



HAUTE AUTORITÉ DE SANTÉ

Transparency Committee doctrine


Principles of medicinal product assessments and appraisal for reimbursement purposes

Adopted by the TC on 2 December 2020

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1. Introduction

In France, the scientific and medical assessment of medicinal products for reimbursement purpose is performed by an independent scientific committee, the Transparency Committee (TC) of the French National Authority for Health (Haute Autorité de santé or HAS).

This document outlines the main elements and criteria taken into account by the Committee in its assessments¹.

1.1. Definitions

1.1.1. General definition

The term “doctrine” can be defined as the basic principles underpinning a strategy and theoretical concepts, adopted to guide actions or help interpret facts.

The doctrine described hereafter does not include an ideological or dogmatic dimension.

1.1.2. Definition of the Transparency Committee’s doctrine

The doctrine is a work tool designed to provide benchmarks and visibility with respect to the main criteria for the assessment of medicinal products with a view to issuing a recommendation relating to their funding and, consequently, the expectations concerning submissions by companies.

The doctrine explains the basic principles of the scientific and methodological rationale adopted by the TC when it analyses data and incorporates it in its assessments, in view of the medical context. This doctrine forms a general framework to be applied to assessments. It is designed to be updated if deemed necessary by the TC, notably in order to take into account methodological, regulatory or contextual changes.

1.2. Context

This presentation of the assessment methods applied by the TC is a reflection:

- **firstly, of the TC’s determination to outline the basis for its assessments – and, in particular, for the assessment of clinical added value (CAV) – within a framework that is flexible enough to maintain the required balance between general aspects and the singular context of each individual medicinal product;**
- **secondly, of a demand on the part of public authorities, patient and consumer associations and manufacturers.**

The objective is to guarantee a transparent, reproducible and fair assessment.

The TC’s medical and scientific assessment is based on an analysis of all the clinical data available at a given time for the medicinal product in question and in the indication assessed. The

¹ The regulatory framework for the assessment of medicinal products is laid down in articles R. 163-1 et seq. of the French Social Security Code and in the Transparency Committee’s internal regulations.

assessment is, by definition, temporary; it corresponds to a snapshot at a given point in time and is liable to evolve on the basis of new data concerning the product's efficacy and safety.

Numerous national studies – including the report by Dominique Polton in 2015² – have demonstrated the importance of improving the reproducibility and transparency of assessments with a view to reimbursement, particularly the assessment of the CAV, which has a direct impact on the negotiation of medicinal product prices. Whilst it is true that regulations explicitly lay down a list of criteria for the assessment of the clinical benefit (CB), this is not the case for the CAV, which is based on an overall assessment of the progress provided by a medicinal product compared with existing treatments.

Furthermore, for the past few years, the TC has been faced with an increase in the number of requests for assessment of new medicines presenting a high level of uncertainty (uncertain clinical benefits, poorly demonstrated given the early nature of the data) or very rapidly changing therapeutic strategies. In response to the multiplication of these situations that do not meet the usual methodological requirements, the TC considered it useful to specify the main principles underpinning its assessments and its expectations.

This approach, designed to provide clarification and transparency, also fits squarely with the international context of comparison of assessment and analysis methods underpinning the decisions taken in different countries.

² Polton D. Rapport sur la réforme des modalités d'évaluation des médicaments. [Report on medicinal product assessment method reform]. November 2015. Available online at: http://solidarites-sante.gouv.fr/IMG/pdf/rapport_polton_-_evaluation_medicaments.pdf

2. Clinical added value

2.1. Determinants of CAV

In accordance with article R. 163-18 of the French Social Security Code, the TC's opinion includes an assessment of the CAV. The CAV is an assessment of the therapeutic (or diagnostic) progress provided by a medicinal product – notably in terms of efficacy or safety – compared with existing alternatives. It measures the medical added value of the medicine compared with existing therapies: this assessment is a snapshot at a given point in time within an environment that may evolve. It may be rated major (CAV level I), substantial (CAV level II), moderate (CAV level III), minor (CAV level IV) or no improvement (CAV level V), with the latter level corresponding to no therapeutic progress. In particular, the CAV is used to define the framework for price negotiations.

Particular attention is paid to the following criteria:

- **the quality of the demonstration**, which includes the comparison and the choice of comparator(s), the methodological quality of the study, the appropriateness of the population included for the indication, the relevance of the clinical endpoint and its significance, etc.;
- **the effect size in terms of clinical efficacy, quality of life and safety** in view of the robustness of the demonstration;
- **the clinical relevance** of this effect compared to clinically relevant comparators;

in view of the medical need.

The TC's main expectations with respect to these three criteria are detailed below.

2.1.1. Quality of demonstration

2.1.1.1. The comparison and the choice of comparator

Since the CAV is a relative approach, the first step in assessment of the quality of the demonstration therefore assumes that:

1. a comparison is available;
2. a clinically relevant comparator has been identified;
3. and that the available data enables assessment of the medicinal product's contribution compared to this comparator.

A clinically relevant comparator may be a medicinal product (active substance or placebo, with or without MA), a medical device, a procedure or any other non-medicinal therapy (or diagnostic method). It plays the same role in the therapeutic strategy as the new medicinal product and is aimed at the same patients.

Hence, a medicinal product subject to an early access programme such as a temporary authorisation for use (ATU) or a temporary recommendation for use (RTU), or used off-label in routine practice in the indication assessed may be considered to be a clinically relevant comparator.

Comparison with the clinically relevant comparator corresponds to an important step in the TC's rationale for assessment of the CAV.

A direct comparison with the clinically relevant comparator, conducted within the framework of a double-blind, randomised trial, is expected wherever possible.

Double-blind, randomised controlled studies remain the prerequisite and the essential reference for the assessment of any medicinal product. This is because only randomisation and double-blind comparison can guarantee the similarity of the groups compared throughout the study and thus make it possible to attribute the differences observed to the medicinal product studied in a given treatment regimen. Double-blinding makes it possible to avoid assessment of biases related to the subjectivity of follow-up, the assessment of outcome measures, etc.

