by the fact that the FDA just very recently approved the MitraClip® (in March 2013). The coverage database only lists a new technology add-on-payment application document for the fiscal year 2014. The document states that an application for the coverage of the MitraClip® has been submitted under the acute inpatient prospective payment system (IPPS).

no information about evidence basis

No information is available on the evidence that will be used for the coverage decision for the MitraClip®. It is expected that more information will be accessible through the CMS after the decision for the application is made in 2014.

Aetna

no information available

On the homepage of the Aetna health insurance program, no information or evidence about the device can be found when searching with the keywords Mitra Clip® OR mitral regurgitation.

device covered if considered "necessary" for indication

The Aetna health insurance program consists of various health plans for different population groups. In general, a device is covered if the insurance program considers the device "necessary" for the intended indication.

coverage decisions of other valve implantations accessible

Coverage decisions are generally available for aortic or pulmonary valve implantation, but not for mitral valve implantation. Nevertheless, the procedure for mitral valve replacement surgery is explained in detail by the Aetna health expert group [133].

BCBS

no information available

The homepage was searched using the keywords MitraClip® OR mitral regurgitation. No information about the MitraClip® can be found on the BlueCross and BlueShield Association homepage.

Healthcare United

coverage decision about transcatheter heart valve procedures

On the Healthcare United homepage, a medical policy document with coverage decisions about transcatheter heart valve procedures can be found. The document provides assistance in interpreting the benefit plan of the insurance program. Moreover, the document includes coverage decisions about aortic valves, pulmonary valves and mitral valves.

MitraClip® classified as investigational and unproven

The document came into effect on July 1, 2013, yet FDA approval information from devices was taken as of April 2013. In the document it is stated that mitral valves such as the MitraClip® are investigational and unproven devices due to lack of FDA approval [134].

evidence basis for decision

The evidence to reach this coverage decision is presented in the following:

- EVEREST I, a multicenter, prospective, single-arm study from 2004. — RCT, EVEREST I (2004)
- EVEREST II, the two-part multicenter, randomized controlled trial from 2005. — RCT, EVEREST II (2005)

RCT, EVEREST II – randomized arm (2011)

- EVEREST II, the randomized arm, separate study conducted by Feldman et al. in 2011.

RCT, EVEREST II – High-Risk Registry (2012)

- EVEREST II, the high-risk registry arm, established by Whitlow et al. in 2012.

referred to NICE guidance document

Further, the document refers to a guidance document created by the National Institute for Health and Care Excellence (NICE) from England. This document states that the evidence on safety and efficacy for percutaneous mitral valve leaflet repair for mitral regurgitation is currently inadequate in quality and quantity.

Kaiser Permanente

recommendation for mitral valve repair for subpopulations

On the Kaiser Permanente homepage, a report is available about the recommendations for treatment of mitral regurgitation. The report distinguishes between mitral valve repair and replacement. Patient criteria are connected to certain recommendations. The MitraClip® device is not explicitly mentioned, but the treatment option mitral valve repair with device is recommended for subpopulations [135].

AHRQ

AHRQ – MitraClip® potential high impact device

In December 2012, the AHRQ published a horizon scanning report about emerging medical technologies and the possible impact they will have. The MitraClip® was included in the report and considered as a device with an expected high impact. It was stated that experts see the unmet patient need and that the MitraClip® has the potential to improve patient health.

evidence for AHRQ report

Within the report, the following evidence is considered [136]:

EVEREST II (2005)

- EVEREST II, randomized controlled trial from 2005

expert opinion (2011)

- Seven expert opinions about the device.

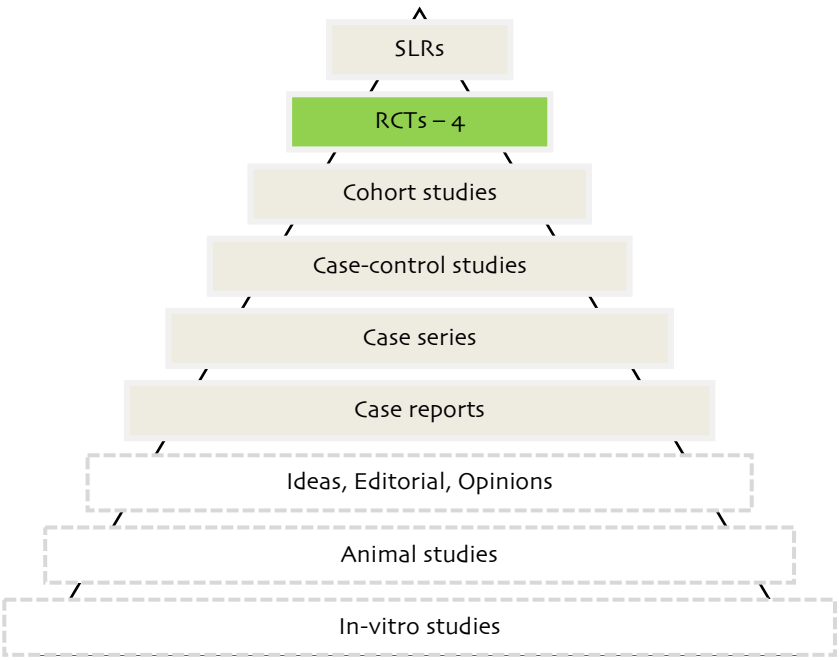

Figure 5.1-1: Evidence pyramid for reimbursement of MitraClip® in the USA

From the five insurance programs selected, only one has published a medical policy document with associated evidence as the basis for the reimbursement decision. The United Healthcare program used four RCTs to reach their coverage decision. Moreover, no information was available from the Aetna and the BSBC insurance programs. CMS and Kaiser Permanente provided fiscal application, a financial coverage document and a recommendation, but no coverage decisions. In addition, the AHRQ considered the device as high impact on the basis of the EVERST II trial and expert opinions given by seven professionals.

coverage decision from 1 insurance program : rejection
AHRQ high impact report

It is expected that more information will be available in 2014, as the device has just recently approved by the FDA.

more information expected in 2014

5.2 Europe

Within the 28 Member States of the European Union, healthcare has remained the responsibility of the separate national healthcare systems. Therefore, a great variety of different healthcare systems and reimbursement practices exists [137]. For the ease of this research, six countries and their associated reimbursement or advising HTA institutes were selected (see Table 2.4-2).

28 Member States with 28 different healthcare systems

The European authorization system is characterized by the ability to grant market authorization to the whole European Single Market, contrary to national reimbursement practices, which only concern national decisions.

EU authorization vs. national reimbursement decisions

It is very common in Europe that governmental public health bodies are responsible for the reimbursement decisions and the implementation of new medical devices or services into the healthcare system. Nevertheless, national HTA advising institutes are often in charge of the evaluation and the assessment of the new medical devices or services. These institutes conduct assessments and provide independent recommendations and guidance to the governmental bodies about the reimbursement decision. This research does not focus solely on the governmental bodies, but rather on the guidance provided by the national HTA advising institutes [138].

Ministries of Health often have independent advisory institutes – HTA institutes

Following an overview of the six selected countries and their healthcare system, advising HTA institutes are briefly introduced. All seven exemplary medical devices have obtained the CE marking. Consequently, guidance and recommendations of the national HTA institutes for all devices, if accessible, are provided.

6 selected countries and national HTA institutes are introduced

5.2.1 The healthcare system in The Netherlands

The healthcare system in the Netherlands is based on a combination of a national health insurance for “exceptional medical expenses,” a social compulsory health insurance and private supplementary insurance programs. The Ministry of Public Health, Welfare and Sport (VWS) is the key authority for health policy. The Ministry, in cooperation with local authorities, is responsible for public healthcare. The system is based on the Exceptional Medicine Act (AWBZ) and the Sickness Fund Act (ZFW). In total, there are 22 sickness funds that are all regulated by the Healthcare Insurance Board (CVZ). Additionally, private health insurance programs exist. In cooperation, the VWS

social and private insurance programs

compulsory social insurance scheme

and the Sickness Fund Council determine the level of income-related premiums that Dutch citizens would have to contribute. It is important to recognize that all budgetary decisions are subject to approval by the Parliament [139].

CVZ is main reimbursement advising body

focus on therapeutic effect

The CVZ carries the responsibility of providing the evidence base for the reimbursement decisions in The Netherlands. Within the CVZ, a committee designated for medical devices will conduct an assessment of the device in question. The assessment focuses on the therapeutic effect, which is defined by five criteria specified by the CVZ: negative effects, positive effects, experience with the device, applicability and ease of use. Based on the recommendations of the committee, the CVZ issues an advice to the ministry of health. Within the ministry, the final decision is taken as to whether the medical device will be allowed for reimbursement by the insurance companies.

Guidance for medical devices in The Netherlands

all 7 medical devices have the CE marking

In the European Union, all seven exemplary medical devices were authorized by the Notified Bodies. The CVZ publishes assessments made on medical devices in Dutch and English on their homepage. Following are the results.

Table 5.2-1: CVZ recommendations

Medical device	Guidance from CVZ
Zephyr® Endobronchial Valve	No recommendation (2012)
Paracor Ventricular Support System (PVSS)	No assessment available
Annular repair device Barricaid®	No assessment available
Rheofilter ER-4000	No recommendation (2010)
BSD-2000 Microwave Hyperthermia System	No recommendation for bladder carcinoma (2006)
Amplatzer™ PFO Occluder	No assessment available
MitraClip®	No assessment available

Zephyr® Endobronchial Valve

Zephyr® not recommended for reimbursement

The CVZ has assessed the endobronchial lung volume reduction therapy for emphysema. It is stated that this therapy, based on the current literature, cannot be seen as clinically effective with an added therapeutic value for the patient. Therefore, the recommendation on the therapy including the Zephyr® Endobronchial Valve is negative and the CVZ advises to not allow reimbursement. Further, it is recognized that there might be subpopulations that benefit from the therapy and that current research for those groups is being conducted. The guidance was published on December 21, 2012 [140].

The following evidence was considered within the reimbursement decision:

case series (2006)

- 19 patients were included in the case study published by de Oliveria in 2006 [141].

case series (2009)

- Springmeyer et al. published a case series with 98 patients from 2009 [142].

RCT (2010)

- A randomized controlled trial from Sciurba et al. in 2010 [65].

pilot study (2010)

- A pilot study from Sterman et al., inclusion of 91 patients in the year 2010 [143].

