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Methodology note

Guideline for the economic evaluation of medicines: a proposal by the Spanish National Health System's Advisory Committee for Pharmaceutical Financing

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ABSTRACT

In 2023, the General Directorate of Pharmacy of the Ministry of Health commissioned the Advisory Committee on the Financing of Pharmaceuticals for the National Health System (CAPF, *Comité Asesor para la Financiación de la Prestación Farmacéutica del Sistema Nacional de Salud*) to produce a guideline for the evaluation of the efficiency of medicines. The aim of this methodological note is to present their main points. The guideline includes 17 dimensions that an economic evaluation of medicines must encompass, the design of a reference case, and a checklist for evaluating the methodological quality and reporting. This guideline should serve as a foundational document for reforming the health technologies evaluation processes of the Ministry of Health. The guideline can also assist researchers, public health professionals, health technology companies and decision makers in assessing the validity of findings and conclusions from health economic evaluations.

Guía para la evaluación económica de medicamentos: propuesta del Comité Asesor para la Financiación de la Prestación Farmacéutica del Sistema Nacional de Salud español

Palabras clave:
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Precio y financiación
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RESUMEN

En el año 2023, la Dirección General de Farmacia del Ministerio de Sanidad encargó al Comité Asesor para la Financiación de la Prestación Farmacéutica del Sistema Nacional de Salud (CAPF) la realización de una guía para facilitar la evaluación de la eficiencia de los medicamentos. El objetivo de esta nota metodológica es presentar los principales puntos que desarrolla. La guía incluye 17 dimensiones que debe incluir una evaluación económica de medicamentos, diseñando un caso de referencia y definiendo una lista de comprobación para evaluar la calidad metodológica y su presentación. Esta guía debe servir como documento básico para el Ministerio de Sanidad en la reforma de los procesos de evaluación de tecnologías sanitarias. La guía también puede ayudar a investigadores, profesionales de la salud pública, empresas de tecnología sanitaria y personas encargadas de tomar decisiones, a evaluar la validez de los hallazgos y de las conclusiones de las evaluaciones económicas en salud.

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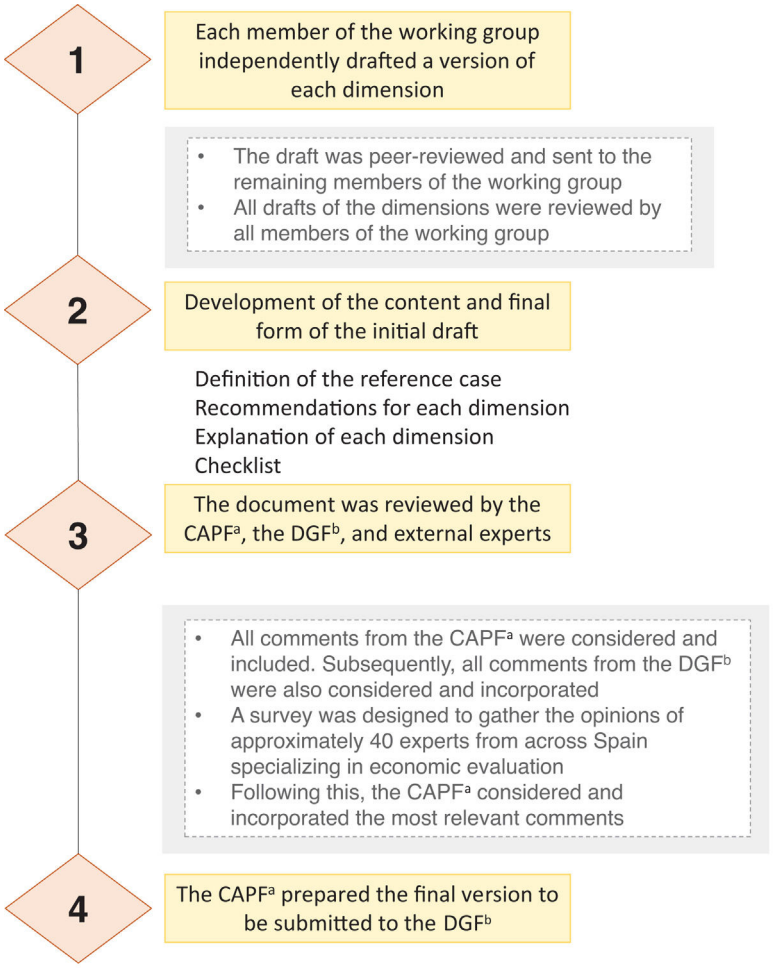
Introduction

