



HAUTE AUTORITÉ DE SANTÉ

Medical device assessment in France

Guidebook

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Preface

The use of medical devices (MD) is constantly increasing, thanks so the ingenuity of designers who themselves are, often health professional.

Other reasons why the MD sector is growing is the wish to improve the health status of patients and to shorten hospital stays by encouraging patients to return home.

The clinical assessment of MDs is based on completely different methods from that applied to medicinal products; additionally, the stage involved in the assessment are not clear for researchers or health professionals carrying out a project.

The aim of this document is to assist these new operators in conducting a clinical assessment adapted not only to the demands of CE marking but also to that of reimbursement. Recent developments in the regulatory environment must be taken into account by the manufacturer who must also plan to conduct studies that are adapted to the expectations of the health authorities from the moment he starts to develop his product. To do this, he has to surround himself with expert clinicians and methodologists. A protocol will enable useable clinical data to be collected as soon as the first patients are recruited. A quality clinical evaluation whose methodology is adapted to the features of the MD is a key factor in the assessment of its overall value.

This document is the product of HAS's experience since its creation. It will be updated regularly and examples added. The aim is to be able to make properly-evaluated medical devices available to patients as soon as possible and to respond to the challenges of the medicine of the future.

Jean-Michel Dubernard

Summary

List of abbreviations	6
Introduction	7
Assessment of the medical device within the health service	9
1. Preamble	9
2. Assessment of the medical device for marketing	10
3. Assessment for reimbursement by National Health Insurance	14
4. The challenges of clinical development	27
5. Conclusion	39
Annex 1. Working practice	41
Annex 2. Bibliography	43
Participants	45

Liste des abréviations

AB	Actual benefit (SA "Service Attendu" and SR "Service Rendu" in french)
ACV	Added clinical value (ASA "Amélioration du Service Attendu" and ASR "Amélioration du Service Rendu" in french)
Afssaps	French Healthcare Safety Product Agency
CCAM	Joint classification of medical procedures
CHAP	Committee of hierarchical structures of procedures and services
CE	European conformity
CEPP	Committee for the evaluation of products and services
CNEDiMTS	National committee for the evaluation of medical devices and health technologies
CEAP	Committee for the evaluation of medical procedures
CEPS	Healthcare products pricing committee
CNAMTS	National Health Insurance Fund for Salaried Employees
COMEDIMS	Committee on medicinal products and sterile medical devices
DGS	<i>Direction générale de la santé</i> (part of the French Ministry of Health devoted to public health)
DHOS	Hospitalisation and Organisation of Care Directorate
DSS	Social Security Directorate
DRG	Diagnosis-Related Group
MD	Medical device
AIMD	Active implantable medical device
DMDIV	<i>in vitro</i> diagnostic medical device
ETM	Evaluation of medical technologies
GHM	Homogeneous group of patients
GHS	Homogeneous groups in health establishments
HAS	<i>Haute Autorité de Santé</i> (French National Authority of Health)
HTA	Health Technology Assessment
INCa	National Cancer Institute
ISP	Assessment of public health benefit
LPPR	List of products and services qualifying for reimbursement
NABM	Nomenclature of procedures in laboratory medicine
NGAP	General nomenclature of medical procedures
OECD	Organisation for Economic Cooperation and Development
SEAP	Department of medical procedures assessment
SED	Department of assessment of medical devices
T2A	New fee-for-service pricing system
UNCAM	National Association of Health Insurance Funds
UNOCAM	Association of Co-payment Health Insurance Funds
UNPS	National Union of Health Professionals

Introduction

The medical devices (MD) sector is not well known. Yet it is a **dynamic** market, of the order of 19 billion euros in 2006, irrespective of MD, i.e. accounting for more than 12% of the overall consumption of medical care and medical products (1) in France. This dynamism is also notable on an international level, particularly in the United States of America (2).

A study conducted in France by National Health Insurance¹ on medical devices included on the list of products and services approved for reimbursement (LPPR) reveals a **rapid growth** in the field, with a mean increase in expenditure of 9.2% from 2000 to 2007 (3). In 2006, the LPPR² accounted for 15% of the growth in expenditure on ambulatory care (4).

In parallel with this, clinicians, researchers and manufacturers deplore the **lack of clarity** in the process of making a MD available to patients. Moreover, various people involved in healthcare have commented on the fact that the **methodology** of the trials is **weak** (1,2,5).

The OECD (Organisation for Economic Cooperation and Development), in its 2005 report (6), stated that **encouraging the adoption of effective and efficient medical technologies** remains a major political challenge for many OECD countries.

The HAS states in its 2009-2011 project (7), that it is working to **improve the quality of healthcare**, on behalf of **patients** and users, both from an individual viewpoint, in the management of each patient, as well as from a collective viewpoint, in the lasting quality of an equitable and interdependent health service. In fact, the quality of a health service improves when the preventative and curative care is as effective, safe and accessible as possible, in conditions that are as equitable and efficient as possible. It is with this objective in mind that HAS decided to develop a guidebook on medical devices for **new operators and for those carrying out projects** (very small companies) undertaking the development of a new MD, especially for individual usage.

The aim of this guide is to **improve the standard of scientific evidence of clinical trials** in the interest of the **patient**. This evidence will enable us to assess, in an optimal manner, the role of a new MD in the corresponding therapeutic strategy.

One further objective of this guidebook and technical accompaniment for clinicians and researchers is to **improve our understanding of the rules surrounding marketing and reimbursement**, in order to optimize the availability of MD by new operators.

1. French Health Insurance System

2. Article L.165-1 of the Social Security Code

Moreover, the objective of improving the standard of scientific evidence of trials will have the effect of improving **efficiency of the health service** by providing those elements that will enable one to assess the validity of the nationally refunding of MD.

After a preamble on the definition of a MD, this guidebook presents:

- assessment for **marketing**;
- assessment in the event of a request for **reimbursement by National Health Insurance**;
- and finally the **challenges of clinical development**.

Assessment of the medical device within the health service

1. Preamble

A medical device is a product that must correspond to the following definition of the **Public Health Code**³: "A medical device is understood to be any instrument, appliance, equipment, material, product, with the exception of products of human origin, or other article alone or in combination, including the accessories and software involved in its functioning, intended by the manufacturer to be used in humans for medical purposes and whose principal intended action is not obtained by pharmacological or immunological means or by metabolism, but whose function can be assisted by such means. MDs that are designed to be implanted in whole or in part in the human body or placed in a natural orifice, and that depend for their proper functioning on a source of electrical energy or any other source of energy other than that generated directly by the human body or gravity, are called active implantable medical devices."

Medical devices have **specificities** that must be taken into account throughout the strategic planning of their clinical development (Figure 1). In particular, these include:

- the **heterogeneity** of the world of MDs;
- the **status of the device** as a function, for example, of its association or not with a medicinal product;
- the **life-cycle** of a MD, which can be very short because of the rapid technical development or **lifetime of a MD** which is dependent on the obsolescence of the latter (or when appropriate the duration of implantation);
- the **technical performance** must be distinguished from the clinical benefit;
- the clinical benefit that can be dependent not only on the MD itself but also on the **performance of the medical team** (operator-dependent nature, learning curve) and the **technical expertise**, this organisational dimension being an element that must be taken into account as soon as investigations on a new MD start;
- the **number of patients** who may benefit from a MD – this may sometimes be very low.

3. Article L. 5211-1 of the Public Health Code, article one item 2.a) of directive 93/42/CEE. Note that as of March 2010, directive 93/42/CEE will be amended by directive 2007/47/CE, and that the definition of a medical device will be "any instrument, appliance, equipment, software, material or other item used on its own or in combination, as well as any other accessory, including software intended by the manufacturer to be used specifically for diagnostic and/or therapeutic purposes, and necessary for the proper functioning of the former, intended by the manufacturer to be used in humans for the following purposes: the diagnosis, prevention, control, treatment or relief of the illness, - the diagnosis, control, treatment, relief or compensation of a wound or disability, - the study, replacement or modification of the anatomy or of a physiological process, - contraception, and whose principal intended action **in or on the human body** is not obtained by pharmacological or immunological means but whose function can be assisted by such means".

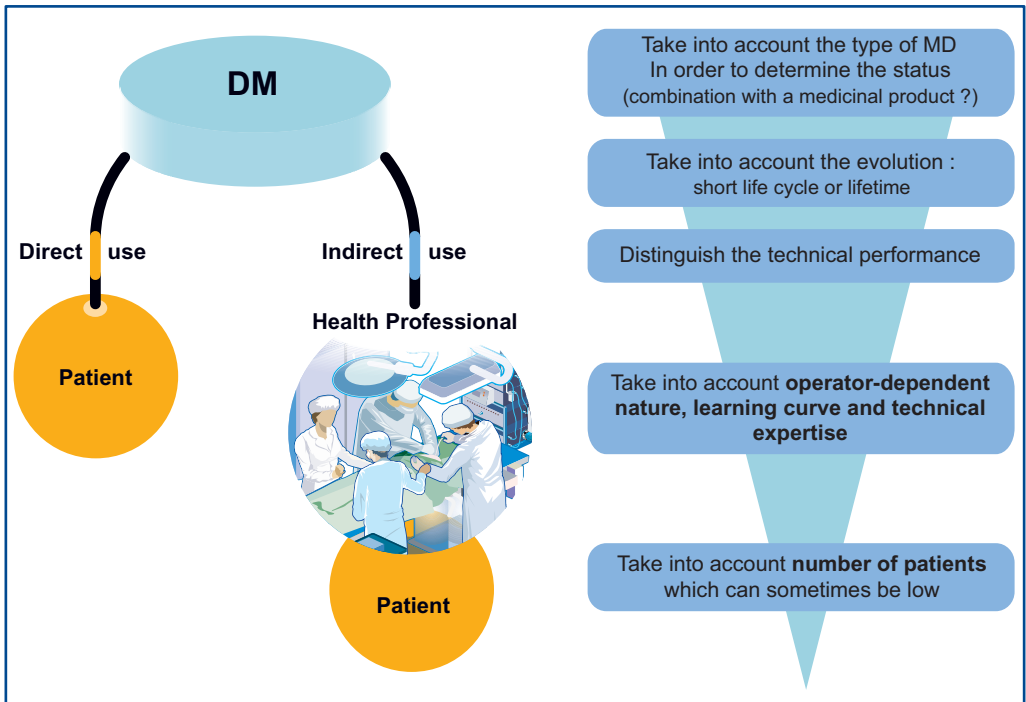


Figure 1. Features of the MD to take into account, when appropriate, during clinical development

When determining the status of a device, if the latter combines a MD with a medicinal product, particular attention must be paid to qualification⁴ of the device which will determine the development plan adapted to the applicable regulation.

