HAUTE AUTORITÉ DE SANTÉ

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HEALTH TECHNOLOGIES

GUIDE

Innovation funding: HAS assessment principles

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Preface

Gene therapy, immunotherapy, messenger RNA vaccines, artificial intelligence, telehealth and smart devices are only a few examples showing the extraordinary development currently taking place in the field of health and the importance of innovation and patients' access to it.

HAS is thus particularly attentive to the subject of innovation, which is at the core of its missions. Indeed, HAS plays a crucial role in ensuring that users and professionals have access to useful innovations, with two priority objectives: on the one hand, identifying/supporting/monitoring medical, technological and organisational innovations and, on the other, assessing them. HAS has thus decided to make innovation a driving force of its action, and a major focus of its strategic project for 2019-2024.

This ambition is perfectly embodied in the work conducted on innovation funding. This scheme enables manufacturers and National Councils of Healthcare Professionals to obtain funding for a medical device, an *in vitro* diagnostic medical device or an innovative procedure, right from the launch of the clinical study that will establish the proof of its efficacy. To this effect, HAS is in charge of assessing funding requests.

This innovation funding scheme has been in place for several years. The scheme was totally reviewed over the years, and most recently in 2019. With the simplification of the steps involved, the setting of a clear and precise timetable, the digitisation of the application process and the support provided to distributors, manufacturers and professionals in their procedures, the scheme is now fully operational and is a real acceleration vector for high-potential health technologies, for the benefit of patients.

This document – which presents the assessment principles used for innovation funding – supports this dynamic. In keeping with its resolve to instil transparency in all of its initiatives, HAS enables manufacturers to learn about and understand the criteria it uses for the assessment of the innovation funding applications submitted to it. We hope that this presentation will give them a better grasp of the scheme, enable them to submit appropriate applications and, consequently, offer greater chances of success to provide patients with quicker access to innovative technologies.

D. LE GULUDEC and I. ADENOT

1. Innovation funding

1.1. Implications

In this document, the word technology covers the medical devices (MDs) and health products stipulated in articles L. 5211-1 or L. 5221-1 of the French Public Health Code (CSP) and medical procedures.

Innovation funding (*Forfait Innovation* – FI) is an exceptional process dedicated to the funding of innovative technologies. It was created by the French Social Security Financing Act for 2009.

Article L. 165-1-1 of the French Social Security Code (CSS) thus 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.* ".

Acceptance into the innovation funding scheme thus provides fast-track access to the market. Indeed, a technology which is accepted into the innovation funding scheme is disseminated across the French market *via* the inclusion of patients in the study, with the assurance that there won't be any interruption of funding for patients between the clinical study and the request for coverage by the mainstream health system.

The 3 main principles of innovation funding are the following:

- **exceptional funding**, ahead of coverage by the mainstream health system;
- **for a limited period of time**;
- **to conduct a clinical or medico-economic study**, which means that the project leader's study protocol must be included in the application for innovation funding.

This procedure is designed to:

- facilitate French patients' early access to promising technologies;
- also facilitate early access to promising technologies for the French health system when such technologies address non-covered medical needs or significantly reduce medical expenses;
- facilitate the collection of the data required to demonstrate the technologies' added value, since innovation funding will allow the early collection of the data that will be decisive upon submission of an application for mainstream funding, i.e. inclusion in the LPPR [1] for individual-use MDs or in the CCAM[2], NABM[3] or NGAP[4] nomenclatures for medical procedures that may or may not be associated with other types of technologies (medical devices for collective use or *in vitro* diagnostic medical devices (IVDMDs)).

Over the years, innovation funding implementation methods underwent a series of modifications to make the process fully operational. The Decree of December 2019 laid down specific time limits for each of the stages in the assessment of the funding application: HAS has a maximum of 75 days to

[1] LPPR: Liste des Produits et Prestations Remboursables (List of products and services qualifying for reimbursement)
[2] CCAM: Classification commune des actes médicaux (Joint classification of medical procedures)
[3] NABM: Nomenclature des actes de biologie médicale (French nomenclature of medical laboratory procedures)
[4] NGAP: Nomenclature générale des actes professionnels (General nomenclature of medical procedures)

issue an opinion, following which the Ministry of Health has 75 days to decide on the implementation of innovation funding.

1.2. Eligibility criteria

The innovation funding scheme targets technologies which are likely to have a significant impact, either on the clinical or medico-economic level.

