HAUTE AUTORITÉ DE SANTÉ

ASSESS
HEALTH TECHNOLOGIES

GUIDE

Innovation funding: submission of an application for exceptional funding for an innovative product

– L.165-1-1 of the French Social Security Code (CSS) – Medical device, in vitro diagnostic medical device or procedure

Validated by the HAS Board on 8 April 2015

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Contents

This document and its bibliographic reference are available to download at www.has-sante.fr

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Introduction

Article L. 165-1-1 of the French Social Security Code (CSS) provides that "Any innovative healthcare product mentioned in Articles L. 5211-1 or L. 5221-1 of the French Public Health Code or innovative procedure likely to provide a clinical or medico-economic benefit may, as an exceptional measure and for a limited period of time, be partially or fully funded, on the condition that a clinical or medico-economic study is carried out. This funding comes under the national health insurance system. The innovative character of the product or procedure is established by its degree of novelty, its degree of risk diffusion and characterisation for the patient, and its potential ability to significantly fulfil a relevant medical need or significantly reduce healthcare spending. ".

This exceptional funding or **"innovation funding"** consists of exceptional, temporary funding aimed at facilitating access to innovative technologies.

With respect to innovation funding and thus in this Guide, the term "technologies" either refers to healthcare products (medical devices or in vitro diagnostic medical devices) or healthcare procedures. Multi-technology solutions (combining a medical device or an in vitro diagnostic medical device with a healthcare procedure) are also eligible for innovation funding.

The technologies concerned are those that supply, at the time of submission of the application, the data establishing that they can provide a significant health benefit or reduce healthcare spending, but which are not sufficient to justify public funding under the ordinary rules of law. This exceptional funding via innovation funding is thus conditional upon the conduct of a clinical study or cost-minimisation study aimed at confirming the interest of the technology. This study may be national or international.

In brief:

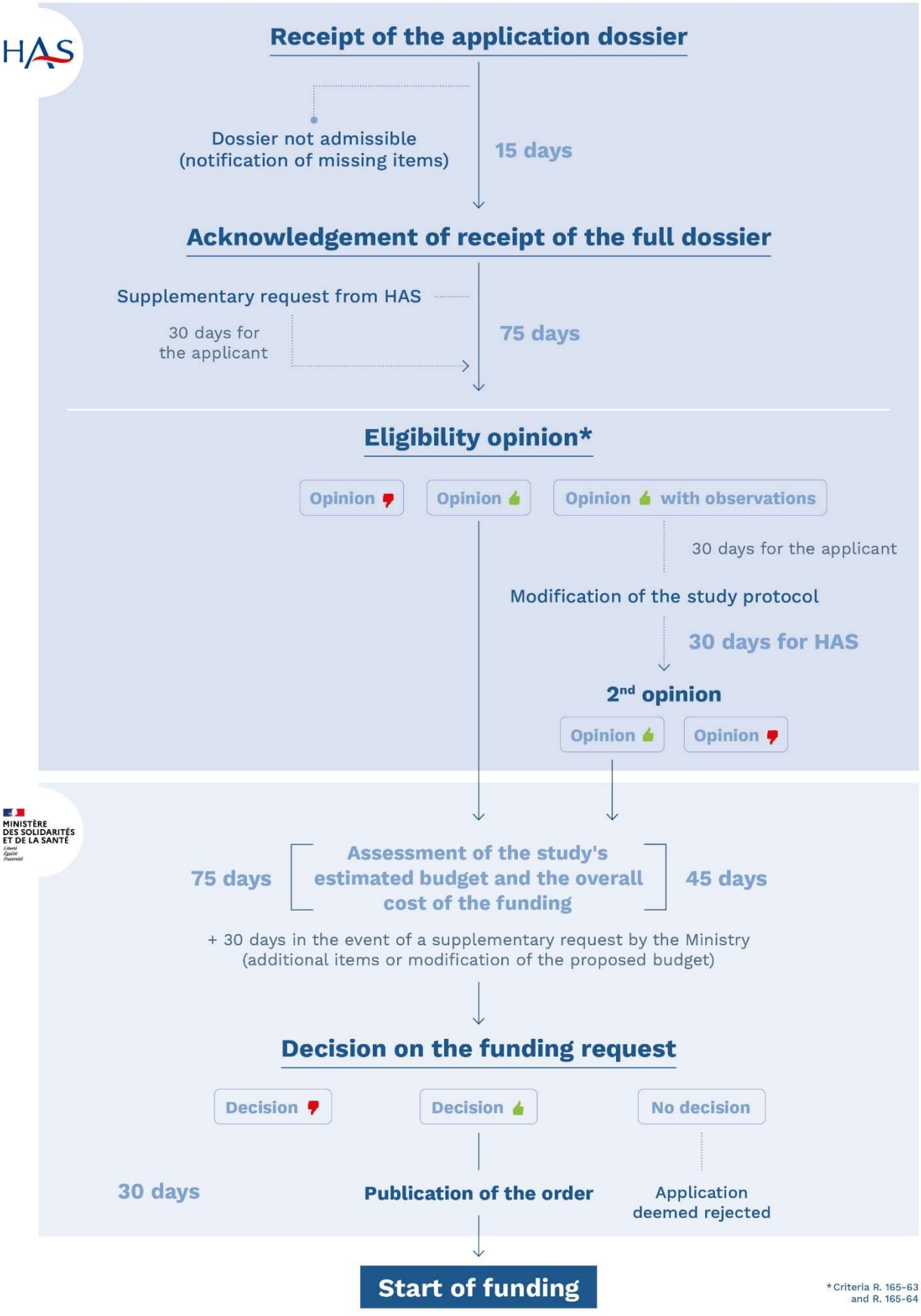
The eligibility of an application for exceptional funding is appraised by HAS in respect of a combination of three types of criteria:

- the type of technology involved, out of the categories of healthcare technologies eligible for innovation funding, i.e. medical devices (MDs), in vitro diagnostic medical devices (IVDMDs), and medical procedures;
- the technology's innovative character (4 conditions defined in Article R.165-63 of the CSS);
- the relevance of the clinical or medico-economic study proposed by the applicant (conditions defined in Article R.165-64 of the CSS).

The HAS Board issues an opinion on the request (procedure available on the HAS website).

The Ministers of Health and Social Security assess the admissibility of the estimated budget of the study proposed by the applicant and decide on whether to grant exceptional funding.

Innovation funding – **Examination procedure**



* Critères R. 165-63 et R. 165-64

The purpose of this Guide is to help you prepare your application for exceptional funding. It also details all of the items you need to provide to enable HAS to process your application.

Before submitting your application, you can request two types of meetings with HAS, depending on the progress of your application:

- early dialogue: the purpose of these meetings is to discuss any queries you may have in relation to the methodology of the clinical study you are envisaging;
- pre-submission meetings: the purpose of these meetings is to discuss any technical/regulatory queries you may have during the preparation of your application or in its finalisation phase (especially concerning the content of your dossier).

No HAS members are present for these two types of dialogue.

General instructions for dossier submission

Where and how do you submit your application?

The whole of the dossier concerning your application for exceptional funding for an innovative healthcare product or procedure (Parts I, II, III, IV and V) should be sent simultaneously to HAS and to the Ministries of Health and Social Security.

In actual practice:

- For the **Ministries of Health and Social Security**: the dossier must be submitted to Bureau Innovation et Recherche Clinique - Direction Générale de l'Offre de Soins (DGOS), in accordance with the procedures described on the following webpage: https://solidarites-sante.gouv.fr/systeme-de-sante-et-medico-social/recherche-et-innovation/forfait-innovation;
- For **HAS**: via the SESAME platform (see additional information below on how to access the SESAME platform).

You should specify **a single designated contact** who will be the sole recipient and point of contact with HAS throughout the dossier examination phase.

SESAME platform access procedure

To be able to submit a dossier via the SESAME platform, the applicant (company or national professional council) must have previously requested to **set up an account for access**. This account set-up request is also made via the SESAME platform using the relevant form. HAS creates a dedicated account, with authorised access for no more than two individuals designated by the company. These individuals become their company's account managers. They can then set up **contributors**, who will be able to access/submit/track dossiers via the SESAME platform on behalf of the company in question. Each contributor will have their own ID and password, which will be their responsibility.

You will only have to enter most of the personal details once; they will subsequently be automatically pre-populated for each new application.

To set up an account for access, you will need the company's or professional council's SIRET number and a statement stamped and signed by the legal representative authorising the individuals mentioned to act as "account manager".

The company can also commission a consultant to submit/track a dossier on its behalf. In this case, HAS sets up access for the individual designated by the company's legal representative. This user will only be able to submit and track dossiers that they have created.