The device (10) may be qualified as:

- a MD (e.g. a reusable MD intended for administration of a medicinal product);
- a **combined medical MD** (combination of MD and medicinal product, the medicinal product having an additional effect);
- a **medicinal product** (predominant medicinal product effect vis-à-vis device).

2. Assessment of the medical device for marketing

The first step in launching of a MD is to obtain the CE marking. This step is integral to the overall marketing and reimbursement strategy.

4. Refer to the guide for qualification published on the European Commission website: MED-DEV 2.1/3 rev.3 *Borderline products, medicinal product-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative (8) as well as the manual on borderline and classification in the Community. Regulatory framework for medical devices (9).*

2.1. Principles of CE marking

The MD (medical devices "MD" and active implantable medical devices "AIMD") and in vitro diagnostic medical devices (IVDMD) market is based on a European⁵ regulatory framework governed by **three directives**, the so-called new approach⁶. These specify that MDs and IVDMDs can be marketed only if their manufacturers have previously appended the CE marking. This requirement does not apply to devices intended for clinical investigation, to custom-made medical devices⁷, or to *in vitro* diagnostic medical devices for evaluating performance (11).

The CE marking defines the conditions for marketing of MDs. This marking is appended under the **responsibility of the manufacturer** (or his representative). The manufacturer must prove that his device conforms to the requirements of the directive in question, before appending the CE marking to his device. The CE marking symbolizes compliance of the device with the **essential requirements** of the directives (Figure 2).

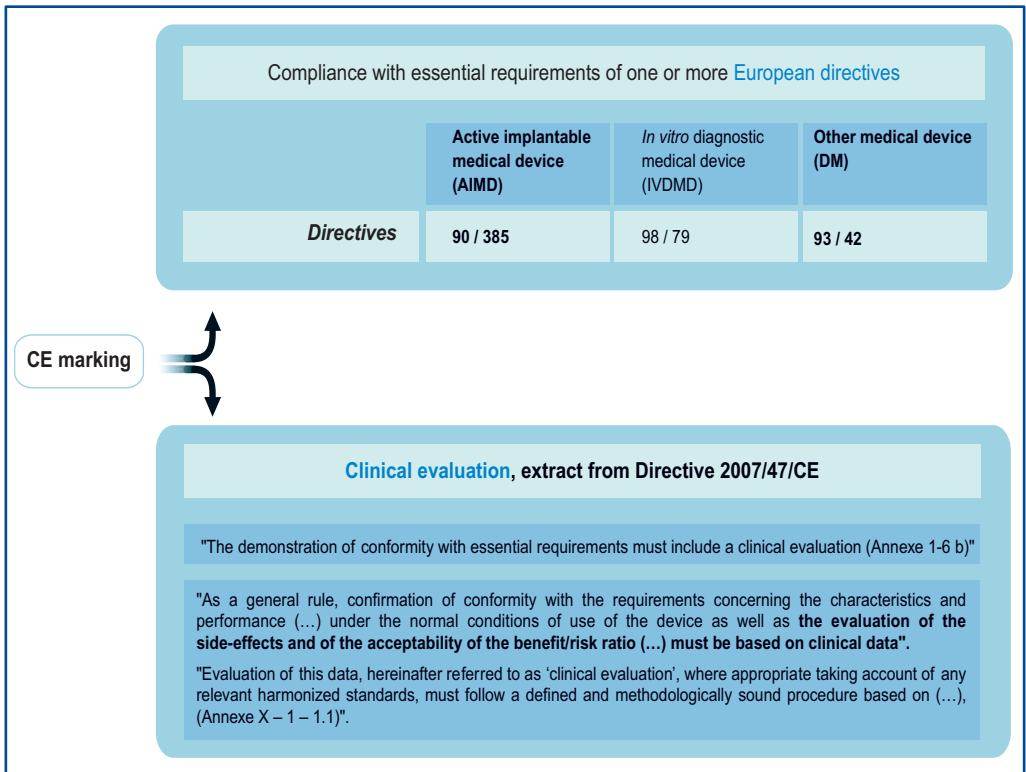


Figure 2. CE marking and associated directives

- The principal texts of the European regulations that apply to MDs are available on the European Commission website at the following address: http://ec.europa.eu/enterprise/sectors/medical-devices/regulatory-framework/legislation/index_en.htm
- 90/385/CEE for AIMD, 98/79/CEE for IVDMD and 93/42/CEE for the others
- Definition of these two categories in directive 93/42/CEE. Note that these devices do not carry the CE marking but that all the requirements of CE marking are applicable to them, with the exception of those that are the subject of clinical investigation, for example, or are not required for a device manufactured individually.

MDs are divided into **four classes**, known as class I, class IIa, class IIb and class III,^{8,9} **as a function of their level of risk** (Table 1). This categorization takes into account duration of use, whether or not it is invasive and to what extent it is invasive, whether or not it can be reused, the therapeutic or diagnostic aim and the body part in contact with the device. The class is determined by the manufacturer as a function of the claims and classification rules of the directive¹⁰.

Table 1. Classification of MDs as a function of risk¹¹

Class I	Low degree of risk
Class IIa	Medium degree of risk
Class IIb	Increased potential for risk
Class III	Very significant potential for risk (includes active implantable MDs)

Non sterile MDs, or those with no measurement function, are self-certificated by the manufacturer.

The majority of MD classes require the intervention of a **notified body**¹², chosen from those on the European Commission list¹³:

- Class IIa, IIb, III AIMDs and MDs and class I sterile MDs or those with a measurement function;
- IVDMDs specified in annex II of directive 98/79/CE as well as those intended for self-diagnosis.

The procedures certifying compliance include both audit of the manufacturer's quality system and control of the design dossier, which is only systematic for AIMDs, class III MDs and IVDMDs in annex II list A. This process is long and restrictive; it should therefore be anticipated.

The certificate of compliance issued by the notified body is valid for a maximum of 5 years and is renewable. During this period, **follow-up audits** are carried out; and an **in-depth audit takes place at the time a certificate is renewed**. This process enables account to be taken of the continuous development of devices as well as data collected during this interval.

The more innovative a device, the more strategic the application of regulations. For this reason, Afssaps (the French Healthcare Product Safety Agency) has implemented a structure to accompany those conducting innovative projects to facilitate access to the market of devices which are of significant clinical benefit.

8. Article R. 5211-7 of the Public Health Code

9. Rules of classification defined in annexe IX of directive 93/42/CEE, choice of different possible procedures in annexes II to IV of directives 90/385/CEE and 93/42/CEE

10. To assist in determining the class of MD, there are MEDDEV 2.4/1 guidelines (12)

11. According to annexe IX of directive 93/42/CEE

12. In France, there is G-Med (appointed by and supervised by the Afssaps – French Healthcare Product Safety Agency)

13. NANDO (New Approach Notified and Designated Organisations) Information System <http://ec.europa.eu/enterprise/newapproach/nando>

2.2. Evolution in CE marking: directive 2007/47/CE

Directive 2007/47/CE¹⁴ of 5 September 2007, which amends directives 90/385/CEE and 93/42/CEE, will apply as of 20 March 2010.

Among the changes introduced in the legislation, is an insistence on the need for those responsible for marketing to provide **clinical data**. This is the sense underlying the basic requirement of 6 b of annex I of this directive (Figure 2).

The new annex X clarifies the use of literature in clinical evaluation conditional on a demonstration of equivalence between the device to be evaluated and the device referenced in the available clinical data.

Moreover, **the clinical trial is the norm for implants and class III devices**, except where an exemption can be justified. Therefore there is a reversal from the responsibility of proof, the clinical chapter having to be henceforth systematically documented in any dossier on the CE marking of a MD.

Clinical evaluation of the CE marking aims to justify the claim for medical use as regards risk/benefit ratio.

However it is essential that the person conducting the project designs the clinical development by **anticipating the requirements to be satisfied, not only as regards CE marking but also the reimbursement by National Health Insurance** in the conditions described in the following section. In fact, as a function of the final marketing strategy selected for the MD, the objective of demonstrating compliance to the essential requirements could be associated with an **objective of demonstrating the clinical or health-economic impact**. In order to **save time and optimise the conditions for marketing of the MD**, it is essential to **integrate from the outset those elements that will enable the clinical benefit of the device to be demonstrated**, as well as the role of the latter in the **therapeutic strategy**.

2.3. Afssaps's areas of intervention in terms of assessment in the context of CE marking

Afssaps intervenes during the clinical trial phase of studies conducted in France by evaluating and authorizing biomedical research. It does not, however, intervene directly in the marketing of MDs and IVDMDs.

Afssaps' Clinical Trials Unit is responsible for the authorisation and follow-up of interventional clinical trials of MDs and IVDMDs conducted in France. By follow-up of trials is understood the analysis of serious events that occur during clinical trials and authorisation of amendments during the trial.