The absence of direct comparison with a clinically relevant comparator must be justified by the company and may be accepted by the TC in certain situations, such as concomitant developments, specific populations for whom extrapolation of efficacy can be performed on the basis of pharmacokinetic data or real-life data, etc.

In the absence of direct comparison, an indirect comparison, conducted on the basis of defined and validated methodological principles, may be taken into account^{3,4}. Indirect comparisons that are not performed in accordance with these methods are not generally considered to be appropriate for claiming a CAV. However, new methods of indirect comparison may be used to specify the position in the treatment strategy, for example.

Data from real-life studies may also be taken into account (see Chapter 5 Real-life studies).

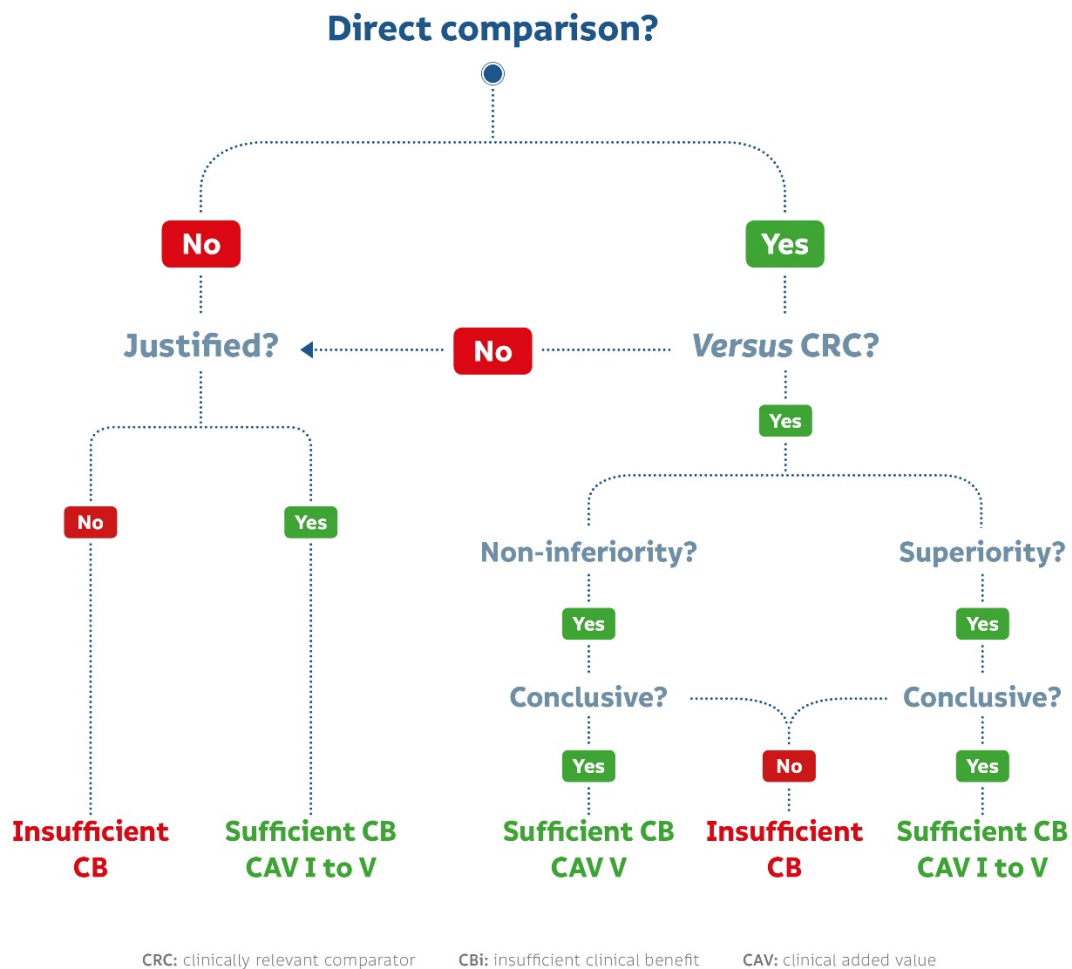
In practice, the rationale adopted by the TC generally follows the approach presented in Figure 1. This rationale is not immovable and can be adapted to the context of each assessment.

The absence of any direct comparison when the TC deems that it would have been possible may lead to allocation of a CAV level of V. In this context, the CB may be considered to be sufficient if a loss of opportunity can be eliminated (see “Insufficient CB” paragraph).

³ Haute Autorité de santé. Rapport de synthèse. Les comparaisons indirectes. Méthode et validité. Available online: https://www.has-sante.fr/portail/jcms/c_998793/fr/les-comparaisons-indirectes-methodes-et-validite

⁴ EunethTA. Guideline. Comparators and comparisons: direct and indirect comparisons. Adapted version 2015. Available online: https://www.eunetha.eu/wp-content/uploads/2018/01/Comparators-Comparisons-Direct-and-indirect-comparisons_Amended-JA1-Guideline_Final-Nov-2015.pdf

Figure 1. Comparison in the Transparency Committee's assessment



2.1.1.2. The outcome measure

The TC considers that the **primary outcome measure** of a study must be a relevant clinical endpoint wherever it is possible to collect one. If a relevant clinical endpoint is not used in the trials, justification by the company explaining this choice is expected.

The use of a **surrogate endpoint** – in particular a biomarker – is considered to be a relevant clinical endpoint on condition that a link with a clinical morbidity and mortality endpoint has been demonstrated in the disease concerned, in accordance with the definition of a surrogate endpoint.

The use of an **intermediate outcome measure** (without demonstration of a link with a relevant clinical endpoint) may be taken into account in assessment of the CAV.

For example, in the field of oncology, the TC may take into account progression-free survival in situations whereby overall survival cannot be documented in the short or medium term (long life expectancy, multiple subsequent therapeutic conditions, etc.) or where a link has been demonstrated between these two endpoints.

2.1.1.3. The study design

The study design must be consistent with the objective and, wherever possible, the statistical analysis plan must schedule appropriate control of the alpha risk.