For more information, a dedicated FAQ section and a dossier submission guidance procedure are available in the dossier submission section of the HAS website.

You can consult the status of a dossier on the platform at any time, allowing you to track its progress in real time. Each time the status changes, you will be sent an email notification (if you have enabled this option).

Dossier structure

➔ **Format**

The full dossier must be written in French, with the exception of appended reports, protocols, and publications which may be in English.

Your application for exceptional funding must comprise 5 documents, in keeping with the **template plan described on the following pages**.

The **"Identification of the application" parts I, II and III** will need to be submitted as a single document in Word or accessible PDF format

The **appendices** may be submitted in separate documents.

Each document

- must have numbered pages;
- must comply with the template plan and formats described above;
- must comply with the rules relating to electronic documents (see page 39).

Upon receipt of the application via SESAME, HAS will check that the documents required for the processing of your application are present and valid. The Innovation Funding Secretariat may inform you of any missing documents and request them within 15 days following the submission of your application. The assessment of the eligibility of your application will only start once the dossier is admissible in both administrative and technical parts.

➔ Content

- All targeted data (clinical, epidemiological, etc.) must be referenced[1] and transmitted.
- Relevant studies must be summarised in tabulated abstract form as per the template (on page 35).
- In accordance with Article R.165-66 III of the CSS, except in the event of a request from the department in charge of examining the dossier, the applicant will not be able to make any change to the dossier once its administrative admissibility has been established by HAS.

However, the applicant is required to send HAS and the Ministers of Health and Social Security any information they may be aware of that may alter the efficacy or safety of the healthcare product or procedure under consideration in the application.

[1] Bibliographic references must adhere to the recommendations adopted by the International Committee of Medical Journal Editors (Vancouver guidelines):

Authors*. Title. Subtitle. Title of journal; Year of publication; volume (issue or supplement): start page-end page. [*For up to six authors, the authors' names must be given; from seven, the first six should be cited, followed by a comma and the words "et al.". "*]*

Dossier template plan

Identification of the application

Part I – Arguments confirming compliance with eligibility criteria

The arguments confirming compliance with the eligibility criteria must be summarised, along with a list of the clinical or medico-economic data (they will be detailed in Part II).

Part II – Application assessment dossier

This section includes information that supports the arguments presented in Part I. A systematic documentary search must be conducted to identify the main clinical or medico-economic data available. The search strategy and data selection criteria must be described and justified. The clinical or medico-economic data analyses must be mentioned in this section.

Part III - Full draft protocol of the study

Depending on the case, the full draft protocol put forward must be:

- a clinical study aimed at demonstrating the clinical benefit of the technology,
- a cost-minimisation study following a demonstration of the clinical equivalence of the technology with respect to comparators.

Part IV – Estimated budget

In accordance with the template laid down by decree by the Ministers of Health and Social Security, available via the following link:https://solidarites-sante.gouv.fr/systeme-de-sante-et-medico-social/recherche-et-innovation/forfait-innovation

Part V – Applicant's commitment to communicate the results of the study and provide access to the data

In accordance with the template laid down by decree by the Ministers of Health and Social Security.

Appendix 1 – Administrative documents

- Letter of application to HAS (the French National Authority for Health)
- Copy of the letter of application to the Ministries of Health and Social Security
- Certificate of transfer of authority for the application, where applicable
- For a medical device or an in vitro diagnostic medical device, if available on the application date, the Declaration of CE conformity and certification (an application may be submitted even if the device does not yet bear the CE mark), and, as required:
- CE declaration of conformity to Directive 93/42 for medical devices or to Directive 90/385 and the amendments to Directive 2007/47 for active implantable medical devices
- Declaration of conformity to Directive 98/79 for in vitro diagnostic medical devices
- EU declaration of conformity as per Regulation 2017/745 or 2017/746.
- CE certificate(s) issued by a notified body or self-certification where applicable – with, if available, the basic UDI-DI
- CE marking instructions/information in French

For connected medical devices:

- for personal data processing, the declaration of conformity to the requirements of the General Data Protection Regulation (GDPR);
- where the data processing gives rise to the hosting of health data as per Article L.1111-8 of the French Public Health Code (CSP), the certificate of conformity of the host.

Where the application concerns a multi-technology solution (e.g. a solution involving a medical device and a medical procedure) for which the main applicant wishes to delegate authority to another party, the certificate of transfer of authority for

the application using the template available on the following web page; https://solidarites-sante.gouv.fr/systeme-de-sante-et-medico-social/recherche-et-innovation/forfait-innovation).

Appendix 1 must be submitted in the form of a single document, with numbered pages, in PDF format.

Appendix 2 - Studies and tabulated abstracts

Clinical or medico-economic data justifying the relevance of the request:

- clinical or medico-economic data justifying the relevance of the request, written in English or in French and provided under one of the following formats:
- publication or text accepted for publication (providing proof)
- failing that, the protocol and study report
- failing that, an international conference summary, poster or presentation accompanied by the study protocol, exclusively for studies registered on ClinicalTrials.gov and for which the follow-up period ended less than one year ago
- tabulated abstracts, written in English or in French, according to HAS templates (see p. 35) for each of the clinical or medico-economic studies attesting to the relevance of the request

Appendix 2 must be submitted in the form of a single document, with numbered pages, in Word or accessible PDF format.

Appendix 3 - Other documents

A copy of the other reports or publications mentioned in the dossier (not covered by a tabulated abstract)

Appendix 3 must be submitted in the form of a single document, with numbered pages, in Word or accessible PDF format.

Identification of the application

Name of the technology	
Commercial models and references targeted by the application, if relevant	
Applicable discipline(s)	

The application concerns:

- ☐ a medical procedure
- ☐ a medical device
- ☐ an in vitro diagnostic medical device

The applicant is:

- ☐ the distributor
- ☐ the manufacturer
- ☐ a national council for healthcare professionals (for a procedure)
- ☐ in partnership with a service company
- ☐ in partnership with a healthcare institution

Identification of the applicant	Company name: Address: Tel./Fax/email: SIREN No.: And/or SIRET No.:
Identification of the healthcare facility or service company, where relevant	Company name: Address: Tel./Fax/email: SIREN No.: And/or SIRET No.:
Contact [2] (one contact person per dossier)	Name, capacity and contact details: Address: Tel./Fax/email:
Applicant's legal representative	Name, capacity and contact details:

[2] If the contact belongs to a different legal entity than the applicant, please provide a mandate.

	Address: Tel./Fax/email:
Identification of the manufacturer (if different from the applicant)	Company name: Address: Tel./Fax/email: SIREN No.: Name and capacity of contact:

1. Part I: Eligibility arguments

The eligibility of your application for exceptional funding is appraised in respect of a combination of three types of criteria:

- the type of technology involved, out of the categories of healthcare technologies eligible for innovation funding, i.e. medical devices (MDs), in vitro diagnostic medical devices (IVDMDs), medical procedures;
- the technology's innovative character (4 conditions defined in Article R.165-63 of the CSS);
- the relevance of the clinical or medico-economic study proposed by the applicant (conditions defined in Article R.165-64 of the CSS).

A healthcare product or procedure is considered as innovative if it meets the following 4 conditions (Article R. 165-63 of the CSS):

- its novelty goes beyond that of a mere technical upgrade in relation to the healthcare technologies used for the indications claimed
- it is in an early phase of dissemination, does not justify sufficient clinical benefit in view of the available clinical or medico-economic data available, is not and has never been publicly funded for the indications claimed
- the risks for the patient and, if relevant, for the operator in charge of its use, have already been characterised, as confirmed by available clinical studies
- clinical or medico-economic studies confirm that its use is likely to fulfil one of the following objectives:
  - provide a significant clinical benefit in terms of therapeutic, diagnostic or prognostic effect[3], thus meeting a medical need not yet covered or insufficiently covered
  - reduce healthcare spending, due to the medico-economic benefit, appraised in terms of cost-effectiveness or budget impact on the cost of the care provided. The medico-economic benefit is only taken into consideration when the healthcare product or procedure considered is deemed to be at least as clinically useful as the reference healthcare technologies.

The proposed clinical or medico-economic study underlying the exceptional funding is considered as relevant if it meets the following 3 conditions (Article R. 165-64 of the CSS):

- It makes it possible to gather the missing data to establish an improvement of the clinical benefit and confirm the interest of the innovative healthcare product or procedure. It is comparative, except if there is no relevant comparator, or if this is impossible for ethical reasons,
- Any other similar studies under way or scheduled are identified in order to assess the relevance of carrying out this study,
- The feasibility of the proposed study appears to be reasonable, especially in view of the draft protocol and budget estimate.