14. Directive 2007/47/CE of the European Parliament and Council of 5 September 2007 (13)

Moreover, like its counterparts in other competent national authorities within the European Union, Afssaps is responsible for appointing and controlling the notified bodies in France (LNE/G-Med 0459). Afssaps is also notified of the arrival on the market of new class IIb and III MDs and AIMDs, thus enabling compliance checks when appropriate¹⁵.

Assessment of MD for marketing

- Importance of **qualifying** the status of the health product from the outset.
- **Reinforcement** of the requirement for clinical data within the framework of directive 2007/47/CE.
- **Strategic planning** in the clinical development process starting from the initial trials: integrate those elements which will enable **clinical benefit** to be demonstrated and thus save time by optimizing the conditions for final marketing of the MD.

3. Assessment for reimbursement by National Health Insurance

In the event of a request for refunding, MDs are subjected to additional assessments to those relating to CE marking, which depend on a variety of procedures for listing and pricing (1).

3.1. Different methods for refunding

► Medical devices integrated into *groupes homogènes de séjour (GHS)* / homogeneous groups in health establishments (DRG)

Since 2004 and as a result of gradually scaling, public and private health establishments are financed within the framework of **tarification T2A**. As a result, expenditure on certain MDs is integrated into hospital services (in the DRG in health establishments). Hence MDs such as ophthalmological implants, osteosynthetic materials, digestive tract sutures and staples are included in the cost of the DRG-based fee.

In accordance with articles R. 5126-48 and following of the Public Health Code, the committee on medicinal products and sterile medical devices (COMEDIMS) (14) participates as an advisor in the drafting in particular of a list of sterile MDs, whose use is advocated within the health establishment.

HAS can initiate an assessment itself and evaluate certain MDs integrated in the DRG-based fee. This evaluation has started already with haemostatics for surgical use and healing devices that use negative pressure.

15. Decree no. 2002-1221 of 30 September 2002

► Medical devices included on the LPPR

List of products and services qualifying for reimbursement¹⁶ (LPPR)

This list concerns the medical device itself (for example an auditory prosthesis) and also the service necessary for its proper use (for example the service of an audio-prosthetist to adjust and regulate the prosthesis for a particular patient). The complementary nature of the appliance (the MD) and the equipment (the service) is one of the characteristics of the LPPR.

The LPPR is divided into four parts:

Section I : Materials and treatments in the home, dietary products, items for dressings

Section II : External orthotics and prostheses (spectacles, frames, appliances for correcting deafness, ocular and facial prostheses, orthopedic shoes, corsets, prostheses for amputation, etc.)

Section III : Implantable medical devices (internal prostheses)

Section IV : Vehicles for physically-handicapped people

Inclusion on the LPPR is for a maximum duration of **5 years and can be renewed**.

If the manufacturer of a MD for individual use and used by the patient himself, or the people around him want it to be reimbursed by National Health Insurance, he must request that the MD be included on the LPPR. There are two ways in which a MD can be included on the LPPR¹⁷: under the generic or brand name.

☞ The general method is by **generic description**.

- this method of inclusion identifies a type of product according to its indications and technical specifications without mentioning the brand name or company. If the manufacturer feels that his product or service matches one of the generic definitions in the LPPR, all he has to do is label the product according to the LPPR nomenclature.
- any MD of this type fulfilling the definition and the technical specifications of one of the generic definitions of the LPPR will be refunded by National Health Insurance.
- the product is not evaluated by the national committee of medical devices and health technologies (CNEDiMTS) when first included but, must nevertheless be **declared to Afssaps**¹⁸.

Up until 2004, inclusion using the generic form was valid for an indefinite period. The 2004-1419 decree of 23 December 2004 introduced a **limit of 5 years** for listing of generic descriptions¹⁹, and as a result an annual programme of **review of the latter**, defined by decree, is currently undertaken by the CNEDiMTS.

16. Article L. 165-1 of the Social Security Code

17. Article R. 165-3 of the Social Security Code

18. Article 11 of law no. 2008-337 of 15 April 2008 pending publication of the enforcement decree

19. The decree temporarily extends the duration of validity of inclusion of products and services using the generic description form until 31 July 2015. Each year, the list of homogeneous categories of products and services that has to be reexamined in order to renew inclusion is fixed by decree and published in the official gazette of the French Republic.

☞ Registration can either be under the **brand name** or the trade name.

This method is used:

- for products which are **innovative in nature** (e.g.: myoelectrical prostheses of the limbs);
- or when the impact on health insurance payments (e.g. implantable cardiac defibrillators), public health requirements (e.g.: metal-metal total hip prostheses), the control and/or the difficulty of defining minimal technical specifications (e.g.: in the prevention of pressure sore with motorized air) require **specific monitoring** of the product

The validity of the request for inclusion on the LPPR is evaluated by the **CNEDiMTS** which bases its decision in particular on the **dossier requesting reimbursement** that is submitted by the manufacturer or distributor. The MD **reimbursement tariff** is then negotiated between the economic committee on healthcare products (CEPS) and the manufacturer.

In the case of an innovative MD, inclusion using the brand name is intended to be temporary²⁰. In fact, as soon as a competitor appears for the innovative product, inclusion using the generic description form could be justified. On the other hand, inclusion using the brand name for public health reasons is not intended a priori to be temporary.

An exemption is planned to the principle of integration of the MD in the DRG in health establishments: some MDs that are likely to introduce a **heterogeneity in hospitalization costs** because prescription of them within the same DRG varies, can be invoiced in addition to the hospital services tariff. This is the case for example with cardiac and vascular implants (including coronary stents) and implantable cardiac defibrillators. Therefore these devices are included on an "additional list" (decision of the ministry after the hospital council²¹ has given its guidance).

To be included on this list, the devices must also be included on the **LPPR²²**. Inclusion on LPPR is the decision of the Minister of Health after CNEDiMTS has given its guidance. As before, the MD **reimbursement tariff** is then negotiated between CEPS and the manufacturer.

► **Specific case of innovative medical devices in health establishments**

Within the framework of a recent legislative measure of 24 June 2009 (2009,44), MDs that are not integrated in the DRG in health establishments, and which could be considered to be **innovative MDs**, could be refunded **exceptionally and temporarily**.

20. Article R. 165-3 of the Social Security Code "(...) At any time, registration using the generic description form can be substituted for registration of one or more products using the brand or trade name by decree of the minister of health after the national committee for the assessment of medical devices and health technologies has given its guidance. "

21. Decree of 7 May 2007 taken in conjunction with article L. 162-21 -2 of the Social Security Code which establishes the composition and the working practices of the hospital council

22. Article L. 165-1 of the Social Security Code

In fact, article L. 165-1-1 of the Social Security Code²³ specifies in particular that "Any innovative product, service or procedure can exceptionally and for a limited time, be refunded in part or in full within the budget provided for in article L. 162-22-13²⁴. The refund is decided by decree of the ministers responsible for health and social security after the Haute Autorité de Santé has given its guidance (.)". Application of this mechanism remains exceptional.

► Medical devices refunded within the framework of the procedure

The committee for evaluating medical procedures

The assessment of medical procedures enables one to give a guidance on the opportunity for including these in the refund procedure of National Health Insurance (NGAP, general nomenclature of medical procedures, CCAM, joint classification of medical procedures, NABM, nomenclature of procedures in laboratory medicine), and on the conditions of this inclusion and possible removal from inclusion.

The procedures in question range from the insertion of dental implants (NGAP) to osteodensitometry for the diagnosis of osteoporosis (CCAM), and researching HIV or the hepatitis C virus in sperm (NABM). Medical devices are widely used in these procedures.

This medical assessment is conducted by the **committee for the assessment of medical procedures (CEAP)**, a specialist committee at HAS. CEAP relies on the work of the SEAP (Department of medical procedures assessment), also part of HAS.

The CEAP generally assesses requests for the inclusion that are made by external bodies like the national Association of Health Insurance Funds (UNCAM), less frequently by the learned societies, the Ministry of Health, the Association of Co-payment Health Insurance Funds (UNOCAM), the National Cancer Institute (INCa), the National Union of Health Professionals (UNPS) and the associations of registered users. **It is important to point out that manufacturers may approach the learned societies when appropriate.** The CEAP can also initiate an assessment itself if the dossier for reimbursement is submitted to the CNEDIMTS.

Requests for assessment are made directly via the HAS website by completing the online form for registration with the work programme.

Committees of hierarchical structures of procedures and services (CHAP)

The purpose of these committees is to define the regulations for the hierarchical structures of procedures and services refunded or reimbursed by National Health Insurance and to validate the resulting hierarchical structure. These committees may request help as necessary from experts in learned societies or economics experts.

23. An amendment to this article will apply as of 1st March 2010, in particular refunds will no longer come under the jurisdiction of MIGAC but under the governance of expenditure mentioned in article L. 162-22-9 of the Social Security Code

24. MIGAC (missions of general interest and assistance with contractualisation)

They rely on the medical assessment studies carried out by the CEAP within HAS, and on the technical studies conducted by CNAMTS (National Health Insurance Fund for Salaried Employees).

Principal reimbursement procedures

- General case of MDs integrated in the **DRG** in health establishments: guidance of COMEDIMS (committee on medicinal products and sterile medical devices) +/- assessment by HAS
- MDs included on **LPPR**: guidance of CNEDiMITS (MD used in the community by patient and those reimbursed in addition by the DRG)
- MDs reimbursed within framework of the procedure: guidance of CEAP

3.2. Medical technology assessment by CNEDiMITS

► CNEDiMITS

CNEDiMITS^{25, 26} (Figure 3 and Figure 4), previously the CEPP (committee for the evaluation of products and services), is one of the 7 **specialist committees** of HAS (15). The chair of the CNEDiMITS as well as 6 other chairs of specialist committees comprise the **HAS Board**, presided over by Professor Laurent Degos. The scientific management and administration of the committee is overseen by the department for assessment of medical devices (SED) within the medical, economic and public health assessment division of HAS.