The eligibility of an application for exceptional funding is appraised on the basis of **cumulative criteria** of three types, defined in 2015 by Decree (No. 2015-179 of 16/02/2015):

➔ **The type of technology concerned, in view of the health technology categories eligible for innovation funding;**

The innovation funding scheme is open to MDs, IVDMDs and medical procedures.

Multi-technology solutions (combining a medical device or an in vitro diagnostic medical device with a medical procedure) are also eligible for innovation funding.

➔ **Innovative character of the technology**

The following four conditions – defined in Article R. 165-63 of the French Social Security Code (CSS) – must be met for the characterisation of the innovation within the meaning of the innovation funding eligibility criteria:

- the innovation's novelty goes beyond that of a mere technical upgrade;
- it is in an early phase of dissemination;
- the risks have already been characterised;
- clinical or medico-economic studies confirm that its use is likely to fulfil one of the following objectives:
  - provide a significant clinical benefit, thus meeting a medical need not yet covered or insufficiently covered;
  - reduce healthcare spending, appraised in terms of cost-effectiveness or budget impact on the cost of the care provided (this benefit is only taken into consideration if the technology is deemed to be at least as clinically useful as the reference healthcare technologies).

➔ **The relevance of the clinical or medico-economic study proposed by the applicant**

The study proposed by the project leader must be relevant and feasible. It must meet the three conditions defined in 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 technology;
- any other similar studies under way or scheduled have been 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.

2. Assessment by HAS: general principles

2.1. Entire process associated with innovation funding

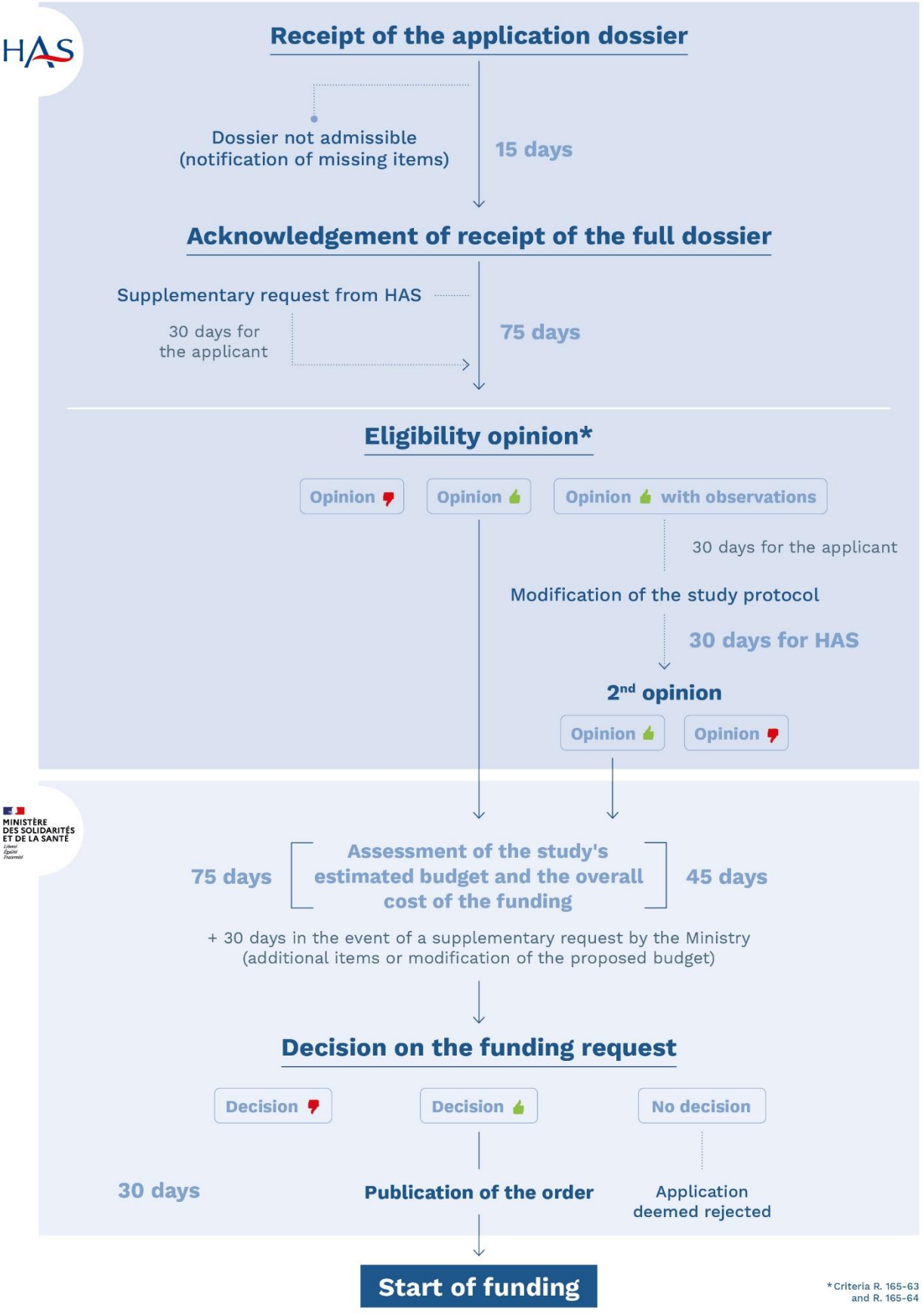
The process schematically comprises four steps, divided into two sequences, following receipt of the application submitted simultaneously to the Ministry of Health and to HAS:

- HAS is in charge of:
  - determining the admissibility of the application;
  - analysing the eligibility of the innovation funding request in view of the criteria defined in Articles R. 165- 63 and R. 165-64 of the CSS. It either issues a favourable or an unfavourable opinion on the request for exceptional funding of the product or procedure targeted by the application. The opinion of the HAS Board is reasoned. The opinion is addressed to the applicant and to the Ministers of Health and Social Security. It is published on the HAS web-site.
- Following this:
  - the Ministry conducts the budget analysis (budget estimate and overall cost of the study);
  - the Ministers decide whether to grant exceptional funding or not.

The diagram provided on the next page summarises the various steps of the overall process.

Moreover, the main stages in the formulating of an opinion by the HAS Board are detailed in a specific document (Procedure used by the HAS Board to formulate opinions on the exceptional funding of an innovative medical device, in vitro diagnostic medical device or medical procedure (in French)).

Innovation funding – **Examination procedure**



2.2. Reliance on expertise

In addition to Board members, one or more external experts may be called upon. They are appointed on a case-by-case basis, based on the advice of the HAS Board's Innovation Funding Officers and that of the Committee for the validation of declarations of interest.

The experts, who are bound by confidentiality rules, receive the applicant's dossier. The experts' contribution takes the form of a written report. External experts do not attend the meetings of the Board.

The Board conducts its own appraisal and compares it with the analysis of HAS services and external appraisals before issuing its opinion.

2.3. Phases of communication with the applicant

During the evaluation of an application for exceptional funding, three phases of communication with the applicant may take place:

- after submission of the dossier, during the so-called administrative admissibility phase;
- during the analysis of the eligibility of the request;
- after HAS' issuing of a favourable opinion with remarks.

2.3.1. Administrative admissibility phase

Upon receipt of the dossier, HAS has 15 days to evaluate its administrative admissibility. This phase consists in verifying that the application complies with the following technical points:

- the request concerns an MD, IVDMD or medical procedure;
- the applicant is among those mentioned in Article R. 165-65 of the CSS;
- the applicant is the sponsor of the study;
- the dossier submitted is complete, as laid down in the guide for the submission of an application for exceptional funding.

If the dossier submitted is complete, the application is deemed admissible. HAS notifies the applicant of the admissibility of their application. This is the simplest case.

If the dossier submitted is incomplete, the application is initially deemed non-admissible. HAS notifies the applicant of the non-admissibility of their application, pointing out the missing items. In such a case, the applicant is given the opportunity to complete their application by providing the stated missing items within 15 days following receipt of the HAS notification. If the items are not provided by that deadline, the application is deemed non-admissible. Should the applicant be unable to respond by the deadline, the application may also be withdrawn. Such a withdrawal will not impede a subsequent application submission at a more suitable time for the applicant.

The missing items may be purely administrative or linked to a certain part of the dossier. They may also be other items which are needed to understand the dossier.

Practical examples

Below are a few examples of missing items or insufficiently detailed items in certain dossiers:

- certificate of transfer of authority for the application when the main applicant chooses to transfer its authority to another entity (e.g. when a National Council of Healthcare Professionals wishes to ask a manufacturer to handle the task of applying for innovation funding for a new medical procedure);
- the description of the associated procedure in the case of an MD;
- role in the diagnostic or care pathway;
- the indications claimed if these are worded differently in different parts of the dossier or not consistent with the inclusion criteria of the proposed study;
- estimation of the target population (in numbers);
- the publications or study reports corresponding to the initial data supporting the request. For example, an application for innovation funding had been submitted in late 2020. An observational study report dating back to late 2019 with a 1-month patient follow-up was provided, indicating the production of another report after 6 months of patient follow-up. The applicant was asked to provide the latest data in its possession.
- …

2.3.2. During the eligibility analysis

Once the admissibility of the application has been established, HAS has 75 days to issue an opinion on the eligibility of the technology for exceptional funding.