[3] The diagnostic or prognostic value is defined in terms of proven improvement of the diagnosis or clinical utility (i.e. the outcome for patients). Utility thus combines diagnostic and therapeutic aspects.

In this section, you will need to **provide a summary of the arguments which confirm the compliance of your application with the eligibility criteria** by filling in the eligibility arguments form set out below.

The elements supporting your arguments will need to be detailed in Part II: Application assessment dossier.

Name of the technology	Name of the technology (medical device, in vitro diagnostic medical device or medical procedure) covered by the application
Type of technology	Type of technology, stating the CE marking class or type of procedure, where relevant For a technology combining a medical device and a procedure: List the similar medical devices that may be involved
Indication(s) claimed	Wording of the indication(s) claimed
Reference strategy	Describe the standard strategy used in the care provided for the indication(s) claimed Describe how it is funded by the community
Target population	Provide an estimate of the number of people liable to benefit from the technology
Anticipated coverage following the exceptional funding	□ LPP □ CCAM □ other: To be specified

1.1. Novelty aspect

Type of innovation	Identify the nature of the technological innovation: ☐ A new form of action that transforms the care provided for a pathology or disability ☐ A radical transformation of a medical procedure for the use of an existing device ☐ A radical transformation of a medical procedure through the use of a device ☐ A radical transformation of the way in which the care associated with a pathology or disability is organised ☐ The introduction of a new technology in an existing class ☐ Other type of innovation: To be specified
Technology development history	Give details of the technology development stages and upgrades
Current development stage	☐ Specific pre-clinical data available ☐ Specific clinical data available

Availability

CE mark	– Date on which CE marking was granted or expected timeline for obtaining CE marking – Class – Name, code and country of notified body

Dissemination in France	– Expected or effective date of the launch of marketing or dissemination for the indication(s) claimed – Annual units provided free of charge or sold, or procedures performed and number of centres involved over the past 5 years – If the technology is already marketed or disseminated for other indications, please provide details
Prior funding in France	Pursuant to Section III of Article R.165-72 of the French Social Security Code, innovation funding is exclusive of any other type of public funding. Here, you need to confirm the absence of current or prior public funding of any type. In the event of such prior funding for a different indication to that targeted by your application, please provide details. As a reminder, care coming under the following categories is considered as publicly funded and excluded[4]: – hospital services (Diagnosis-Related Groups (DRGs), flat-rate fees, etc.) mentioned in Articles L.162-22-6 and L.162-22-1 of the CSS; – nomenclatures: CCAM (joint classification of medical procedures), NABM (nomenclature of medical laboratory procedures), NGAP (general nomenclature of medical procedures) mentioned in Article L.162-1-7; – LPPR (the list of products and services qualifying for reimbursement) mentioned in Article L.165-1 of the French Social Security Code (CSS); – the “additional list” mentioned in Article L.162-22-7 of the CSS; – funding under MIGAC missions (general-interest and contracting assistance missions) as defined in Article L.162-22-13 of the CSS, except for funding granted under the PRT (translational research programme) and PHRC (hospital clinical research programme); – experiments covered by Article L.162-31-1 of the CSS; – funding under the regional intervention fund (FIR) defined by Article L.1435-8 of the CSP. – for innovative medical laboratory and anatomocytopathology examinations, the RIHN (list of innovative procedures outside existing nomenclature).

International dissemination

Country	Authorisation type[5]	Date of expected or effective launch	Annual units provided free of charge or sold, or number of procedures performed over the past 5 years	Funding (No/Yes, date, modalities)
United Kingdom, USA, Germany, Scandinavian countries				

[4] According to Instruction N°DGOS/PF4/DSS/1C/DGS/PP3/2015/279 of 4 September 2015 relative to applicable procedures in respect of exceptional funding as provided in Article L.165-1-1 of the French Social Security Code [http://circulaires.legifrance.gouv.fr/pdf/2015/09/cir_40023.pdf]

[5] e.g.: CE mark, FDA approval procedure (Premarket approval (PMA), 510(k)), etc.

Other				

1.2. Benefit of the Technology

Goal for the use of the technology	☐ Significant clinical benefit: Specify the nature of the medical need that the technology aims to fulfil. Specify whether this medical need is: ☐ an unmet need ☐ an insufficiently covered need ☐ Reduction of care costs with equivalent clinical efficacy: Specify the nature of the costs that the technology aims to reduce
Benefit of the technology	How can the technology fulfil this medical need? How can the technology reduce healthcare spending? These 2 goals may be achieved either directly through the use of the healthcare product or procedure, or indirectly through the organisational changes induced by their use.

1.3. Data available on the technology

The relevance of your application will be assessed on the basis of the clinical or medico-economic studies identified in this section. You need to provide these studies in one of the authorised formats (see description in Appendix II p. 13) and they must be summarised in tabulated abstracts (templates p. 35).

Specific clinical and/or medico-economic studies available	
List the specific clinical studies available on the technology (bibliographic references)	
List the specific medico-economic studies available on the technology (bibliographic references)	
Non-specific clinical and/or medico-economic studies available (similar technology)	
List the non-specific clinical studies available on the technology (bibliographic references)	
List the non-specific medico-economic studies available on the technology (bibliographic references)	
Summary of the clinical or medico-economic data available	
Identified risks	Characterise the nature of the risks for the patient and any risks for the operator in the use of the technology, as identified in available clinical studies Other potential risks (e.g. linked to the type of action) to be correlated with the analysis of the CE marking risk, if applicable
Clinical benefit	Specify the nature and extent of the suggested clinical benefit in terms of therapeutic effect or diagnostic interest, defined as proven diagnostic improvement or clinical utility (i.e. the outcome for patients) in relation to the relevant medical need claimed The diagnostic or prognostic value is defined in terms of proven improvement of the diagnosis or clinical utility (i.e. the outcome for patients). Utility thus combines diagnostic and therapeutic aspects.
Reduction of care costs with equivalent clinical efficacy	Specify i) the nature and extent of the suggested reduction in care costs for the community and ii) the data confirming the equivalent clinical efficacy of the technology in the therapeutic strategy.

1.4. Identification of missing critical data

Identification of missing data	Once the interest of the technology has been characterised through available data, you will need to specify the nature of the missing clinical or medico-economic data that must be collected to confirm the interest of the innovative technology: Specify the nature of the clinical data that must be collected to confirm the interest of the technology: – either in terms of clinical benefit – or in terms of reduction of care costs; in this case, please demonstrate the equivalent technical effectiveness of the technology in relation to the comparator(s)

1.5. Proposed study underpinning the exceptional funding

The proposed study for innovation funding may be a **national study** or an **international study**. In the case of an international study, the whole of the international study must comply with the innovation funding requirements; **however, the innovation funding will only concern the patients cared for in the study's French centres**.

1.5.1. Superiority clinical study

Identification of similar clinical studies	Identify any similar clinical studies that may be under way or scheduled in France or any other country - Specify the search strategy used (databases and key words tested)
Comparator(s)	Provide full details of relevant comparator(s) in the treatment strategy
Research question	Clearly explain the rationale of the proposed study in light of the identified missing data
Objective of study	Describe the precise objective to be addressed by the study
Expected time frame	Specify the expected dates for the start of enrolments and end of the study follow-up

1.5.2. Cost minimisation study after demonstrating clinical equivalence

Identification of similar medico-economic studies	– List any similar medico-economic studies under way or scheduled in France or in any other country – Specify the search strategy used (databases and key words tested)
Comparator(s)	Provide full details of relevant comparator(s) in the treatment strategy
Research question	Clearly explain the rationale of the proposed study in light of the identified missing data
Objective of study	Describe the precise objective to be addressed by the study
Expected time frame	Specify the expected dates for the start of enrolments and end of the study follow-up

2. Part II: Application assessment dossier

In Part 2, you will provide details of the elements supporting your eligibility arguments presented in Part I.

2.1. Detailed description of the technology

You will need to provide all the descriptive details you deem useful for the assessment of the technology covered by your exceptional funding request. The items listed in this section will need to be adapted according to the nature of the technology. These items are listed by type of technology (depending on whether the technology involves an innovative MD, IVDMD or medical procedure). In the case of a multi-technology solution, please use the various dedicated items, combining them and adapting them as required.

2.1.1. For a medical device

This section is intended to **specifically describe the technology** under consideration in the application: composition, technologies involved and technical characteristics (weight, size, diameter, materials, origin of materials (particularly in the case of constituents of biological origin), shape, battery or cell service life under the various conditions of MD use, warranty period, shelf-life, etc.).

In view of the broad range of medical devices liable to be assessed, you will need to adapt the required descriptive information in order to convey:

- **the composition of the product under assessment;**
- **its technical characteristics;**
- **if applicable, the devices or technologies liable to be used alongside the product or required for its operation.**

The exact product description may be supplemented by drawings, diagrams, photos.

