



HAUTE AUTORITÉ DE SANTÉ

Medical device evaluation
by the CNEDiMTS (Medical Device
and Health Technology Evaluation
Committee)

**Guide to the specific features of
clinical evaluation of a connected
medical device (CMD) in view of its
application for reimbursement**

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Contents

Abbreviations and acronyms	4
Introduction	5
Connected medical devices evaluated by the CNEDiMITS and covered in this guide	7
CNEDiMITS evaluation criteria for access to reimbursement of a MD.....	9
CMD common features	10
Adaptation of the clinical development of CMDs	13
Evaluation by the CNEDiMITS	16

Abbreviations and acronyms

ACB	Actual Clinical Benefit
ANSM	Agence nationale de sécurité du médicament et des produits de santé (French National Agency for Medicines and Health Products Safety)
CAV	Clinical Added Value
CEESP	Commission évaluation économique et de santé publique (Commission for Economic Evaluation and Public Health)
CEPS	Comité économique des produits de santé (French Healthcare Products Pricing Committee)
CMD	Connected medical device
CNEDiMST	Commission nationale d'évaluation des dispositifs médicaux et des technologies de santé (Medical Device and Health Technology Evaluation Committee)
CNIL	Commission nationale de l'informatique et des libertés (French Data Protection Authority)
CSS	Code de la sécurité sociale (French social security code)
DSS	Direction de la sécurité sociale (French social security division)
FDA	Food and Drug Administration
GDPR	General Data Protection Regulation
HAS	Haute Autorité de santé (French National Authority for Health)
LPPR	Liste des produits et prestations remboursables (List of products and services qualifying for reimbursement)
MD	Medical device
PHB	Public health benefit
RCT	Randomised controlled trial
SED	Service évaluation des dispositifs (HAS medical device assessment department)

Introduction

Warning: this guide applies to a very small number of connected medical devices (CMDs). They are those for assessment by the Medical Device and Health Technology Evaluation Committee (CNEDiMETS), including those already with CE marking and for which the company which manufactures them or operates them wishes to apply for individual funding by the French health insurance scheme.

Digital use is widespread in health system users and also in the structures for which it is intended, as much in private practices as in hospitals.

For patients and health care professionals alike, the digital provides for a new way of working, treating, being treated and looking after one's health.

Digital technologies are used to simplify numerous tasks (patient access to their personal record, appointment making, computerisation of the patient's medical record or information, assistance for health care professionals in decision-making, flow management, etc.), and major changes in organisation or running of the health care system through radically new practices.

One of the promises made by connected medical devices is to contribute to improving the quality and efficiency of patient management by providing users with the possibility to do away with time and space-related constraints. Ultimately, they aim not only to simplify use or reinforce personalisation of prevention, diagnosis, treatment and support/follow-up, but also to improve coordination within the patients' healthcare pathway or life.

Beyond the direct benefit for the patient, the data generated, where they are shared in accordance with the texts in effect for the protection of personal health care data, are a source of new knowledge for companies, researchers, patients' associations and governments.

Thus, connected medical devices should contribute to the convergence of individual and societal benefits. Their use implies selecting useful and efficient technologies. Their evaluation, which must adapt to the pace of technological developments, is therefore important. We must all be able to trust in connected medical devices.

One of the challenges for the CNEDiMETS is to conciliate between evaluation requirements and the pace of development of CMDs, in order to promote the rapid introduction of those likely to bring benefit in the health care system.

Before embarking on the clinical development of a CMD, it is important for the project leader to question their reimbursement strategy.

A certain number of questions can be asked beforehand, such as:

- Is the connected medical device (CMD) for individual use or not?
- How and where is it used (before or after, for or during a medical procedure, used at the patient's home or in hospitals)?
- What is its mode of action?
- What is the ultimate medical purpose?
- With which "interlocutors" is the CMD intended to (or designed to) interact: other MDs or CMDs, data platforms, patient and their family, health care professionals, etc.?
- Which type of process (i.e. collection, recording, storage, release or any other form of disclosure, destruction, etc.) and what data security?
- Which population is likely to use it?
- Is a learning phase necessary?
- Is it interoperable with the information system designed to manage coordination of treatment by health care professionals?
- What is the gold standard therapeutic, diagnostic or disability compensation strategy?
- What is the expected added value of the CMD with respect to the gold standard and pre-existing technological solutions?
- What are the possible reimbursement conditions?

Also, CMDs can obviously have specific features related to their mode of action, their impact on patients, carers, health care professionals or organisation. Their clinical development must take these specific features into account.

The objective of this guide is to help companies manufacturing or operating CMDs to include clinical trials for determining their usefulness in view of their reimbursement by national solidarity in their development strategy.

This guide is based on a systematic review of literature that the reader will find in a separate report (see the guide preparation report).

To answer the questions from companies on the clinical development to be led with respect to clinical evaluation, and therefore to answer their need to anticipate, this guide takes account of the general safety and performance requirements of [European regulation 2017/745](#) for medical devices¹.