During that time, a first analysis is carried out. The applicant may be asked to provide additional items. Such items may concern any part of the dossier, **in particular the protocol**.

The applicant has 30 days to answer the questions and provide the additional items requested. The applicant also has the possibility of amending their protocol or withdrawing their application if they so wish or if they are unable to respond by the given deadline.

At the end of the additional period, the HAS Board may issue three types of opinions: favourable opinion, favourable opinion with remarks, unfavourable opinion.

Practical examples:

- During the eligibility analysis phase, HAS asked an applicant to provide further arguments concerning the added value of the study for which the innovation funding was requested, with respect to a study already under way, and to make, in view of these additional arguments, certain adjustments to the proposed study to bring together the still necessary data to confirm the improvement of the benefit provided by the technology.
- For another dossier, HAS asked the applicant to enhance their dossier by providing arguments or adapting the layout of the proposed study in keeping with the stated primary endpoint.

In both of these cases, the applicants were given the opportunity to amend their applications in line with the questions raised by HAS and adjust the protocol of the study underpinning the request.

2.3.3. After HAS' issuing of a favourable opinion with remarks

In the case of a favourable opinion with remarks, the HAS Board deems that the health technology would meet the innovation criteria defined in Article R. 165-63 of the CSS. However, the Board has questions concerning certain points of the protocol of the proposed study for which exceptional funding is requested. It thus issues remarks implying that **minor** changes may need to be made to the study protocol. The applicant then has 30 days to respond to the remarks, state the reasons for their choices, or make changes to the protocol.

If the applicant is unable to respond by the given deadline, they may withdraw their application if they so wish at this stage and re-apply at a later date. In the event of voluntary withdrawal, no further opinion is issued by HAS.

Upon receipt of the new items requested, HAS issues a final reasoned opinion. This may be a favourable opinion or an unfavourable opinion as to the exceptional funding of the product or procedure covered by the application.

3. Criteria-based appraisal

To be eligible, a health technology must **comply with all of the eligibility criteria** of the innovation funding scheme. The criteria are thus cumulative and HAS' opinions cover:

- each of the four criteria used to characterise the innovation (within the meaning of Article R.165-63 of the CSS);
- each of the three criteria defined in Article R.165-64 to characterise the relevance of the clinical or medico-economic study proposed by the applicant.

Eligibility is appraised in view of the technology, the disease concerned and its frequency, and the available diagnostic or care pathway.

The purpose of this document is to provide guidance to future project leaders and explain how HAS appraises the regulatory criteria defined.

> You will note that many of the chosen examples are negative. This is done on purpose. Indeed, those cases illustrate situations that were unsuccessful. They are thus particularly instructive, as the objective is to provide the right keys to obtaining a favourable opinion.
>
> To date, no application has been submitted exclusively for a medico-economic benefit. The examples thus focus on the clinical benefit approach.
>
> This document will be reviewed on a regular basis to provide clarity to applicants.

In all cases, HAS drafts its opinions with great care, whether they are positive or negative. It takes special care when it issues an unfavourable opinion, as an unfavourable opinion does not mean that the technology is of no interest or is not innovative. This opinion only means that, at the time of the assessment, the application fails to meet at least one of the innovation funding scheme's eligibility criteria (e.g. concerning the proposed protocol or prior dissemination).

Note that, after a negative opinion, the applicant may submit a new innovation funding application. This application – which obviously needs to be modified with respect to the previous one – may lead to a favourable recommendation of exceptional funding; this has already been the case for a dossier.

3.1. Innovative character of the technology

3.1.1. Novelty aspect

Criterion: "the technology's novelty goes beyond that of a mere technical upgrade".

Examples of appraisals:

- ➔ A breakthrough technology is eligible for innovation funding but mere technological upgrades are not.
- ➔ A technology which is already disseminated may be eligible for innovation funding if new indications are targeted.
- ➔ Technologies which have been under FDA approval or CE marking procedures in the claimed indications for numerous years have been appraised as non-eligible for innovation funding.