Where applicable, conformity to guidelines, standards, specifications, tests, or analyses (attach specifications document if applicable) or proof of conformity to the technical specifications set out in the LPPR may be documented or attached.

You will need to give details of any conditions that may apply to the use of the medical device (instructions for use, user training, organisation of care, etc.). If a procedure is required for its use, the subsequent dedicated items will enable you to provide precise details of the associated procedure and its implementation.

If the application concerns connected technology, as part or all of the device is digital, a specific description is required according to the recommendations.

According to the type of MD and according to its medical purpose(s), you will need to identify the appropriate descriptive information in the sections listed below.

The description of the different product data should make it possible to define the hardware or software technical specifications of the MD. As regards the specific section relating to software or connectivity, the following information is particularly expected:

- description of the different functions:
  - user interfaces (patients and healthcare professionals);
  - components (e.g. a messaging module, data import and export modules).

  The functions for which any modification (with the exception of corrections associated with functional defects) or deletion would be liable to result in a substantial modification of the CMD during app updates must be identified.
- Description of any data specifically collected by the solution and the purpose of the collection of each item.
- Concerning the data:
  - collection and transfer procedures (frequency, human intervention or not);
  - access procedures according to user profiles;
  - processing procedures (time limit, data circuit) and data consultation, rectification and/or deletion procedures;
  - storage period.
- Description of the technical environment required for installation (installation and update procedures, compatible operating system) and for data transfer (characteristics of network used). Requisite conditions for interoperability with other solutions, where possible, must be described.
- The description of service characteristics (maximum number of simultaneous logins, guaranteed range of service, guaranteed restoration time, availability rate, description of restoration procedures, etc.).
- Description of update and maintenance procedures (upgrade and corrective maintenance procedures).

In order to gain an understanding of the software architecture, a general diagram mentioning the different components and their relationships is requested.

For electronic services, apps or software, the descriptive data provided can be supplemented with access provided to the tool in simulation mode, using fictitious profiles enabling access to the different functions, included in the dossier, with a view to shedding more light for the HAS Board on its characteristics or on its use.

Concerning MDs involving a learning algorithm

For medical devices embedding decision-making systems based on machine learning processes, it is required to provide a description of the functions built or subject to change using these technologies.

For this purpose, you must use the specific descriptive grid appended from page 38 . This will provide you with a base to particularly describe the role of each function concerned, the characteristics of the data processed, the results obtained, and the algorithm operating procedure.

MRI compatibility, if applicable

For implantable MDs liable to give rise to artifacts, the potential impact of these artifacts on MRI interpretation and the associated recommendations for use must be documented.

For active implantable medical devices (AIMDs) specifically, you should specify the limits of compatibility with MRI procedures and the main precautions to be taken. Where applicable, the AIMD deactivation measures, required to conduct the test, must be specified.

2.1.2. For an in vitro diagnostic medical device

You will need to describe the key characteristics of the IVDMD, providing details of each phase, in particular the pre-analysis phase (collection and preparation of the sample), analysis phase (measurement type and method) and post-analysis phase (interpretation), stating the duration of each phase.

Concerning the interpretation of tests, please provide the following information:

Methods used to rate the results or preferred positive threshold value (state whether several thresholds or categories must be used)	
Any "grey area" to be prioritised	
Non-interpretable test circumstances and frequencies	
Expected approach in the event of positive results	
Expected approach in the event of negative results	
Expected approach in the event of non-interpretable results	
Predictable consequences of false-negative results	
Predictable consequences of false-positive results	

Since the use of an IVDMD is associated with a medical procedure (except for IVDMDs intended for self-monitoring by the patient), you will also need to fill in the section relating to the associated medical procedure (see below).

2.1.3. For a new medical procedure

Function(s) of the procedure to be assessed for the indication claimed	□ Therapeutic □ Diagnostic □ Prognostic □ Mixed

A description of the procedure giving details of each stage should be provided. You will also need to state the duration of each stage.

N.B. If the medical procedure is an existing one, this section shouldn't be filled in (you will need to provide details of the procedure required for the use of the MD or IVDMD in the next section).

To describe the innovative procedure, **use the items described in the following table, adapting them to suit the type of technology concerned** (delete the descriptive items that are irrelevant to your application):

– approach used	
– role of associated healthcare technologies (MD or medicinal products),	
– whether the intervention is able to treat the entire lesion(s) or not,	
– the intervention frequency and number of repetitions required, if applicable,	
– whether the intervention has a bilateral character or not	
– whether the intervention can be carried out on a scheduled or emergency basis.	
– Does the intervention require anaesthesia?	□ NO □ YES Specify the anaesthesia methods to be used (general, locoregional, local, sedation, analgesia, etc.)
– Does it require imaging?	□ NO □ YES Specify which type(s) (radiology, ultrasonography, CT scan, MRI, Doppler ultrasonography, etc.)
– Does it require other associated procedures when it is carried out?	□ NO □ YES Specify which ones
– What environment is required to carry out the intervention?	□ Full hospitalisation. Specify the average duration (number of days): □ Outpatient care □ Hospitalisation at home. Specify the average duration (number of days): □ Hospital consultation □ Intervention in a nursing home or healthcare centre □ Intervention in a doctor's office or a private laboratory □ Intervention at the patient's home

	□ Intervention carried out remotely (telemedicine). Specify the type of procedure: teleconsultation, remote assessment, remote monitoring, remote assistance, call handling
Description of the technical platform required at each stage of the intervention.	Specify the technical environment (operating theatre, interventional suite, etc.) and technical facilities required
Description of the composition of the medical and paramedical team required for each stage of the intervention	Please specify: – the type of medical professional, their speciality and their role, – the number of medical professionals required
Description of the qualification(s) and training required	for the person performing the intervention and for any other medical professionals. This description should also include the learning curve for the operator.
Specifically for diagnostic or prognostic procedures: – Describe the nature of the sample, the place of harvesting, and the method used	
– Describe the conditions and time frame for the conservation and transport of the required sample	
– Is the diagnostic intervention carried out and interpreted by the same person?	□ YES □ NO Specify:
– Can the interpretation of the diagnostic intervention require several people?	□ NO □ YES…..Specify:
– Does the interpretation of the diagnostic intervention require specific equipment, dedicated software or an algorithm?	□ NO □ YES…..Specify:
– Are other tests taken into account in the interpretation?	□ NO □ YES…..Explain the expected rationale
Other useful information to describe the procedure and the required care environment	

2.1.4. Medical device, medicine or non-innovative procedure required for the use of the technology under consideration in the application

Provide details of any healthcare products that may be required for the use of the technology under consideration.

- For a procedure: If the required procedure is already listed in the NGAP (general nomenclature of medical procedures), CCAM (joint classification of medical procedures) or NABM (nomenclature of medical laboratory procedures): Specify the relevant procedure (code and name of the associated procedure) according to the nomenclature in force (date and version) and the price; list any similar medical devices that may be involved in this procedure.
- For a medical device: state whether it is included in the list of products and services qualifying for reimbursement mentioned in Article L 165-1 of the French Social Security Code (specify the code and name according to the applicable nomenclature and the price).
- For a medicinal product: state whether it is already included in the retail formulary list of reimbursed medicinal products and/or the hospital formulary list of medicinal products approved for use (specify the code and name according to the applicable nomenclature and the price).

2.2. Innovative character of the technology

Analytical description of the characteristics of the innovation: provide a detailed description, backed by bibliographic references, of the specific characteristics of the proposed technology that render it innovative in comparison with existing technologies or procedures

2.3. Mode of action of the technology

Description, with bibliographic references, of the technology's mode of action on the pathology or its impact in terms of therapeutic effect, diagnostic effect, prognostic effect, etc.

2.4. Identification and selection of available clinical and/or medico-economic data

2.4.1. Systematic documentary search

You will need to conduct a systematic documentary search and describe its results.

The purpose of this systematic documentary search is to identify all available clinical or medico-economic data in published literature on the technology under consideration.

Your documentary search must involve the query of international bibliographic databases.

The websites of national and international assessment agencies and learned societies should also be used to find any relevant technology assessments, meta-analyses, systematic reviews and guidelines.

A non-exhaustive list of links that can be consulted for the systematic documentary search is available in the appendix (see. p. 33).

The search strategy used must be explicitly described and justified: search period, sources consulted, terms used.

2.4.2. Selected clinical and/or medico-economic data

You should then select the relevant documents in respect of the theme of your application. Your selection method must be explicitly described and justified (selection criteria used).

The results of your search and selection should be presented in diagram form (number of references identified by data type, number of references selected based on title and abstract, number of references retained based on full text). Negative data in respect of the technology must be selected according to the same criteria as other data.