2.1.2. Additional effect size and clinical relevance

The effect size measures the magnitude of the medicinal product's effect compared to the clinically relevant comparator, usually in terms of morbidity and mortality, quality of life and safety. The clinical relevance corresponds to the substantial nature of the effect provided to patients (a statistically significant difference alone may not be clinically relevant).

The additional effect size is assessed on a case-by-case basis by the TC, in terms of the following conditions, in particular:

- when the outcome measure is a dichotomous qualitative variable, by the absolute risk reduction and its confidence interval;
- when the outcome measure is a variable such as time to onset of an event, by the difference in time-to-onset medians and its confidence interval;
- when the outcome measure is a quantitative variable with normal distribution, by the difference in means and its confidence interval;
- when the outcome measure is a quantitative variable with non-normal distribution, by the difference in medians and its confidence interval.

The clinical relevance of this effect is assessed on a case-by-case basis depending on the medical context. Hence the TC does not wish to predefine clinical relevance thresholds or systematically correlate these with CAV levels since this assessment depends on the context of the assessment.

The effect size and its clinical relevance are also assessed on the basis of the medicinal product's safety and the medical need in the indication assessed. For example, a low effect size in terms of morbidity and mortality could lead to a CAV level of V when the medical need is already met or to a CAV level higher than V⁵ when the medical need is not met. Similarly, a low effect size in terms of morbidity and mortality could lead to a CAV level higher than V in the event of a clinically relevant improvement in safety and/or quality of life. However, it should be noted that at the date of the initial assessment, the lack of experience means that it is rarely possible to reach a formal conclusion with respect to better medium or long-term safety. In the event of any doubt, the patient's interests will always take precedence in the TC's conclusions.

2.1.3. Quality of life

Quality-of-life data contribute to assessment of the medicine's clinical effect.

In addition to efficacy and safety data and depending on the medical context, if an improvement in quality of life is demonstrated, this could lead to a CAV level of higher than V in situations in which this finding is based on:

- the use of validated scales appropriate to the objective (preferentially specific);
- a rigorous methodology: objective and clinical relevance threshold pre-specified in the protocol, double-blind conditions, management of multiplicity of the analyses, appropriate analysis frequency, time and duration, few missing data.

Quality-of-life data collected using different methods may be useful for the assessment but is not generally considered to be appropriate for claiming a CAV.

The absence of quality-of-life data may have a negative impact on the CAV if it is expected by the TC, particularly for chronic and/or incapacitating diseases and end-of-life patients.

⁵ A CAV level of higher than V may correspond to a CAV level of I (major), II (substantial), III (moderate) or IV (minor).

2.1.4. Medical need

Assessment of the CAV is performed in view of the medical need in the indication assessed A need that is unmet or is inadequately met may be considered favourably, without being the only justification for concluding that the CAV level is higher than V.

Addressing an unmet medical need is one of the elements taken into account in the assessment, on three levels:

- as an element for assessment of the CB and hence access to reimbursement (number of alternatives, public health benefit);
- as a criterion informing the clinical data, within the CAV;
- as an element in favour of an accelerated assessment procedure.

2.2. Details concerning CAV levels

2.2.1. Major therapeutic progress (CAV I)

The TC may recognise a medicinal product as representing major therapeutic progress if it has a new action mechanism, has demonstrated, with a high level of evidence, its superiority, combined with a clinically relevant effect in terms of mortality and morbidity, compared to a clinically relevant comparator, in a context of an inadequately met medical need for a serious disease.

This assessment corresponds to therapeutic breakthrough situations (that save or change the lives of patients with a serious disease) for which all the CAV determinants are judged to be satisfactory by the TC.

2.2.2. Substantial and moderate therapeutic progress (CAV II and III)

The TC may recognise a medicinal product as representing substantial or moderate therapeutic progress if it has a demonstrated superiority combined with clinical efficacy in terms of mortality and morbidity, in a context of an inadequately met medical need. The evaluation of this efficacy may be positively adjusted by a substantial improvement in quality of life and/or safety.

A moderate or substantial CAV will qualify the clinical added value, depending on its intensity, the quality of the demonstration and the severity of the disease or symptom. Hence, the value attributed to the progress increases along with the effect size, the quality of the demonstration and the seriousness of the disease.

2.2.3. Minor therapeutic progress (CAV IV)

A minor CAV is allocated to progress that is small compared to existing therapies It reflects a non-optimal demonstration and/or effect size (efficacy, quality of life, safety) in view of the medical context.

It may concern a medicinal product having demonstrated relevant efficacy with a slight and acceptable decrease in quality of life or safety. Conversely, it may concern a medicinal product with little or non-optimally demonstrated additional efficacy but which is associated with an improvement in terms of quality of life or safety. It may also concern a major improvement in care conditions, either demonstrated or expected by the TC (see “Focus” paragraph).

2.2.4. No improvement (CAV V)

The TC may conclude that there is no therapeutic progress, particularly in any of the following situations:

- demonstration founded on a noninferiority trial,
- a medicinal product that is a generic medicine, a biosimilar or a range supplement.

In the absence of therapeutic alternatives or when the alternatives are limited, a CAV level of V may also reflect a **deficiency or uncertainty related to the choice of comparator, the quality of the demonstration, the effect size or its clinical relevance that does not indicate an insufficient CB** (see “Insufficient CB” paragraph).

2.3. CAV wording

The CAV is worded compared to one or more comparators or with respect to the therapeutic strategy.

The wording specifies the population or subpopulation of the indication liable to benefit from the identified progress. It usually summarises the justification of the CAV level obtained, particularly in view of the quality of the demonstration, the effect size and the clinical relevance, the safety and/or care conditions or the medical need.

While quantification of the CAV level from I to V indicates the contribution of a medicinal product, the CAV wording explains it. For example, a CAV level of IV compared to a medicinal product with a CAV level of II differs in terms of its additional contribution, to a CAV level of IV compared to a medicinal product with a CAV level of V. In the former case, the medicinal product provides a minor benefit compared to a medicinal product with an important benefit, while in the latter, the contribution is minor compared to no improvement. Therefore the CAV wording and level need to be considered jointly.