Finally, as the technologies, knowledge, legislation, standards, good practices and charters etc. related to the digital are rapidly changing, especially concerning artificial intelligence, **this guide will be amended over time, and will be updated as many times as is necessary.**

The [VILLANI report](#)² emphasises in effect that “systems using artificial intelligence make decisions on models built from data. Therefore, protocols must be developed and include new metrics to be applied to data, performances, interoperability, usability, safety and confidentiality”. And the [report by the working group sponsored by the CCNE with the contribution of the CERNA](#)³, published on 19 November 2018, notes that “however, the certification and standardisation work on artificial intelligence and robotisation in health, despite their usefulness, remain, as they are, at a highly incomplete stage”.

1. European regulation 2017/745 entering into force on 26 May 2017 and applicable from 26 May 2020 unless otherwise provided for (see art. 123 “entry into force and date of application”).

2. Villani C. Donner un sens à l'intelligence artificielle: pour une stratégie nationale européenne. Parliamentary mission from 8 September 2017 to 8 March 2018.

3. Comité consultatif national d'éthique pour les sciences de la vie et de la santé-National ethics advisory board for life and health sciences, commission de réflexion sur l'éthique de la recherche en sciences et technologies du numérique d'Allistene-Allistene discussion group on research ethics in digital sciences and technologies. Numérique et santé. Quels enjeux éthiques pour quelles régulations? Paris: CCNE; 2018. www.ccone-ethique.fr/sites/default/files/publications/rapport_numerique_et_sante_19112018.pdf [viewed on 21/12/2018].

Connected medical devices evaluated by the CNEDiMITS and covered in this guide

The Medical Device and Health Technology Evaluation Committee (CNEDiMITS) is the Haute Autorité de santé (HAS) committee **which evaluates, in particular, medical devices (MD)** and other health products **in view of their reimbursement by the French health insurance scheme** ([article L. 165-1 of the CSS](#)). It plays an advisory role to decision-makers recommending the reimbursement of the MDs or not (inclusion on the List of products and services qualifying for reimbursement – LPPR), helping to determine the conditions for their proper use and their role in the therapeutic, diagnostic or prevention strategy.

The CNEDiMITS' scientific evaluation mission takes place only when **CE marking has been granted** ([article R. 165-4 of the CSS](#)). Its evaluation is complementary to that of CE marking: beyond demonstration of performances and safety, it aims to evaluate the usefulness of the MD for the patient and for public health, and its place in the arsenal available in France. Other than CE marking, other prerequisites are necessary. Therefore companies submitting an application for reimbursement of a CMD must ensure they first meet French and European legal and regulatory requirements, especially in terms of data hosting and data processing^{4,5}.

The connected medical devices area is vast, however, in light of the CNEDiMITS' missions, the medical devices (MDs) it evaluates only represent a small part of connected medical devices (CMDs).

The scope of this guide fully underpins the CMDs subject to evaluation by the CNEDiMITS, that is to say those with CE marking and candidates for individual⁶ funding from the French health insurance scheme.

Therefore, numerous products used in health, although they are connected, are not covered in this guide:

- **applications and connected objects that are not CE-marked medical devices⁷** (e.g. software or apps used to increase physical activity by calculating the number of steps per day);
- **medical devices which are not for individual use and which are not subject to individual funding** (e.g. connected balances, thermometers or blood pressure monitors used in hospitals for more than one patient);
- **medical devices used exclusively by a health care professional or between health care professionals** (e.g. professional decision aid tools, prescription or dispensing aid software, teleconsultation software, diagnostic or therapeutic decision aid medical imaging devices, etc.);
- **software for general uses, even when used in a healthcare environment** (e.g. administrative management software).

4. General Data Protection Regulation (GDPR) – [Regulation \(EU\) 2016/679 of the European Parliament and of the Council of 27 April 2016](#) [viewed on 21/12/2018].

5. Personal health data hosting. [Article L. 1111-8 of the French Public Health Code](#) [viewed on 21/12/2018].

6. Individual funding in addition to existing procedures or health care packages.

7. Medical purposes stated in the medical device definition in: [article 2 of Regulation \(EU\) 2017/745 of the European Parliament and of the Council of 05 April 2017 on medical devices](#) [viewed on 21/12/2018].

CMDs eligible for evaluation by the CNEDiMTS meet the following four criteria.

1. They are intended for use for medical purposes, their end-use implying they are CE-marked.
2. They are for individual use (implanted or used by the patient themselves).
3. They have a telecommunication function.
4. The company has submitted an application for reimbursement by national solidarity.

It is the fourth condition that triggers evaluation of a CMD by the CNEDiMTS: the company takes the initiative to register a new technology on the list of products and services qualifying for reimbursement (LPPR) ([article R. 165-7 du CSS](#)).

To illustrate this scope, some examples of CMDs likely to qualify for individual reimbursement by the French health insurance scheme MDs:

- used for **medical telemonitoring purposes** (e.g. an implantable cardiac defibrillator and remote medical monitoring);
- prompting action from the patient for **self-treatment or self-monitoring purposes** (e.g. nerve stimulator to treat pain connected to a smartphone application allowing the patient to manage their treatment themselves);
- producing or receiving information in view of treatment optimisation (e.g. an insulin pump combined with a sensor for the continuous measurement of interstitial glucose using the patient's electronic diary to optimise their treatment).

CNEDiMETS evaluation criteria for access to reimbursement of a MD

The CNEDiMETS evaluation criteria are regulatory criteria which apply regardless of the type of MD, connected or not⁸.

