Rapid access to innovative medicinal products while ensuring relevant health technology assessment. Position of the French National Authority for Health


➢ To cite this version:

Antoine Vanier, Judith Fernandez, Sophie Kelley, Lise Alter, Patrick Semenzato, et al.. Rapid access to innovative medicinal products while ensuring relevant health technology assessment. Position of the French National Authority for Health. BMJ Evidence-Based Medicine, 2024, 29 (1), pp.1-5. 10.1136/bmjebm-2022-112091 . hal-04056273

HAL Id: hal-04056273
https://univ-rennes.hal.science/hal-04056273
Submitted on 30 May 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License
Rapid access to innovative medicinal products while ensuring relevant health technology assessment. Position of the French National Authority for Health

Antoine Vanier,¹,² Judith Fernandez,³ Sophie Kelley,³ Lise Alter,¹ Patrick Semenzato,¹ Corinne Alberti,³,⁴ Sylvie Chevet,⁵ Dominique Costagliola,⁶ Michel Cucherat,⁷ Bruno Falissard,⁸ François Gueyffier,⁹ Jéréôme Lambert,⁵ Etienne Lengliné,¹⁰ Clara Locher,³,¹¹ Florian Naudet,³,¹²,¹³ Raphael Porcher,¹⁴ Rodolphe Thiébaut,¹⁵ Muriel Vray,¹⁶ Sarah Zohar,¹⁷,¹⁸ Pierre Cochat,¹⁹ Dominique Le Guludec¹⁹

The challenge of accelerated clinical developments

In France, decisions for reimbursement taken by the Ministry of Health are based on appraisal by an independent Health Technology Assessment body (HTAb): the ‘Haute Autorité de santé’ (HAS). HAS grades the clinical added value of any medicinal product for which a manufacturer seeks reimbursement. This appraisal considers different types of clinical and patient-centred outcomes, including patient-reported ones. Under certain conditions, a concomitant economic assessment which accounts for patients’ preferences in the form of utility values is also performed.

As providing fast access to breakthrough therapies is a critical expectation from patients, clinicians and health policy makers, the European Medicines Agency and the Food and Drug Administration have established various accelerated approval pathways. These procedures lead to conditional approvals frequently based on uncontrolled (ie, single arm) pivotal trials.¹–⁴ Approvals based on uncontrolled trials are also motivated by randomisation sometimes being considered unfeasible or unethical, or because the pathophysiological rationale is assumed to be important when proving effectiveness (eg, a treatment with molecular target in oncology).⁵ ⁶

However, expected benefits based on uncontrolled trials as evidence are frequently not confirmed. The results of meta-epidemiological studies illustrate that appraisals based on such evidence entail a high level of uncertainty leading to ethical concerns.⁷ ⁸ For patients, this may have deleterious consequences such as the use of products for which the benefits remain unknown,⁹ ¹⁰ the overestimation of benefits with no further confirmation¹¹ ¹² or the increased risks of adverse events.¹² ¹³ This high level of uncertainty may also impact health system sustainability.

While ensuring rapid access to valuable treatments is of utmost importance to patients, maintaining an adequate balance with the performance of relevant HTA in this context is highly challenging. Thus, the French Minister of Health requested HAS to provide recommendations. A consultation of patient associations, academics, manufacturers and various institutions was conducted from October 2021 to January 2022. With the support of an expert committee, a qualitative summary of the consultation has led to the prioritisation of recommendations, which are developed below (details on the consultation process are available in an online supplemental appendix 1).

Need for evidence from comparative designs allowing causal interpretation of treatment effect estimation

Performing relevant HTA requires that an unbiased estimate of the treatment effect is available. Thus, the additional effect must be disentangled beyond effects due to the natural course of the medical condition, the placebo effect, various sources of bias and the effect of alternative(s). To produce such an estimate, the simplest and most consensus methodological choice is a comparison of the treatment of interest to a control by conducting a randomised controlled trial (RCT). Randomising treatment allocation balances both known and unknown confounders between groups, which enables the causal attribution of an observed effect to the investigated treatment. Other characteristics such as blinding and intention to treat analysis principles reduce the risk of bias and thereby lead to an estimation of treatment effect with the highest certainty of results.