The committee generally assesses requests for inclusion that are made by external bodies, but can also initiate an assessment itself.

CNEDiMITS gives a guidance on **requests for inclusion or renewal of inclusion of MDs for individual use on the LPPR**, human tissues and cells irrespective of their degree of transformation and materials derived therefrom, healthcare products other than medicinal products and associated services, in particular dietary products intended for special medical purposes, as well as on **changes to the conditions for inclusion on the list of products and services qualifying for reimbursement**, provided for in article L. 165-1 of the Social Security Code²⁷.

25. Article R. 165-18 of the Social Security Code

26. Decree no. 2009-1088 of 2 September 2009 relating to the committees mentioned in articles R. 5212-7 of the Public Health Code and L.165-1 of the Social Security Code

27. Decree no. 2004-1419 of the 23 December 2004 amending the Social Security Code, in particular articles R. 165-1 to R. 165-6, R. 165-11 to R. 165-13, R. 165-21 and 22

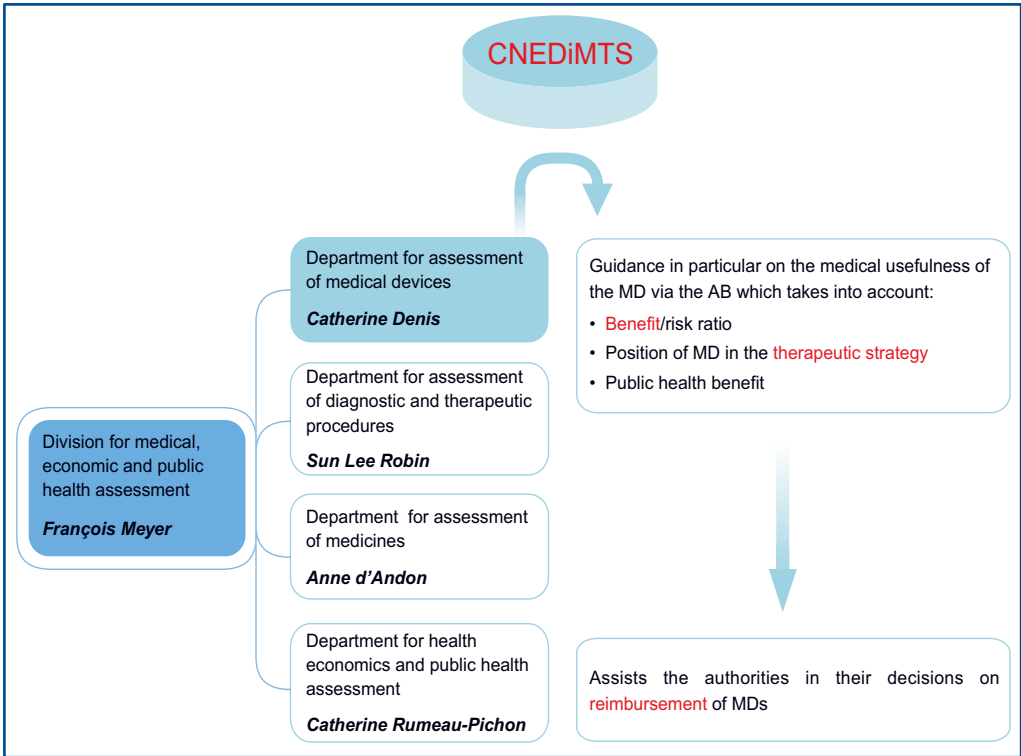


Figure 3. **Departments in the Division of medical, economic and public health assessment at the HAS (including the department for assessment of medical devices) and CNEDiMTS**

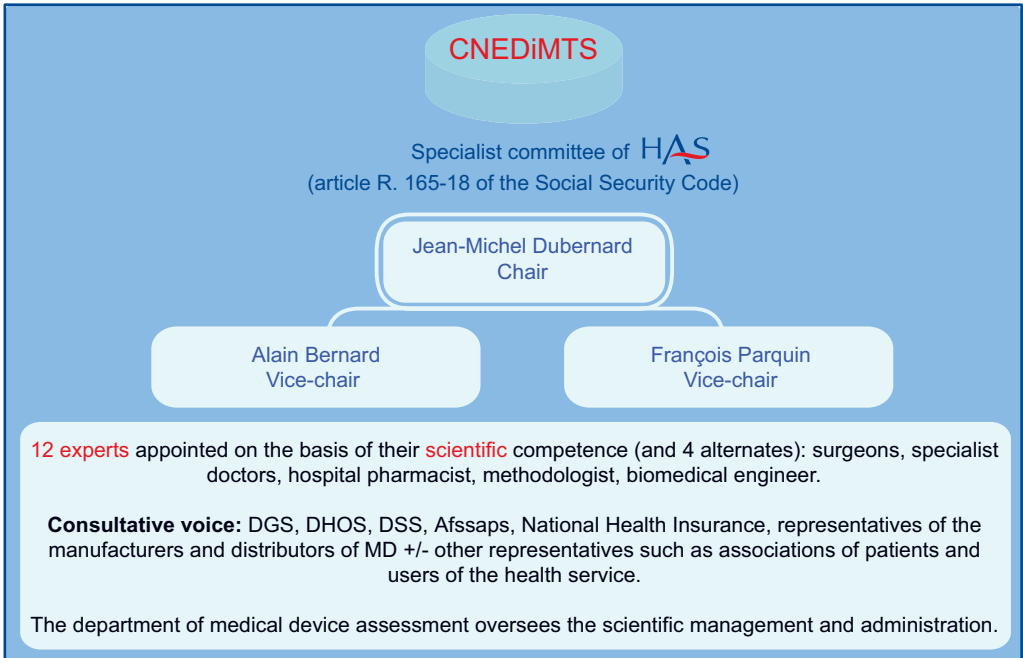


Figure 4. **CNEDiMTS 2009 composition**

In the case of an initial request for inclusion, the guidance of the committee is based in particular on assessment of the **actual benefit (AB)** and, if this is sufficient, on assessment of the **added clinical value (ACV)**. Then, when a request is made to renew inclusion, this guidance will be based on **reassessment** of the actual benefit (AB) and, if appropriate, of added clinical value (ACV).

► **Assessment of actual benefit (AB)**

The guidance of the committee is based on assessment of the **AB** of the product or the service (16). The latter is a clinical benefit responding to the needs of health professionals and patients.

"The actual benefit is evaluated, for **each of the indications** of the product or service and, when appropriate, per group of the population, as a function of the two following criteria:

- **The significance of the product or service** as regards, on the one hand, its **therapeutic or diagnostic effect or compensation for a disability** as well as **undesirable effects or risks** linked to its use; on the other hand, the **role of the product or service in therapeutic or diagnostic strategy or compensation for a disability**, taking account of **other available therapeutic or diagnostic methods or means to compensate for the disability**;
- **Its expected public health benefit**, in particular its impact on the health of the population, in terms of mortality, morbidity and quality of life, its ability to fulfill a therapeutic or diagnostic need or to compensate for a disability, its impact on the health service and its impact on public health policies and programmes.

The products and services for which the actual benefit is insufficient to justify inclusion for reimbursement do not appear on the list²⁸."

- ☞ The assessment of AB is therefore based on analysis of the following criteria (16):
- a qualitative and/or quantitative determination of the medical need fulfilled by the MD with a determination of the current strategy and the **role of the MD within this strategy** or changes to the strategy likely to be induced by MD;
 - **the risk/benefit ratio** of the MD: relationship between one or more benefits and one or more risks established from scientific evidence. The assessment seeks to quantify the results of the risk/benefit ratio observed during use of the MD after taking into account the reimbursement by National Health Insurance. It takes into account results observed during clinical trials and possible limits to the generalisability of these results to the population likely to be treated with the MD in common usage situation;
 - **benefit to public health at the level of the French population in everyday life.**

28. Article R. 165-2 of the Social Security Code

This assessment is done for each indication claimed, when appropriate per group of the population (Figure 5).

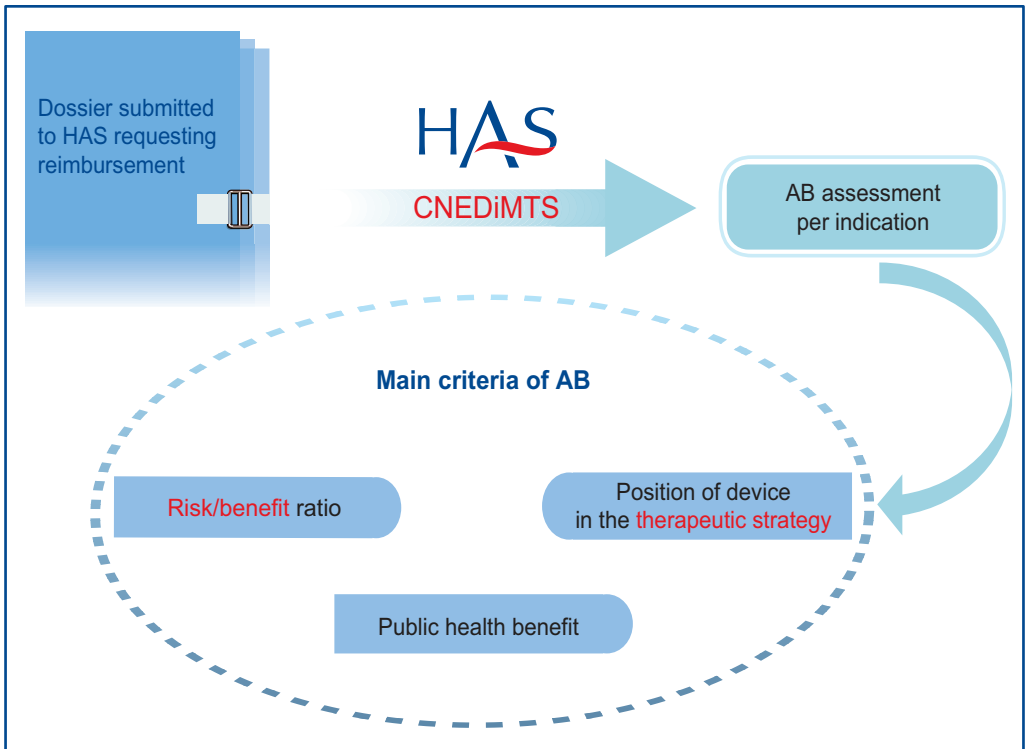


Figure 5. Assessment of actual benefit by CNEDiMTS

► Assessment of added clinical value (ACV)