► Evaluation of actual clinical benefit

The actual clinical benefit (ACB) of a health product is evaluated in each of the indications claimed, according to the following two criteria: **benefit of the MD for the patient and its public health benefit**. The ACB is a binary criterion: it is deemed to be “sufficient” or “insufficient” at the end of the evaluation. If the actual clinical benefit is sufficient, the opinion issued by the CNEDiMETS is favourable to inclusion of the MD on the LPPR; if the benefit is insufficient, the opinion is unfavourable to inclusion of the MD on the list.

■ Benefit of the medical device

The benefit of the medical device is used to determine its **effect at individual level**, firstly, its therapeutic, diagnostic or disability compensation effect, secondly, its role in the therapeutic, diagnostic or disability compensation strategy, given other therapies or other diagnostic or compensation methods available. The data are analysed according to evidence-based medicine criteria. The CNEDiMETS determines clinical relevance.

■ Public Health Benefit

The Public Health Benefit (PHB) **takes the collective aspect into account**. Its objective is to understand the impact of the medical device on the improvement of the state of health of a population, in terms of mortality, morbidity and quality of life, response to an unmet or insufficiently met therapeutic or diagnostic or disability compensation need, its impact on public health policies and programmes.

► Evaluation of clinical added value

Where ACB is sufficient to justify registration for reimbursement, the CNEDiMETS must also issue an opinion on “the evaluation of clinical added value [...] (CAV [...]) with respect to a specifically designated, comparable product, procedure or service or comparable set of procedures, products or services, considered to be a gold standard according to the current state of knowledge of science, whether accepted or not for reimbursement”⁹.

This evaluation concludes on the CAV as **major (I), important (II), moderate (III), minor (IV) or as showing no improvement (V)**. It is conducted for each therapeutic, diagnostic or disability compensation indication in which the Committee considers there is evidence to justify registration. CAV has an impact on the MD tariff, negotiated by the French Healthcare Products Pricing Committee (CEPS) with the company.

Patients and users associations have the possibility [to contribute to this evaluation](#).

The CNEDiMETS evaluation procedures are described in detail in the document [“Procedures for evaluation of medical devices for individual use in view of their application for reimbursement”](#).

Inclusion of a product under brand name on the LPPR is granted for 5 years maximum. It can be shorter if the Committee sees there is a need for additional data to confirm the benefit of the MD.

The opinion issued by the CNEDiMETS is sent:

- to the CEPS (**see CEPS missions**), in view of setting the reimbursement tariff;
- to the ministry in charge of social security, which takes the decision to accept it or not for reimbursement.

8. [Article R. 165-2 of the French Social Security Code](#) [viewed on 21/12/2018].

9. [Article R. 165-11 of the French Social Security Code](#) [viewed on 21/12/2018].

CMD common features

By their nature or function, connected medical devices are a heterogeneous group of medical devices.

However, they have in common the remote sharing of data for monitoring clinical or technical indicators in order to adjust patient management.

One of the expectations of these devices resides in what they bring in terms of additional information (e.g. more frequent measures or alerts) or in terms of interaction with other technologies or with medical staff, enabling continuous or more frequent monitoring, or even anticipating intervention by health care professionals if necessary.

Therefore, as they are connected, CMDs have common features. In particular, these relate to:

- **the very high rapidity of technological development;**
- **their interaction with other devices/objects/platforms** (medical devices or other) including data collection, transmission and data processing between the various components;
- **the existence of expert information processing systems**, from the more conventional, such as programmed decision-making algorithms, to the most innovative, such as those using artificial intelligence algorithms.

These specific features can have an impact on various aspects, especially on the patient's health, quality of life or organisation of care. These features can also have an incidence on the way in which the CMD is evaluated.

Rapidity of technological development

The MD sector is already seen to be rapidly developing. CMDs enter into this momentum in an even more marked manner due to their plasticity. For example:

- **CMDs can use technologies that are highly scalable.** Technical improvements non-specific to health, such as information processing digitising, the development of data sciences models or voice assistants, can be used to design or improve the CMD. Downsizing of certain components, the development of new sensors, or even energy consumption optimisation can be used to measure parameters that were inaccessible until now, and send the result from a remote site;
- **the need for or the possibility of having a remote connection to use them can enable developers to rapidly upgrade their technological solution;**
- The possibility of monitoring the use or performance of CMDs, through indicators integrated in the technological solution or through interactions with users, can make it possible **to reduce the length of certain development steps related to setting up or to the system test.**

Interaction with other devices/objects/platforms

By doing without wired connections, CMDs make multiple interactions between patients, carers, medical staff and machines possible. They enable a health care professional or a patient to interpret data from a remote site, and where applicable, to take decisions on treatment. Data recording and transmission can be automated or performed by the patient themselves, by their carer or a health care professional or other individual.

CMDs can receive or transmit data at a few centimetres (e.g. where the patient uses two devices with complementary functions and which communicate with one another) as at a few hundred kilometres (e.g. in the case of remote medical monitoring, where the patient is monitored via software by which they transmit information to the doctor looking after them).

Therefore, by removing the constraints related to distance between users and medical staff, **and by offering potentially shared access to the data collected, in real time or more often by conventional monitoring**, CMDs can also have an **impact on work methods and on interactions between medical staff, patients or their carers.**

These impacts depend on the methods of access to the data (access rights, server availability rate, guaranteed range of service, maximum number of simultaneous logins, etc.), on the monitoring organisation in place (depending on the protagonists, their role in monitoring and the sequence of their interventions), on the attitude of the health care professionals and also the patient's role in managing their health.