Therefore, RCTs should still be systematically considered by manufacturers during clinical development.

Accelerating rapid access to innovative treatments by adapting the traditional RCT design

While RCTs are the gold standard for producing clinical evidence, HAS acknowledges that the strict
adherence to the traditional fixed-sample RCT design can lead to
long delays before patients access treatments. Several alternatives
to the traditional design, such as adaptive designs, platform
trials, seamless trials, pragmatic trials or cross-over designs, can
be better suited choices for accelerating clinical developments. An
overview of main strengths and methodological points of atten-
tion is described in table 1. All these adaptations are considered
compatible with the principles of RCT design and can produce
evidence with high certainty of results.

They should, therefore, be encouraged first when considering
the issue of balancing rapid access to beneficial medicinal prod-
ucts to patients while performing relevant HTA.

Increasing the certainty of results when uncontrolled
trials are pivotal studies
Apart from the exceptional condition where an unequivocal
response on a patient-centred outcome for almost all patients
compared with an otherwise certain pejorative evolution is
observed, the value of uncontrolled trials alone is strongly limited
when estimating the effect of a treatment. Nonetheless, market
approval relying on uncontrolled trials is prevalent, as is the
number of dossiers submitted for HTA based on these trials.
Thus, HAS proposes points of attention that should be consid-
ered providing a manufacturer wants to submit a dossier based
on uncontrolled trial(s) only. They are summarised below and are
detailed in box 1. Any deviation from these points of attention
will further impair the certainty of results.

Justifying the suitability of the data generation programme
Lack of randomisation is a major deviation from evidence-based
medicine principles and should remain an exceptional option.
Therefore, a rationale for the lack of randomisation must be

Table 1  Adaptation of randomised controlled designs leading to good enough certainty of results that can accelerate treatment access to patients

<table>
<thead>
<tr>
<th>Type of design</th>
<th>Brief description and usage</th>
<th>Some methodological points of attention for HAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adaptive designs in clinical trials</td>
<td>Their design can be modified in several aspects prospectively (eg, sample size, stopping rules due to effectiveness, futility or safety, enrichment of subgroups that are the most susceptible to exhibit effectiveness), which can decrease the number of patients to be included compared with what was initially expected.</td>
<td>They require the frequent review of accrued data at multiple time points to decide or not for modifications, which may reveal information about effectiveness to stakeholders. Defining adequately the role, process and interactions of the unblind independent data monitoring committee and blind trial steering committee is therefore crucial.</td>
</tr>
<tr>
<td>Platform trials</td>
<td>A subset of adaptive designs allowing the comparison either simultaneously and/or sequentially of multiple interventions to a common or multiple control groups, with possible addition and dropping of interventions, and adaptation of the control to new standard of care.</td>
<td>The design of the trial must ensure the control group is contemporaneous of the intervention(s) of interest(s). Blinding of patients and investigators can be difficult to achieve as it can require the use of multiple dummies.</td>
</tr>
<tr>
<td>Seamless trials</td>
<td>A subset of adaptive designs where there is no interruption between the conduct of different phases such as between phase 2 and phase 3, allowing reuse of data from patients from phase 2 for which the investigated treatment appeared to be beneficial.</td>
<td>It could be argued a seamless phase 2/3 trial does not allow the phase 3 to be an independent confirmation of the results of suggested effectiveness of the phase 2.</td>
</tr>
<tr>
<td>Pragmatic trials</td>
<td>An umbrella term that can define trials which try to enhance enrolment and applicability by defining less stringent eligibility criteria that ‘traditional’ randomised controlled trials, or the partial or complete use of real-world data allowing the conduct of ‘trials within a cohort’, ‘registry-based randomised controlled trials’, ‘contactless trial’ or ‘direct-to-patient trial’ (when all data are collected using real-world data and data coming from fully remote pathways).</td>
<td>Relying partially or completely on sources of data that were not primarily designed for research purposes can lead to issues regarding data validity, integrity, and monitoring. The follow-up of patients may not be as standardised as de novo clinical studies. Assessment of endpoints is at risk to be unblinded and/or adjudicated in a decentralised manner. Collection of safety data can be problematic.</td>
</tr>
<tr>
<td>Cross-over designs</td>
<td>Trials where the sequence of interventions is randomised and therefore each patient receives all interventions and is its own control, leading to the enrolment of fewer patients to conclude than the parallel-group design for a given effect of interest.</td>
<td>They assume an identical baseline state at the start of each treatment exposure, no effect of the first treatment to which a patient is exposed during the period of exposition to the second treatment, and no interaction between treatments and periods of exposure.</td>
</tr>
</tbody>
</table>