If the actual benefit is sufficient to justify listing for reimbursement, the guidance of the Committee²⁹ (16) will also be based on "the assessment of the added clinical value (ACV) in relation to a comparable product, procedure or service or a group of comparable well-defined procedures, products or services, considered to be the current gold standard according to available scientific data and regardless of whether this gold standard is, or not, reimbursed. This assessment classifies the added clinical value as major (I), substantial (II), moderate (III), minor (IV) or absent (V) for each indication for which the committee considers that there is evidence to justify listing." (Figure 6)

29. Article R. 165-11 of the Social Security Code

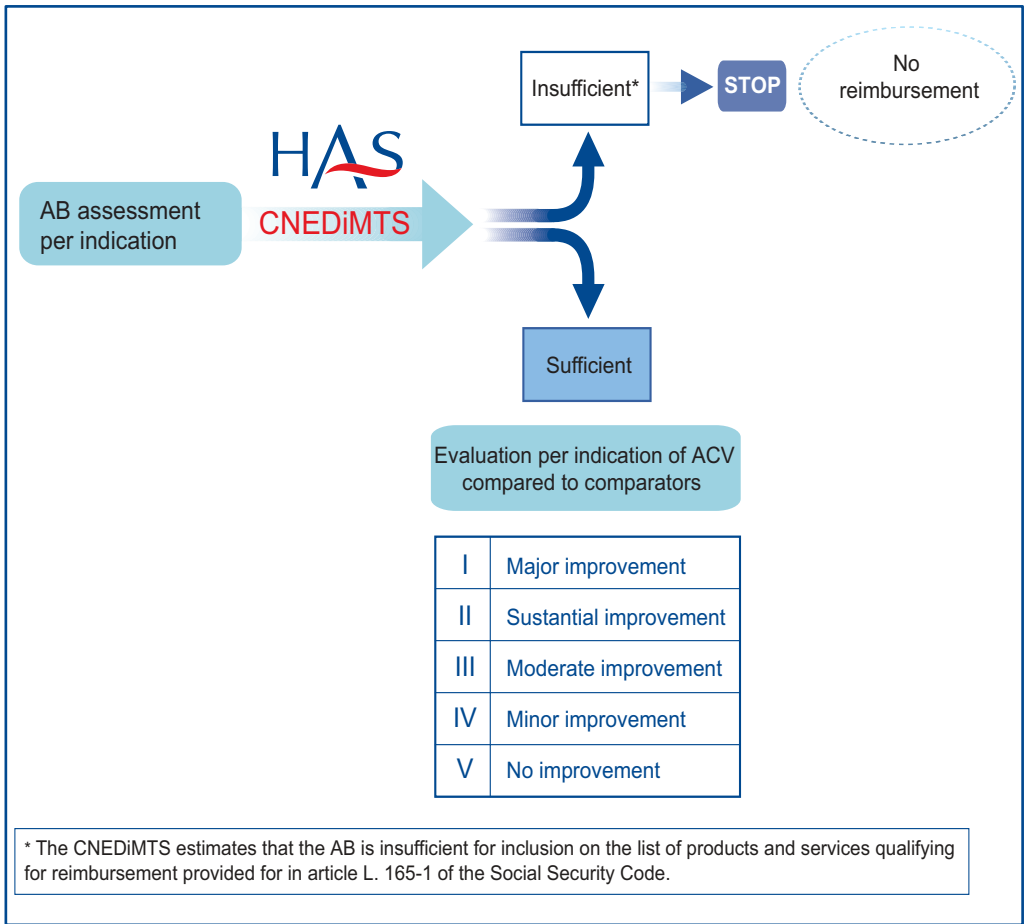


Figure 6. Assessment by CNEDiMts of the added clinical value when the actual benefit is sufficient

- ☞ The relevant comparator is derived from the reference strategy, or the strategy used in routine practice in the absence of scientific evidence, or absence of treatment if the need for treatment is unfulfilled. It may correspond to another medical device, whether or not included on the LPPR, medicinal product, service or procedure whether or not accepted for reimbursement.
- ☞ These criteria are clinical criteria (mortality, morbidity, compensation for a disability, reduction in undesirable effects), relating to quality of life, convenience of use with clinical benefit to the patients.
- ☞ ACV is demonstrated with the aid of randomised, controlled clinical trials using a primary validated judgement criterion; except in situations where such data cannot be obtained and this is supported by sound bibliographic references.

► **Renewal of inclusion on listing**

Reassessment of actual benefit

"Inclusion can only be renewed, according to CNEDiMTS, if the product or service provides sufficient actual benefit to justify continuing to reimburse it.

AB is determined again by **reevaluating criteria** (Figure 5) used in the initial assessment, taking into account the results of studies that were requested at inclusion, and all other new data available on the product or the service and the condition treated, diagnosed or compensated, other products and services included on the list and other available therapies or methods. Assessment of actual benefit is evaluated in each of the indications accepted for reimbursement³⁰."

In the case of **generic** descriptions, the review carried out by CNEDiMTS evaluates **justification of continued inclusion as a function of criteria previously cited and when appropriate defines their conditions of use.**

Reassessment of added clinical value

"[...] When actual benefit is sufficient to justify renewal of inclusion, a reassessment of added clinical value is undertaken. This assessment is done in relation to a comparable product, procedure or service or a group of well-defined comparable procedures, products or services currently considered to be the 'gold standard' according to current scientific data. This is done regardless of whether or not the comparator is reimbursed. This comparator can be the one used to assess added clinical value. This assessment classifies the improvement in actual benefit as major (I), substantial (II), moderate (III), minor (IV) or absent (V) for each indication for treatment, diagnosis or compensation for a disability for which the committee considers that there is evidence to justify listing³¹."

► **CNEDiMTS recommendations for clinical studies**

CNEDiMTS requests that the following be provided in the dossier submitted for inclusion: **relevant publications or reports**, as well as a **summary of each study** (16) in the form of a table containing among other things the **study reference, type of study, date and duration of study, study objective, method and results**. CNEDiMTS has also published **methodological requirements relating to comparative trials** (16).

The randomised controlled trial is the optimal study design to demonstrate the superiority of a product in relation to the reference strategy. It can also be used to show equivalence or "non-inferiority" of the product in question.

30. See article R. 165-11-1 of the Social Security Code

31. See article R. 165-11-1 of the Social Security Code

Assessment in the case of a request for reimbursement Medical technology assessment by the CNEDiMTS

- CNEDiMTS is a specialist committee of the **Haute Autorité de Santé**.
- CNEDiMTS gives a guidance on the **requests for inclusion** or renewal of inclusion of MDs on the **LPPR**.
- Inclusion on the list is for a maximum duration of **5 years** in a **specific indication**.
- For a new MD, the guidance of CNEDiMTS is based in particular on assessment of the **actual benefit (AB)** and, **if the latter is sufficient**, on the assessment of **added clinical value (ACV)**.
- Assessment of the AB is by indication and is essentially based on an assessment:
 - of the **risk/benefit ratio**;
 - of the **role of the device within therapeutic strategy**;
 - of its **benefit to public health**.

Assessment of **ACV** is done, per indication, in relation to a **comparator** (a product, procedure or service) considered to be the gold standard according to **current scientific data or absence of treatment if the need for treatment is unfulfilled**.

- CNEDiMTS requests that the following be provided in the dossier submitted for inclusion in the list: **relevant publications or reports**, as well as a **summary of each study** (16) in the form of a table containing among other things the **study reference, type of study, date and duration of study, study objective, method and results**.
- CNEDiMTS has published **methodological requirements** relating to **comparative trials**. The optimal type of study for this clinical investigation is the **randomised controlled trial**.

3.3. Setting tariffs and establishing prices within the framework of a procedure by the economic committee on healthcare products

Within the framework of a negotiation with CEPS (17), the tariff assumes that a decision has been made on whether to use the generic nomenclature or the trade name. This decision is made by the minister, but CEPS can make proposals based on the recommendation from CNEDiMTS.

‘Tarifs de responsabilité’³² and when appropriate limits on sale prices are then determined in compliance with the general principles; **these are applied differently according to the situation encountered**.

There are three regulations that govern the tariffs and prices of MDs.

32. ‘Tarifs de responsabilité’ is an expression which describes the practice of the social security bodies and insurance companies of designating that part of the cost of services which is refunded under the social security system. This is done according to a scale resulting from a ministerial decision or agreement concluded at the national level between the social security funds and the bodies representing the medical and paramedical professions concerned.

Two relate to the tariffs:

- Article R. 165-4 of the Social Security Code specifies that "**products and services (...) that do not provide any improvement in the actual benefit or economy in the cost of treatment, or which are likely to involve unjustifiable expenditure to the French National Insurance scheme cannot be included on the list provided for in article L. 165-1**".

In practice, this regulation only applies to new MDs without ACV which do not fulfill an existing generic definition or which are not regarded as belonging to generic definitions.