Furthermore, the TC highlights that it may consider that two medicinal products have an identical CAV level in the following situations:

- therapeutic class reassessments;
- concomitant developments.

CAV wording following therapeutic class reassessments

In a therapeutic class reassessment, the TC reaches a conclusion concerning the value of having access to the medicinal products in this class as well as their relative value in the therapeutic strategy. It may therefore consider that several medicinal products have a similar value and allocate them the same CAV level in the therapeutic strategy.

For example, a medicinal product with a CAV level of V compared to its clinically relevant comparator, which has itself obtained a CAV level of higher than V at its initial assessment may obtain the same CAV level in the therapeutic strategy following a class reassessment. This same CAV level then means that the two medicinal products make an equivalent contribution to the strategy without it being possible to rank them in order on the basis of clinical data following the reassessment.

CAV wording in the event of concomitant developments

Identical CAV levels may be allocated to medicinal products having been the subject of concomitant development.

For example, the TC considers that two medicinal products have been the subject of concomitant development when their respective pivotal clinical trials were performed totally or partially during the same period or when they were begun before one or other became available.

In practice, these medicinal products can be cited among the clinically relevant comparators at the time of the assessment but a direct comparison will not be expected in the initial assessment.

2.4. Assessment of innovation

The elements characterising a health innovation are, in particular:

- the **novelty of the mechanism of action in the indication concerned;**
- **and** the existence of **an inadequately met medical need;**
- **and** the **response to the medical need** thanks to a demonstrated additional efficacy that is clinically relevant for patients. For example, in oncology, the medicinal product should provide a response in terms of overall survival and quality of life.

A new medicinal product may be considered to be an innovation **if it saves or changes the lives of patients with a serious or progressive disease in the context of an inadequately met medical need** (no alternative or alternatives not very effective).

The “new” nature alone of a medicinal product cannot, therefore, define innovation. Likewise, addressing a need is not itself systematically an eligibility criterion for innovation.

3. Clinical benefit

3.1. Determinants of CB

In accordance with article R. 163-3 of the French Social Security Code, the clinical benefit of a medicinal product in a given indication is assessed on the basis five factors:

- the efficacy and adverse effects of the medicinal product;
- its place in the therapeutic strategy, particularly with respect to the other therapies available;
- the seriousness of the disease targeted by the medicinal product;
- the preventive, curative or symptomatic nature of the medicinal product;
- the public health benefit of the medicinal product.

3.2. Focus on certain determinants of CB

3.2.1. Role in the care pathway

When it assesses a medicinal product, the TC describes the therapeutic strategy for the disease concerned and specifies the place of the medicinal product in this strategy. For example, and depending on the clinical data available, the place of the medicinal product assessed may be ranked or put into perspective with respect to the other therapies available.

This is dependent on the context of the assessment and may therefore evolve. Consequently, it is reconsidered at each new assessment, and particularly during therapeutic class reassessments.

The place in the therapeutic strategy is also a vector for evaluation of a medicinal product, particularly in situations where the quality of the demonstration and the effect size do not enable evaluation of the CAV.

3.2.2. Public health impact

The aim of the PHB is to indicate the benefit provided by the medicinal product to the community in terms of public health, compared to that of the alternatives.

The TC considers that a medicinal product is liable to have a PHB when it provides a service to the community, either because it helps markedly improve the state of health of the (or a) population, or because it addresses a public health need, or because it reduces the consumption of resources (see Table 1).

The various dimensions that can be used to assess the PHB are, in particular:

- the medical need, the seriousness of the disease concerned and the prevalence of the target population;
- the potential impact of the medicinal product on the health of the population considered in terms of morbidity and/or mortality, compared to the therapeutic alternatives;
- the impact on the organisation of care or improvement of the care pathway and/or life course for the patient or his/her family.

3.2.2.1. Partially met medical need

When the need is partially met (existence of clinically relevant comparators(s)), the additional potential impact can be assessed compared to the comparator(s).

In this case, when the indication concerns a **serious disease with a high prevalence**, the situations in favour of recognition of a PHB are, in particular:

- the demonstration of an additional impact on morbidity and mortality and the absence of any deterioration in the care pathway and/or life course;
- a substantial change in the care pathway and/or life course without deterioration in morbidity and mortality.

When the indication concerns a **serious disease with a low prevalence** in the target population, the demonstration of an additional impact on morbidity and mortality combined with a substantial improvement in the care pathway and/or life course are, for example, in favour of recognition of a PHB.

3.2.2.2. Unmet medical need

When the need is not met, the additional potential impact can be assessed relative to the usual care (“best supportive care”) **independently of the prevalence**. For example, when the indication concerns a serious disease, the situations in favour of recognition of a PHB may be:

- the demonstration of an impact on morbidity and mortality and the absence of any deterioration in the care pathway and/or life course;
- a substantial change in the care pathway and/or life course without deterioration in morbidity and mortality.

Table 1. Examples of elements for assessment of the public health benefit depending on the context

PHB criteria	Partially met need (existence of clinically relevant comparator)		Unmet need (absence of clinically relevant comparator)
	High prevalence Prevalence rate > 1 / 2,000 Number of cases > 30,000	Low prevalence Prevalence rate ≤ 1 / 2,000 Number of cases ≤ 30,000	Independently of prevalence
High seriousness	Case 1 – additional impact on morbidity and mortality and absence of deterioration in the care pathway and/or life course Case 2 – substantial improvement in the care pathway and/or life course without deterioration in morbidity and mortality	Additional impact on morbidity and mortality and substantial improvement in the care pathway and/or life course	Case 1 – additional impact on morbidity and mortality and absence of deterioration in the care pathway and/or life course Case 2 – substantial improvement in the care pathway and/or life course without deterioration in morbidity and mortality
Lower seriousness	additional impact on morbidity and mortality and substantial improvement in the care pathway and/or life course		additional impact on morbidity and mortality and substantial improvement in the care pathway and/or life course
Specific cases	<ul style="list-style-type: none"> – vaccines and preventive treatments – concomitant development of two comparable medicinal products – other exceptional situations, on a case-by-case basis, depending on the assessment of the TC 		

Based on the criteria detailed above, the TC assesses whether the medicinal product is liable to have an impact on public health or not, on a case-by-case basis. In certain situations (negative impact on the organisation of care without morbidity and mortality benefit, increased toxicity compared to available treatments), the TC may consider that a negative impact on public health cannot be excluded for the medicinal product.