HAS, Haute Autorité de santé.

Gathering source(s) of data for external comparison
Performing an adequate comparison vs an external control, using
for example data from cohorts or other clinical trials, can be an
option for mitigating uncertainties in the absence of RCTs. Avail-
ability of external controls may be scarce (eg, in case of targeted
therapies for very rare mutation(s) in oncology). Real-world data
generation should therefore be anticipated by the manufacturer
during the early stages of the clinical development if no pre-
existing data set has been identified for the comparison.

Performing transparent and appropriate analyses
To follow an hypothetico-deductive approach, external compar-
ison must be planned as early as possible during clinical develop-
ment. The framework of the emulation of a target trial can help
to define the appropriate estimand, eligibility criteria as well as
exposition and outcome(s) of the targeted (ie, ideal) RCT that the
external comparison tries to emulate. It also helps to avoid the
occurrence of immortal-time bias that results from a failure to
align start of follow-up.

To avoid a post hoc selection, the choice of an external control
must be done prior to conducting the trial, after a well-performed
systematic search. It must fit the standard of care. The retained
external source of data must be chosen because it fits best the
research question and not because it would arbitrarily favour the
treatment of interest.

When performing an external comparison, the attribution of the observed effect to the treatment (causal statement) supposes the
absence of any confounders. It requires a well performed
1. Justification of the lack of randomisation
   - A rationale appraised as acceptable by Haute Autorité de santé is provided.

2. Study design
   - Early planning during clinical development and before the conduct of the uncontrolled trial of the treatment of interest.
   - A priori definition of the clinical question, study population, intervention, comparator and outcomes in a protocol and statistical analysis plan.
   - An emulatation of a target trial can enhance eliciting the appropriate clinical question (estimand) and designing the external comparison.

3. Search and selection of relevant sources of data
   - Well-performed systematic review identifying relevant prognostic variables, confounders and effect modifiers.
   - Well-performed systematic review (with eligibility criteria defined a priori) identifying relevant sources for external control.

4. Choice of the external control
   - The comparator and external source(s) of data has been chosen independently of the results of the uncontrolled trial, fit best the clinical question (does not arbitrarily favour the treatment of interest) and correspond to standard of care.

5. Analysis of the results
   - The study protocol, statistical analysis plan and report allow a transparent and appropriate assessment of the study.
   - A model for causal inference controlling an appropriate set of confounders and targeting the predefined estimand has been properly specified and estimated.
   - The model is preferably based on a method using individual patient data only such as propensity scores, g-computation or doubly robust estimation.
   - Underlying assumptions have been explored and seems to be met (such as positivity, sufficient overlap and sufficient balance for propensity scores).
   - If ‘trimming’ (ie, excluding patients in areas of the propensity score without overlap) have been performed, the resulting target population for which results can apply is described.

6. Grading the clinical added value
   - The clinical added value of the treatment of interest is appraised considering the certainty of results, the relevance and magnitude of treatment effect and safety.

Additional points:
- Study characteristics of the uncontrolled trial and external control are sufficiently similar for excluding other sources of bias such as selection bias, attrition bias, measurement bias.
- Safety can be properly documented for both groups.