- Article R. 165-14 requires that CEPS establishes by agreement, or failing that by decision, the MD tariffs mentioned in article L. 165-1. "**Determination of these tariffs mainly takes into account actual benefit, any added clinical value**, when appropriate additional studies requested, tariffs and prices of comparable procedures, products and services included on the list, the volume of anticipated sales and predicted and real conditions of use".

As for prices, these must be determined by applying the very general provisions of article L. 162-38 of the same Code, according to which the final price and margins for products and services refunded by subdivisions of the social security system are fixed by decree "taking into account changes in charges, revenue and volume of activity of the practitioners or companies concerned".

**Assessment in the case of a request for reimbursement
Setting tariffs and establishing prices within the
framework of a procedure by the CEPS**

- **Determination of the MD tariffs** mainly takes into account **AB, and ACV**, when appropriate additional studies requested, tariffs and prices of comparable procedures, products and services included on the list, the volume of anticipated sales and predicted and real conditions of use.

3.4. Medical devices for individual use for which the associated procedure has not been evaluated

If the new MD is associated with a procedure, this procedure must be listed on the CCAM (joint classification of medical procedures) to be reimbursed in the ambulatory care or in a hospital.

If this procedure is new, there must be a **double assessment: assessment of the MD by the CNEDiMTS and assessment of the procedure by CEAP**.

It is important to **anticipate this request for inclusion of the new procedure** in the overall marketing strategy of the MD. In fact, this classification is used for invoicing the new procedure, to pay for the procedure of the health professional in the private sector (in the ambulatory care or in a hospital) and to allocate resources to the health establishments.

Medical assessment of the procedure is carried out by **CEAP** who relies on studies by HAS's SEAP.

The committees of hierarchical structures of procedures and services (CHAP) then define the rules for hierarchical structures of procedures and services refunded or reimbursed by National Health Insurance and validate the resulting hierarchical structure. These committees rely in particular on the medical assessment studies carried out by CEAP within HAS and on the technical studies conducted by CNAMTS. The procedure can only be refunded if its use complies with the indications specified for inclusion of the new MD on the LPPR³³.

**Assessment in the case of a request for reimbursement.
Example of a MD for individual use for which the
procedure has not been evaluated**

- **Double assessment in consultation of:**
 - MD by **CNEDiMTS**
 - procedure by **CEAP**
- Remember to **anticipate this request for inclusion**

3.5. Medical technology evaluation in Europe

On a European level, as on an international level (6), **the evaluation of medical technologies** (ETM) or Health Technology Assessment (HTA) was designed to evaluate the wider repercussions of medical technologies, their benefits and their costs.

There are usually three stages involved:

- identification of questions;
- systematic collection of **scientific data and analysis**;
- and analysis of data, including judgements on the **significance** of the results obtained, the data and their assessments subsequently serving as a basis for the decision process.

On an international and European level, the institutions can vary in terms of distribution of competences in relation to these three stages (Table 2). HTA and in particular HTA of MDs is implemented in the main European countries today (5,18,19).

In France, the national institution is HAS. For the time being, it only takes into account the medical scientific dimension on first inclusion. The main national institutions abroad are IQWiG (institute for quality and efficiency in healthcare) in Germany, KCE (healthcare knowledge centre) in Belgium, and NICE (national institute for health and clinical excellence) in the UK.

33. Decision of 11 March 2005 by the National Union of Health Insurance Funds relating to the list of procedures and services refunded or reimbursed by National Health Insurance, book 1: general provisions, article L-4 "Moreover, a procedure or a service can only be refunded if its use complies with the indications pursuant to article L. 165-1 of the Social Security Code concerning medical devices, tissues and cells, health products other than medicinal products and associated services, and article L. 165-17 of the same code concerning specialist medicinal products (...)"

Table 2. HTA Institutions in the main European countries (5)

	Institution	National system ?	Data taken into account
Belgium	KCE	Yes	S, E and CE
France	HAS	Yes	S, E and ± CE^c
Germany	G-BA^a and IQWiG	Yes	S, E and CE
Spain	AETS^b	No	
United Kingdom	NICE	Yes	S, E and CE

S = safety data, E = efficacy data, CE : cost/efficacy data

- Gemeinsamer Bundesausschuss – the highest committee in the joint self-administration of the German health service
- Agencia de Evaluación de Tecnologías Sanitarias – Health technology evaluation agency in Spain
- Economic analysis performed in selected cases only

HAS uses assessments from the different European institutions to carry out its recommendations.

Only France insists on a systematic medical assessment before inclusion of a MD on the LPPR, but the procedures are evolving in other European countries, especially in the United Kingdom.

Health Technology Assessment in Europe

- HTA exists in the main European countries.
- Assessment of medical technologies is based on the collection and analysis of scientific data with an **assessment** of the **significance** of the results which subsequently serve as a basis for the **decision process**.
- The main institutions in Europe practising HTA are **HAS** in France, **IQWiG** in Germany, **KCE** in Belgium and **NICE** in the United Kingdom.
- HAS can refer to assessments made by other HTA institutions in Europe.

4. The challenges of clinical development

4.1. Key stages in clinical development

Industrial development and updating of prototypes constitute crucial stages in the development of a new MD³⁴.

These stages must be prepared as early as possible (20). Anticipating the stages enables relevant clinical studies to be suggested that demonstrate the benefit of this new MD and will eventually optimise its valuation.

34. The stages of clinical development are described in the harmonised standard NF EN 14155. European Commission recommendations are also available on MEDDEV http://ec.europa.eu/enterprise/medical_devices/meddev/meddev_en.htm

It is important to **identify from the outset what clinical data are already available within the domain of the new MD** in question and any recommendations through systematic research.

The **preclinical** phase comprises not only the **technological revisions** but also the implementation of ***in vitro* tests** and sometimes **animal experiments**.

The clinical phases comprise feasibility studies (safety and performance) and finally studies that provide evidence of clinical benefit (Figure 7). Clinical data should be collected as soon as the first patient is recruited and a protocol drawn up to ensure the quality of this data collection.

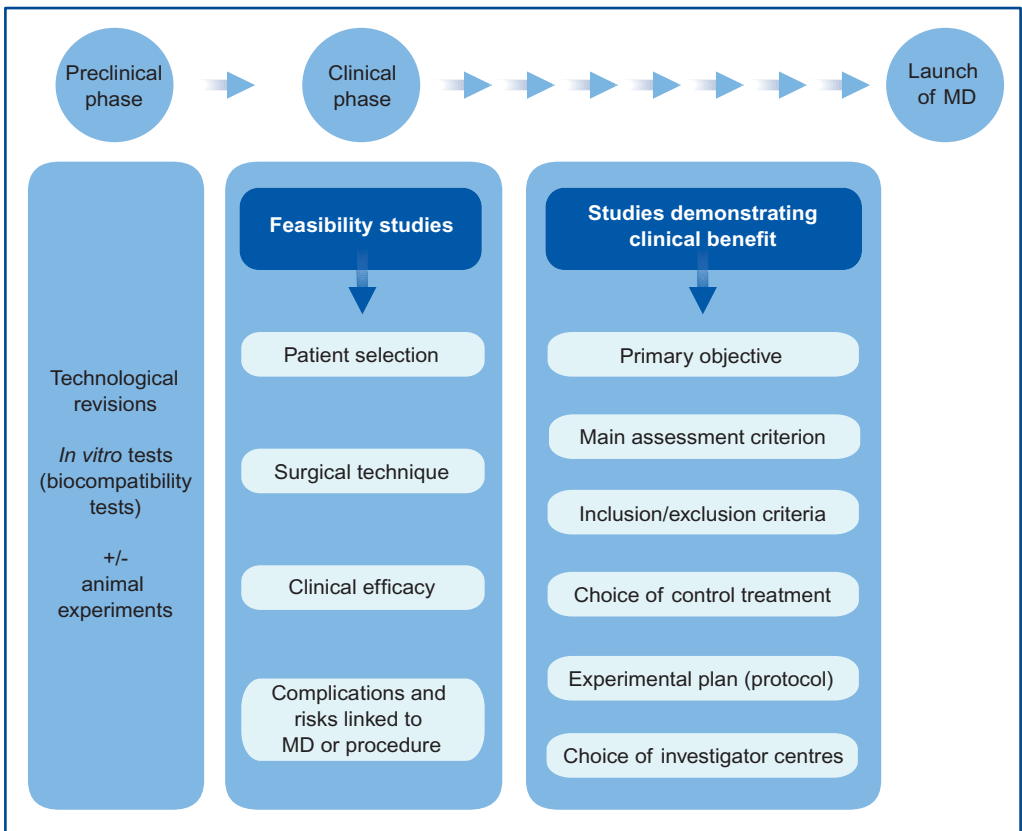


Figure 7. **Key stages in clinical development**

► Feasibility studies

It is proposed that these are conducted immediately following the preclinical phase or in parallel with industrial development, depending on the type of MD. Often, the type of study most appropriate from a methodological viewpoint at this stage is the non-comparative prospective study.

Depending on the context, one or more studies are necessary to answer different questions, in particular those outlined below:

- selecting patients who will benefit from the new MD;
- development of the surgical technique, in particular implantation;
- clinical efficacy;
- the complications and risks associated with the MD and the implantation technique.

Selecting patients who will benefit from the new MD

This stage enables one to **specify the clinical forms of the pathology** in which the new device would bring about the expected therapeutic efficacy in the patients.

This stage must also specify the characteristics of the patients (age, sex, acceptable comorbidities) which would have the **least possible effect on the result in order to select a sufficiently homogeneous patient group**.

However, even at this early stage of development, it is advisable to make a choice, often delicate, between a very narrow selection of patients which optimises *a priori* the risk/benefit ratio of the device, and a wider selection which optimises the recruitment options and the possibility of being able to generalise the study results

Development of the surgical technique, in particular implantation

One or more studies are necessary to develop the implantation technique of a new MD and **describe the different operating times, the technical expertise and the personnel necessary** for the procedure to succeed.