- Kotecha et al. conducted a retrospective cohort study in 2010 including 23 patients [144]. — cohort study (2010)
- Case series from Venuta et al. from 2011 – 40 patients included [145]. — case series (2011)
- One double-blinded sham controlled randomized controlled trial conducted from Ninane et al. in 2012 [146]. — RCT (2012)
- Randomized controlled trial from Herth et al., published in 2012 [66]. — RCT (2012)

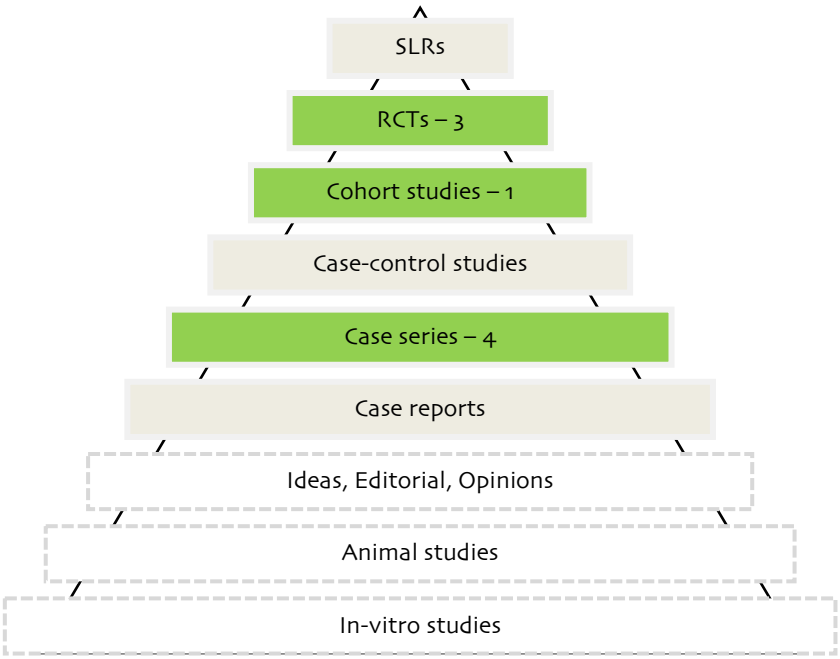

Figure 5.2-1: Evidence pyramid reimbursement Zephyr® in The Netherlands

The Zephyr® device was assessed on the basis of three randomized controlled trials, one cohort study and four case series. The device was not seen as safe and effective by the CVZ. The device was rejected from reimbursement in the year 2012. — 3 RCTs, 1 cohort study, 4 case series basis for rejection

Paracor Ventricular Support System (PVSS)

No assessment for the PVSS could be found on the CVZ homepage. It can be assumed that the device has not been assessed and is therefore not subject to reimbursement in The Netherlands. — no assessment available

Annular repair device Barricaid®

No assessment for the annular repair device could be found on the CVZ homepage. It can be assumed that the device has not been assessed and is therefore not subject to reimbursement in The Netherlands. — no assessment available

Rheofilter ER-4000

The CVZ has published guidance about the Rheopheresis therapy for dry AMD. On the basis of a systematic literature review focusing on the effectiveness of the therapy, the CVZ has concluded that no acceptable evidence — Rheopheresis not recommended for reimbursement

exists to support the effectiveness of the Rheopheresis therapy. In the guidance, the CVZ outlines that there are questions about the rationale of this therapy, that there are no guidelines standardizing the therapy and that many other countries do not reimburse and cover the therapy. Therefore, the CVZ summarizes that Rheopheresis should not be provided in The Netherlands, as the therapy is not confirmed by sound scientific studies. The guidance of published on October 5, 2010 [147].

The CVZ considered the following evidence in its evaluation:

RCT (2000)
- A randomized controlled trial, the MAC-1, published by Brunner et al. in 2000 [148].

SLR (2009)
- A systematic literature review published by Wild et al. in 2009 [81].

RCT (2010)
- The ART-trial, a randomized trial published in 2009 by Koss et al. [83].

RCT (2009)
- Randomized controlled trial by Rencova et al. from 2010 [149].

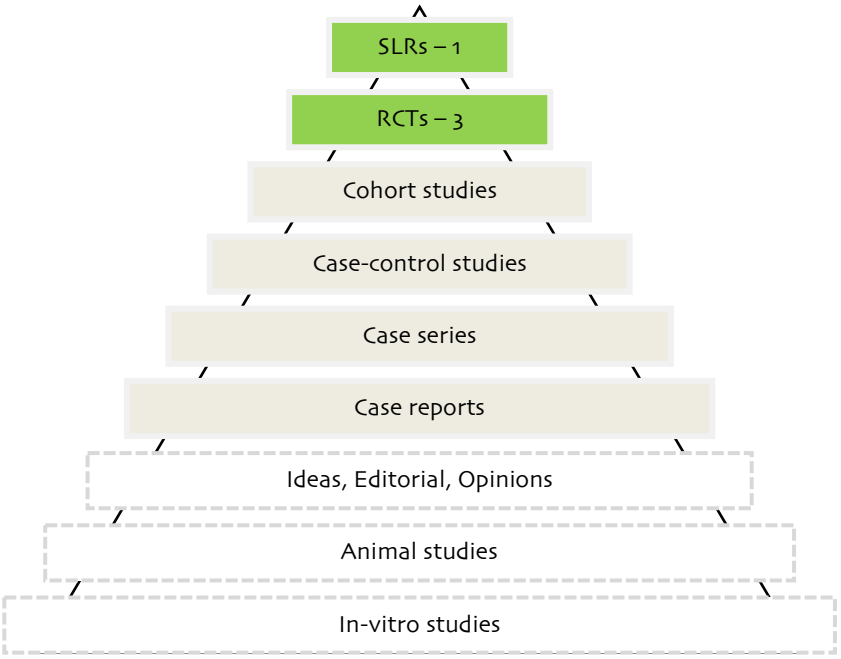

Figure 5.2-2: Evidence pyramid reimbursement Rheofilter ER-4000 in The Netherlands

1 SLR, 3 RCTs basis for rejection

The Rheofilter ER-4000 was assessed by the CVZ considering one systematic literature review and three randomized controlled trials. On the basis of the available evidence, reimbursement cannot be approved by the CVZ.

BSD-2000 Microwave Hyperthermia System

hyperthermia not recommended for reimbursement for bladder carcinoma

The published guidance from June 24, 2011 focuses on the combination therapy of hyperthermia and chemotherapy for bladder carcinoma. The CVZ concludes that this therapy cannot be considered a therapy conforming with the scientific standards. Reimbursement is not advised [150].

In the evaluation report the following evidence is included:

- In 1998, Colombo et al. published another case series [151]. — case series (1998)
- A guidance report from NICE about hyperthermia from 2007 [152]. The NICE SR included the following clinical trials: — guidance report (2007)
  - Gofrit et al. published a case series in 2004 [153]. — case series (2004)
  - In 2004, another case series was published by van der Heijden et al. [154]. — case series (2004)
  - In 2003, a randomized controlled trial was published by Colombo et al. [155]. — RCT (2003)
  - In 2001, a comparative study was published by Colombo et al. [156]. — comparative study (2001)
  - Colombo et al. published a randomized controlled trial in 1996 [157]. — RCT (1996)
  - In 1995, Colombo et al. published an article about a case series [158]. — case series (1995)
- In the same year, 2011, another case series was published by Nativ et al. [159]. — case series (2009)
- Witjes et al. published a case series in 2009 [160]. — case series (2009)
- In 2011, a randomized controlled trial was conducted by Colombo et al. [161]. — RCT (2011)

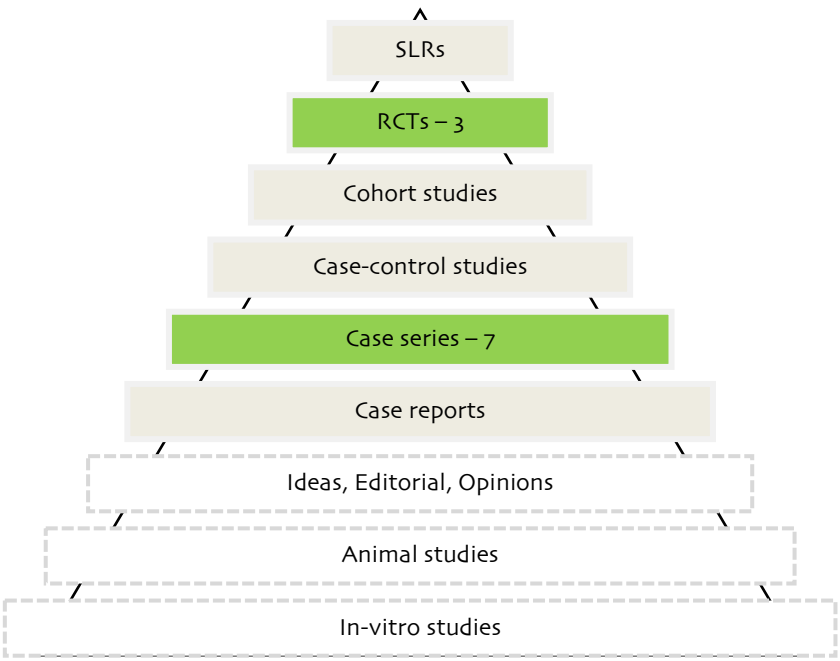

Figure 5.2-3: Evidence pyramid reimbursement BSD-2000 in The Netherlands

The CVZ considered all the evidence from a SR from the NICE and conducted an additional literature search. In total, the reimbursement decision is based on three randomized controlled trials and seven case series. The evidence from all these studies is not enough to support the hyperthermia treatment for reimbursement limited to the indication of bladder carcinoma. — 3 RCTs, 7 case series as basis for rejection

Amplatzer™ PFO Occluder

no assessment available

No assessment for the Amplatzer™ PFO Occluder System could be found on the CVZ homepage. It can be assumed that the device has not been assessed and is therefore not subject to reimbursement in The Netherlands.

MitraClip®

no assessment available

No assessment for the MitraClip® could be found on the CVZ homepage. It can be assumed that the device has not been assessed and is therefore not subject to reimbursement in The Netherlands.

3 devices not recommended for reimbursement, no assessment available for other 4 devices

From the seven authorized high-risk medical devices, three have been subject to negative guidance and were not recommended for reimbursement by the CVZ. The other four have not yet been assessed.

5.2.2 The healthcare system in Germany

obligatory social insurance system

The Statutory Health Insurance Funds (SHIs) are responsible for the costs of healthcare delivery to their insured members. Private health insurance exists and can be used for extra services or if the income of the insured member exceeds a certain threshold.

medical devices in inpatient and ambulatory use – different reimbursement

Medical devices are used in inpatient and ambulatory settings, and the reimbursement and funding mechanisms for the both settings are different. It can be recognized that all medical devices and diagnostics are subject to contracts, yet these contracts differ between the inpatient and ambulatory setting.

for the inpatient sector the state negotiates contracts with the hospitals

The inpatient sector mechanism is regulated by the "hospital funding act." The principle mechanism of the reimbursement by the SHIs is based on a prospective payment system (PPS), also called the German Diagnosis Related Group (DRG). The ambulatory setting is served by physicians that are paid in accordance with the EBM (Einheitlicher Bemessungsmassstab), which includes a mix of services delivered, number of patients served and a fixed budget distribution system.

three important institutes involved in the reimbursement assessment: G-BA, IQWIG and MDS

Three institutes are responsible for the pre-reimbursement assessments and coverage decisions: The G-BA, (Gemeinsamer Bundesausschuss – Federal Joint Committee) is the main governmental body responsible for taking decisions about reimbursement of pharmaceuticals and medical devices. It is the highest decision-making body of the joint self-government of health insurance funds, hospitals, physicians and dentists in Germany. The G-BA conducts and performs assessments of new medical devices or services and issues directives for the benefit catalogue of the statutory health insurance funds. Through these directives, the G-BA specifies which medical services are reimbursed by the statutory health insurance funds. However, some assessments are forwarded to the second selected institute, the IQWIG (the Institute for Quality and Efficiency in Healthcare). The IQWIG is an independent HTA institute assessing medical technologies and giving recommendations about their characteristics. The third body, the MDS, is an umbrella organization of German sickness funds; the MDS assessments are not publicly available.