The challenge is to improve standard of care, to reduce inequality of access to care for users in isolated geographical areas or in social isolation, to simplify monitoring and to improve quality of life. In these conditions and in a context of an ageing population and increase in chronic diseases, these technologies contribute to treatment as close to home as possible.

The functioning of the device and the behaviour of the persons involved, whether using the CMD or the data it generates, can therefore vary depending on the context of use.

Expert data processing systems

Warning: health data are specific personal data and are thus considered to be sensitive. To this effect they are specifically protected by law (European personal data protection regulation, French data protection act, French Public Health Code, etc.) in order to protect personal privacy (www.cnil.fr/fr/sante).

CMD data processing requirements (collection, recording, storage, dissemination or any other form of disclosure, destruction, etc.) are covered by current legislation, especially the General Data Protection Regulation (GDPR), whether the company is located in the European Union or not (due to the fact that their activity applies to European patients).

The French data protection authority (Commission nationale de l'informatique et des libertés – CNIL) is in charge of providing information to and answering requests from private individuals and professionals. It offers tools (www.cnil.fr/fr/quelles-formalites-pour-les-traitements-de-donnees-de-sante-caractere-personnel). **As a result, data processing requirements are not discussed in this guide.**

The CNIL has the authority to conduct inspections and to issue authorisations relating to data protection. The CNE-DiMETS therefore ensures straightforward watch as to application submissions and reserves the right to alert the CNIL in the event of justifiable doubt on an application.

In the conditions provided for by law, data collected can be processed for medical purposes. In this context, alerts can be generated, triggering, if necessary, changes in the patient's management or health care pathway.

For data processing, CMDs may use various types of algorithms, more or less complex, more or less autonomous in their learning. Among the algorithms¹⁰, conventional algorithms do not have the ability to self-modify. **The so-called learning algorithms (machine learning) have the ability to evolve over time.**

Pending new methodologies, the main machine learning methods are said to be supervised or unsupervised. These methods can be combined together. When used in real-life situations, the algorithms can be temporarily fixed, then updated sequentially and regularly by persons in charge of their development, according to predetermined version management. The algorithms can also not be fixed and can update dynamically when used and when processing new data.

10. Algorithm: "description of a finite and unambiguous series of steps or instructions for producing a result on the basis of input elements"¹¹. A learning algorithm is able to autonomously develop the parameters of the instructions of which it is made up over time, according to the results previously received. It is the opposite of conventional algorithms which do not have the ability to self-modify.

Supervised machine learning

“The algorithm learns input data qualified by humans and thus defines rules on the basis of examples which are as many validated cases.”¹¹

Supervised learning takes place in two steps. During the first, the algorithm learns, on the basis of solved cases, to adjust its parameters in order to enhance its predictive performances (e.g. case classification). The second step consists of verifying that the resulting algorithm is generalisable by applying it to a set of new cases, the result for these cases having to be validated by an expert. We thus check that the algorithm has learned properly, if the learning was biased (over learning) or, conversely, if it requires more examples (under learning).

Unsupervised machine learning

“The algorithm learns from raw data and creates its own classification which is free to develop into any final state where a pattern or element is presented to it. Practice which requires instructors to teach the machine how to learn.”¹¹

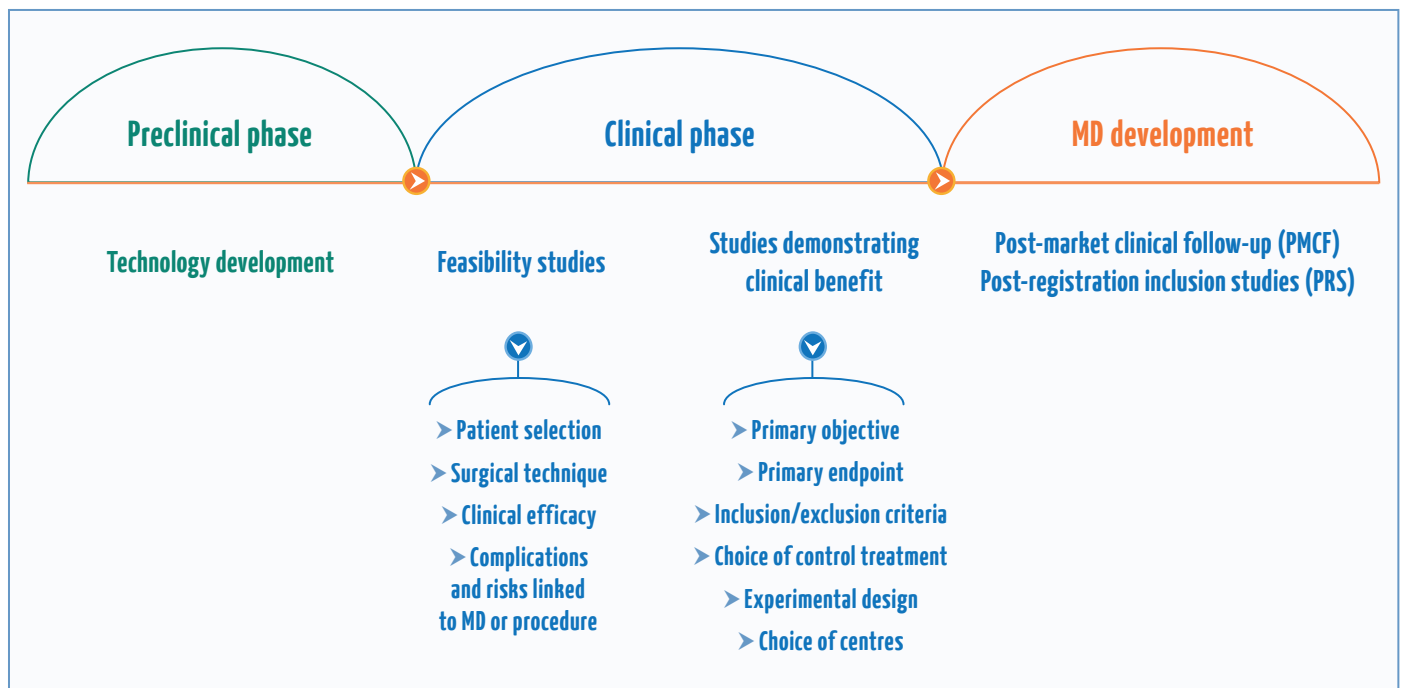
In the case of unsupervised learning, the data provided to the algorithm are unsolved cases (we do not know the conclusion). The algorithm relies on functions of similarity, differences etc. between the cases to pool them into groups. The expert then verifies later on that the resulting groups effectively classify the data (by comparing the algorithm result and its own decision on new data) in order to decide whether the algorithm is valid and can be used in real life.