In general, a medicinal product indicated in a non-serious disease is not eligible for a PHB, irrespective of its target population and efficacy.

3.3. Details concerning CB levels

3.3.1. Insufficient CB

The factors that may result in an insufficient CB are, in particular:

- **a loss of opportunity demonstrated for the patient or that cannot be excluded in view of the clinically relevant comparators, defined by:**
 - an efficacy judged to be too low and/or not clinically relevant and/or inadequately established compared to that of the comparator, even if the disease is serious and the medical need substantial. In particular, this may concern:
 - a non-statistically significant comparative study (“negative study”) and, even more so, several negative studies,
 - a comparative study versus a non-clinically relevant comparator without acceptable justification of this choice,
 - a demonstration less robust than that performed with the clinically relevant comparators, that cannot eliminate the possibility of a loss of opportunity for the patient,
 - a non-comparative study when a comparative study could have been performed,
 - a demonstration of efficacy in a selected specific population for which transposability to the patient population to be treated in France is not guaranteed,
 - a demonstration of efficacy using an outcome measure judged to not be relevant to quantify the efficacy for patients,
 - the accumulation of several methodological biases leading to a high level of uncertainty with respect to the real efficacy of the treatment for patients,
 - an effect size that is not clinically relevant,
 - and/or unacceptable toxicity, particularly if this is greater in terms of severity or frequency to that of the comparators or in view of a modest efficacy;
- **the absence of any place in the therapeutic strategy or a place judged to be “not established” by the TC**, including all situations in which the TC considers that there is a risk of loss of opportunity for patients (see above);
- **a medicinal product aimed at a non-serious symptom of a benign, non-progressive disease, for which the demonstration of efficacy presents a low level of evidence and/or for which the safety is poor.**

Any one of these factors may lead to allocation of an CB insufficient to justify funding by the national health insurance fund.

However, they are assessed in view of the medical need (i.e. the presence or absence of an alternative and their quality). In fact, **the medical need will provide additional information to the efficacy, the**

adverse effects and the place in the therapeutic strategy of the medicinal product assessed. Hence, an effect size will be assessed on the basis of the medical context. For example, a medicinal product having demonstrated weak or uncertain efficacy of moderate quality and/or a low effect size, may have a place in the therapeutic strategy in the absence of any alternative whereas it may not have a place in the presence of recommended and/or better studied alternatives, in order to avoid a potential loss of opportunity for the patient.

An insufficient CB does not mean that no patient may benefit from this medicinal product; however, on a collective level and in view of the alternatives, this medicinal product does not present sufficient medical benefit for the national health insurance fund to contribute financially.

3.3.2. Sufficient CB

The clinical situations not covered by the abovementioned scenarios may lead to allocation of a sufficient CB. In practice, this applies to **any medicinal product having demonstrated clinically relevant efficacy and an acceptable safety profile with a sufficient level of evidence in view of the clinical context** (i.e. based on an appropriate study design in terms of population, comparator, outcome measure and duration, in particular).

The CB level is modulated, in view of the available alternatives and clinical context, by the quality of the demonstration and/or the effect size and adverse effects.

3.4. Assessment of the CB in the event of major uncertainties

The assessment of some medicinal products is based on the analysis of early or still limited data, in a context of major uncertainty with respect to the real effect of the latter. In addition, the safety profile of these medicinal products is generally associated with high levels of uncertainty, particularly in the medium and long term, given the early nature of the data.

In this case, the TC may consider that additional data will be essential to reassess the medicinal product. It may then specify in its opinion the information and additional studies essential for reassessment of the clinical benefit of the medicinal product that must be submitted by the pharmaceutical company, within a period stipulated in the opinion (article R. 163-18 of the French Social Security Code).

Pending new data, an CB may be allocated in situations in which the absence of reimbursement in view of the preliminary data is liable to result in a loss of opportunity for patients:

- **serious disease**, irrespective of its prevalence, and
- **unmet medical need, and**
- **initial data suggestive of a clinical utility** for the patient, and
- **development plan enabling the elimination of uncertainties in the short term** on the basis of:
 - clinical studies: in this case, the development plan must be predefined by the company and known at the time of the initial assessment to enable the TC to assess whether it will be able to eliminate the uncertainties,
 - and/or real-life studies capable of eliminating uncertainties.

The maintenance of a sufficient CB level following reassessment may then be envisaged only if the results eliminate the uncertainties identified in the initial assessment, in accordance with article R. 163-3 of the French Social Security Code.

4. Estimation of target population

One of the TC's missions is to estimate the target population of the medicinal product liable to be treated. It is calculated for the **population corresponding to the sufficient CB**, which may sometimes be smaller than that of the MA indication.

Determination of the target population is based on:

- available epidemiological data concerning the disease and the effects of existing treatments (obtained from observatories, registries, prescription, hospital activity or reimbursement databases, the number of patients with registered chronic conditions, the scientific literature, etc.);
- a rationale leading, in stages, to the population liable to receive the medicinal product proposed for reimbursement.

The choice of the incidence or prevalence for this estimation is made on a case-by-case basis as a function of the actual conditions of use of the medicinal product: the target population of a medicinal product used once over a short period may be based on the incidence whereas in the case of chronic use, the prevalence will be required.

Data concerning the population reached is not generally used, except in certain situations – for example when the therapeutic strategy is well established.

Dynamic modelling of the target population may be conducted in exceptional cases and at the request of the *Comité Economique des Produits de Santé* (CEPS – Healthcare Products Pricing Committee).

5. Real-life studies

Real-life studies correspond to data obtained from observational studies. This data may have different sources (ATU, registries, queries of databases such as the National Health Data System (SNDS), post-registration studies, etc.).