Guidance on the medical devices in Germany

In the European Union, all seven exemplary medical devices were authorized by the Notified Bodies. The G-BA, the IQWIG and the MDS were searched for assessments and published guidance. The reimbursement decisions are provided in German or English.

all seven devices carry CE marking

Table 5.2-2: G-BA, IGWIQ and MDS recommendations

Medical device	Guidance from G-BA	Guidance from IQWIG	Guidance from MDS
Zephyr® Endobronchial Valve	Report about therapies for COPD	Guidelines for the treatment of COPD	No information available
Paracor Ventricular Support System (PVSS)	No assessment	No assessment	No assessment
Annular repair device Barricaid®	No assessment	No assessment	No assessment
Rheofilter ER-4000	No recommendation (2003)	No assessment	No assessment
BSD-2000 Microwave Hyperthermia System	No recommendation (2005)	No assessment	No assessment
Amplatzer™ PFO Occluder	No assessment	No assessment	No assessment
MitraClip®	No assessment	No assessment	No recommendation (2012)

Zephyr® Endobronchial Valve

The G-BA published a decision about therapies for COPD. Within this decision, it is stated that operative procedures for the treatment of emphysema should be used with caution. The Zephyr® device is not explicitly mentioned. The decision is dated September 21, 2004 [162].

operative procedure for COPD used with high caution

The IQWIG recently published a preliminary report with guidelines for the treatment of COPD on May 8, 2013. However, the treatment with any endobronchial valve and its assessment were not included [163].

guidelines for the treatment of COPD

No assessment was available from the MDS.

no assessment available

The manufacturer has provided a complete literature list and explanation of how to access treatment with the endobronchial valve. The treatment can be organized by contacting the manufacturer.

access to device through manufacturer

Paracor Ventricular Support System (PVSS)

No assessment for the Paracor Ventricular Support System could be found within the G-BA, IQWIG or MDS databases. It can be assumed that the device has not been assessed and is therefore not subject to reimbursement in Germany.

no assessment available

Annular repair device Barricaid®

No assessment for the annular repair device Barricaid® could be found within the G-BA, IQWIG or MDS databases. It can be assumed that the device has not been assessed and is therefore not subject to reimbursement in Germany.

no assessment available

Rheofilter ER-4000

report about Rheopheresis treatment

For the treatment of AMD with Rheopheresis, a 2003 evaluation report by the G-BA is available. A broad range of indications for Rheopheresis treatment are discussed in the report. In addition, the report states that currently the Rheopheresis treatment cannot be advised for inclusion into the standard of care [164].

The evidence considered within the report is summarized as follows:

RCT (1999)

- In 1999, an article about a prospective randomized controlled trial was published by Swartz and Rabetoy [165].

RCT (2000)

- Brunner et al. published a prospective randomized controlled trial in 2000 [148].

summary (2011)

- A summary of the MIRA-I randomized trial presented at a conference in 2011 [166].

No assessment for the Rheofilter ER-4000 could be found within the IQWIG or MDS databases.

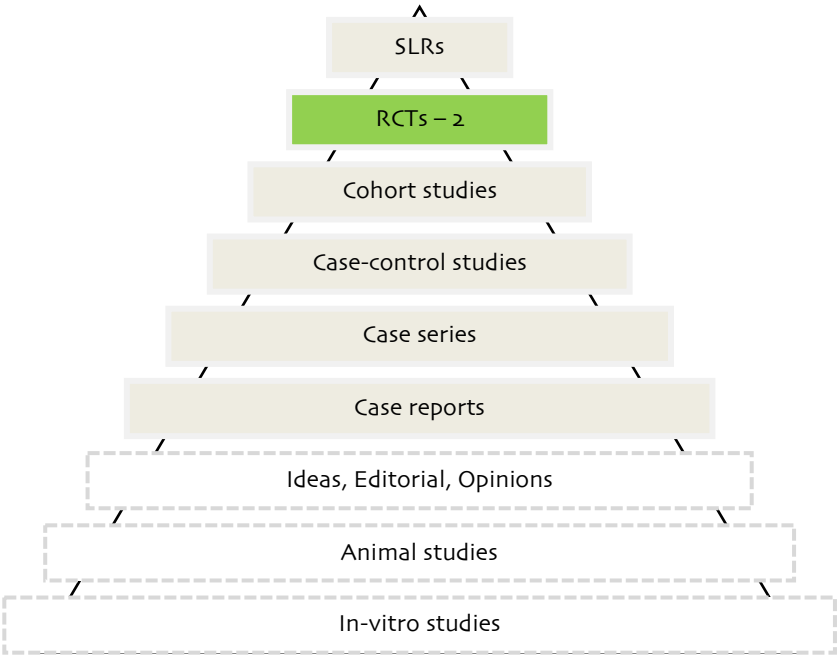

Figure 5.2-4: Evidence pyramid reimbursement Rheofilter ER-4000 Germany

2 RCTs, 1 summary basis for rejection

The G-BA has assessed the Rheopheresis treatment for AMD based on two randomized controlled trials and one summary of an on-going trial. With this evidence as basis, the treatment is not recommended for reimbursement.

BSD-2000 Microwave Hyperthermia System

G-BA report about hyperthermia treatment

The G-BA published an evaluation report about whole-body or partly hyperthermia treatment in 2005. The report focuses on different indications for the treatment, concluding that currently hyperthermia should only be used under investigational circumstances with caution [167].

The evidence used for this report is indication-specific, but special attention was paid to cervical cancer and the treatment with hyperthermia. Five primary studies were evaluated in more depth for the report:

- A prospective randomized study published by Sharma et al. in 1990 [168]. — RCT (1990)
- A randomized controlled trial as well from Sharma et al. in 1991 [169]. — RCT (1991)
- Case series by Gupta et al. from 1999. Included were 69 patients [170]. — case series (1999)
- A randomized controlled trial published in 2001 by Harima et al. [171]. — RCT (2001)
- Van der Zee and Gonzales reported about the Dutch Deep Hyperthermia Trial, a multicenter, randomized clinical trial in 2002 [172]. — RCT (2002)

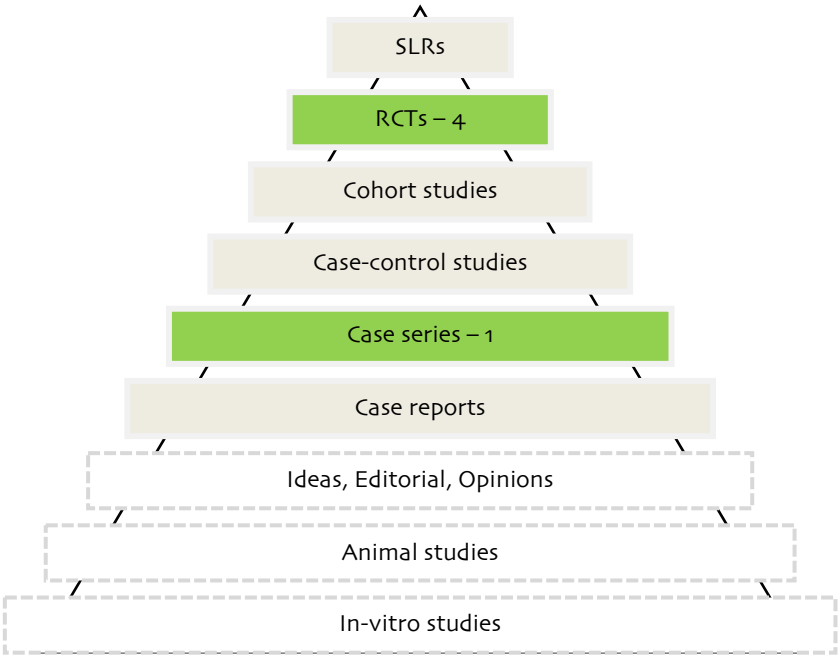

Figure 5.2-5: Evidence pyramid reimbursement BSD-2000 Microwave Hyperthermia System Germany

4 RCTs, 1 case series basis for no reimbursement

The G-BA published a report concluding that hyperthermia cannot be reimbursed on the basis of the available evidence. The decision was taken with primary focus on four randomized controlled trials and one case series.

Amplatzer™ PFO Occluder

no assessment available

No assessment for the Amplatzer™ PFO Occluder could be found within the G-BA, IQWIG or MDS databases. It can be assumed that the device has not been assessed and is therefore not subject to reimbursement in Germany.

MitraClip®

MitraClip® not recommended for reimbursement

Within the MDS database, a summary of newly evaluated medical technologies includes the assessment of the MitraClip®. After assessing the device, the summary states that the device is currently not recommended for reimbursement, as no clear beneficial therapeutic value can be identified. The assessments summary was published in August 2012. The assessment was carried out in collaboration with the LBI-HTA.

No assessment for the MitraClip® could be found within the G-BA and IQWIG databases. It can be assumed that the device has not been assessed and is therefore not subject to reimbursement in Germany.

3 devices not recommended for reimbursement, 4 no assessments available

From all seven medical devices that have been approved by the accredited Notified Bodies, three have received negative recommendations for the reimbursement. Four devices have not been assessed so far.

5.2.3 The healthcare system in England

healthcare system based on NHS – funded by population taxes

In England, the healthcare system is based on the National Health Service (NHS). The NHS is funded by taxes and NHS coverage for health services is comprehensive and, in most cases, free of charge. The Secretary of State of Health is responsible for the provision of health services within the NHS. Further, the NHS is divided into ten so-called strategic health authorities (SHA). The SHAs are in charge of supervising the NHS trusts in their respective areas.

NICE main advising body in reimbursement decisions to the NHS

The central advising body to the NHS is the National Institute for Health and Care Excellence (NICE). The department of the Medical Technologies Advisory Committee (MTAC) is the main body responsible for medical devices within the NICE. The main criteria the NICE uses for the assessment of a product are clinical evidence and economic evidence. Each assessment can lead to recommendations that are classified in four categories: recommended, optimized, only in research or not recommended. A specified program for medical technologies and their evaluation exits. This program, the "Medical Technologies Evaluation Programme," selects and evaluates new or innovative medical technologies to help the NHS adopt efficient and cost effective medical devices more rapidly and consistently.

Guidance on the medical devices in England

All seven devices were granted the CE marking for Europe. The NICE was searched for guidance reports available for the devices.