In March 2024, the Spanish Ministry of Health published the guideline for the health economic evaluation of medicines proposed by the Advisory Committee on the Financing of Pharmaceuticals for the National Health System (CAPF, *Comité Asesor para la Financiación de la Prestación Farmacéutica del Sistema Nacional de Salud*).[1] This guideline was developed in response to a 2023 request from the General Directorate of Pharmacy (DGF, *Dirección General de Farmacia*) of the Ministry of Health, aiming to provide and formalize a methodological framework for conducting and critically appraise health economic evaluations informing the introduction of innovative medicines in Spain. These evaluations can be crucial for decision-making regarding the positioning, public reimbursement, pricing, and subsequent reassessments of medicines. Furthermore, the development of this guideline was also previously recommended by CAPF.[2,3] The health technology assessment (HTA) mechanisms in Spain can be contextualized and further explored in previously published documents.[2,4,5] Additionally, the HTA mechanisms are currently under review by the Ministry of Health, with the publication of two related Royal Decrees, regulating HTA and price and the selective financing process, expected by the end of 2024 or the beginning of 2025.

Previous health economic evaluation guidelines have been developed in Spain,[6–8] but to our knowledge, this is the first one commissioned by the Ministry of Health's Pharmacy Directorate to serve as a foundational document for the Ministry's own guideline, as part of its strategy in modifying and reforming the health technologies evaluation process.

With the aim of improving the transparency and quality of future economic evaluations of medicines, and to enhance the international dissemination of the guidelines, this article presents the official English translation of the economic evaluation guideline published on the Ministry of Health's website, to enhance access by the international community.[1] In particular, the content of the guideline includes identifying and defining the sections or dimensions that a health economic evaluation must encompass, the design of a reference case, and a checklist for evaluating the methodological quality of health economic evaluations, by researchers, public health professionals, and potential decision makers. Further details on the in-depth discussions surrounding each dimension of the guidelines can be found in the original document published by CAPF in Spanish (https://www.sanidad.gob.es/areas/farmacia/comitesAdscritos/prestacionFarmaceutica/docs/20240227_CAPF_Guia_EE_definitiva.pdf).



[a]CAPF: Advisory Committee on the Financing of Pharmaceuticals for the National Health System (CAPF)
[b]DGF: General Directorate of Pharmacy

Figure 1. Stages in the development of the proposed health economic evaluation guideline.

Table 1
Sections or dimensions and reference case for a health economic evaluation.