5.1. Requests for post-registration studies by the TC

During the initial assessment of a medicinal product, the available data primarily comes from clinical trials and data obtained in real-life use conditions is rare. The TC may therefore identify uncertainties or questions concerning the clinical benefit of the medicinal product, its place in the therapeutic strategy in view of the alternatives, misuse, as well as the short or long-term consequences of introduction of the medicinal product on public health.

In application of article R. 163-18 of the French Social Security Code, the TC may request that additional data essential for subsequent reassessment of the clinical benefit or clinical added value of the medicinal product be collected. This involves post-registration studies (PRS), which may concern any medicinal product and are generally requested at the time of the initial assessment or an indication extension but may also be requested during a reassessment. The results of PRS must be submitted to the Committee by a date stipulated by the Committee in its opinion.

5.1.1. Objectives

These requests made by the TC usually have the objective of documenting:

- the methods of use of the medicinal product in real-life conditions: patient characteristics, place in the therapeutic strategy, treatment duration, dosage, co-prescription, conditions for stopping or continuing treatment, misuse, etc.;
- the efficacy in real-life conditions (*effectiveness*) in the context of an observational study;
- the safety (although this is never the sole objective of a PRS request insofar as follow-up of the safety of medicinal products falls within the scope of the missions performed by the French National Agency for Medicines and Health Products Safety).

5.1.2. Wording of requests

When it requests a PRS, the TC takes particular care to:

- limit the number of objectives;
- rationalise the number of real-life studies by encouraging the use of any study already under way liable to provide answers to the questions asked (RMP study, secondary analysis of cohort data or academic registries, studies on the basis of the National Health Data System (SNDS), all pre-identified studies);
- specify the time-frame for results, which are usually expected within a maximum period of 5 years.

5.1.3. Study methodology

The methodology of a PRS depends on the TC request. It is usually a descriptive observational study to assess the use and impact of the medicinal product in non-selected populations, over prolonged durations or with different criteria from those in the clinical studies available at the time of the initial

assessment. If it deems it necessary and possible, the TC may request the performance of randomised clinical studies or analytical observational studies.

5.1.4. Assessment of studies

The results of these studies are systematically assessed and contribute to reassessment of medicinal products by the TC.

The TC therefore pays particular attention to this data, which supports the data obtained in investigational conditions and supplements knowledge concerning the actual conditions of use, potential misuse, potentially modified therapeutic strategies, the methods for initiation or discontinuation of treatments, etc. Although it is rarely appropriate in terms of the level of evidence for a claim for a CAV level higher than that initially obtained on the basis of investigational data, **this data can contribute to an increase in or maintenance of the CB or the CAV and generally provides crucial information for the recommendation of good practice conditions for medicinal products.**

5.2. Other real-life data

Independently of requests for a PRS, real-life data – especially ATU data – contributes to assessments (PHB, target population, therapeutic strategy, etc.) and can also be taken into account in the assessment of the CB and the CAV, for example in situations where the TC considers that a comparative clinical study cannot be performed (see “Quality of demonstration” paragraph).

The TC recalls the fact that it is not appropriate to compare randomised clinical trials with observational studies. Randomised clinical trials remain the reference design to demonstrate the efficacy of a medicinal product. This means that observational studies cannot be a substitute for clinical studies in situations in which the latter are expected or provide evidence of efficacy that clinical studies have failed to demonstrate.

Observational studies are always analysed in view of all the efficacy data available concerning the treatment and may be one of the elements leading the TC to increase or maintain a CAV.

6. Focus

6.1. Improvements in care conditions

Potential improvements in care conditions, related, for example, to new administration conditions, dosage forms, follow-up, etc. are taken into account by the TC in its assessments. These may lead to an increase in the CAV when a major modification in care conditions (improvement of care pathway, reduction in hospitalisations, improvement in compliance, etc.) is demonstrated or expected by the TC.

6.2. Fixed combinations

The assessment by the TC of fixed combination of active substances already available separately takes into account the logical nature of the combination, as well as evidence of the pharmacodynamic equivalence of the fixed combination compared to the free combination of the active substances at the same doses (or of their synergy when the doses are lower).

These combinations may be considered to be progress if a significant clinical consequence in terms of efficacy, compliance or safety is demonstrated.

6.3. Medicinal products combined with a medical device or procedure

In some cases, the use of the medicinal product to be assessed may be combined with a medical device or a diagnostic or therapeutic procedure (for example, an insulin to be specifically used with a pump, a radiopharmaceutical used in the context of an imaging exam, a test to be performed to identify the patients to be treated, etc.). In this case, if the medical device or diagnostic or therapeutic procedure is not included in the list of products and services reimbursable by the French National Health Insurance system, it is assessed by the National Committee for the Evaluation of Medical Devices and Health Technologies (CNEDIMTS) and/or the HAS College in parallel with assessment of the medicinal product.

6.4. Targeted therapies

6.4.1. General principles

Targeted therapies can be understood in two ways:

- a medicinal product for which the mechanism of action has a specific target;
- a medicinal product aimed at specific patients, identified by a marker, which is usually biological.

In oncology, targeted therapies designate medicinal products designed to stop the growth and/or spread of tumour cells by specifically attacking some of their abnormalities. Their main mode of action

is heterogeneous and is based on inhibition of the mechanisms of oncogenesis, with a high level of specificity for cancer cells or their microenvironment⁶.

The identification of patients eligible for targeted therapy may be based on an associated diagnostic test (or “companion test”) enabling selection of those patients most likely to benefit from the medicinal product in terms of efficacy or safety. The medicinal product and the test must then be assessed jointly on the basis of the principles outlined in the methodological guidelines produced by the HAS⁷. These guidelines present the ideal method that the development of a companion test should aim to follow. Any differences with respect to this method must be justified.

The TC’s requirements concerning targeted therapies are common to all medicinal products and their assessment is based on the same criteria (see “Clinical added value” and “Clinical benefit” chapters). Hence, as for other medicinal products, the TC considers that a direct comparison with the clinically relevant comparator, conducted within the framework of a double-blind, randomised trial, is expected wherever possible.