Continued

causal inference analysis, suing appropriate methods. Approaches based on the use of individual patient data only are preferred (eg, propensity scores analysis, g-computation, doubly robust estimation). Indeed, population-based adjusted methods using individual patient data from an uncontrolled trial and aggregate statistics from external data are sometimes considered. However, they rely on the assumption of the conditional constancy of absolute effects (ie, the absolute treatment effects are assumed constant at any given level of the effect modifiers and prognostic variables), which is unlikely to be met. To select the appropriate set of covariables to use for conditioning the statistical analyses, a well-performed systematic search of prognosis variables, confounders and effect modifiers must be conducted.

The possibility of residual confounding must be discussed. All methods assume exhaustivity of the confounders considered, a property that will ultimately remain unverifiable. This discussion should not be based on expert opinion only and should be documented, for example, using either negative or positive controls, or a quantitative bias analysis. Sources of bias (eg, selection bias, measurement bias) due to the characteristics of the trial and external control(s) must be discussed.

Safety must be properly documented, including for the external control.

Discussion of cross-cutting implications

This paper delineates proposals for an adequate balance between fast access to valuable medicinal products and performing relevant HTA. RCT, as the simplest and most consensual design for allowing causal reasoning, must be systematically considered for clinical development. However, various adaptations of its design, as proposed in table 1, may accelerate clinical development and are encouraged whenever appropriate.

Conducting uncontrolled trials is regularly justified by arguing that randomisation is deemed unfeasible, or that there is a conflict between individual and collective ethics because there is no other alternative than best supportive care. However, results from meta-epidemiological studies showed that RCTs are regularly conducted when investigating rare diseases, even vs placebo, providing clinical equipoise (ie, the genuine uncertainty regarding the benefit of a new treatment) is appropriately explained to patients. Urgent response to an emergent disease, or a strong pathophysiological rationale, are also frequently argued to justify the absence of RCTs. But, randomising the first patients when an emergent disease occurs has been considered ethically appropriate for decades, as it leads to the quickest generation of evidence with the highest certainty of results. A strong pathophysiological rationale does not necessarily translate into clinical
value and what is considered an ‘innovative’ treatment should be based on clinical evidence. Therefore, HAS cannot propose a definitive list of conditions where absence of randomisation would be de facto acceptable.

To some extent, HAS acknowledges that exceptional conditions may exist that make it unreasonable to conduct an RCT. From the HAS perspective, evidence must, however, still comply to a hypothetico-deductive approach allowing causal reasoning. Should an uncontrolled trial with a comparison vs an external control be provided, the methodological points of attention HAS should consider are described in box 1 to reduce uncertainty. Most of these points of attention (sections 2–5 of box 1) allow assessing factual elements according to good clinical and statistical principles. As such, they could be proposed as consistent points of attention applicable by different HTAs when assessing external comparisons. However, the acceptance of the rationale justifying the lack of randomisation, as well as some elements leading to the appraisal of clinical added value (eg, relevance and magnitude of treatment effect, impact on public health), are relative to the organisation of health systems and must be assessed considering the national context.

A consequence of relying increasingly on uncontrolled trials as pivotal evidence would be a shift in demonstrating the effectiveness of medicinal products during clinical development towards post-approval. In this context, the use of real-world data, as primary or complementary source of data, is a possible way to address remaining uncertainties. Regardless of the source of data, quality of study design is a cornerstone for certainty of results. To close evidence gap quickly, appropriate studies must thus be anticipated and not limited to uncontrolled designs. Usage of real-world data and compliance to RCT design should not be seen as antinomic. When appropriate, the conduct of RCTs can be facilitated by collecting some of the necessary data from pre-existing databases (see table 1). In addition, HAS calls for greater transparency in the whole process of generating evidence through initiatives such as registered report publications, data and clinical study reports sharing.