The documents obtained following this selection (based on full text) must be referenced[6] and appended.

Besides the systematic documentary search, other data may be relevant. The applicant must justify the choice of the data retained.

The clinical and/or medico-economic data retained to justify the relevance of the request must be presented in one of the following formats:

- publication or text accepted for publication (providing proof)
- failing that, the protocol and study report
- failing that, an international conference summary, poster or presentation accompanied by the study protocol, exclusively for studies registered on ClinicalTrials.gov and for which the follow-up period ended less than one year ago.

These studies must be appended and summarised in tabulated abstracts according to the template on p. 35.

2.5. Interest of the technology as suggested by available data

- ➔ Exact wording of the indication(s) claimed
- ➔ Correlation with CE marking indications, if relevant

The assessment of the interest of the technology relies on the analysis of the following criteria:

- The relevance of the medical need that the technology fulfils and/or the relevance of the reduction in healthcare spending generated by its use,
- The presentation of the current care strategy and the determination of the place of the proposed technology in this strategy or the changes liable to be introduced in the strategy by the technology,

[6] Bibliographic references must adhere to the recommendations adopted by the International Committee of Medical Journal Editors (Vancouver guidelines):

Authors*. Title. Subtitle. Title of journal; Year of publication; volume (issue or supplement): start page-end page. [*For up to six authors, the authors' names must be given; from seven, the first six should be cited, followed by a comma and the words "et al.". "]

- The determination of risks for the patient (and for the operator, if applicable) arising from its use,
- The qualitative and quantitative determination of the clinical benefit, or reduction in the cost of care with equivalent clinical efficacy, that the technology is likely to provide in view of available data.

2.5.1. Pathology concerned

In this section you should describe:

- The nature and severity of the pathology in terms of morbidity and mortality (life-threatening, acute/chronic, etc.), disability (severity, duration, temporary or permanent), quality of life, health state perceived by the patient, and medico-social consequences.
- As a preference, you should use the quantitative and qualitative measurement scales or classifications validated in the pathology, if these are available.
- The characteristics of the patients concerned by the technology in the French population for the indication claimed: age, sex, stage of severity of the pathology, etc.

2.5.2. Therapeutic/diagnostic/prognostic alternatives

This section is devoted to identifying and describing the alternatives available for the treatment or diagnosis of this pathology in routine practice.

You thus need to describe the alternative(s), or the standard diagnostic approaches that may exist, specifying the possible limitations to their use.

Such alternatives may be a medical device, a medicinal product or a procedure addressing the same indications as the proposed technology. When there is no existing therapeutic/diagnostic/prognostic solution, the need is unmet.

The expected place of the technology in the therapeutic strategy will be established after assessment of the available data (see Section 2.5.5).

2.5.3. Risks associated with the use of the technology

Based on the available data, in particular the initial clinical data available, you will need to qualitatively and quantitatively characterise any identified risks posed by your technology for the patient and for the operator, if any.

Two types of risks may be reported:

- those associated directly with the technology, including the risks associated with poor patient compliance or misuse
- and those inherent to the operating technique (particularly the team's experience, the technical platform, the training required, etc.)

You will need to provide an analysis of any adverse events, particularly those having occurred in clinical trials (including the data relating to prior versions of the technology in the event of its development).

Any other potential risks (e.g. linked to the mode of action) should be identified and correlated with the CE marking risk analysis, where relevant.

2.5.4. Clinical benefit or reduction in the cost of care with equivalent clinical efficacy to the reference healthcare technology

➔ **For the technology, please state the therapeutic, diagnostic or prognostic effect suggested by the available clinical trial data**, in relation to the relevant medical need claimed.

The arguments should be based on identified clinical data (see paragraph 2). They will distinguish between:

- specific clinical data concerning the technology,
- non-specific clinical data concerning prior versions of the technology, where applicable. Their use must be scientifically justified (characteristics of the technology under study compared to those of the technology under consideration in the application).

The choice of the studies taken into consideration and their methodological quality should be discussed in the dossier.

The extrapolation of the clinical trial data to the population liable to be treated with this technology should be justified.

➔ **For each selected study, you must provide an analysis of the study findings**: this analysis should be based on the assessment of the primary endpoint. Its relevance will need to be justified. The relevant endpoints consist of clinical endpoints and preferences in terms of effect on mortality/morbidity, quality of life or disability compensation. They correspond to those advocated by the state of the art. In all cases, please provide arguments justifying the choices made.

The use of intermediate endpoints requires that these endpoints also be scientifically validated as corresponding to an effect on morbidity/mortality, quality of life or disability compensation. An intermediate endpoint is validated if the literature provides evidence of the close correlation between the latter and a robust clinical endpoint.

In addition to the primary endpoint, other secondary endpoints may be used.

Please specify:

- the **clinical benefit suggested by the clinical studies** in terms of therapeutic, diagnostic or prognostic effect within the treatment strategy.

The diagnostic or prognostic value is defined in terms of proven improvement of the diagnosis or clinical utility (i.e. the outcome for patients). Utility thus combines diagnostic and therapeutic aspects.

- The proposed **comparator(s)**:

A relevant comparator may be the gold standard, or the strategy used in routine practice in the absence of scientific evidence, or the absence of treatment if the need is unmet. It may consist of a medical device, listed in the LPPR or not, a medicinal product, service or medical procedure qualifying for reimbursement or not, lifestyle/dietary measures, etc.

- **Endpoints on which added value is based**:

Clinical endpoints (mortality, morbidity, disability compensation, reduction of adverse effects), quality of life, constraints linked to the care environment if they provide a clinical benefit for patients, etc.

- **where applicable, the reduction in care costs for the community** provided by the technology in comparison with the relevant comparators, as well as the degree of equivalence in terms of clinical efficacy.

2.5.5. Expected place of the technology in the therapeutic or diagnostic/prognostic strategy

In view of the current treatment used for the pathology and the clinical or medico-economic data provided, please provide a justified description (backed by bibliographic references) of the expected place of the technology in the therapeutic, diagnostic or prognostic strategy (1st, 2nd or nth-line treatment,

adjuvant treatment, preventive treatment, etc.).(see 2.5.2.Therapeutic/diagnostic/prognostic alternatives).

2.6. Target population

The target population is the population liable to benefit from the technology in France.

A quantitative estimation should be made and justified. Please state the sources used and the rationale followed.

The following should be mentioned in the justification:

- type of data: epidemiological study, survey or observational study, cohort follow-up, database, clinical studies, etc.…
- dates on which these data were compiled and published, and their geographic origin (countries concerned).
- bibliographic references (documents to be appended)

By way of indication, a list of epidemiological data websites is proposed (see p. 33).

2.7. Identification of missing critical data

The interest of the technology shall have been characterised:

- either using clinical data that establish that the use of the technology is liable to provide a significant clinical benefit in relation to the relevant comparator(s) in terms of therapeutic, diagnostic or prognostic effect with respect to the relevant medical need claimed;
- or using clinical and medico-economic data that establish that the use of the technology is liable to reduce the cost of care in relation to the relevant comparator(s), with equivalent clinical efficacy.

You will need to identify the missing data to confirm either the clinical benefit or cost reduction for equivalent clinical efficacy, suggested by the available clinical or medico-economic data.

Please specify the nature of such missing clinical or medico-economic data which need to be obtained to confirm the interest of the innovative technology.

2.8. Identification of similar clinical studies under way or scheduled

Please provide a list of similar clinical or medico-economic studies, either under way or scheduled, that could provide the critical missing data identified. Please specify the search strategy you have used (databases and key words tested) to identify the studies and your search results.

Databases of registered studies (clinicalTrials.gov, clinicaltrialsregister.eu, International Clinical Trials Registry Platform (ICTRP), etc.) must be consulted. The search should not be limited to key words relating to the name of the technology under consideration in the application, but should at least combine the technology used and the indication considered.

3. Part III: full draft protocol of the study

3.1. Identification of the research question

You will need to clearly explain the research question (main objective) of the proposed study in relation to the missing critical data.

The research question should provide unambiguous answers to the uncertainties raised by the absence of data identified as critical and deemed necessary to confirm the benefit suggested by the clinical or medico-economic data available.

If the existing data suggest a clinical benefit of the technology, the study will be one of clinical superiority in relation to the relevant comparator(s) identified. In that case, we recommend that the trial also involve the collection of the required data that will allow, during the subsequent application for coverage by the mainstream health system, a cost-effectiveness analysis if clinical superiority is demonstrated during the trial. Indeed, if a claim of improvement of the clinical benefit (ASA I, II or III) is liable to be filed for the technology and if a significant impact on costs is recognised, a cost-effectiveness analysis will need to be submitted to HAS. To prepare for this analysis, we recommend that you consult the HAS methodology guide "Choices in methods for economic evaluation – HAS" in order to plan for the collection of the required data at an early stage. Such data may consist of cost and quality-of-life data.