The fact that a treatment is a targeted therapy does not automatically mean that it will be granted a favourable recommendation for reimbursement.

6.4.2. Methodological assessment of “basket” trials in oncology

Within the scope of its missions, the Transparency Committee (TC) would like to provide benchmarks and visibility with respect to its assessment methodology for “basket” trials, which are increasingly frequent in the field of oncology.

These benchmarks consequently define what is expected of manufacturers concerning applications for medicinal products with an “agnostic” independent “tissue/organ” indication submitted to the Transparency Committee.

The increasing discovery of molecular or genetic subtypes for common cancers has led to the definition of subgroups, which correspond to orphan or niche indications, even within broad tumour types. These subtypes are considered to be biomarkers potentially predictive of a therapeutic effect in multiple histologies and locations. Hence the basic hypothesis of “precision medicine” is that by using the tumour’s genetic composition, therapies specifically targeting the resulting molecular abnormalities could improve the prognosis of cancer patients.

A “basket” trial involves testing a medicinal product or a combination of medicines in a population of patients who have different types of cancer but that all have the same alteration or molecular profile (irrespective of their histology). Basket trials therefore assess targeted medicines assumed to act selectively on the molecular or genomic profile involved in the carcinogenesis of all these types of cancers. A basket trial assumes that the molecular subtype is more decisive than histology, and therefore that the anti-tumour benefit is exclusively or predominantly related to this molecular mechanism.

Basket trials were initially designed to study the anti-tumour activity of a drug targeting a genetic alteration, assuming a homogeneous effect between tumour types. Basket trials make it possible to test a

⁶ Institut National du Cancer (French National Cancer Institute). Les thérapies ciblées dans le traitement du cancer en 2015. Etat des lieux et enjeux. Available online: <http://www.e-cancer.fr/Expertises-et-publications/Catalogue-des-publications/Les-therapies-ciblees-dans-le-traitement-du-cancer-en-2015-Etat-des-lieux-et-enjeux>

⁷ Haute Autorité de santé. Guide méthodologique. Test compagnon associé à une thérapie ciblée : définitions et méthode d’évaluation. Available online: https://www.has-sante.fr/portail/jcms/c_1735034/fr/test-compagnon-associe-a-une-therapie-ciblee-definitions-et-methode-d-evaluation-guide-methodologique

targeted therapy on molecular profiles for a broad spectrum of cancers and possibly on a limited number of patients in the same “basket”, whereas the performance of specific trials in each could be limited by their rarity depending on the frequency of the alteration.

These trials have been used in the early phases of clinical development, with non-comparative study designs aimed at identifying populations for which the anti-tumour activity appears to be significant compared to a historical value on an intermediate primary endpoint (such as response rate) and generally with a small number of patients (<30) per cohort.

Now, in the context of early and accelerated development programmes, so-called "agnostic" MAs (independent of tumour location and histology) are granted on the basis of overall results for all cohorts combined, from preliminary trials, and without any confirmatory comparative trials for all cohorts or separate cohorts being scheduled.

In this context, the TC wishes to specify methodological benchmarks for the assessment of basket trials provided in support of an application for reimbursement in an agnostic indication.

These methodological benchmarks will be taken into account by the TC to determine the clinical benefit (CB) and the clinical added value (CAV) of the medicinal product assessed from the time of application for inclusion of the medicinal product in the list of reimbursed products.

6.4.2.1. Key messages for assessment of the CB and CAV for inclusion of the medicinal product in the list of reimbursed products

Ensure these trials are part of a genuine comparative strategy

– Confirmatory basket trials

The implementation of a basket trial does not, in itself, justify not following a rigorous methodology based on comparative and preferably randomised trials as described in the TC doctrine and universally accepted. Indeed, the Committee points out that a scientific rationale supporting the value of a treatment - even a strong one - does not justify the absence of comparison - direct or indirect - with the standard of care.

Presenting a pivotal trial based on a poor methodology with preliminary non-comparative data represents a major risk when recommending the reimbursement of a new treatment, whether or not it is a basket methodology, and, in particular, when the prognostic value of the targeted genetic/molecular alteration is not known or when it is variable depending on location and/or histology.

The assessment of the level of evidence resulting from a basket trial provided in support of an agnostic indication will be evaluated based on the same methodological elements as for any other type of trial (in accordance with the TC doctrine).

- **Randomised comparative basket trials or comparative basket trials versus an external control**

The TC highlights the importance of ensuring basket trials - like any other trial - are part of a genuine comparative strategy wherever possible. Basket trials should not be seen as a way of bypassing rigorous clinical trials for accelerated access to a treatment of unproven efficacy.

Randomised controls should therefore be favoured⁸. If it is impossible to make a direct comparison this must be duly documented and supported and data from indirect comparisons must be supplied, e.g. a comparison with an external control scheduled in advance⁹. The implementation of an external comparison should be anticipated as soon as any non-randomised basket clinical trial is launched in order to improve its robustness and ensure it is part of a deductive reasoning approach.

Randomisation or, if this is impossible, a comparison versus an external control must be scheduled in advance.

- **Study populations and their sizes**

The choice of cohorts in the basket trial should be based on preliminary data documenting the relationship between the targeted molecular mechanism and the expected anti-tumour benefit.

In the context of randomised comparative basket trials, in addition to the value of randomisation, which makes it possible to control the heterogeneity factors of the populations included, it seems important to stratify randomisation on the basis of cohorts in order to guarantee a balanced distribution of the different types of tumours, which may have different prognoses.

However, if a direct comparison cannot be scheduled, the inclusion in the basket trial of patients who are as homogeneous as possible - particularly in terms of age, course and stage of the disease - is preferable in order to minimise the risk of potential confounding bias (at the cost, however, of a loss of transposability of the results). The inclusion of patients at the same prognostic stage avoids artificially prolonging survival time by including forms that may have a better prognosis or have been diagnosed at an earlier stage of the disease. Solid data to document the prognostic value of the genetic alteration is expected.