At the end of this stage, specifications are established to **standardize** best practice of the technique. They include a description of the procedure and the resources necessary. This will facilitate development of the following stage in the demonstration of clinical benefit.

Clinical efficacy

At this stage of development, the choice of **criterion for assessment** for measuring the **quantity of therapeutic effect** is essential. The criterion must be clinical and relevant, e.g. mortality, onset or evolution of a disease or compensation for a disability. This allows one to assess whether the MD keeps all its promises in terms of clinical efficacy.

The use of an intermediate criterion may be justified by the time that obtaining more relevant clinical criteria would necessitate. However, the use of intermediate criteria must always be carefully weighed as it might call into question the overall demonstration of efficacy. Intermediate criteria should be based on the predictive validity of the expected clinical effect.

The results of the feasibility studies can provide the basis for **estimating the number of patients** that would be needed in future trials.

The complications and the risks

Two types of undesirable events may be reported:

- those **linked directly to the MD**;
- and those that are related to the **implantation or surgical technique**.

At this stage, the objective of the studies is to come up with an estimate of the **main complications**. This estimate is essential in establishing the future risk/benefit ratio.

► Studies demonstrating clinical benefit

The organization of the trials necessary to demonstrate the clinical benefit of the new MD must be based on **the different feasibility studies** (21).

The trials chosen may be trials of superiority, equivalence or non-inferiority³⁵.

The type of trial that allows one to demonstrate clinical superiority of a new MD compared to the current gold standard is the randomised, controlled trial (2,22). This type of trial, when it can be conducted, optimally add value on a new MD up. The randomised, controlled trial can also be used to show equivalence or non-inferiority of the MD.

The randomised, controlled trial, apart from the fact that it has to adhere to the usual methodological criteria, must also be clinically relevant. When the study protocol is being drawn up, particular attention must be paid to a certain number of points. These various points must be systematically addressed and **questions must be asked when constructing any trial intended to demonstrate the clinical benefit** of a new MD.

Primary objective

It is important that the primary objective is defined before the study protocol is drawn up (23). This must be unique. The wording of the objective is important in terms of the final indication of the MD in the market.

The difficulty is choosing the right objective to demonstrate the clinical benefit of the new MD. In fact, the entire trial is constructed around **formulation of this primary objective**, which must be clear, precise, and based on relevant and valid clinical criteria.

The following aspects are specified:

- the treatment being tested;
- the control treatment that will ideally correspond to the gold standard;
- whether this is a superiority, equivalence or non-inferiority study;
- the patients concerned.

35. Trial of superiority: the new MD is supposed to be more effective than the control treatment. Equivalence: the new MD and the control treatment are medically equivalent. Non-inferiority: the new MD is not worse than the control treatment.

For example, "demonstrate that the aortic endoprosthesis reduces perioperative mortality compared with open surgery in patients suffering from an unruptured aortic aneurysm of more than 5 cm in diameter."

The main criterion for assessment

In all cases, identification of a single main criterion for assessment is proposed in conformity with the study's primary objective. It must be defined before the protocol is drawn up (23) and must enable one to **quantify the therapeutic effect** of the new MD **in relation to the control treatment**.

The choice of criterion for assessment is dependent on the pathology being treated and the clinical action of the new MD and the control treatment. To obtain a valid demonstration of the clinical benefit of the new MD, the main criterion for assessment should be **clinical** (if at all possible), **relevant and validated**.

An intermediate criterion is valid if the literature provides evidence of a **close correlation between the latter and a robust clinical endpoint**, as for example the glycosylated haemoglobin level and the appearance of degenerative complications in the diabetic. Conversely, "late loss" is an intermediate criterion in angiography that is often used in trials on new vascular endoprostheses; there is no evidence that it formally demonstrates a close correlation between this and the appearance of relevant clinical events, such as myocardial infarction or a recurrence of angina necessitating revascularisation.

The characteristics of assessment criteria that can be used in various trials can be summarised as follows:

- short, medium or long-term reduction in mortality;
- reduction or improvement in morbidity: myocardial infarction, stroke, pain, scarring etc.;
- improvement in disability;
- reduction in complications or undesirable events with the surgical procedure or technique: number of hospitalisations, infections, haemorrhages, re-interventions, etc.;
- impact on the organisation of care: reduction in duration of hospitalisation, decrease in consumption of healthcare products or decrease in number of procedures, etc.

Inclusion and exclusion criteria

The study population must correspond to the patients for whom this new MD is intended in **current practice**. Eligibility criteria are based not only on the identification of the **clinical forms of the pathology** but also on the **characteristics of the patients**: age, sex and comorbidities.

The patients included in the trial must be sufficiently homogeneous so as not to increase variability and have too great an effect on the outcome of the trial. Trials already carried out should assist in the description of inclusion and exclusion criteria.

The eligibility criteria must correspond to the same indications as the gold standard and the patients likely to participate in the trial must be suitable for one or other of the treatments being compared.

Finally, the clinical forms of the pathology must be sufficiently common to enable patient recruitment within a realistic timeframe

The choice of control treatment

This refers to the strategy(ies) or reference treatment which may be either **another MD**, or a **medicinal product**, or a **surgical intervention**, or another care service (physiotherapy, nursing care).

The reference strategy is based on **data from reputable literature sources**. In the absence of valid scientific evidence, the reference strategy is defined as that used in routine practice according to expert guidance. This reference strategy should be that which is supposed to give the **best results**, in the absence of the new MD, in eligible patients in the trial.

The final important point is to specify the **role of the control treatment within the therapeutic strategy**. This precision has the benefit of reinforcing the importance of completing this trial in order to ensure demonstration of the potential clinical benefit of the new MD in the management of patients suffering from the pathology in question.

The choice of whether to conduct a trial of superiority, equivalence or non-inferiority takes into consideration both the existence of a control treatment and the supposed contribution of the new MD as regards efficacy compared with this control.

The choice of investigator sites

Trials should preferably be **multicentre**. There is a dual objective to this rationale:

- to facilitate patient recruitment in order to ensure the inclusion period is as short as possible (23);
- so that study results can be extrapolated. In fact, different teams participating in the trial may be more representative of a certain variability in medical practice.

The teams likely to participate in a multicentre trial must master the implantation or surgical intervention technique (23). At the time the protocol is being drawn up, a **specification** is proposed for the **eligibility** of the teams that can take part in the trial. The **specification** comprises standardisation of the implantation technique, experience of the medical team, the required technical expertise and quality control of the medical data.

In the case of the application of procedures or prescription of certain MDs which necessitate specific conditions for public health reasons or that are likely to involve unjustifiable expenditure³⁶, rules fixed by inter-ministerial decree by the ministers responsible for health and social security, can be applied, after HAS has given its guidance.

36. Article L. 1151-1 of the Code of Public Health

These rules concern in particular the **training and qualifications** of professionals and the technical conditions for implementation. The use of these MDs and the application of these procedures can be restricted for a **given period to certain health establishments** (24)

Calculating the number of subjects required

It is essential that the number of patients to be included be estimated in advance. The population size is dependent on two variables: the size of therapeutic effect and the prevalence of the event being researched. In fact, the greater the therapeutic effect, the fewer the patients needed to show a difference. On the other hand, for rare events, the population will be large.

Given the features of the MD, sometimes patient recruitment may be limited. In this case, it may be beneficial to set up **international multicentre studies** and emphasise the role of assessment agencies.

Managing protocol deviations and missing values

There may be bias in the follow-up. This can translate into a difference at the level of study "drop-outs" – notably treatment withdrawals, patients lost to follow-up or those forced to take concomitant treatments.

Study "drop-outs" can be caused by undesirable events or ineffective therapies. This may result in treatment effects disappearing or conversely false differences appearing.

The experimental plan (protocol) design should lead to as few drop-outs or treatment withdrawals as possible. The manufacturer, in cooperation with the investigators, should use all possible means **to minimise the number of patients lost to follow-up**.

A **systematic approach** will enable a trial to be designed which will best evaluate the new MD. In fact, it will enable the design of the optimal trial appropriate to the features of the MD. It may be that this trial, given the **features of the MD**, cannot be carried out as a controlled randomised trial; the systematic approach will then enable one to **explain the options chosen for which the interpretations will take account of any bias** (19).

4.2. Clinical development strategy

It is essential to have a **strategic and anticipatory vision** right from the time the clinical development plan is conceived. This means anticipating from the outset those aspects which will add value to the MD up until it is made available to the patient. This approach enables the person carrying out the project to **save time**, for instance by avoiding having to start a new trial, if the trial conducted to obtain the CE marking (safety and safety data) does not necessarily demonstrate the clinical benefits from a therapeutic strategy viewpoint.