Table 5.2-3: NICE recommendations

Medical device	Guidance from the NICE
Zephyr® Endobronchial Valve	No recommendation (2013)
Paracor Ventricular Support System (PVSS)	No assessment available
Annular repair device Barricaid®	Assessment in progress (2013)
Rheofilter ER-4000	Not used within NHS care (2010)
BSD-2000 Microwave Hyperthermia System	Only for use in clinical settings (2007)
Amplatzer™ PFO Occluder	No safety concerns – efficacy not proven (2005)
MitraClip®	Not recommended for reimbursement (2009)

Zephyr® Endobronchial Valve

Zephyr is not recommended for reimbursement

Guidance and recommendations for the usage of the therapy with endobronchial valves were found on the NICE homepage. The NICE states that current evidence on the efficacy and safety of insertion of endobronchial valves for persistent air leaks is limited in both quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit, or research. The guidance is from September 2013 [173].

Evidence that was used within the report is as follows:

- Sternman et al. published about a case series in 2010 [143]. — case series (2010)
- A randomized controlled trial by Sciurba et al. in 2010 [65]. — RCT (2010)
- Case series by Venuta et al. in 2011 included 98 patients [62]. — case series (2011)
- Hopkinson et al. reported about a case series including 19 patients in 2011 [174]. — case series (2011)
- Herth et al. reported about a randomized controlled trial in 2012 [66]. — RCT (2012)
- Another randomized controlled trial by Ninane et al. in 2012 [146]. — RCT (2012)
- Herth et al. published a case series including 96 patients in 2012 [175]. — case series (2012)

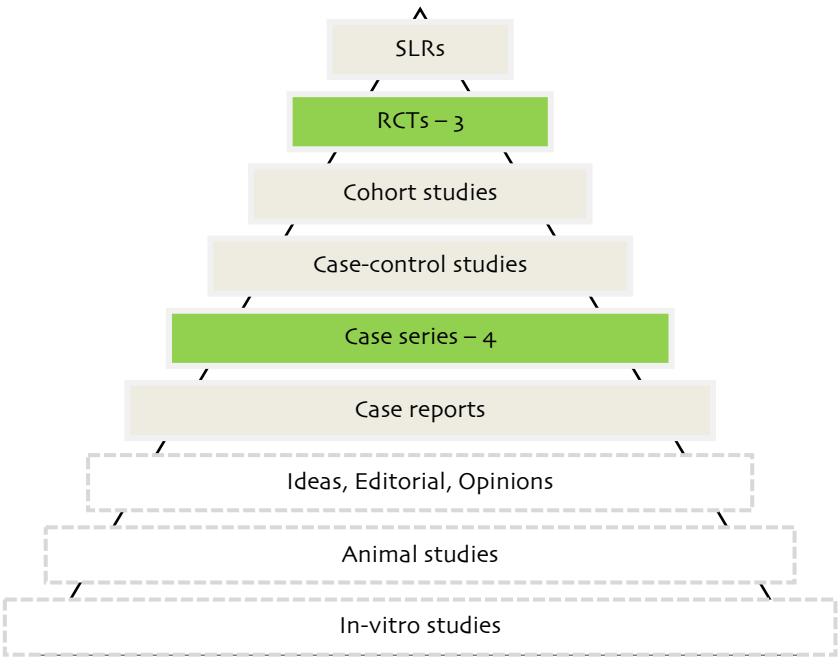

Figure 5.2-6: Evidence pyramid reimbursement Zephyr England

4 RCTs, 1 case series basis for no reimbursement

The decision from the NICE was based on four randomized controlled trials and one case series. The evidence presented within those five articles was not enough to support reimbursement.

Paracor Ventricular Support System (PVSS)

no assessment available

Many different assessments were presented on the NICE homepage for cardiovascular technology guidance, but no report focused on the PVSS system. Therefore, no information about the device is available.

Annular repair device Barricaid®

assessment in progress

It is stated on the NICE homepage that the Institute has been informed about the annular disc implant lumbar discectomy procedure and the guidance report is in progress. NICE is still waiting for further publications on this topic.

Rheofilter ER-4000

not used within NHS care

NICE stated that the Rheopheresis treatment is not used within the NHS care. The treatment is limited to official UK research centres. The notice is from March 30, 2010.

BSD-2000 Microwave Hyperthermia System

only for use in clinical trial settings

The NICE published a guidance report in 2007 about the treatment of bladder cancer with microwave hyperthermia and chemotherapy. It concluded that the treatment should only be used in clinical trial settings, since evidence is very limited [176].

Evidence that was used in the report:

case series (1995)
- A case series by Colombo et al. in 1995 [158].

RCT (1996)
- A randomized controlled trial by Colombo et al. from 1996 [157].

case-control study (2001)
- In 2001, a non-randomized controlled trial by Colombo et al. [156].

RCT (2003)
- A randomized controlled trial in 2003 by Colombo et al. [155].

case series (2004)
- Case series by Gofrit et al. in 2004 [153].

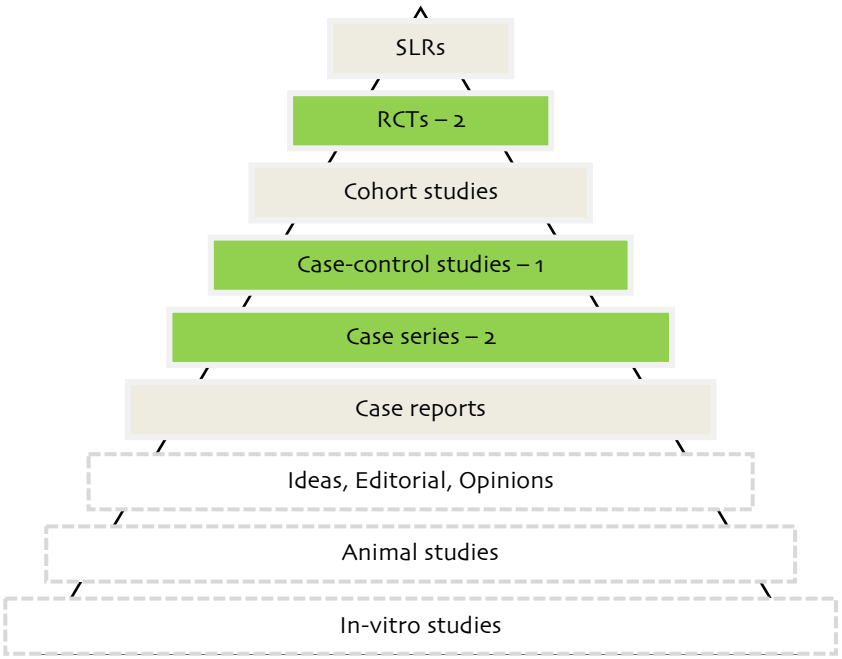

Figure 5.2-7: Evidence pyramid reimbursement BSD-2000 Microwave Hyperthermia System England

2 RCTs, 1 case-control, 2 case series for decision

The NICE considered two randomized controlled trials, one case-control study and two case series for the guidance report about hyperthermia treatment for bladder cancer. The NICE reached the decision that the treatment should only be used within clinical trial settings.

Amplatzer™ PFO Occluder

A guidance report from January 2005 by NICE for the percutaneous closure of patent foramen ovale for the prevention of cerebral embolic stroke states that current evidence suggests that there are no major safety concerns and that percutaneous closure of patent foramen ovale for the prevention of cerebral embolic stroke is efficacious in achieving closure of the foramen. However, its efficacy in preventing future strokes has not been clearly shown [177].

no major safety concerns, but efficacy is not proven

Evidence sources used for the guidance document are not accessible – it is stated on the NICE homepage that the requested document is currently not available and that it was last updated on February 8, 2011.

MitraClip®

The NICE issued a guidance report on percutaneous mitral valve leaflet repair for mitral regurgitation in August 2009. The report states that evidence on the safety and efficacy of the procedure is currently inadequate in quantity and quality. It is explained that the procedure should only be used with special arrangements and in the context of clinical research [178].

evidence is inadequate in quality and quantity

Evidence that was used in the guidance report is:

- Dang et al. reported about a case series in 2005 with six patients included [179]. — **case series (2005)**
- A phase I trial including 27 patients by Feldman et al. in 2005 [180]. — **phase I trial (2005)**
- Herrmann et al. published an article about a phase I trial in 2006 including 27 patients [113] — **phase I trial (2006)**
- A case study was presented by Condado et al. in 2006, looking at one patient [181]. — **case study (2006)**
- A multicenter case series from 2008 published by Silvestry et al. [104]. — **case series (2008)**

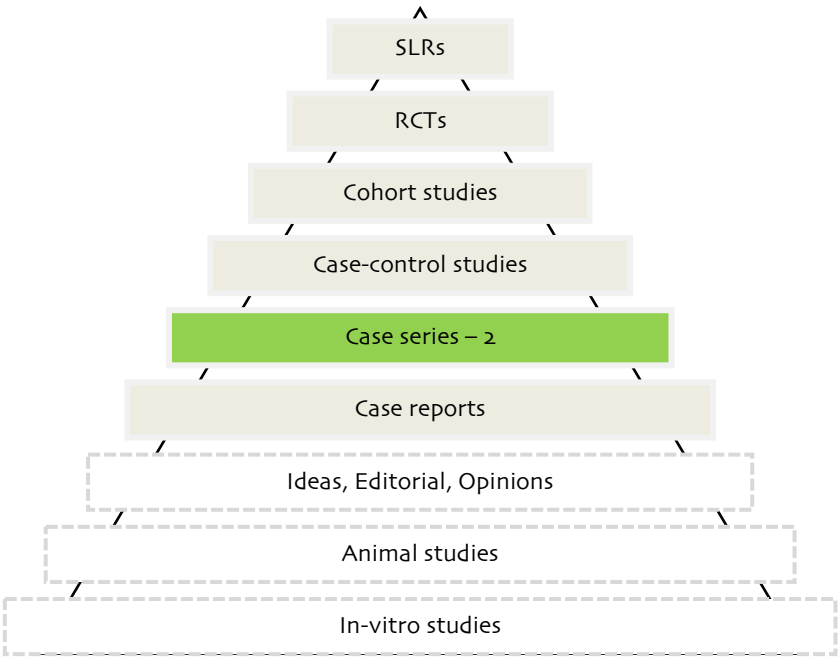

Figure 5.2-8: Evidence pyramid reimbursement MitraClip® England

2 case series, 2 phase I trials as evidence

NICE based the guidance report on two case series and two phase I trials. The Institute considered the evidence as inadequate and the procedure was therefore not recommended.

5.2.4 The healthcare system in Austria

social security system based on mandatory public insurance

The Statutory Health Insurance Funds (SHIs) are responsible for the costs of healthcare delivery to their insured members. Private health insurance exists and can be used for extra services or if the income of the insured member exceeds a certain threshold.

highly decentralized system

The system is highly decentralized with the Ministry of Health formulating the policy framework and the nine federal states managing the healthcare delivery. The main association of the Austrian Social Security Institutions (Hauptverband der österreichischen Sozialversicherungsträger) and the associated 19 sickness funds ensure the implementation of this social insurance system. In general, healthcare contributions are based on the income of the insured person, with exemptions made for low-income and severely ill individuals. There are three different benefit catalogues (for drugs, for ambulatory care and for hospital interventions).