Practical examples:

- A device under the 510(k) marketing clearance process in the United States obtained an unfavourable opinion. Indeed, that procedure implies a demonstration of substantial equivalence in terms of efficacy and safety in relation to techniques already marketed (*predicate*). However, substantial equivalence does not mean an innovation other than a mere technological upgrade.
- The grouping of two already marketed devices into a kit was not considered as an innovation.
- An implantable neurostimulation system obtained an unfavourable opinion on the criterion that the system was already disseminated across the world with a significant number of implanted patients.
- A device can be deemed an innovation when it is the only existing device for the indication concerned or when there is no routine technique with an equivalent mode of action used for the indication claimed. For instance, a device obtained a favourable opinion for its novelty as none of the techniques under development was funded by the health system and all of these techniques were at the clinical research stage.

3.1.2. Early dissemination phase

Criterion: "the technology is in an early phase of dissemination".

The interpretation of this criterion involves several aspects.

Practical examples of appraisals:

To appraise the dissemination level, HAS takes account of:

- The national and international context. For example, a technology that was practically non-existent in France was not considered as being in its early dissemination phase as it was widely disseminated internationally.
- The number of devices already disseminated. For example, a positive opinion was issued as the technology had only been used in feasibility studies and the number of units sold or provided free of charge was still very limited.

As a reminder, the CE marking for the indication claimed is not a prerequisite for obtaining innovation funding. Therefore, a **technology which does not yet have the CE marking** can be considered as being in an early stage of dissemination. The clinical study can start before the CE marking is obtained, but the procedures to obtain the CE marking will of course need to be undertaken since the CE marking will be required once all patients have been included in the study, for the treatment of any additional patients.

Moreover, the technology covered by the application must never have been publicly funded for the indications claimed. Nevertheless, a technology having been the subject of research funding under the hospital clinical research programme (PHRC) may be eligible for innovation funding provided that the study funded under the PHRC has been completed.

3.1.3. Characterisation of risks

Criterion: "the risks have already been characterised".

The characterisation of risks is based on the initial data available. To this effect, all available clinical data, including the most recent (publications, study report along with its protocol) must be provided. For technologies (MD or IVDMD) that have already been granted the CE marking, the

materiovigilance / reactovigilance data collected in France and internationally must also be provided as they contribute to the characterisation of risks. This criterion covers the risks incurred, firstly by the patient and possibly by the operator also.

There is no golden rule as to the type of initial data to be provided (such as the minimum number of patients or other threshold). HAS analyses the initial data, taking into consideration the epidemiological and pathophysiological context. Note that the characterisation of risks is appraised in view of the incidence of the disease. It is obvious that there will be less data available for rare diseases.

Practical examples:

- For an application concerning a widespread disease, HAS deemed that providing solely one series of cases relating to a prior version of the technology and covering less than 10 patients was insufficient to characterise the risks of the technique.
- For a non-invasive technology, a favourable opinion was issued, as it was deemed that the risks for patients were lower than those of the standard invasive technique.
- The risk characterisation criterion is appraised solely on the basis of the risks directly generated by the use of the technology itself. In the phase of analysis of a technology's eligibility for innovation funding, the aim is not to assess the risks inherent in decisions resulting from the use of the proposed technology. For an *in vitro* diagnostic test on a blood sample, the risks associated with the use of this diagnostic test were thus deemed already characterised without waiting for the demonstration of the benefit or risk resulting from its use (e.g. based on its predictive value). The results of the innovation funding study will provide that answer.

3.1.4. Available clinical studies

According to the regulatory criteria, the available clinical or medico-economic studies must show that the use of the technology is likely to fulfil one of the following objectives:

- ➔ provide a significant clinical benefit in terms of therapeutic, diagnostic or prognostic effect, thus meeting a medical need not yet covered or insufficiently covered;
- ➔ or reduce healthcare spending, due to a medico-economic benefit.

The expected benefit thus directly depends on what is expected from the use of the technology.

Concerning the clinical benefit, the term clinical is to be interpreted in a broad sense: the patients' **quality of life** and the **optimisation of the care pathway** to improve therapeutic management are some of the benefits that may incite HAS to recognise the interest of a technology.

The medico-economic benefit (cost-effectiveness or budget impact) is only appraised if the technology is deemed to be at least as clinically useful as the reference care pathway. To date, no application has been submitted exclusively in that objective.

Practical examples:

- For the proposed technology, the applicant claims a substantial clinical benefit, while available preliminary clinical data show a clinical efficacy which is comparable to the standard care pathway. In that case, the technology cannot be deemed as likely to provide a substantial clinical benefit that would fulfil a medical need not yet covered or insufficiently covered.