Finally, HAS will remain attentive to emerging methods to reduce evidence gaps and accelerate clinical developments. In particular, the increasing use of artificial intelligence, in silico trials and disease modelling, might become a complementary path to optimising clinical development, as illustrated by CRESIM in helping to choose the best design in rare diseases.

Conclusion

Decisions for reimbursement in France are based on an assessment and appraisal process performed by an independent HAS committee which includes healthcare providers, methodologists and patients’ representatives. Members of HAS and especially this committee are eager to secure rapid patient access to valuable medicinal products and that must be weighed against the duty to propose treatment with a clear demonstration of their clinical added value. As evidence-based medicine is an impartial decision model for coverage authorisations and as causal reasoning is essential for continuous improvement of care, HAS reaffirms the importance of RCTs to establish the value of new treatments. However, to balance rapid access for patients with evidential uncertainties, the traditional fixed-sample RCT design can be adapted. Moreover, properly conducted external comparisons as detailed in this paper may represent reasonable alternatives under exceptional conditions.

Author affiliations
1Health Technology Assessment Department, Haute Autorité de Santé, La Plaine Saint-Denis, France
2UMR U1246 Sphere, Inserm - Nantes Université - Université de Tours, Nantes, France
3ECF, Inserm - Université Paris Cité, Paris, France
4CIC 1426, UEC, Inserm - AP-HP Robert-Debré Mother-Child University Hospital, Paris, France
5UMR U1153 - ECSTRA Team, Inserm - Université Paris Cité, Paris, France
6Hematology Department, AP-HP Hospital Saint-Louis, Paris, France
7Pharmacology Department, Université Claude Bernard Lyon 1, Villeurbanne, France
8UMR U1018 CESP, Inserm - UVSQ - AP-HP - Université Paris-Saclay, Paris, France
9Pôle de Santé Publique - Unités des Bases de Données Cliniques et Épidémiologiques, Hospices Civils de Lyon, Lyon, France
10Hematology Department, AP-HP Hospital Saint-Louis, Paris, France
11CIC 1414 - Service de Pharmacologie Clinique - Iriset UMR S1085, Inserm - CHU de Rennes - EHESS - Rennes 1 University, Rennes, France
12CIC 1414 - Iriset UMR S1085, Inserm - CHU de Rennes - EHESS - Rennes 1 University, Rennes, France
13Institut Universitaire de France, Paris, France
14Centre de Recherche Épidémiologie et Statistiques (CRESS-UMR1153), Inserm - Université Paris Cité, Paris, France
15Bordeaux Population Health - SISTM - Service d’Information Méridionale, Inserm - Inria - Bordeaux 1 University - CHU de Bordeaux, Bordeaux, France
16Unité d’Épidémiologie des Maladies Emergentes, Institut Pasteur - Inserm, Paris, France
17Centre de Recherche des Cordeliers, Inserm - Université Paris-Cité - Sorbonne Université, Paris, France
18HeKa, Inria, Paris, France
19Scientific Board, Haute Autorité de Santé, La Plaine Saint-Denis, France

Twitter Judith Fernandez @JudithFerBen and Florian Naudet @NaudetFlorian

Contributors AV, JF, SK and LA were responsible for the organisation and synthesis of the consultation of stakeholders as detailed in the online supplemental appendix. Preliminary scientific work on the issue of the methodological qualities of external comparisons was performed for HAS by PS and MC. All authors have participated in producing the recommendations proposed in the paper. AV, JF, SK and LA wrote the initial draft and oversaw subsequent steps of the writing process. All authors contributed to the conceptualisation and revisions of this analysis and approved the final version.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests DC reports an HIV grant from Janssen (2019–2020), personal fees from Gilead (2020) and Pfizer (2022) for lectures outside the submitted work. RT has been the coordinator of the IMI2 EBOVAC2 project in collaboration with Janssen (2014–2021). Other authors have no competing interests to disclose.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of
the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Judith Fernandez http://orcid.org/0000-0003-3760-3801
Clara Locher http://orcid.org/0000-0002-8212-4351
Florian Naudet http://orcid.org/0000-0003-3760-3801

References