If the existing data suggest cost reduction and equivalent clinical efficacy in relation to the relevant comparator(s), the study to be conducted will be a cost minimisation study which also demonstrates clinical equivalence. Indeed, since innovation funding concerns technology which is not backed by sufficient data to claim coverage by the mainstream health system, clinical efficacy data are expected to be insufficient at this stage to claim coverage by the mainstream health system. Data will thus need to be collected to confirm clinical equivalence with the comparator(s) and reduction of the cost of care.

3.2. Full draft protocol of the study

3.2.1. Case 1: Superiority clinical study

- Study name and title;
- Entities in charge of the study (laboratory, service company, etc.);
- Contact details of the main investigator;
- Composition of the Scientific Committee, methodology expert;
- Type of study and justification in relation to the issue and other possible strategies (randomised/controlled/blind/multi-centre trial, parallel/crossover trial, exposed/unexposed study, cohort study, etc.);
- Description of the main objective and secondary objectives;
- Primary endpoint and secondary endpoints retained and justified in respect of the study's objectives;
- Study population
  - Population covered,
  - Inclusion/exclusion criteria,
  - Calculation of the number of subjects required,
  - Patient sampling/selection modalities and their justification;
- Data collected and methods used to obtain the data;

- Study timetable: start date, inclusion period, follow-up, total duration, date of release of analysis report;
- Statistical analysis strategy: variables to be explained, explanatory variables, tests used, confounding factors, management of missing data and patients lost to follow-up, etc.
- Discussion on the limitations of the study (extrapolation capacity, etc.);
- Quality Assurance procedures;
- List of concomitant treatments authorised and not authorised;
- List of participating centres;
- Procedures for obtaining authorities' approval;
- Investigator brochure, information sheet to inform the patient and get their consent;
- Book of comments.

3.2.2. Case 2: Cost minimisation study with simultaneous demonstration of clinical equivalence

- Study name and title;
- Entities in charge of the study (laboratory, service company, etc.);
- Composition of the Scientific Committee, methodology expert;
- Description of the main objective and secondary objectives;
- Primary endpoint and secondary endpoints retained and justified in respect of the study's objectives;
- Study population
  - Population covered,
  - Inclusion/exclusion criteria,
  - Calculation of the number of subjects required,
  - Patient sampling/selection modalities and their justification;
- Data collected and methods used to obtain the data;
- Study timetable: start date, inclusion period, follow-up, total duration, date of release of analysis report;
- Statistical analysis strategy: variables to be explained, explanatory variables, tests used, confounding factors, management of missing data and patients lost to follow-up, etc.
- Discussion on the limitations of the study (extrapolation capacity, etc.) and, in particular, discussion on expected differences in costs between the experimental environment and standard practice;
- Quality Assurance procedures;
- List of participating centres;
- Procedures for obtaining authorities' approval;
- Investigator brochure, information sheet to inform the patient and get their consent;
- Book of comments.

Table of appendices

Appendix 1.Non-exhaustive list of links that can be consulted for the systematic documentary search and the epidemiological data search

French data sources

- ANS
- ANSM
- ANSES
- French national health insurance system
- French national health insurance system/Open Data
- ASIP Santé
- FNMF
- FNORS
- HAS
- HCSP
- INCa
- INED
- Santé publique France
- INSEE
- INSERM
- IRDES
- IRSN
- French ministry of health
- Observatoire de médecine générale
- ORPHANET
- French Sentinelles Network
- SNDS/Open Data

International data sources

- AHRQ
- AHRQ/Guidelines and measures
- CADTH
- CDC
- CMA Infobase
- Cochrane
- CRD databases (HTA database)
- DIMDI
- ECRI INSTITUTE
- EUROSTAT
- Eunethta
- FDA
- Finotha
- HIQA
- HPA
- IARC
- INAHTA
- INESSS
- IQWIG
- ISC
- KCE
- MSAC
- NICE
- OECD
- OEAW
- WHO
- RIVM
- SBU

Databases

- Public health database
- BML
- CHU Rouen
- ENCEPP
- Medline
- Epidemiology portal

Appendix 2.Template of tabulated abstract to be completed

The clinical and medico-economic data provided to justify the relevance of the request should be identified in the eligibility arguments (Part I) and analysed in the assessment dossier (Part II). These studies must be provided in Appendix 2 and summarised in a tabulated abstract according to the following template below:

Template 1: Tabulated abstract of a clinical study

Reference	XXXXX study Authors (up to 6 authors, and then et al.). Title. Subtitle. Name of the journal. Year of publication; volume (issue): start page-end page
Type of study	Specify the study type
Study date and duration	Specify the dates and time period between the start of enrolments and end of the follow-up.
Objective of study	Objective stated in a precise way in terms of comparable or greater efficacy than the reference strategy.
METHOD	
Selection criteria	Describe the significant inclusion/exclusion criteria.
Study framework and location	Specify the number of centres, the country or countries concerned, whether the patients concerned are hospitalised or outpatients.
Products studied	Provide details of the products for each group.
Primary endpoint	Describe the primary endpoint (generally the criterion used for the calculation of the number of subjects required).
Secondary endpoints	Mention the secondary endpoint(s).
Sample size calculation method	Provide the calculated number of subjects required in each group and the number of patients included in each group.
Randomisation method	Describe the randomisation method and blinding method.
Results analysis method	Describe the statistical tests used and the type of analysis (intention-to-treat or other). If the analysis is not an intention-to-treat analysis, give the reasons why.

RESULTS	
Number of subjects analysed	Provide the number of patients per group included in the analysis, particularly in the intention-to-treat analysis in comparative trials.
Follow-up period	Duration of follow-up, number of patients lost to follow-up, reasons.
Patient characteristics and group comparability	Describe the patients' relevant initial characteristics such as age, sex, comorbidities, potential confounding factor(s), etc. Specify whether the groups are comparable or not at the start of the study.
Inherent results for primary endpoint	Describe the results inherent to the primary endpoint in each group and between groups by stating the difference, test value (p) and confidence interval if they are available or another method measuring the extent of the effect.
Inherent results for secondary endpoints	Describe the results inherent to the secondary endpoint in each group and between groups by stating the difference, test value (p) and confidence interval if they are available. Describe the sub-group analysis if relevant.
Adverse events	Provide the number of patients per group included in the analysis, particularly in the intention-to-treat analysis in comparative trials.

Please note:

- "Not applicable" when an item does not need to be entered (depending on study type);
- "Not described" when an item is to be entered but no information is provided

Template 2: Data extraction sheet for an economic study

REFERENCE
Article title
Source
Main author
Date of publication
GENERAL METHOD
Study type (summary review, meta-analysis, modelling study)
Country or countries in which the economic evaluation was conducted
Perspective
Analysis method (CUA, CEA, CBA, cost minimisation, disease cost, etc.)
Time horizon
Cost and result update
Population
Interventions compared (intervention under study, comparator)
EVALUATION OF RESULTS
Data collection dates
Result measurement (event avoided, life years, QALY, etc.)
Description of data:
- Data sources (study, meta-analysis, summary review, expert opinion)
- Method and tools (study design, QL scale, direct measurement, author's assumption, etc.)
- Clinical data
- Preference score
Presentation of results
Subgroup analyses
COST ASSESSMENT
Reference year
Reference currency
Costs included in the assessment (direct medical costs, direct non-medical costs, indirect costs)
Source of cost data

Cost valuation method
Cost data
CONCLUSIONS OF THE ASSESSMENT
Cost-outcome ratios
Subgroup analyses
Conclusion
Sensitivity analysis
Acceptability analysis
Limitations
Funding
COMMENTS:

Appendix 3.Rules in relation to the electronic documents associated with applications for exceptional funding for an innovative product – medical device, in vitro diagnostic medical device or procedure

File type

The source files drafted by the applicant should also be provided in a text format compatible with Microsoft Word 2007. All files submitted in PDF format must be compatible with Acrobat Reader 9.0 and later.

Files containing figures in Excel format, if they are compatible with version 2007 of the program, may be accepted, as well as those in ASCII format (use the extension *.txt).

For other files, the following formats are accepted:

- images: *.jpg, *.gif, *.tip, *.bmp
- video: *.avi, *.mpg, *.mpeg, *.wmv, *.flv
- bibliography: *.ris

For any other format, approval from the department responsible for dossier examination is required.

For file compression or grouping, *.zip format is accepted.

Character fonts

The character fonts must all be included in PDF type files.