- Preliminary clinical data from a series of cases relating to the first generation of the device were provided. In relation to the version of the study, the technology had undergone substantial technological changes that modified the efficacy profile. The available clinical data made it possible to estimate the benefit of the first generation of the device but it was impossible to extrapolate this data for the proposed generation.
- Concerning the interpretation of the clinical benefit, let's examine the case of an application for which the expected benefit was **organisational** with an improvement of the care pathway. This was recognised for a technique whose potential benefit rested on rapid access to the diagnosis. The expected benefit may also concern the **quality of life** of patients. This was recognised for a solution whose aim was to reduce pain, with a major impact on patients' quality of life.

3.2. The relevance of the clinical or medico-economic study proposed by the applicant

3.2.1. Capacity of the proposed study to gather the missing data

The study covered by the application for innovation funding must allow the collection of the missing data to confirm the improvement of the expected benefit. It will thus confirm the interest of the healthcare product or procedure and its added value. The study must therefore be ambitious **and be suited to the clinical context**.

HAS does not define minimum requirements for the study. However, in accordance with regulatory requirements, the study must be comparative. Ideally, the study should be comparative in relation to the optimal care pathway, except if no relevant comparator is available or if such a study cannot be conducted for ethical reasons. As a minimum, comparison with a clinically documented performance target is desirable. The primary endpoint(s) should be in line with the objective of the study, and be relevant for the disease treated and the intended use of the technology.

In all cases, the dossier must **provide arguments for the choices made** for the experimental design of the proposed study. The assumptions made must be clinically relevant and justified. The sample size must be calculated in view of the study's assessment criterion/criteria. In particular, in the face of the frequently observed trend which consists in multiplying criteria, it is better to opt for valid statistical techniques such as hierarchical sequential methods or other appropriate methods in order to test secondary endpoints in an adequate way.

The protocol must also anticipate the technology upgrades. As we all know, the MD sector evolves rapidly. It is essential to integrate the technology's life cycle in the draft study and anticipate the assessment of successive generations.

Practical examples:

- An unfavourable opinion was issued for a protocol submitted for a technology which made it possible to collate the diagnostic performance data of the proposed technology and reference care pathway, but failed to demonstrate its clinical utility.

- On the other hand, a study protocol concerning the direct comparison of a new IVDMD with a reference technique was accepted as it was of a good methodological quality, with clear objectives and relevant endpoints, allowing the collection of the missing critical data concerning diagnostic and sensitivity performance data.

The innovation funding scheme can fund the French arm of an international study. In such a case, the draft protocol must allow any modifications that may be required to meet the criteria of the innovation funding scheme. In the case of an international comparative study, the comparator and the reference care pathway must be the same in France in order to ensure the extrapolation of the results.

Note:

- The protocol submitted to HAS is a draft protocol. No innovation funding request may be submitted for a study already under way and having started its inclusions. For example, an unfavourable opinion was issued for a research project already authorised by the Food and Drug Administration and already under way, with the effective inclusion of patients.
- Certain draft protocols included a medico-economic aspect on top of the clinical aspect, which constituted the main objective of the study. HAS only takes the medico-economic benefit into consideration when the healthcare product or procedure considered is deemed to be at least as clinically useful as the reference healthcare technologies.

3.2.2. Relevance of conducting the proposed study

The dossier submitted must mention any other similar studies under way or scheduled concerning the technique covered by the application or other analogue techniques for the indications claimed. Their provisional timetable must also be described. This stage is crucial to assess whether the conduct of the study proposed by the applicant is relevant.

Practical examples:

- An application for innovation funding was submitted with preliminary clinical data consisting of a randomised control study conducted abroad. This study aimed to compare the technology concerned by the innovation funding request with the standard care pathway. Since this pathway was the same as in France, the results of the preliminary study could be extrapolated to the French healthcare context and support a request for mainstream funding. The conduct of a new study was therefore useless.
- Two similar competing techniques are under clinical development. Since randomised, controlled clinical trials are already under way in France and abroad for these techniques, there is no need to fund a new study under the innovation funding scheme.

3.2.3. Study feasibility

The feasibility of the proposed study must seem reasonable, especially in view of the draft protocol and budget estimate.

Practical example:

- A draft study is submitted with multiple endpoints without any ranking or documentation of the chosen target values. Moreover, the number of subjects to be treated was set arbitrarily and independently from the effect sought. These major limitations called into question the feasibility of the proposed study.