LBI-HTA advising body in reimbursement process

The Ludwig Boltzmann Institute for Health Technology Assessment (an independent academic institute) is contracted by the Ministry of Health to evaluate medical interventions delivered in hospitals. The institute focuses on clinical effectiveness and safety.

Guidance on the medical devices in Austria

In the European Union, all seven devices have been granted CE marking. In the following, the evidence from guidance reports for Austria for the seven devices is summarized.

Table 5.2-4: LBI-HTA recommendations

Medical device	Guidance from the LBI
Zephyr® Endobronchial Valve	No recommendation (2010)
Paracor Ventricular Support System (PVSS)	No information available
Annular repair device Barricaid®	No recommendation (2013)
Rheofilter ER-4000	No recommendation (2008)
BSD-2000 Microwave Hyperthermia System	No recommendation (2012)
Amplatzer™ PFO Occluder	No assessment
MitraClip®	No recommendation (2012)

Zephyr® Endobronchial Valve

The LBI-HTA published a decision support report in February 2010 about the endobronchial valve implementation for COPD. This report states that it is not recommended to reimburse the procedure with the valve. Available evidence could not prove whether there is a therapeutic benefit for the patient [182]. **not recommended for reimbursement**

The report considered the following evidence in its recommendation:

- Toma et al. published a case series in 2003 including eight patients [183]. **case series (2003)**
- In the same year, 2003, Sabanathan et al. likewise published a case series with eight patients [184]. **case series (2003)**
- Snell et al. reported about a case series including ten patients in 2003 [185]. **case series (2003)**
- In 2004, a case series was published by Yim et al. including 21 patients [186]. **case study (2004)**
- In 2005, Venuta et al. published an article about a case series including 13 patients [187]. **case series (2005)**
- In the same year, 2005, Hopkinson et al. reported about a case series including 19 patients [61]. **case series (2005)**
- In 2006, de Oliveira et al. published a case series including 19 patients [141]. **case series (2006)**
- Wan et al. included 98 patients in a case series in 2006 [62]. **case series (2006)**
- In 2007, Wood et al. reported about a case series including 30 patients [188]. **case series (2007)**
- The randomized controlled trial VENT from 2010. **RCT (2010)**

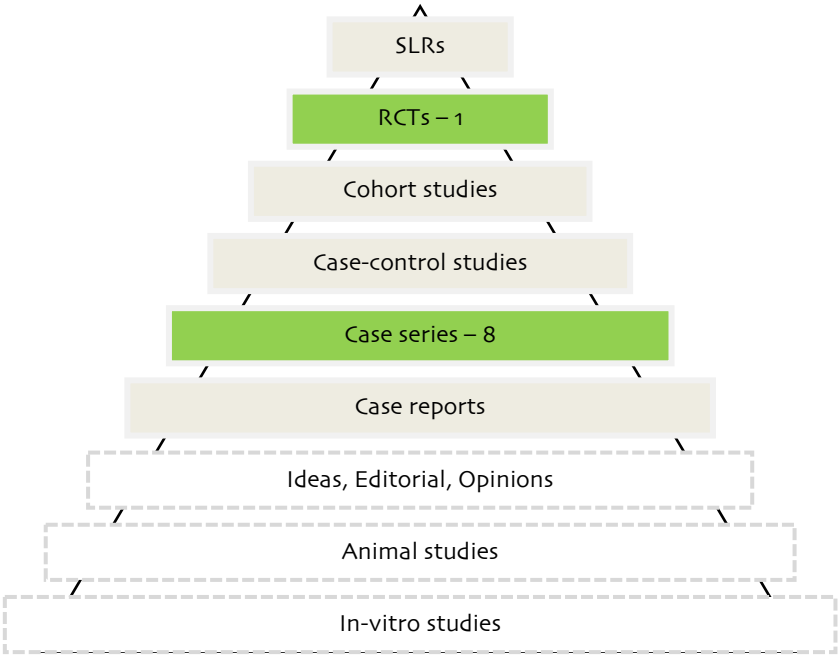

Figure 5.2-9: Evidence pyramid reimbursement Zephyr® Endobronchial Valve Austria

The recommendation by the LBI-HTA is based on one randomized controlled trial and eight case series. It is currently not recommended to reimburse the device in Austria, as the available evidence is not strong enough. **recommendation based on 1 RCT and 8 case series**

Paracor Ventricular Support System (PVSS)

no assessment available

No assessment for the PVSS could be found within the LBI-HTA decision support documents. It can be assumed that the device has not been assessed and is therefore not subject to reimbursement in Austria.

Annular repair device Barricaid®

not recommended for reimbursement

The LBI-HTA recently published a decision support document in March 2013 about the therapy with the Barricaid® device. The report states that current evidence cannot ensure the safety and effectiveness of the procedure and, therefore, the reimbursement recommendation is negative [189].

Evidence considered within the report is as follows:

case series (2012)
- Multicenter prospective case series by Lequin et al. in 2012 [75].

case series (2012)
- Case series from Intrinsic Therapeutics – a Clinical Evaluation Report including 30 patients from 2012.

abstracts
- Ten conference abstracts focusing on the two studies.

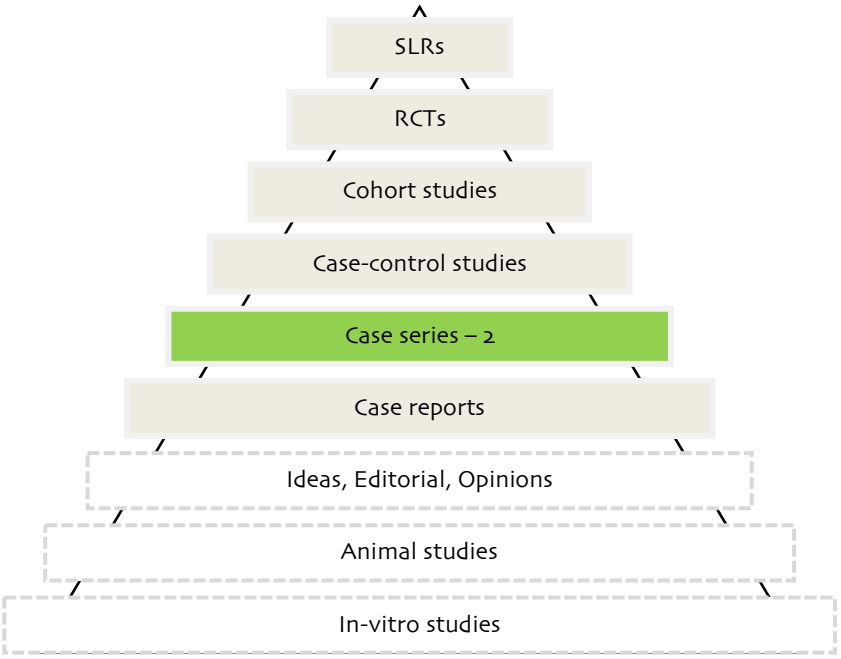

Figure 5.2-10: Evidence pyramid reimbursement Barricaid® Austria

2 case series basis for recommendation

The report from the LBI-HTA considers two case series as the basis for the recommendation. It is currently not advised to reimburse the device, but a re-evaluation in four years (2017) is recommended as two more clinical trials are still on-going.

Rheofilter ER-4000

not recommended for reimbursement

In March 2008, a decision support document by the LBI-HTA stated that it is not recommended to reimburse the Rheopheresis procedure. The current evidence is not enough to ensure a therapeutic benefit for patients [190].

The evidence included in the report is listed below:

- Brunner et al. published an article about a randomized controlled trial in 2000 [148]. — RCT (2000)
- Interim results published by Pulido in 2002 from the MIRA-I trial. — interim results – RCT (2002)
- Klingel et al. published a prospective open label trial in 2003 [79]. — case series (2003)
- The RheoNetRegistry report from Klingel et al. in 2005 [82]. — registry (2005)
- Pulido et al. published preliminary results of the MIRA-I trial in 2006 [80]. — final RCT (2006)

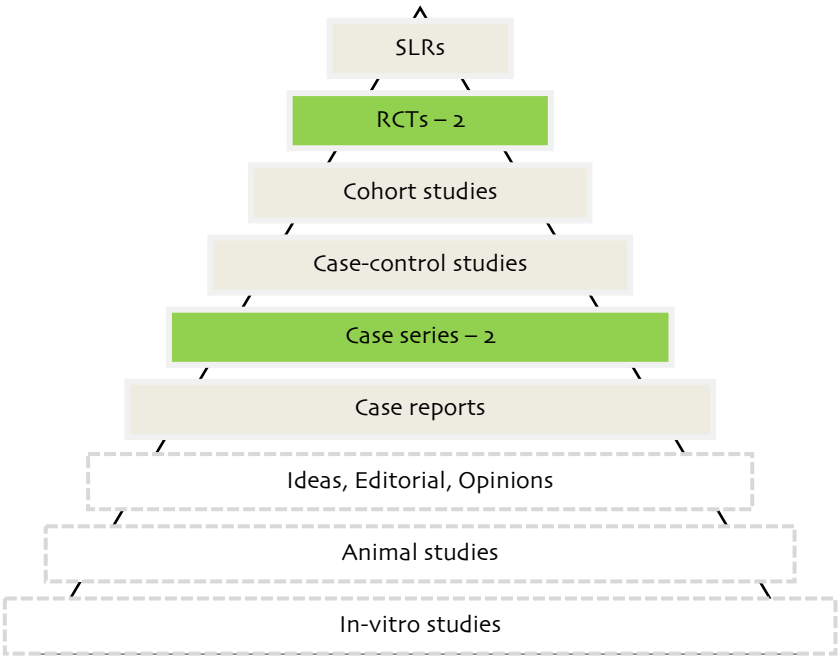

Figure 5.2-11: Evidence pyramid reimbursement Rheofilter-ER 4000 in Austria

2 RCTs and 1 case series/registry basis for recommendation

The negative decision is based on two randomized controlled trials, from one of which only interim results were available, and on one case series and one registry study. It is currently not advised to reimburse the procedure.

BSD-2000 Microwave Hyperthermia System

not recommended for reimbursement

Two decision support documents were published by the LBI-HTA, both focusing on the hyperthermia procedure. The first document, from March 2010, recommended not to reimburse the procedure for several cancer indications. The second document from December 2012 confirmed the first report by stating that current evidence is insufficient to make a judgment about the procedure's clinical benefit and possible associated risks.

The evidence that was used in the latter report from 2012 splits the studies included over four indications, namely breast cancer, bladder cancer, cervix cancer, and soft tissue sarcoma. All studies are presented in the following [191]:

RCT (1989)
- A randomized controlled trial from Sharma et al. in 1989.

RCT (1991)
- A randomized controlled trial for breast tumors from 1991, published by Perez et al. [192].

RCT (1996)
- A randomized controlled trial from Colombo et al. in 1996 [157].

RCT (1996)
- A randomized controlled trial from Vernon et al. published in 1996 [193].

RCT (2001)
- A randomized controlled trial from 2001 by Harima [171].

RCT (2002)
- Van der Zee et al. published a randomized controlled trial in 2002 [172].

RCT (2003)
- Published by Colombo et al. in 2003, a randomized controlled trial. [155].