11. Commission nationale informatique et libertés. Comment permettre à l'homme de garder la main? Les enjeux éthiques des algorithmes et de l'intelligence artificielle. Summary of the public debate led by the CNIL as part of discussions on ethics mandated by the French law for a digital republic. Paris: CNIL; 2017. www.cnil.fr/sites/default/files/atoms/files/cnil_rapport_garder_la_main_web.pdf [viewed on 21/12/2018].

Adaptation of the clinical development of CMDs

MD evaluation must follow the usual clinical development phases.

- **The preclinical phase** evaluates the characteristics, the **performances** and **safety** of the MD, during the technology design and development phase.
- **Clinical feasibility phase** on the first use of the MD in humans, which makes it possible to make an initial estimation of efficacy and adverse effects. Feasibility is also used to:
 - evaluate its acceptability in its operating environment;
 - identify relevant endpoints and criteria for the selection of patients to include;
 - develop the implantation technique where applicable.
- **The clinical phase which follows feasibility is used to demonstrate its therapeutic, diagnostic or disability compensation effect along with any adverse effects or risks related to its use**, via the essential compilation of clinical trials. These trials are based on the various feasibility and technology development studies.
- **Post-registration monitoring requested for certain MDs via post-inclusion studies in view of renewal of their inclusion on the LPPR** is used to evaluate the MD in the medium- to long-term in real life (NB, post-market clinical follow-up introduced by European regulation 2017/745).



The clinical development of a CMD must also take account of the features specific to CMDs described previously.

Rapidity of technological development

Two key questions on this specificity have been identified:

- how to manage CMD evolution during the study?
- will the data collected on a previous version be able to be used for the evaluation of the latest generation of the CMD by the CNEDiMITS?

In all cases, during the clinical phase, the study protocol must take account of the scheduled evolution of the CMD. The feasibility of an evolving CMD during the study and extrapolation of the clinical data from the study implemented, to a more recent version of the CMD must be anticipated.

The clinical requirements depend on the type and extent of the modifications made.

- If the modifications made to the CMD are minor or cover secondary components (such as identification, data encryption, text or mail message service modules, etc.), the protocol can plan to include several versions of a CMD where:
 - the main component does not undergo major changes;
 - the non-regressiveness¹² of results is ensured (in order to guarantee that component replacement has not affected the functionality, reliability or the performances of the system and has not led to additional faults).
- Conversely, a major technological change requires a new study. For example, a change is considered to be major in the following situations:
 - change of the system's architecture by addition or removal of components or interfaces for which maintenance of the quality of service is not established;
 - replacement, addition or removal of a function or parameter used by the algorithm(s) with an effect on the results;
 - change of organisation of care.

Interaction with other devices/objects/platforms

Use of a CMD implies above all having precise knowledge of the system in which it is to be integrated, in particular organisation of care, in order to construct the relevant clinical development.

Two key points to be considered before starting a clinical evaluation:

- identify the stakeholders involved (patients/medical staff or other protagonists involved), their role according to logic of the type "Who does what? When? How?";
- define the scope for the technological solution to be evaluated: for certain CMDs, the evaluation to be implemented shall be that of the CMD if its specific effect can be customised in the system in which it is integrated. Nevertheless, in most cases, it is the evaluation of the technological solution that will be the most relevant, that is to say one or several devices together, collecting, processing and transmitting information from a remote site taking account of the organisation of care in place.

Expert data processing systems

CE marking¹, prerequisite to evaluation by the CNEDiMTS, ensures that the medical device is compliant with the general safety and performance requirements. Manufacturers have to set up, enforce and maintain a risk management system, throughout the device's life cycle.

The European Regulation also specifies that:

- electronic programmable systems shall be designed to ensure repeatability, reliability and performance in line with their intended use;
- technical documentation drawn up by the manufacturer in view of its CE marking shall present, among other elements, the verification and validation of any software (description of the software design and development process and proof of its validation).