4. Dossier strong points

In the preparation of your dossier, carefully anticipate your strategy. This will ensure the coherence of your request.

The Guide for the submission of an application for exceptional funding was produced to enable you to provide HAS with all the information required to analyse your request and appraise your chances of success in your project. It is totally based on the eligibility criteria.

Below are a few watchpoints relating to common difficulties encountered in applications:

- Provide details of the technology, its mode of action and its technical characteristics. Where relevant, provide a certificate of health data hosting by an approved or certified data host.
- In the event of incremental changes in the technology over time, draw up comparative tables between any prior version(s) and the version covered by the request, specifying, for each clinical study available and provided, the version involved in the study. Provide details of the marketing history of the various generations available.
- Anticipate the upgrade of the technology and include it in the ensuing study protocol.
- In the case of a new procedure associated with the use of an individual-use MD, describe with precision all the procedures associated with the use of the device.
- Determine the indications to be claimed in a clear and precise manner.
- Carry out a rigorous analysis of the therapeutic or diagnostic strategy. Justify the place of the technology in this strategy and estimate the corresponding target population, in keeping with the indications claimed.
- For technologies that have already been granted the CE marking, provide the materiovigilance data used for the characterisation of the technology's risks. Also provide the marketing history.
- For the studies mentioned that are already under way, give details of their provisional timetable.
- Provide all the publications mentioned in the dossier.
- In the case of a technology using artificial intelligence, provide precise details of the algorithm(s) using the dedicated descriptive grid. These items are obviously technical. We advise you to call on the developers of the algorithm so that the information is filled in correctly.

Likewise, concerning the draft protocol provided, recurrent shortcomings are to be noted. We strongly recommend that you refer to good clinical practice guidelines to provide a comprehensive high-quality draft protocol. The most common reasons for contacting applicants are the following:

- Describe the Scientific Committee (identity and speciality) and ensure that all specialities are properly represented. Systematically involve a methodologist and, where relevant, a health economist.
- The objective of the study must be consistent with the primary endpoint.
- If the study is international, specify the number of French patients.
- Take account of the technology learning curve and include roll-in phases.

- Take account of the technology's life cycle by including successive generations in the protocol.
- Provide details of the analysis populations and data collection methods.
- Draw up lists of authorised and non-authorised treatments.
- Provide for the management of missing data and lost to follow-up subjects and describe the means used to limit them.
- Provide details of the sensitivity analyses planned.
- Discuss the limitations of the study and its external validity.
- Provide for a register of non-included patients.
- Provide the list of centres participating in the study and discuss their representativeness.
- Provide the statistical analysis plan and CRFs/e-CRFs if available.

5. Support from HAS

On the practical level, HAS can assist you prior to the submission of your dossier. Two types of meetings are possible for technologies coming under the medical device category or involving the creation of a new medical procedure, depending on the progress of your project:

5.1. Pre-submission appointments

Applicants who wish to obtain information on the required technico-regulatory aspects to prepare their dossier can request a pre-submission appointment (in French).

These meetings are arranged by HAS (on request) prior to the submission of an application for exceptional funding. Only HAS services are involved in those meetings.

This type of appointment is not intended as a means of obtaining advice about the company's strategy. They are optional, non-binding, confidential and free of charge. A distinction should be drawn between these meetings and the early dialogues designed to give an insight into the methodological elements regarding the device development.

5.2. Early dialogues

The applicant may request an early dialogue on matters connected with the clinical development of the technology concerned or a joint early dialogue also touching on issues relating to the conduct of a medico-economic study, if an assessment of the technology's cost-effectiveness is envisaged. Only HAS services are involved in those meetings.

The early dialogue processes organised by HAS are optional, non-binding, confidential and free of charge.

The answers provided by HAS services during the course of these early dialogues in no way constitute an assessment and should not be taken as predicting the conclusions of any assessment by the HAS Board at the time of submission of the dossier.

Appendix 1 – Practical tips before submitting a dossier

Who can apply?

For innovation funding, the **applicant must be the sponsor of the proposed study** (**for an MD**: manufacturer or distributor, in association, where relevant, with any service provider; **for a procedure**: a National Council of Healthcare Professionals (CNP), in association, where relevant, with any healthcare institution). For multi-technology or technological solutions involving, for instance, an MD and a procedure, the application may be submitted by several entities. In such cases, the main applicant is determined according to predefined rules. Authority for the application may be transferred, for instance from the CNP to the manufacturer or vice versa.