A minimum number of patients included per tumour type is preferable. Calculation of this number should be based on the effect size sought, with a type-1 error risk adapted to any scheduled multiple analyses¹⁰.

- **One or more appropriate comparators**

The comparator must be adapted to each cohort, based on histology or tumour location, cancer stage and treatment line. The use of standard(s) of care should be favoured. In the event of last-line treatment, the comparators should be supportive care.

⁸ Saad E, Paoletti X, Burzykowski T, Buyse M. Precision medicine needs randomized clinical trials. *Nat Rev Clin Oncol* 2017; 14(5): 317-23.

⁹ Cucherat M, et al. Des études mono-bras aux études de comparaison externe. *Considérations méthodologiques et recommandations*. *Therapies* 2020; 75(1): 13-19.

¹⁰ Li W, Chen C, Li X, Beckman RA. Estimation of treatment effect in two-stage confirmatory oncology trials of personalized medicines. *Stat Med* 2017 ;36(12):1843-61.

– Patient-centred endpoints

As with any trials in the field of oncology, the endpoints must be able to demonstrate that the medicinal product assessed is of clinical utility for the patient. Hence the preferential endpoint is overall survival in advanced-stage cancers. Quality of life data with a demonstrative value is also required.

When the primary endpoint is the response rate, the assessment must be standardised and the duration of response analysed. The Committee points out that it expects a demonstration of the impact of the tumour response on overall survival (surrogate endpoint) in order for a substantial therapeutic contribution to be recognised.

– Interpretation of the results obtained

The TC reiterates that a deductive reasoning approach must be adopted and accompanied by an intention-to-treat (ITT) analysis.

Analysis in the global population

In the context of an agnostic indication, the objective is to use the whole population of the main analysis in order to obtain a broad indication in all types of tumours. In this respect, the implementation of a basket trial in support of an agnostic indication leads to a global analysis of the results (all cohorts combined) being scheduled as the primary objective. This analysis is based on the hypothesis of homogeneity of effect between cohorts, which, if not respected, leads to a biased estimation of the overall response rate. Consequently, an assessment of the heterogeneity of results between cohorts is crucial and should therefore be systematically provided (e.g. with presentation of the effects per cohort and the overall effect in graph form, with confidence intervals by forest plot).

Subgroup analyses

A specific “subgroup” analysis of one or more cohorts may be scheduled in the protocol as a secondary objective; it should be associated with an interaction test and take into account the inflation of the alpha risk and thus limit the risk of false positive results related to the multiplicity of analyses¹¹.

Validate the reliability and utility of the companion test

– Diagnostic test reliability

The performance of the test (sensitivity, specificity, predictive values, or probability reports), as well as its accessibility throughout the territory must be documented.

The HAS will be attentive to the method to be used for the detection of the molecular alteration (recent or archived samples, method and reliability of sample preparation for molecular analysis, analysis methods, standardisation, etc.). Hence, the tumour sample that has been used for investigation of the driver genetic modification must be as representative as possible of the disease stage (in practice, justify the choice of a metastatic sample or a sample from the primary tumour, a recent sample, for example less than six months old, or an archived sample). It should be noted that for continuous biomarkers, the choice of the threshold differentiating between positive and negative biomarkers can vary between histological types. The choice of threshold must be justified.

¹¹ Renfro LA, Mandrekar SJ. Definitions and statistical properties of master protocols for personalized medicine in oncology. *J Biopharm Stat* 2018; 28(2): 217-28.

The discriminatory capacity of the diagnostic test is essential, including when the genetic alteration is rare.

– Clinical utility of the companion test

A diagnostic test is considered to be a “companion test” if it permits the selection only of patients in whom the treatment is likely to provide a benefit from among those diagnosed with a given illness, according to their status for a predictive marker identified by this test. Hence the TC stresses that validation of the clinical utility of the treatment is indissociable from validation of the clinical utility of the companion test (joint assessment of the test and the treatment)¹². In this respect, it points out that an application for registration of a medicinal product targeting a molecular alteration - assessed in a basket trial, in particular - must be accompanied by an application for assessment of the companion test ([the standard application annex](#) available on the HAS website must be completed).

6.4.2.2. Conclusion

In the field of oncology, the concept of treatment based on a “driver” molecular anomaly, independently of tumour location and/or histology, represents a fundamental change in the therapeutic approach, usually considered on the basis of the organ and not in a transversal manner based on a molecular abnormality shared by different tumour locations or histologies.

Although this is a change in clinical management strategy, it does not significantly modify the methodological fundamentals, which need to be maintained in order to obtain quality data on the efficacy and safety of medicines assessed with a view to their public funding.

The specificity of basket trials is essentially due to the combination of a relatively innovative concept with uncertainties linked to this novelty (such as the validity of the definition of the target population, defined by one or more biomarkers) and the heterogeneity of the histology or organ cohorts. **However, this specificity does not justify any change in the TC’s methodological requirements.**

Consequently, when a basket trial is submitted in support of a request for reimbursement in the context of an agnostic indication, **the Committee expects this trial to adopt a comparative approach and to provide a sufficient level of evidence for the targeted therapy to be incorporated into the therapeutic strategy.**

In accordance with the Committee’s assessment principles, recognition of therapeutic progress will be assessed on the basis of the quality of the demonstration and the extent of the results of the basket trial.

6.4.2.3. References

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¹² https://www.has-sante.fr/jcms/c_1735034/fr/test-compagnon-associe-a-une-therapie-ciblee-definitions-et-methode-d-evaluation-guide-methodologique

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Abbreviations and acronyms

ANSM	<i>Agence Nationale de Sécurité des Médicaments et des produits de santé</i> (French National Agency for Medicines and Health Products Safety)
ATU	Autorisation temporaire d'utilisation (Temporary authorisation for use, a French early access programme)
CAV	Clinical added value
CB	Clinical Benefit
CNEDiMTS	= Medical Device and Health Technology Evaluation Committee
HAS	Haute Autorité de santé (French National Authority for Health)
MA	Marketing Authorisation
PHB	Public health benefit
PRS	Post-registration study
TC	Transparency Committee

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