CMDs can integrate various types of algorithms for data processing, some being more "explainable" than others. Where the algorithm is based on machine learning methods or develops complex predictive models, it can be difficult to fully explain the mechanism having led the algorithm to provide a solution. However, for decisions proposed/taken by the model with impacts on patients' health, **the algorithm must be intelligible and interpretable.**

12. [Standard ISO62304](#) [viewed on 21/12/2018]. "Regression test: test required to ensure that a change of a system component has not affected the functionality, reliability or performances and has not led to any additional faults."

For **conventional algorithms** (see p. 11) to be intelligible and explainable, their principles must be sufficiently documented. As a result, the descriptive information enabling it to be understood by users is to be provided on application submission. Also, the data description used to validate the algorithm (completeness, quality and representativeness) is expected, along with the estimation of its performance where applicable (e.g. through the positive or negative predictive value of the parameter evaluated).

For **learning algorithms**, other requirements come into play as their performances are based on models, the stability or non-regressiveness of which over time must be anticipated and verified regularly. It is not the CNEDiMITS' responsibility to evaluate the mathematical functioning of the model, however it is responsible for evaluating its clinical relevance. As a result, the company shall include any information explaining both the way in which the algorithm was created (choice and selection of variables, model selection and learning) and monitoring of the relevance of the algorithm created and set up (regular verification, lack of bias, etc.) in their application. These points must be taken into account in the model design.

► **The selection and quality of the input data taken into account in the CMD are to be explained**

The design of these algorithms or their modification is generally based on a learning database (predictive model production phase) and another test (predictive error determination phase). In order to minimise prediction errors, **the CMD developer shall ensure in particular that their learning algorithm is relevant and robust, that the predictive model generated is relevant as is the quantity and quality of the learning data used** (selection of variables, error detection, exceptions and inconsistencies, representativeness and completeness of the cases).

As a result, the method for compiling learning databases and test databases, patient and disease characteristics are to be explained by the company (prevalence and clinical forms of the disease, necessary number of subjects and selection criteria, origin, sampling methods, recruitment phase, centre location, etc.). These elements are highly important for the subsequent clinical evaluation of the CMD, especially for ensuring that the databases used contain sufficiently diverse information in order to ensure performance for the entire target population.

► **Quality monitoring throughout the use of the CMD is necessary**

Evaluation of a medical device or other health product is based on the principle according to which the product, designed for medical purposes, undergoes clinical evaluation and is marketed in the form in which it was tested. Evolving CMD, especially in the case of learning algorithms, brings this paradigm into question.

Therefore, the methods in place for testing the permanent upgrade of CMD performance are to be explained, especially the methods ensuring that the MD is not upgraded in a way that could be harmful to the patient and that it remains beneficial and useful. Also, the rapid evolution of CMD may lead to data collection in actual conditions of use.

► **The decision-making processes leading to the result and the means in place to evaluate the quality of the predictive model should be explained, especially to ensure its non-regressiveness¹².**

During evaluations by the CNEDiMITS, in light of the developments in the intelligibility and interpretability of algorithms, developments in the good practices for model, ethics and methodology creation, **this guide will be updated as often as necessary**.

Evaluation by the CNEDiMTS

Evaluation of the healthcare technologies benefits is based on a joint approach which involves **assessment of their efficacy and their adverse effects** (quality of the demonstration, quantity of effect and relevance of the criterion taken into account) with regard to the medical context (disease and/or disability, its severity, standard care and the medical need). The pivotal study submitted to support the application for reimbursement above all depends on the end purpose of the CMD and the project leader's strategy with respect to the gold standard.

The CMD developer or company can request early dialogue with the HAS services on issues related to the **clinical or medical and economic development of the CMD** in question.

The evaluation must in theory cover the technological solution as a whole, that is to say all elements collecting, processing and transmitting information from a remote site, taking treatment organisation into account. For example, if a CMD is combined with remote medical monitoring, the evaluation will cover the "CMD and remote medical monitoring system" in its context of use.

In certain cases, especially where certain products can run on their own, the company can envisage customising their evaluation.

Depending on the stakes for the developer, the trials selected can be superiority, equivalence or non-inferiority trials. To demonstrate superiority, the non-inferiority or the equivalence of a new CMD compared to the gold standard, the multicentric randomised control trial is the type of trial with the best level of evidence. This type of trial, when it can be carried out and when it is well built, valorises a new CMD in an optimal manner.

Where it is not possible to conduct a randomised controlled trial, the CNEDiMTS has already identified alternative methods and the conditions enabling quality clinical evaluation in the "[Guide to the choice of methodology for the clinical development of medical devices](#)".

The relevance of the improvement criteria is to be optimised according to the medical purpose of the CMD.

CMDs can have:

- **individual benefit** (morbidity-mortality criteria or with an impact on morbidity-mortality, quality of life criteria, acceptability and patient satisfaction criteria);
- **other impacts** on multiple dimensions of organisation of care according to the different stakeholders (especially in terms of access to treatment, treatment quality, professional practices).

Where the CMD involves the intervention of the patient or carer, the individual benefit related to the connected function of the CMD is to be demonstrated in its use environment.