RCT (2005)
- In 2005, a randomized controlled trial from Vasanthan et al. [194].

follow-up (2008)
- A long-term follow-up by Franckena et al. in 2008 [195].

RCT (2010)
- A randomized controlled trial published by Issel et al. in 2010 [196].

follow-up (2011)
- A long-term follow-up by Colombo et al. from 2011 [161].

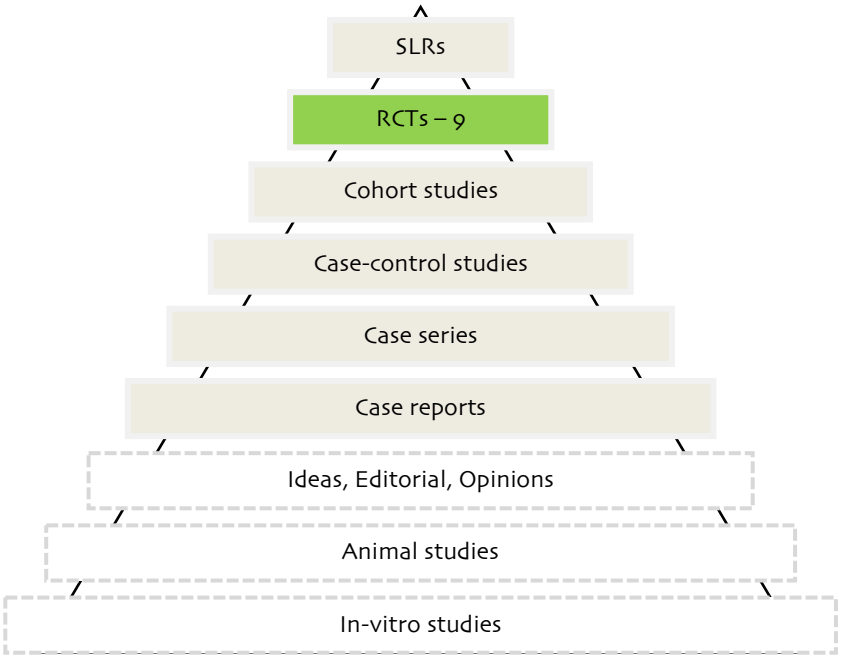

Figure 5.2-12: Evidence pyramid reimbursement BSD-2000 Austria

9 RCTs and 2 follow-ups as basis for recommendation

The (repeated) recommendation to not reimburse hyperthermia treatment was based on nine randomized controlled trials and two long-term follow-up studies. The LBI-HTA states that the evidence available for the therapy is insufficient to make a judgment on its clinical benefit because of the lack of patient-relevant endpoints (rather than surrogate endpoints) and associated risks.

Amplatzer™ PFO Occluder

No assessment for the Amplatzer™ PFO Occluder could be found within the LBI-HTA decision support documents. It can be assumed that the device has not been assessed and is therefore not subject to reimbursement in Austria.

no assessment available

MitraClip®

The MitraClip® was assessed several times (2010, 2012). The updated report concludes that the reimbursement procedure is currently not recommended. The decision is based on insufficient evidence to ensure the efficacy and safety of the procedure [197].

not recommended for reimbursement

The evidence used in the report is as follows:

- EVEREST I – randomized controlled trial from 2005. **RCT (2005)**
- A prospective case series published in 2009 by Feldman et al. [114]. **case series (2009)**
- A randomized controlled trial from 2011 published by Feldman et al. – EVEREST II. **RCT (2011)**

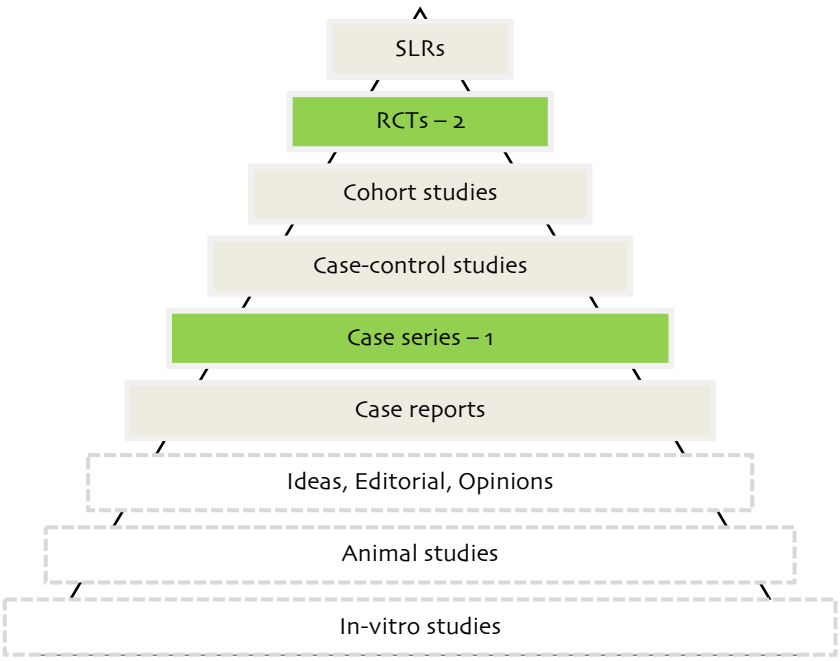

Figure 5.2-13: Evidence pyramid reimbursement MitraClip® Austria

The report from the LBI-HTA bases its decision on one randomized controlled trial and on one case series. The conclusion states that it is currently not advised to reimburse the MitraClip®.

2 RCT and 1 case series as basis for recommendation

From the seven authorized medical devices, five have been assessed by the LBI-HTA and not recommended for reimbursement. No assessment is available for two devices.

5 devices not recommended for reimbursement, no assessment available for 2 devices

5.3 Australia

health responsibility of six states and two territories

In Australia, the federal government is known as the Commonwealth Government. The Australian Government Department for Health and Ageing is a nationwide body that strives to implement uniform regulations in the healthcare sector.

The following chapter introduces the Australian healthcare system and its main features. In addition, the guidance by the Australian Medicare department for the four authorized devices is presented.

5.3.1 The healthcare system in Australia

healthcare provision is ensured through Medicare

The responsibility for healthcare is divided between the federal and the state governments. Yet, Australia ensures its healthcare provision through a large uniform coverage system – Medicare. Medicare is funded through general taxation and includes all hospital and medical services in its coverage scheme. The unique character of Medicare is that it is a governmental coverage system. Medicare is organized within the Department of Human Services.

MSAC advises Medicare about devices to be included into benefit scheme

The Medical Services Advisory Committee (MSAC) is the main body supporting Medicare in its reimbursement decisions. The Australian Government Health Minister has appointed the MSAC to strengthen the role of evidence in health financing decisions in Australia. The main evidence the MSAC focuses on during their assessments is safety, effectiveness, cost-effectiveness and budgetary impact.

Guidance on the medical devices in Australia

Table 5.3-1: MSAC recommendations

Medical device	Recommendation MSAC
Zephyr® Endobronchial Valve	Not supported for public funding (2001)
Annular repair device Barricaid®	No assessment available
Amplatzer™ PFO Occluder	Consultation still on-going (2013)
MitraClip®	Not supported for public funding (2012)

Zephyr® Endobronchial Valve

no public funding supported

The MSAC published a final decision report on lung volume reduction surgery in February 2001. In this report it was stated that the committee does not support public funding of the procedure. In April 2001, this recommendation was adopted by the ministry [198].

The following evidence was used in the assessment:

retrospective analysis (1998)

- Retrospective analysis of emphysema patients published by Licker et al. in 1998 [199].

RCT (2000)

- A randomized study by Geddes et al. from 2000 [200].

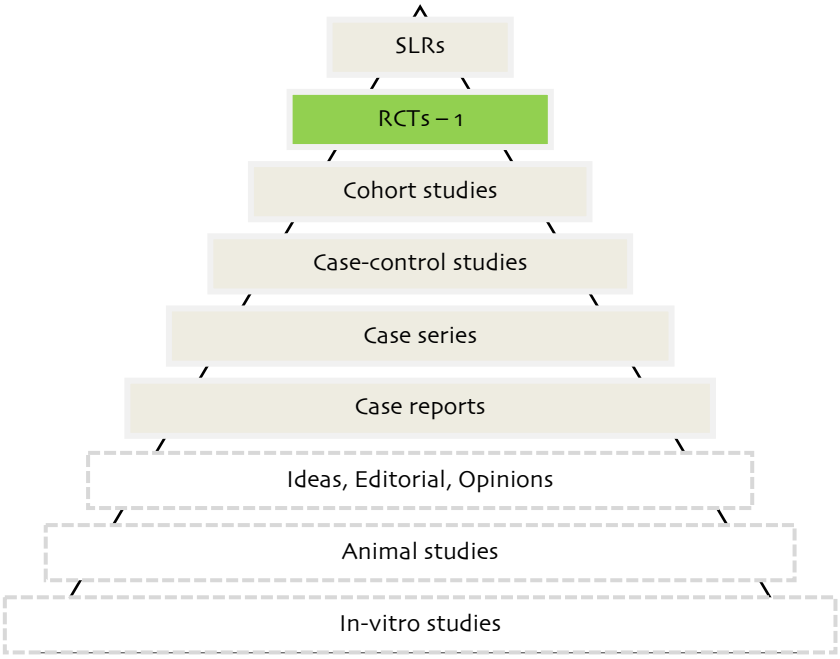

Figure 5.3-1: Evidence pyramid reimbursement Zephyr Australia

The MSAC based its recommendation on two studies – a randomized controlled trial and a retrospective analysis. Based on this evidence, public funding was not supported in 2001.