For more information on this point, Instruction DGOS/PF4/DSS/1C/DGS/PP3/2015/279 of 04 September 2015 provides details on these aspects of the application.

How?

The dossier must be submitted simultaneously to HAS and to the Ministry of Health and Social Security. For practical details on how to do this:

➔ **Submission of the dossier to HAS**

All applications for exceptional funding must be submitted online via the electronic dossier uploading platform SESAME (https://sesame.has-sante.fr/portail). There is no charge for this procedure. Paper applications are not accepted.

➔ **Submission of the dossier to the Ministry of Health and Social Security via Bureau Innovation et Recherche Clinique – Direction Générale de l'Offre de Soins (DGOS)**

Submission instructions are provided on the web page accessible via the following link: https://solidarites-sante.gouv.fr/systeme-de-sante-et-medico-social/recherche-et-innovation/forfait-innovation.

The dossier comprises several parts:

- Identification of the request;
- Part I focusing on the arguments confirming compliance with eligibility criteria;
- Part II focusing on the application assessment dossier;
- Part III focusing on the proposed study's full draft protocol;
- Part IV focusing on the budget estimate;
- Part V focusing on the applicant's commitment to communicate the results of the study and provide access to the data;
- Appendix 1 focusing on administrative documents;
- Appendix 2 focusing on available studies and their tabulated abstracts
- Appendix 3 focusing on the other documents required for the processing of the request.

A guide for the submission of an application for exceptional funding is available on the HAS website to help applicants and guide them through the details of the expected content of each part of the dossier.

Appendix 2- Toolbox

For practical details on the submission of a dossier to HAS

For practical details on the submission of a dossier to the Ministry of Health (DGOS)

Guide for the submission of an application for exceptional funding for an innovative product. HAS – October 2020.	The aim of this guide is to help applicants put together a dossier to apply for exceptional funding for an innovative product (MD, IVDMD or procedure).
Procedure used by the HAS Board to formulate opinions on the exceptional funding of an innovative medical device, in vitro diagnostic medical device or medical procedure (in French).	This document describes the various steps of the internal processing of applications by HAS.
Early dialogue with HAS about a medical device undergoing clinical development, updated November 2017 (in French).	The purpose of this document is to present the practical procedures for submission and the conduct of early dialogues, arranged at the manufacturer's request.
Procedure for applying for a pre-submission appointment and sequence of events, HAS update November 2017 (in French).	The purpose of this document is to explain to prospective applicants the technical and regulatory aspects with which they need to be familiar when preparing or finalising their dossier.
Practical guide to medical device assessment in France, HAS update October 2020 (in French only as of July 2021, English translation in progress).	The purpose of this guide is to help companies better understand the rules concerning medical device marketing and reimbursement. It also presents the key stages of clinical development with a focus on clinical follow-up. An update is coming soon.
Guide to the specific features of clinical evaluation of a connected medical device (CMD), HAS January 2019.	The objective of this guide is to help companies manufacturing or operating CMDs to include clinical trials in their development strategy in order to determine their usefulness in view of their reimbursement through public funding.
Methodology for the clinical development of medical devices, HAS, June 2021 (in French only as of July 2021, English translation in progress).	The purpose of this guide is to provide an update on the methods that can be used to assess the clinical benefit of a new MD or a new health technology and to describe possible study designs for assessing clinical quality.
Companion test associated with a targeted therapy: definition and assessment methods, methodology guide, HAS, April 2014 (in French).	The aim of this guide is to provide a pragmatic summary of HAS' theoretical and methodological principles for assessing a diagnostic test to identify a presumed predictive marker associated with a stratified therapy.

Abbreviations and acronyms

CCAM	Classification commune des actes médicaux (Joint classification of medical procedures)
CNP	Conseil National Professionnel (National Council of Healthcare Professionals)
CSS	Code de la sécurité sociale (French Social Security Code)
CSP	*Code de la santé publique* (French Public Health Code)
DGOS	*Direction générale de l'offre de soins* (French Directorate General of Health Care Provision)
MD	Medical Device
IVDMD	In vitro diagnostic medical device
CMD	Connected Medical Device
FI	*Forfait Innovation* (Innovation Funding)
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)
LFSS	*Loi de financement de la sécurité sociale* (Social Security Financing Act)
NABM	Nomenclature des actes de biologie médicale (French nomenclature of medical laboratory procedures)
NGAP	Nomenclature générale des actes professionnels (General nomenclature of medical procedures)
ONDAM	Objectif national des dépenses d'assurance maladie (National Health Insurance spending objective)

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