► Individual benefit

Individual benefit can related to **morbidity-mortality criteria or criteria with an impact on morbimortality**, but also on **criteria relating to the patient's or carers' point of view** as reported by them.

The challenge is that the clinical development plan has to be in keeping with the CMD's ultimate purpose. In other words, that **the endpoint selected is compatible with the company's claim** when submitting their reimbursement application.

Once the endpoint selected, various tools can be used to measure it. Regardless of the dimension selected, and including for non-clinical criteria, measurement tools must have undergone strict methodological validation.

Criteria relating to the patient's or carer's point of view are relevant criteria in their own right.

According to the end purpose of the CMD, the quality of life criterion¹³ can be envisaged as primary endpoint (e.g. for CMDs compensating for a deficiency, helping to perform tasks and contributing to the individual's social participation) or secondary endpoint (e.g. for CMDs treating patients with life-threatening diseases or affecting the patient's health).

At identical clinical efficacy, quality of life can be a value-creating criterion during evaluation of the CMD by the CNEDiMTS (see "[Procedures for evaluation of medical devices for individual use in view of their application for reimbursement](#)").

Elements selecting this parameter are expected in particular, through general (i.e. EQ-5D, SF-36, etc.) or specific scales.

NB: training is required before certain CMDs can be used. The learning phase is to be taken into consideration when preparing the protocol for the study to be set up (*run in*).

► Other impacts

Whether the technology brings superiority or not at individual level, the development plan can include data collection on aspects **which reach beyond benefit for the patient alone**. In effect, CMDs can have impacts beyond individual benefit which affect the general organisation of care from the point of view of the various stakeholders contributing: methods of management and participation of the patient in their treatment, treatment production process and professional practices, CMD conditions of use, treatment safety, etc.

These impacts may therefore be very different according to the contexts of use and according to the point of view taken into account. It is important that the company identifies these impacts from the point of view of all stakeholders concerned and documents them, via validated methods. Especially, the indirect impacts seen in changes in treatment organisation can back the company's arguments in addition to data demonstrating individual benefit in light of the aspects taken into account by the CNEDiMTS.

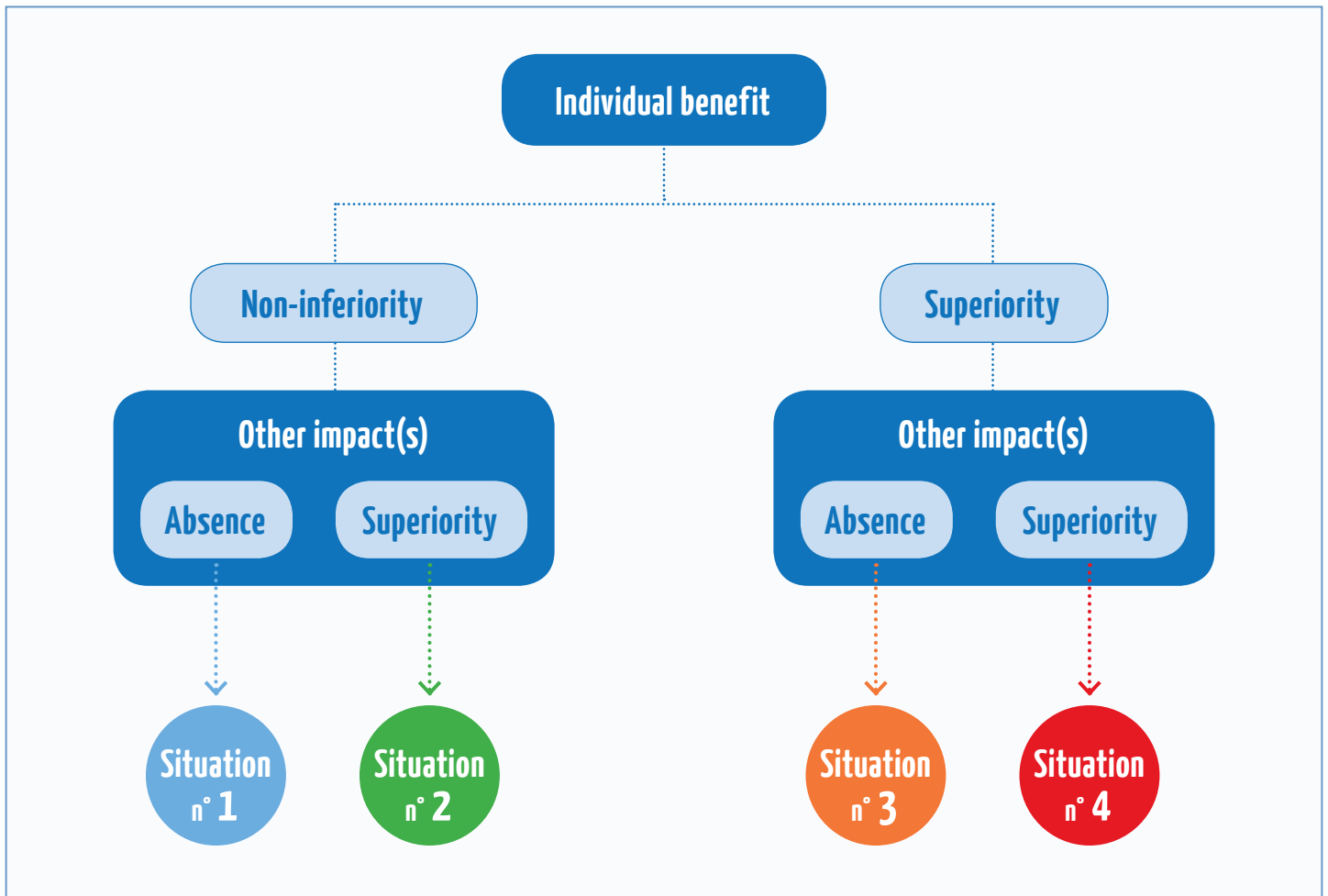
Where other impacts arise without superiority in terms of individual benefit compared to the gold standard, **the lack of harmful effect from the CMD on the individual should be demonstrated.**