1 RCT, 1 retrospective analysis as basis for decision

Annular repair device Barricaid®

No assessment for the annular repair device Barricaid® could be found in the MSAC database. It can be assumed that the device has not been assessed and is therefore not subject to reimbursement in Australia.

no assessment available

Amplatzer™ PFO Occluder

The MSAC has published a consultation report and a final decision report about the application and the assessment of transcatheter closure of patent ductus arteriosus. A decision analytic protocol is attached to guide the further assessment of the procedure. Yet, it cannot be gathered from the report whether the MSAC assessment has been concluded or is still on-going. Therefore, no statements can be made about the reimbursement recommendation. The report was published in April 2013.

consultation procedure still on-going

MitraClip®

The MSAC has provided a public summary document about the MitraClip® device and its application for funding. The document is from November 2012. The MSAC advises the Ministry that, considering the strength of the available evidence, the public funding is not supported by the committee [201].

not supported for funding

The evidence used within the document is:

- A randomized controlled (EVEREST II) trial by Glower et al. in 2011 [202]. — **RCT (2011)**
- The EVEREST I data published by Whitlow et al. in 201 [203]. — **RCT (2012)**

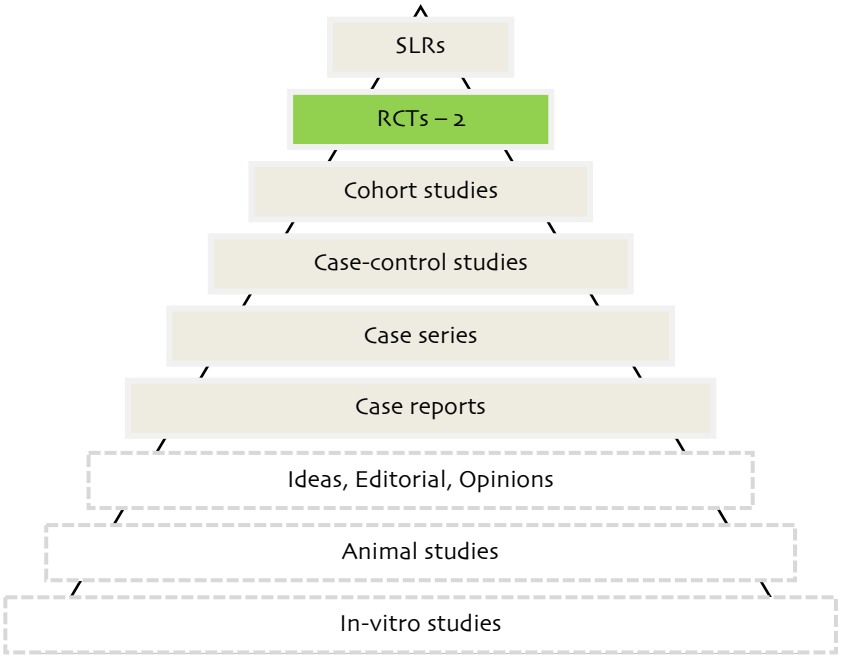

Figure 5.3-2: Evidence pyramid reimbursement MitraClip® Australia

2 RCTs as basis for decision

The MSAC based its decision for a negative recommendation for reimbursement on two available randomized controlled trials.

3 devices assessed with 2 negative recommendations and 1 on-going, 1 device not assessed

Four medical devices have been authorized by the TGA and included into the ARTG. Of the four devices, three have been assessed by the MSAC. Public funding was not supported for two devices. Consultation is still on-going for one device.

5.4 Canada

TPD and CAHR two important bodies

Canada's healthcare system is fairly different from its neighbor country, the United States of America. The TPD, a department within Health Canada, is responsible for the authorization of devices, followed by the CAHR/Canadian Association of Healthcare Reimbursement, where the reimbursement evaluation takes place.

In the following chapter, the healthcare system of Canada is briefly outlined and the guidance given by the CAHR for the one medical device that has been authorized by the TPD is provided.

5.4.1 The healthcare system in Canada

social health insurance plans provide coverage for all citizens

The Canadian healthcare system has a single-payer and mostly publicly funded basis. The system tries to ensure healthcare access for all Canadian citizens. Various social health insurance plans exist that provide coverage for medical items and services. The system is responsible for the administration and is divided on a provincial or territorial basis, with an obligation to adhere to guidelines from the federal government. Under the social health insurance plans, citizens are entitled to ambulatory and hospital care. All citizens qualify for coverage and no distinctions are made regarding medical history, personal income or standard of living.

CAHR provides assessments for pharmaceuticals and medical devices

The CAHR is an institute comprised of members from academia, industry, patient advocacy groups and the government. The association aims at providing a recommendation about the reimbursement for pharmaceuticals and medical devices within the Canadian system.

Guidance on the medical devices in Canada

Table 5.4-1: CAHR recommendation

Medical device	Guidance by the CAHR
Amplatzer™ PFO Occluder	No assessment available

Amplatzer™ PFO Occluder

no assessment available

No assessment for the Amplatzer™ PFO Occluder could be found in the CAHR search function. It can be assumed that the device has not been assessed and is therefore not subject to reimbursement in Canada.

6 Discussion

This research had two main objectives: Firstly, to explore and explain the authorization (premarket approval) systems for medical devices and their respective requirements for clinical evidence in the four selected regions, namely Europe, the United States of America, Canada and Australia. Secondly, to analyze the level of evidence (along the commonly used hierarchy of evidence) used for authorization and reimbursement decisions. As examples, seven high-risk medical devices were selected.

The research has several limitations that have to be recognized. It has been decided to only include high-risk medical devices into this research, because they are the ones most often in the focus of a new regulation of market approval in Europe. There are hundreds of high-risk devices on the markets, and to concentrate on a few only gives a limited, hardly generalizable picture. In addition, only the four selected regions are being considered, because for the time being they represent the most important markets for high-tech medical interventions. Though the Asian and Latin American markets for medical devices are growing fast, their premarket approval systems have not been analyzed. Finally, only seven medical devices have been chosen as an exemplary basis for detailed analysis.

The information provided here is therefore not generalizable and only applicable for the four regions and for a small scope of medical devices. Within the four regions, data collection was limited to accredited regulatory bodies for authorization and for national reimbursement decisions. Only information that was publicly accessible was included. For all these reasons, the information presented is far from being comprehensive.

Authorization

All seven exemplary medical devices have been approved in the European Union through an appointed Notified Body (not known). Four obtained approval by the Australian TGA/Therapeutic Goods Administration (MitraClip®, Amplatzer, Barricaid, Zephyr) and only one each by the US-American FDA (MitraClip®) and by the Canadian TPD/Therapeutics Products Directorate (Amplatzer) (Figure 6-1).

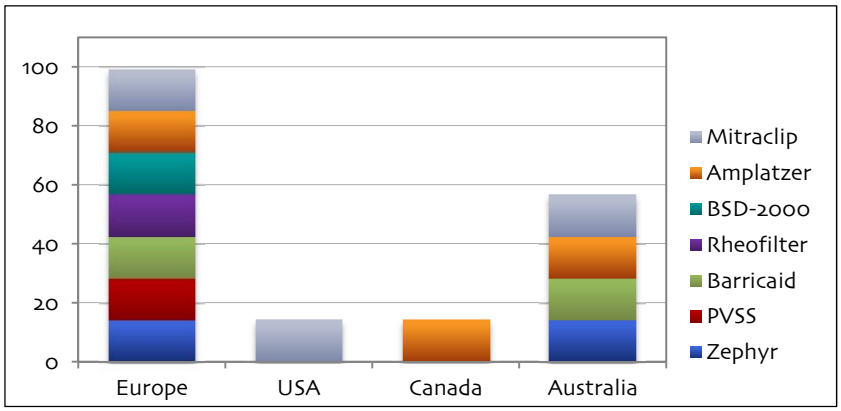

Figure 6-1: Approval of seven selected devices in USA, Europe, Canada, Australia

4 more were assessed in USA (but not generally approved)

In comparison to the other three regulatory systems, the number of approved devices in Europe is strikingly high, especially if additionally considering that four further devices were also assessed by the FDA, but not approved: Two did not obtain approval (Zephyr and PVSS), two received only HDE exemptions (in research only: Hyperthermia and Amplatzer), of which one HDE exemption was withdrawn because of an exceeding number of patients per year. A premarket approval is pending.

CE marking 2-5 years before other approvals

with less mature clinical evidence

In almost all of the analyzed seven examples, the premarket approval in Europe was granted two to five years before authorization in other systems. The evidence used for CE marking is not known in all exemplary devices, due to the highly decentralized authorization system and the lack of transparency of the respective Notified Body that issued CE marking. Even if the clinical evidence used is not known, it is naturally less mature (case studies or non-comparative case series only, interim analysis of RCTs) than later premarket approvals.

Table 6-1: Overview on available evidence for authorization and reimbursement and of recommendations for seven devices in Europe, USA, Canada, Australia

Medical Device	Authorization: year, evidence	Reimbursement: year, evidence, recommendation
Zephyr® Endobronchial Valve		
Europe	2003 (approval), no information	Netherlands (CVZ): 2012, RCT, not recommended Germany (G-BA, IQWIG, MDS): 2004 (operative procedure with caution), 2013 (COPD guideline: valve not mentioned) England (NICE): 2013, RCT, not recommended Austria (LBI-HTA): 2010, RCT, not recommended
USA	2008 (rejection, no authorization), RCT (2007)	No coverage
Canada	No application	No coverage (?)
Australia	No application	MSAC: 2001, RCT, not recommended
Paracor Ventricular Support System (PVSS)		
Europe	2000 (approval), no information	Netherlands (CVZ): no assessment Germany (G-BA, IQWIG, MDS): no assessment England (NICE): no assessment Austria (LBI-HTA): no assessment
USA	2000 (rejection, no authorization), no information	No coverage
Canada	No application	No coverage (?)
Australia	No application	No coverage (?)
Annular repair device Barricaid®		
Europe	2009 (approval), no information	Netherlands (CVZ): no assessment Germany (G-BA, IQWIG, MDS): no assessment England (NICE): assessment in progress Austria (LBI-HTA): 2013, case series, not recommended
USA	No application	No coverage (?)
Canada	No application	No coverage (?)
Australia	2011 (approval), CE marking	No assessment, coverage (?)

Medical Device	Authorization: year, best available evidence	Reimbursement: year, evidence, recommendation
Rheofilter ER-4000		
Europe	1998 (approval), no information	Netherlands (CVZ): 2010, SLR+ RCT, not recommended Germany (G-BA, IQWIG, MDS): 2000, RCT, not recommended England (NICE): 2010, only in research Austria (LBI-HTA): 2008, RCT, not recommended
USA	No application	No coverage (?)
Canada	2002-2005 (approval), withdrawal of authorization on RCT	No coverage
Australia	No application	No coverage (?)
BSD-2000 Microwave Hyperthermia System		
Europe	No information on year (approval), no information	Netherlands (CVZ): 2011, RCT, coverage only cervix carcinoma, not recommended for other indications Germany (G-BA, IQWIG, MDS): 2005, RCT, not recommended England (NICE): 2007, RCT, only in research Austria (LBI-HTA): 2010-2012, RCT, not recommended
USA	Since 2011 (only under HDE, cervix carcinoma), RCT	only in research
Canada	No application	No coverage (?)
Australia	No application	No coverage (?)
Amplatzer™ PFO Occluder		
Europe	No information on year (approval), no infor-mation	Netherlands (CVZ): no assessment, Germany (G-BA, IQWIG, MDS): no assessment England (NICE): 2005 + 2011, not recommended Austria (LBI-HTA): no assessment
USA	Until 2006 (only under HDE), no authorization after 2006	No coverage (?)
Canada	2001 (approval), no information	no assessment
Australia	2006 (approval), no information	MSAC: 2013 assessment, consultation ongoing
MitraClip®		
Europe	2008 (approval), no information	Netherlands (CVZ): no assessment Germany (G-BA, IQWIG, MDS): 2010+2012, RCT, not recommended England (NICE): 2009, case series, not recommended Austria (LBI-HTA): 2010+2012, RCT, not recommended
USA	2013 (approval), RCT	CMS: application for coverage in 2014 Aetna: no information BCBS: no information Healthcare United: coverage, RCT Kaiser Permanente: coverage, no information AHRQ: high impact, RCT
Canada	No application	No coverage (?)
Australia	2010 (approval), no information	MSAC: 2011, RCT, not recommended

? not known, ev. in DRGs included.

low evidence requirements in Europe

Yet, these major differences in the approval of devices support the assumption of a rather easily accessible and low-evidence requirements system for authorization in the European Union [45]. Whereas other countries consider the devices as not safe and effective for the market, they may be legally marketed in Europe. In addition, each of the other systems requires effectiveness data in combination with safety studies during the authorization assessment, except in Europe [47]. Consequently, devices may enter purely on the basis of safety.