If for example it is envisaged that the device will be reimbursed in France, it would be advisable, prior to conducting clinical trials to obtain CE marking, to consider the clinical

requirements that will be demanded by HAS so that these can be anticipated. The studies obtained could therefore be useful throughout the development process (Figure 8)

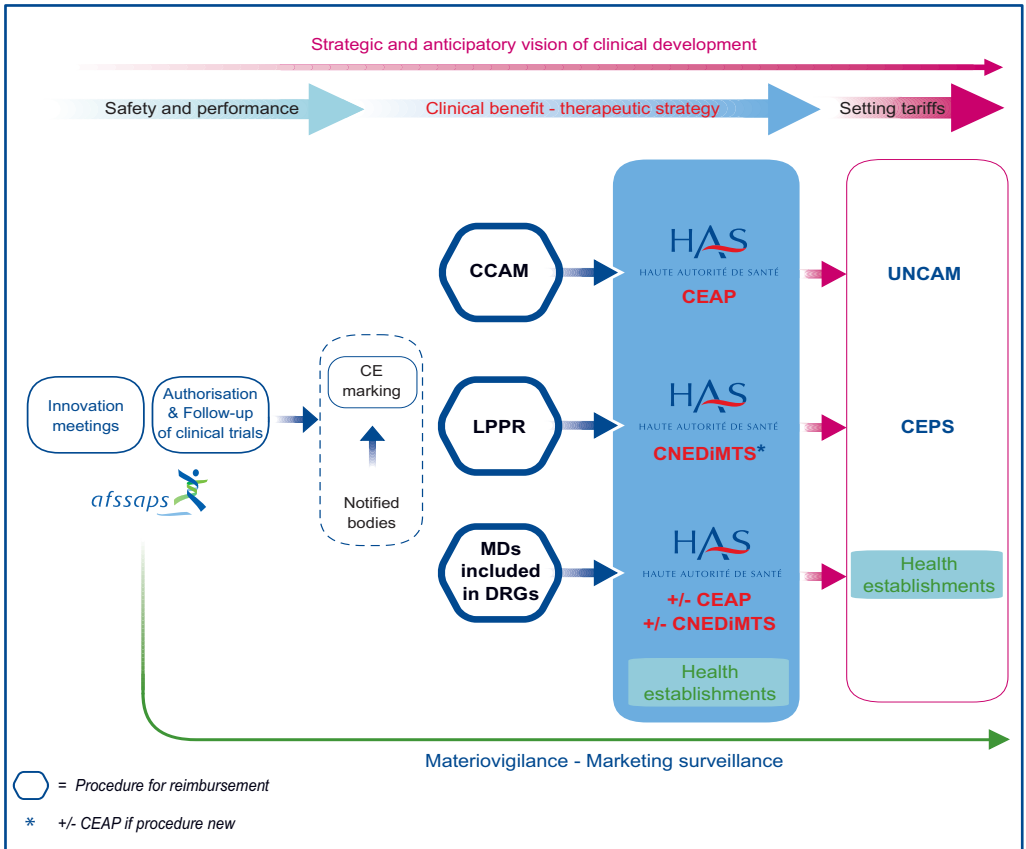


Figure 8. MD process as regards the reimbursement procedure in the French health service (not generic)

In the case of an innovative MD, in terms of clinical development strategy, one should note:

- the **implementation by HAS** of an assessment enabling rapid access to innovative technologies (25);

HAS has implemented a scientific process with four priority objectives **in the interests of the patient**: to locate major potential innovations, to encourage the collection of relevant data thanks to **early contacts with a view to scientific consultation**, to **evaluate** these innovations without delay and finally, to accompany their introduction into the health service.

The truly innovative MD can therefore be made available to the patient while limiting risk-taking by evaluating the MD as soon as it is available.

- the **implementation by Afssaps**³⁷ of a structure to introduce and accompany the innovation.

This structure is composed of an "innovation point of contact" and an internal multidisciplinary innovation network.

4.3. Clinical follow-up after CE and/or after reimbursement by National Health Insurance

► Clinical follow-up after CE marking

The concept of clinical follow-up post-CE was introduced by directive 2007/47/CE which lays down the **principal of collection of clinical data during marketing** to confirm performance and safety of use. Where post-market clinical follow-up as part of the post-market surveillance plan for the device is not deemed necessary, this must be duly justified and documented.

Afssaps can intervene at any time **in the life of a device by evaluating the benefits and risks** within the context of materiovigilance³⁸ and post-marketing surveillance (10).

As far as surveillance of the market is concerned, Afssaps controls the marketing conditions of MDs and ensures that they conform with the specifications for devices declared by the manufacturer. It organizes, on its own initiative or upon notification by the ministry of health permanent actions, ad-hoc surveys and thematic programmes decided annually.

These **market control and assessment** operations are not intended to determine the performance of the devices, which is the responsibility of the manufacturer, but to **reveal possible non-compliance with stated performance** and/or state-of-the-art.

These operations may lead to **requests for making the MD compliant, recommendations for use or restrictions on use or withdrawal from the market.**

► Studies requested by CNEDiMITS after reimbursement by National Health Insurance

The guidance given on first inclusion³⁹ may include a request for additional studies **necessary** to evaluate actual benefit, or added clinical value, which **must be provided** at the time inclusion on the LPPR is renewed

The studies **requested after inclusion on the LPPR** relate to the **MDs registered under their trade name.**

37. Afssaps, accompanying the innovation: <http://www.afssaps.fr/Activites/Accompagnement-de-l-innovation/Afssaps-et-innovation/>

38. Article R. 5212-1 and following of the Public Health Code

37. Article R. 165-11-1 of the Social Security Code

These will enable questions that were unanswered at the time of the assessment by CNEDiMITS to be answered (relating to the opportunity and/or methods for refunding of the MD by the community practice). These questions may concern:

- a need for additional clinical data;
- an estimate of the clinical safety of the devices under actual conditions of use (if there are any doubts);
- a knowledge of the terms of use and verification that in the guidance of CNEDiMITS these are appropriate to those specified;
- a need for health-economic data.

When inclusion on the list is renewed, the analysis of results will provide CNEDiMITS with information on which to base the assessment of the SR of the device. The data provided by these studies are also vital in assessing the ASR of the MD, which was also evaluated at the time of the request for renewal of inclusion.

Requests for post-inclusion studies by CNEDiMITS are usually contained in an **agreement between CEPS and the company**.

In case of a request for post-inclusion studies by CNEDiMITS, the latter will give a guidance on the composition of the scientific committee as well as the methodology envisaged.

Within the framework of **innovative MDs**, CNEDiMITS may recommend reimbursement for a temporary period initially, by controlling prescribing and **making reimbursement conditional on the immediate establishment of additional clinical studies in selected centres**. Analysis of these additional studies will, in this case, be the deciding factor when the time comes for CNEDiMITS to reevaluate the **innovative MD** after it has been made available.

The challenges of clinical development

The methodological principles applied to MDs

- Rules regarding the stages of clinical development exist within the framework of the CE marking.
- The key stages of clinical development are the **feasibility studies** then the studies that demonstrate clinical efficacy; these must be designed as **early** as possible during the preclinical phase.
- **Collection of clinical data must be put in place from the first patient** and a protocol must be drawn up to ensure the quality of this data collection. The most convincing type of study to demonstrate clinical superiority of a new MD is the **randomised controlled trial**.
- Different aspects must be tackled systematically and **questions must be asked at the time any trial demonstrating clinical efficacy of a new MD is being devised**. This systematic approach will enable one to develop a trial that will optimally add value to the new MD up.

... / ...

The challenges of clinical development (continued)

- It may be that this trial, given the **features** of the MD, cannot be randomised and controlled; in such cases, the systematic approach will then enable one to **explain the options chosen** for which the **interpretations will take account of any bias**.
- It is essential that the **primary objective** is defined **before the protocol is drawn up**; it must be **unique**, and its **wording clear and precise**.
- **The main criteria for assessment** must be **unique, valid and clinically relevant**.
- **Multicentre trials** facilitate the extrapolation of results.

Clinical development strategy

- Importance of having a **strategic and anticipatory vision** when the clinical development plan is being designed.
- Case of innovation: existence of a specific process at **HAS** and of a **structure for introducing and accompanying the innovation at Afssaps** to support innovative MDs.

Clinical follow-up after CE and/or after reimbursement by National Health Insurance

- Reinforcement of post-marketing clinical follow-up within the framework of CE marking.
- Follow-up by Afssaps within the framework of **materiovigilance** and **surveillance of the market** following CE marking.
- Possibility of request for post-inclusion studies by CNEDIMTS when renewing inclusion of MD on list.

Conclusion

This document indicates the willingness of HAS to pursue its objective of improving the quality of healthcare in the interests of the patient. This appraisal and this review of experiences by HAS are offered to the researchers and health professionals who participate in the development of medical devices.

This guidebook formalises a proactive approach for researchers and/or very small companies that conduct projects. HAS wishes to engage in a constructive assessment of MDs by encouraging clinical development and providing, without delay, effective and efficient medical technologies to patients.

Annex 1. Working practice

Information sources

Main sources:

- The *Cochrane Library* (United Kingdom);
- *National Guideline Clearinghouse* (USA);
- *HTA Database (International Network of Agencies for Health Technology Assessment - INAHTA)*;
- *Bibliothèque médicale A.F. Lemanissier* – medical library, Le Mans Hospital (France);
- *CISMeF Bonnes Pratiques* – register of GCP conferences and professional recommendations (France);
- *CMA Infobase - Clinical Practice Guidelines* (Canada);
- *National Library for Health - Guidelines Finder* (United Kingdom).

Other sources:

- websites of international ministries of health;
- websites for assessment and regulation of devices and/or medicinal products (e.g.: FDA Food and Medicinal product Administration-USA, PMDA Pharmaceutical and Medical Devices Agency-Japan, MHRA Medicines and Healthcare Products Regulatory Agency-UK);
- internet sites of learned societies competent in the field studied;
- bibliography of selected articles and documents.

Research strategy

The documentary strategy consisted in identifying recommendations and documents that appeared between 1999 and 2009 on the subject of the marketing of medical devices and the process to follow of a MD within the health service.

This research was continued by:

- a systematic review, up until October 2009, of the following journals: *British Medical Journal* (BMJ), *Journal of the American Medical Association* (JAMA), *The Lancet*, *The New England Journal of Medicine*, the daily medical and paramedical press and the *Agence Presse Médicale* (APM);
- as well as by research updates on sites of interest using the same strategy.

The last update was in October 2009.

No **summary document or guidebook was found on the process to follow when marketing a medical device and in the case of a request for reimbursement**. Fragmented documents are usually issued by different institutions within the same country. These provide a reference for just a portion of the process to foresee but not for the entirety process.

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