It is recommended to limit the number of fonts used when creating documents. If the PDF includes images from a digitised source, the image resolution must be the lowest possible without compromising adequate display or print quality.

Protection options

The files must not include protection.

File size

The maximum size of each file submitted in SESAME is dependent on its type, between 100 and 300 MB. Size reduction options must systematically be used for these documents. The naming rules listed above must then allow logical reading of the documents submitted.

For videos, the applicable limit is 150 MB.

File and directory naming rule

Directory and file names must be explicit.

The file names must not exceed 70 characters and must only contain non-accented upper and lower case letters and numbers. Spaces, apostrophes, or special characters must not be used (e.g. “~”, “*”, “|”, ““”, etc.); however, it is recommended to use the underscore character (_) to separate words in file or directory names.

The file or directory names must be preceded by a sequence of two characters and an underscore character (_) in order to retain the logical reading order.

Examples

01_NOM_DU_DOSSIER_Partie_I_Argumentaire_éligibilité

02_NOM_DU_DOSSIER_Partie_II_Evaluation technologie

03_NOM_DU_DOSSIER_Partie_III_Projet_complet_protocole_etude

04_NOM_DU_DOSSIER_Annexe_1_Pièces_administratives

05_NOM_DU_DOSSIER_Annexe_2_Etudes_cliniques_medico-economiques

Etc.

Appendix 4.Specific descriptive information to be provided for medical device functions relying on machine learning processes (technologies falling within the scope of artificial intelligence)

Preliminary observations

If your MD is based on at least one machine learning process, you should complete this grid to provide the committee members with the information needed in this area of your MD. Included in the submission guide in September 2020, it should be amended as needed in line with technological upgrades.

Depending on the case, you should construct one or more grids, the principle being that you complete one grid for each “smart” function of the device:

where there is only one function relying on machine learning processes: you should complete a single grid. This particularly applies when the interlinking, or succession, of several processes can justify their grouping in the same grid when they contribute to the same “smart” function.

in the case of an MD including several functions of this type, you should complete one grid per function.

Depending on the type of technology, some items may not be adapted. In these cases, you should specify this, providing a justification. Conversely, you can also supplement the descriptive information listed with any information deemed useful.

Descriptive grid

		Information to help you complete the grid
Purpose		
1	Note the claimed use and the envisaged scope of the medical device (MD) including one or more machine learning algorithms	Is it used for example to: help the patient adjust the dosage of their treatment? predict or provide early detection of the occurrence of a clinical event? You should specify the pathologies or clinical scenarios addressed, or the multidisciplinary nature of the MD, where applicable. You should also systematically specify the user (patient or professional).
2	Specify the benefit of the information provided or decisions made by machine learning processes	In this section, specify the “smart” function in which machine learning has played a direct role. For example: Determining a severity score? Calculating a dose for treatment adaptation?

3	Note the characteristics of the target population and, where applicable, the characteristics for which use of the MD is unsuitable, due to non-indication, contraindication, or factors influencing the product result	These may be: Demographic (age groups, sex, etc.) Physiopathological (pregnancy, diabetics or asthmatics, etc.) or morphological (lower limb amputees, etc.) Clinical or biological (disease stage, etc.)
4	Describe the operating environment of the smart system	Particularly specify the environmental conditions (meteorological, brightness, temperature, ground conditions, etc.) used to characterise the operating range.

Data		
Description of samples used for initial model learning or relearning		
5	Specify the characteristics of the population on which the initial model learning or relearning data are based	These may be: Demographic (age groups, sex, etc.) Physiopathological (pregnancy, diabetics or asthmatics, etc.) or morphological (lower limb amputees, etc.) Clinical or biological (disease stage, etc.) Differentiate the population on which the initial learning data are based (training, validation, and testing) from that used during the relearning phase (retraining, validation, and testing of updated system), where applicable.
6	Specify the characteristics of each sample used for the initial model learning or relearning data .	Expected: their function, size and composition. Included variables must be cited. The manner in which rare events are taken into account must be described. Differentiate the databases of the initial learning phases (training, validation, and testing) and in the relearning phase (retraining, validation, and testing of updated system), where applicable
7	Specify the methodology for separating or segmenting samples	For example, specify the procedures for separating (methods used and proportions) and segmenting (random, by date, by subject, etc.) the training, validation, and test data sets Differentiate the databases in the learning and relearning phases, where applicable.
Description of input data involved in initial model learning or relearning		
8	Specify the characteristics of the variables (variable type, distribution, etc.)	Differentiate the training, validation and test corpus where applicable.

9	Indicate the method of acquisition of the variables and their origin during the learning process	For example, was a variable entered by a patient? Does it come from a sensor? Was it generated from virtual patient models? Specify whether the variables were extracted from corpora of open or purchased data, and indicate which, where applicable, as well as whether they are long-term or not. Specify the types of sensors used during variable acquisition, where applicable.
10	Describe the pre-processing applied to the data.	For example, tasks to clean, transform, reduce, increase data (additions of artificial noise, artificial interference simulating weather variations or sensor faults, etc.) Specify the data concerned and the proportion of data modified by these pre-processing operations
11	Indicate the proportion of missing data, among the raw data, and describe their management.	Specify the types of missing data (random or anticipated).
12	Explain the procedures in place to detect and manage outliers, where applicable	In particular, specify how outliers (e.g. physiologically impossible data) are distinguished from atypical values (e.g. rare events)
13	Justify the representativeness of the samples used for the initial learning (training, validation, and testing) of the algorithm in relation to the data to which this algorithm will be exposed once deployed	A justification of the representativeness criteria is expected. Particularly specify the tools and methods used to verify the representativeness of the samples and detect potential bias. In the case of incremental or continuous learning, indicate the potential impact of updates on all learning data.
Description of input data involved in decision-making (once the medical device has been deployed)		
14	Specify the characteristics of the variables (type, distribution, etc.)	Indicate the main sources of difference between the training, validation and test data, and the data involved in decision-making, once the system has been deployed (different sensors, different environmental conditions, etc.).
15	Indicate the method of acquisition of the variables and their origin	For example, was a variable entered by a patient? Does it come from a sensor? Indicate the measurement range and sensitivity settings of the measuring devices, where applicable.

16	Describe the pre-processing applied to the data used for decision-making	For example, tasks to clean, transform, reduce data, etc.
17	List the output variables (model prediction objects) and their characteristics (type, unit, etc.)	Specify the variables that will be processed in relation to the objective. Specify whether they are processed by another component of the MD or whether they are communicated to the user (if so, how)

Model: description of training, validation, and testing, before and after MD deployment		
18	Describe the type of learning used	Is this machine learning process: supervised, semi-supervised, unsupervised, by reinforcement, federated, centralised, other? These suggestions are not mutually exclusive.
19	Describe the type of task automated by the algorithm	supervised classification (determine the ranking criteria), unsupervised classification (define classes), ranking (rank in classes), regression (quantitative projection), segmentation, other?
20	Specify the update frequency	Is learning: continuous (system learning autonomously after deployment)? initial (algorithm designed based on learning then fixed after MD deployment)? or incremental (algorithm for which updating of the structure and/or settings after MD deployment is supervised by a human and involves prospective and/or retrospective validation)?
21	Describe the model selection criteria	For example, the error rate, computing time, the number and nature of the data available, explainability or embeddability, etc.

		Do not go into detail on the system input data (covered in questions 5 to 17), or the test methods used (covered in questions 26 to 32)
22	Describe the various training, validation, and test phases, prior to MD deployment	Indicate the various training, validation, and test phases, particularly specifying whether they are based on individual or collective data. Do not go into detail on the test methods in place (covered by questions 26 to 32).
23	Describe the training, validation and test strategies for updates, if applicable	Indicate the various training, validation, and test phases applied once the MD is deployed, particularly specifying whether they are based on individual or collective data. Specify in particular the retraining frequency, the variables involved and the data inclusion period, the retraining computation location (locally on the MD or on server). Do not go into detail on monitoring and/or human intervention in these phases (already covered in questions 24 and 25), or the update test methods (already covered in questions 26 to 32).
24	Describe how parties involved in system development are referenced	Specify whether the human managers or legal entities involved at each stage of the life-cycle of the smart MD (data collection, development, qualification, use and feedback for MDs with AI capability) can be identified.
25	Where applicable, state in which cases a human being is involved in the retraining process	For example, in the case of active learning, specify the frequency and qualification of the person involved. In the case of operator annotation, specify the operator's qualification and role.