These results are in accordance with earlier findings, concluding that the access to new medical devices in Europe is faster with fewer regulatory requirements for high-quality clinical evidence for authorization [16, 204].

evidence collection for authorization is difficult

Further, it has been crucial for this research to access the evidence used for the authorization process in the four selected regions. However, it has been rather difficult to gather enough relevant data from the regulatory authorities in Europe, Australia and Canada, but not so in the USA.

168 decentralized Notified Bodies in EU: no transparency at all

In Europe, with the many (168) decentralized Notified Bodies, all entitled to conduct a conformity assessment and grant the CE marking, no system of transparency is installed, neither for the assessment process nor for the results: There is no publicly available information or summary describing the basis for granting a CE marking. Members of the public, therefore, cannot find out information about the process (place of application, requirements for application, pre-defined criteria for decisions) or the rationale for an approval (efficacy and safety data) [38]. Consequently, the public has no overview of which Notified Body has granted which CE marking, and what evidence has been used to reach this decision.

Australia and Canada: at least of approval

In Australia and Canada, at least publicly accessible databases with information whether the device in question has been approved are installed (as a minimum requirement), but the clinical evidence used for the approvals is also not public. The ARTG listing (Australia) and the TPD device license listing (Canada) can be scanned for information about approved devices. In both systems, every approved device can be found with the respective manufacturer. Nonetheless, evidence that has granted the decision for the approval of the device is not made available for the public.

USA summary of safety and effectiveness data

The FDA is the only regulatory body that has publicly available summaries of safety and effectiveness data for approved or rejected devices. The FDA has a public listing and an accessible database of all approved devices in place. Yet, the evidence gathered for the three devices (MitraClip, BSD-2000 and Zephyr) derived from committee panels. These committee panels were conducted to discuss and review the premarket application of these devices. Generally, it is not the case that such a committee panel is held for every device, but rather only if the FDA urges experts for advice.

Reimbursement

Europe vs. USA, Canada and Australia

The decision making on reimbursement within the four regions and the many countries is very diverse. In the European Union, healthcare has always been regarded as a matter of national sovereignty. Therefore, many (actually 28) different systems exist. In the USA, Canada and Australia, national insurance programs and advisory committees assess devices and give recommendations.

level of evidence ranging from RCTs to case series none of the 7 devices recommended for reimbursement in Europe

In order to facilitate this research, only four countries, namely The Netherlands, England, Germany and Austria and their (national) advising institutes have been selected for a more detailed analysis of health technology assessments as support for reimbursement decisions. In the European Union, all seven medical devices have received CE marking. However, none of the seven medical devices was recommended for reimbursement. Some devices have not been assessed by all bodies, but the majority of those assessed were not supported for (general) reimbursement. Often the reason is that current evidence is not enough to ensure patient benefit and safety. Some devices are recommended for "research only."

patient-relevant outcomes demanded

The evidence levels have ranged from very high – more than one randomized controlled trial – to rather low – uncontrolled case series. However, even after conducting several randomized controlled trials, reimbursement advising institutes looked at the safety and effectiveness in more detail, considering patient-relevant endpoints rather than surrogate endpoints alone.

USA – MitraClip® reimbursement by Healthcare United

The MitraClip®, the only device authorized in the USA, has just very recently been approved and therefore some health insurance programs have not made decisions on the coverage of the device yet. An application for coverage has been submitted and a decision will be taken in 2014. Only Healthcare United has published a final decision paper stating that the MitraClip® will be included in their medical benefit scheme.

Canada: no information Australia: none of the 4 devices recommended for reimbursement

In Canada, no information about the one approved device (Amplatzer) was available. In Australia, all four devices – three of which had been assessed, were not recommended for reimbursement. It was decided that current evidence is not enough for a positive recommendation.

within DRGs the devices are possibly covered

Since diagnostic-related groups (DRGs) are installed in many countries as flat rates for reimbursing medical interventions rather than separate reimbursement of devices, one cannot conclude that – even after negative recommendations – the devices are not in use or not covered.

Evidence requirements in authorization and reimbursement

Europe and Australia – low evidence for authorization vs. strict reimbursement assessment

In this research, it was observed that in Europe the seven medical devices analyzed have received CE marking and passed the gateway of authorization easily, but were then not recommended for reimbursement because of a lack of good quality clinical evidence and relevant outcomes. This can be explained with the very low evidence requirements for the European pre-market authorization and higher requirements for proofs of clinical benefit in national decision-support assessments for reimbursement. The same seems to apply in Australia.

USA – FDA starts with strict assessments

In the USA, the FDA applies much stricter evidence requirements for market authorization. Consequently, it might seem in line that devices that were authorized by the FDA are as well positively recommended by the health insurance programs. But this research generated too little evidence for such a broad conclusion or hypothesis.

Canada no information

In Canada, it is difficult to make observations, as no information was available for the reimbursement assessments of the approved device.

The following figures try to summarize the information on years of approval and development of evidence over the years before and after approval. Only the highest level of evidence available before and after approval of the device is presented.

Table 6-2: Timeline for time of approval(s) and evidence development over the years

Timeline	Device name
2007 – VENT design; 2010 – VENT reporting; 2012 – VENT Europe 2003 – CE marking; 2011 – ARTG inclusion 2008 - PMA rejection FDA	*Zephyr® Endobronchial Valve*
2007– Case series; 2012 – RCT – Rational and design 2000 – CE marking 2000 – PMA rejection FDA	*Paracor Ventricular Support System (PVSS)*
2006 – Prospective, multicenter controlled clinical study 2009 – Benchtop; 2011 – Technical feasibility study 2012 – Non-randomized, partly uncontrolled study 2009 – CE marking; 2011 – ARTG inclusion	*annular repair device Barricaid®*
2003 – SLR; 2005 – SLR; 2009 – SLR 1998 – CE marking; 2002-2005 – Device License	*Rheofilter ER-4000*
1996 – RCT ? – CE marking; 2011 – FDA approval under HDE	*BSD-2000 Microwave Hyperthermia System*
2005/2006 – RCT; 2007/2008 – 3 RCTs; 2011 – RCT; 2012 – RCT; 2013 – SLR 2006 – ARTG inclusion 2001 – Device License ? – CE marking	*Amplatzer™ PFO Occluder*
2005 – RCT; 2011 – RCT; 2013 – RCT; 2013 – SLR 2008 – CE marking; 2011 – ARTG inclusion; 2013 – PMA approval	*MitraClip®*

7 Conclusion

results support change for European authorization system towards a transparent, evidence-based regulation process

It can be mainly concluded that it is strongly recommended that the European authorization (premarket approval) system will need to undergo a change towards transparency in the approval processes and underlying evidence of an authorization result (as access to the market). The requirements outlined in the Open Letter of a number of experts to the EU Commission [38] that Europe needs a "central, transparent, and evidence-based regulation process" holds true especially for high-risk devices when looking at the results of this research. Mutual learning and knowledge exchange monitoring the other authorization systems would enhance improvement.

conditional coverage or coverage under evidence development as instrument between immature data and reimbursement requirements

In addition, several countries have started "conditional coverage" or "coverage under evidence development" programs in order to give "promising" devices with immature or only partly convincing clinical data a chance to prove their promises. These programs should be closely monitored, analyzed and assessed. Moreover, an "early dialogue" between national HTA agencies, reimbursement institutions, regulators and device manufacturers on required clinical evidence and patient-relevant endpoints could be taken into consideration. EUnetHTA/European Network for HTA will possibly play an important role in the field of activities.

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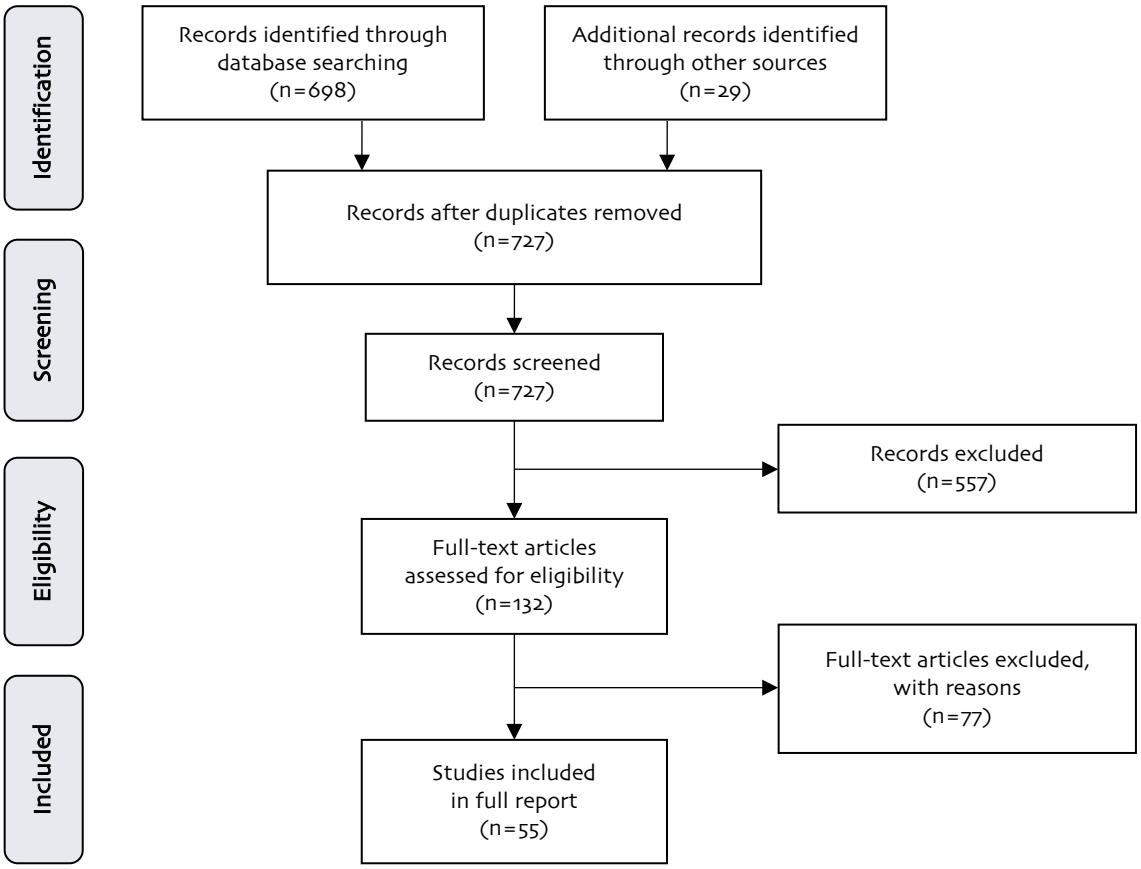
Appendices

Appendix 1: PRISMA Tree for authorization part



Appendix 2: PRISMA Tree for reimbursement part