At least, the non-inferiority in terms of clinical benefit or acceptability by the patient is to be demonstrated. According to the context, the same study can address both endpoints if it is already provided for in the protocol, in other cases, two separate studies may be necessary.

A medical and economic evaluation can also be included on the condition sufficient efficacy data and costs are available. The procedures and methods adopted by the Haute Autorité de santé for the medical and economic evaluation of MDs are described in the guide "[Methodological choices for economic evaluation at the HAS](#)". This evaluation is not conducted by the CNEDiMTS but by the CEESP.

NB: the HAS has included organisational impacts in the healthcare technologies assessment dossier in its work programme. These impacts, and especially their definition and the criteria used to evaluate them, are discussed in a specific document (see [roadmap](#)).

13. Haute Autorité de santé. Évaluation des technologies de santé à la HAS: place de la qualité de vie. Summary note. Saint-Denis La Plaine: HAS; 2018. www.has-sante.fr/portail/jcms/c_2883073/fr/evaluation-des-technologies-de-sante-a-la-has-place-de-la-qualite-de-vie



Clinical trials supporting applications for inclusion on the LPPR are to be in keeping with the claims of the manufacturer or supplier of the technological solution. In effect, data collection based on the design of the planned trial, will make it possible to provide arguments in favour of the added value of the CMD in terms of CAV in light of the gold standard.

Situation n° 1

Clinical trials show non-inferiority of the CMD in terms of individual benefit and lack of improvement from the CMD on the other impacts, compared to the gold standard. **No claim in terms of CAV can be made.**

Situation n° 2

After having confirmed the non-inferiority of the CMD in terms of individual benefit, a superiority study shows a benefit from the CMD on other impact(s) compared to the gold standard (especially in terms of accessibility, professional practice and treatment organisation, standard of care and treatment safety). **A claim to CAV on the other impact(s) can be envisaged.**

Situation n° 3

Clinical trials have shown superiority of the CMD compared to the gold standard and in the use environment, in terms of patient benefit. **A claim to CAV on the individual criteria can be envisaged.** The organisation of care to be set up should be described in detail.

Situation n° 4

Clinical trials have shown superiority of the CMD compared to the gold standard and in the use environment, in terms of patient benefit, but also in terms of benefit on other impacts (especially in terms of accessibility, professional practice and treatment organisation, quality of care and treatment safety). **A claim to CAV on the individual criteria and the other impact(s) can be envisaged.**

Summary

Regardless of the MD, connected or not, the regulatory evaluation criteria for their reimbursement by the French health insurance scheme are the same. According to the MD's ultimate purpose, they take account of the therapeutic, diagnostic or disability compensating benefit of the MD, and its public health benefit.

Such benefits are demonstrated in clinical trials.

Four specific areas to CMD evaluation must be anticipated by the manufacturer or company operating the CMD.

1 The optimised clinical development programme

- The first challenge for the company in question is to create a clinical development programme that is compatible with the CMD's intended ultimate purpose. For all CMDs for individual use, the evaluation of their impact in terms of clinical benefit, acceptability or improvement of quality of life for users is necessary. Other impacts can also be looked for, especially in terms of access to treatment, standard of care and organisation of care.
- The evaluation must in theory cover the technological solution as a whole, that is to say all elements collecting, processing and transmitting information from a remote site, taking treatment organisation into account. In some cases, especially where certain components are self-operating, evaluation of the effect specific to the CMD can be a challenge for developers.

2 Prerequisites in place independently of any evaluations by the CNEDiMETS for application for reimbursement:

- observance of requirements in terms of processing and hosting of data covered by applicable legislation, especially the GDPR;
- being granted CE marking, which aims to ensure general safety and performance requirements are met during the device's life cycle;
- elements set up by the company for ensuring the quality of the results is managed throughout the period of availability of the CMD to the patient.

3 In the event of automatic data processing, the CNEDiMETS is not responsible for evaluating the mathematical functioning of the model. However, information is to be provided both on the way in which the algorithm was created (choice and selection of variables, model selection and learning, etc.) and on monitoring of the relevance of the algorithm created (regular verification, absence of bias, etc.). These points must be taken into account in the model design.

4 Real-life data collection

The rapid evolution of certain CMDs could imply that after inclusion on the list of products qualifying for reimbursement, real-life data collection be set up in order to monitor its non-regressiveness. The objective is to avoid the negative consequences of possible deviation of the evolving technological solution.

In certain other cases, and as long as the technology is evolving, the CNEDiMETS can request that post-registration studies be set up. These studies, paid for by the company manufacturing or operating the technological solution, are used in particular to confirm the benefit of the CMD in a real-life use situation.



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