Functional characteristics		
Performance and qualification		
26	Describe and justify the choice of metrics used to measure performance …	For example: Root-mean-square deviation, Area Under Curve, F1-score, ZoneMap, Jaccard
27	Describe the processing operations applied which have had a substantial impact on performance	For example, in the case of class imbalances in the context of supervised classification, indicate whether class rebalancing has been carried out, as well as the method used.
28	Describe the identified risks of over- and under-learning and the methods in place to remedy this	A link may particularly be established with the responses to question 7 on data separation/segmentation.

29	Specify whether the system returns a confidence rating for each of its decisions	This could for example indicate, for an image classifier, whether it returns the probabilities of the input image to belong to each of the classes
30	Describe the qualification methods of the machine learning system	Particularly specify the test protocol in place and the procedures used to ensure performance measurement repeatability and test reproducibility. If using formal methods to qualify the machine learning system, justify the choice of methods used and how the ranges on which the formal methods were applied were defined.
31	Indicate the performance measurement results on the different data sets	For example, the error rates supplied by the metrics on the training, validation, and test databases, according to the distribution applied. Specify whether a separate database from the training, validation, and test databases was used to qualify the model. Specify, in the case of formal proof analysis, the results obtained and the validity range of these results.
32	Specify the performance thresholds selected (limit values, maximum error rate, etc.) and explain the choice of these thresholds	
System robustness		
33	Specify the tools in place to generate antagonistic examples in the performance evaluation and qualification phase	
34	Specify the tools in place to monitor the performances of the smart system after its deployment	Particularly specify the mechanisms in place to measure model degradation and/or concept drift (regular evaluation campaigns, etc.), as well as performance degradation logging, archival and analysis
35	Specify the thresholds selected (limit values, maximum error rate, etc.) for tracking model degradation and/or concept drift and explain the choice of these thresholds	
36	Specify the measures in place in the case of automatic or user detection of model degradation or concept drift	For example: information sent to the user, substitution of the learning algorithm by an expert system, retraining, etc.

System resilience		
37	Describe the system in place for input data anomaly detection in operational use	This could for example concern the detection of data outside the nominal operating range of the smart system
38	Describe the potential clinical and technical impacts induced by anomalies on the input data of the machine learning system	For example, what will happen: In the event of non-correction of outliers? In the event of a declarative value input error by the patient? Due to the level of uncertainty associated with the input data (physiological, environmental data, etc.)? In the event of data unavailability? In the event of data integrity loss?
39	Specify the measures in place in the case of automatic or user error detection (e.g. malfunction damaging the input data)	For example: information sent to the user, degraded mode, substitution of the learning algorithm by an expert system, clinician or technician intervention, etc.
Explainability and interpretability		
40	Indicate the explainability elements provided by the smart device	Specify, where applicable, the explainability technique(s) in place to help understand the main factors leading to the decision taken or proposed by the machine learning algorithm. Specify the recipient of these explanations: user (caregiver or patient), developer, etc. Also indicate whether the explanations are recorded for retrospective analysis by experts (users and/or developers).
41	Indicate the interpretability elements, i.e. the parameters (input variables, weightings, etc.) influencing decision-making, as well as the method used to identify them	For algorithms with initial or incremental learning, are these parameters identified (e.g. by means of influence functions)?
42	Specify whether the decisions and actions of the smart device are compared to professional guidelines	Particularly indicate whether the machine learning algorithm outputs are compared to professional guidelines in real time or retrospectively. Specify whether these comparisons are made accessible to users. For example, are the machine learning algorithm outputs compared to those of an expert system modelling care guidelines?

Glossary

This glossary is solely intended for use alongside this descriptive grid of machine learning algorithms in the context of CNEDiMTS medical device evaluation.

Term	Definition	Source
Machine learning	Process whereby an algorithm evaluates and improves its performances without programmer intervention, by repeating its execution on data sets, until appropriate results are regularly obtained.	7
Unsupervised learning	Machine learning in which the algorithm uses a raw data set and obtains a result based on the detection of similarity between some of these data items.	7
Supervised learning	Machine learning in which the algorithm practises a defined task using a data set each accompanied by an annotation indicating the expected result	7
Ranking	Action of ranking objects, persons in a certain order.	8
Supervised classification	Technique consisting of categorising data according to their proximity thus making it possible to differentiate among two or more discrete classes.	9
Concept drift	A machine learning algorithm in which the parameters are fixed becomes inconsistent with its environment if the latter has been updated.	10
Range of use	Description of the environment and target population, for which the algorithm or program is designed.	-
Data	Representation of the observation of a variable on an element, individual, or instance of a population, intended to facilitate its processing.	-
Raw data	Data having undergone no transformation since the initial observation.	-
Input data	Data used for model learning or decision-making.	-
Output data	Value representing all or part of the decision made by the algorithm based on the input data.	-

[7] Official Journal of 09/12/2018

[8] https://www.larousse.fr/dictionnaires/francais/classement/16405

[9] Based on ISO definition (drafting in progress)

[10] Tsymbal, A. (2004). The problem of concept drift: definitions and related work. Computer Science Department, Trinity College Dublin, 106(2), 58.

Sample	Representative fraction of a population or a statistical universe	11
Training	Machine learning process through which the artificial intelligence system builds a model from data.	9, 12
Antagonistic example	Borderline case placing the system under evaluation in difficulty.	-
Explainability	Ability to link and explain the elements taken into account by the algorithm, for example the input variables, and their consequences, for example, on the prediction of a score, and thus on the decision. The explanations must be adapted to the comprehension level of the person for whom they are intended.	-
Hyperparameter	Parameters tweaked during successive runs of training of a model in order to check under- and over-learning in particular.	13
Information	Knowledge element expressed by a data set according to a defined code, with a view to being stored, processed, or communicated. An item of information is obtained from the interpretation of one or more pooled data items.	14
Interpretability	Ability to render the operation of an artificial intelligence system comprehensible. An algorithm is “interpretable” when its operation is accurately understood, for example, when an expert system models a decision tree.	9
Data set	Collection of data	-
Model	Mathematical construction generating an inference or a prediction from input data.	9
Parameter	Coefficient of a model that the machine learning system estimates or trains on its own and which impacts the output data.	13
Resilience	Ability of the system to maintain its conformity with performance and/or security requirements in the presence of input data outside its range of use (e.g. due to a sensor fault).	-
Robustness	Ability of a system to maintain its performance level whatever the circumstances.	9

[11] Centre National de Ressources Textuelles et Lexicales www.cntrl.fr
[12] From the Montreal Declaration for a Responsible Development of Artificial Intelligence
[13] https://developers.google.com/machine-learning/glossary
[14] https://www.dictionnaire-academie.fr/article/A9I1218

Segmentation “Data segmentation” “Automatic segmentation task”	Data segmentation: division of a corpus of data into several bases (e.g. training, validation, and testing) either based on objective criteria (date, age, etc.), or at random. Automatic segmentation task: extraction and automatic recognition of zones of interest from input data (e.g. an image).	15
Test	Process consisting of detecting errors associated with running an algorithm or a program based on input data sets not used during the training phase.	-
Validation	Process consisting of testing, observing and optimising (hyperparameters) system behaviour during running so as to ensure, in the range of use, that the output data are in line with the expected results.	9
Variable	Observable characteristics (qualitative or quantitative) of an element.	-

[15] Rakoto–Ravalontsalama, M. (1990). Méthodes de segmentation automatique d'image. Analyse quantitative des formes, Télédétection, pp251-260.

Abbreviations and acronyms

CCAM	Classification commune des actes médicaux (Joint classification of medical procedures)
CNP	French National Council for Healthcare Professionals
CSS	Code de la sécurité sociale (French Social Security Code)
CSP	Code de la santé publique (French Public Health Code)
MD	Medical Device
IVDMD	In vitro diagnostic medical device
AIMD	Active implantable medical device
DGOS	Direction générale de l'offre de soins (French Directorate General of Health Care Provision)
GHS	Groupe homogène de séjours (diagnosis-related group)
HAS	*Haute Autorité de santé* (French National Authority for Health)
JO	Journal officiel (French Official Gazette)
LPP/LPPR	Liste des produits et prestations remboursables (List of products and services qualifying for reimbursement)
MIG	Mission d'intérêt général (General Interest Mission)
NABM	Nomenclature des actes de biologie médicale (French nomenclature of medical laboratory procedures)
NGAP	Nomenclature générale des actes professionnels (General Nomenclature of Medical Procedures)
PHRIP	Programme de recherche infirmière et para-médicale (Nursing and paramedical research programme)
PREPS	Programme de recherche sur les performances du système de soins (Healthcare system performance research Programme)
PRME	Programme de recherche médico-économique (Medico-economic research programme)
PRT	Programme de Recherche Translationnelle (Translational research programme)
RIHN	Référentiel des actes innovants hors nomenclature (List of innovative procedures outside existing nomenclature)

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