Section or dimension	Reference case
1. Objective and scope	The objective and the question to be answered by the health economic evaluation will be clearly defined. It will be specified whether this is an initial evaluation or a re-evaluation of the medication for an indication.
2. Perspective	The main perspective will be that of the healthcare payer perspective (National Health System).
3. Study population and subgroups	The study population will encompass individuals eligible to receive the medication for the evaluated authorized indication, ensuring clarity in patient identification. In the presence of relevant heterogeneity among different subpopulations potentially influencing economic evaluation outcomes, these differences will be explored. Subgroup analysis will be justified accordingly. The consideration of such heterogeneity will be based on a rigorous assessment, leveraging available reports from regulatory bodies (e.g., European Public Assessment Report [EPAR]), joint clinical assessments, and other quality evaluations. In instances of uncertainty, the population and subpopulations to be analysed will be agreed with the health authority before starting the evaluation.
4. Comparators	The evaluated intervention will be compared with standard practice. If different alternatives are used for subpopulations of the indication, these will be considered. Concurrently, the most efficacious/effective alternative, the most cost-effective, and the lowest-priced alternative will be analyzed as comparators. The inclusion/exclusion of alternatives will be extensively justified. For comparator selection, multidisciplinary evaluation results and consensus will be considered.
5. Type of economic evaluation	The specific type of complete health economic evaluation chosen will be clearly identified and justified. Cost-utility analysis (CUA) will be prioritized. In cases where this is not feasible, justifications must be provided, and a cost-effectiveness analysis (CEA) will be conducted. Cost minimization analysis (CMA) will be limited to situations lacking evidence of acceptable quality of clinically significant additional benefits of the medication compared to the appropriate comparator from a clinical and patient perspective. This will be conducted following applicable sections of this guideline.
6. Evidence of efficacy/effectiveness and safety	The evaluation of comparative clinical benefit will be based on randomized clinical trials and systematic reviews with meta-analysis of randomized clinical trials of adequate quality. In the absence of suitable randomized clinical trials for the necessary comparisons, adjusted indirect comparisons may be employed, albeit with increased uncertainty. If direct or indirectly adjusted comparison-enabling clinical trials are unavailable, cohort studies of adequate quality from routine practice may be utilized. If only descriptive studies are available matched adjusted indirect comparison can be conducted. In all cases, study selection will be thoroughly justified, potential biases assessed, their impact on results evaluated, and associated uncertainty addressed. When a model is utilized to extrapolate results to the time horizon analysis, it must be clinically justified, and its uncertainty considered.
7. Measurement and assessment of health outcomes	Quality adjusted life years will serve as the measure of health outcomes in CUA. EQ-5D and SF-6D are the recommended instruments for measuring and assessing preferences. Clinically relevant outcome measures, preferably overall survival or years of life gained, and safety measures will be used in CEA.
8. Identification, measurement and assessment of the use of resources and costs contemplated/consumed	All relevant resources for the analysis will be identified, measured, and valued consistently with the perspective(s) and time horizon(s) considered. Detailed information on resources used, measured (in physical units), and valued (with prices or unit costs) must be transparently presented. Each cost type will be separately presented based on the perspective(s) employed.
9. Time horizon	The time horizon should be long enough to capture all differences in health outcomes and resource utilization between the intervention and its comparators.
10. Discount	Costs and health effects beyond the first year will be discounted to the base year at an annual rate of 3%.
11. Methods of analysis	It is recommended to use modelling techniques to model the treatment effect after the trial period, which must be presented in a clear and transparent manner. Modelling and extrapolations should not overestimate or underestimate the expected clinical effect of the intervention or its comparators in the long term. A quantitative synthesis of the best available evidence should be included. Good practice guidelines for selecting the best model must be applied.
12. Validation of decision models	Validation of the conceptual model, data used and their appropriateness to the Spanish context, as well as correct model implementation and verification should be included. External model validation is recommended.
13. Management of uncertainty	Primary sources of uncertainty will be explicitly identified in the evaluation. Univariate and multivariate deterministic sensitivity analysis of model parameters and structure will be conducted, along with probabilistic sensitivity analysis.
14. Presentation of results	The primary outcome of the economic evaluation will be presented as the incremental cost-utility or cost-effectiveness ratio. In the case of a cost-minimization analysis, cost differences will be presented. Incremental costs, incremental health outcomes, and their confidence levels (dispersion/uncertainty measures) will be separately presented. The results and justifications of conducted sensitivity analyses will be clearly and comprehensively presented.
15. Summary of the main results, their interpretation, limitations, transferability, discussion and other relevant considerations	Main analysis results and areas of uncertainty will be summarized and interpreted within the context for which they were conducted. Limitations of the economic evaluation will be critically enumerated. The applicability to the Spanish context and intracountry transferability of results will be assessed, particularly if nonlocal data are employed. Ethical and equity considerations relevant to the analysis will be clearly articulated.
16. Source of financing and conflicts of interest	A dedicated section will disclose study funding sources and conflict of interest declarations for all economic evaluation participants (authors, consulted experts, reviewers).
17. Re-evaluation	For the first evaluation of a medicine in an indication, areas of uncertainty will be explicitly reported to identify the need for additional evidence beyond what is currently available. In the case of re-evaluation, justifications for changes compared to the previous evaluation will be provided, alongside all relevant elements potentially affecting results and uncertainty. Re-evaluations must include a comparison of their results with those of the previous evaluation.

Method

For its development, CAPF formed an initial working group comprised of five experts (MTB, JO, FCL, LGP and LS), coordinated by one of the CAPF members (MTB). The selection criteria were based on the scientific and technical competence, the multidisciplinary composition of the group, and their expertise in health economic evaluation for informing health decision-making. The development process involved a review of previous Spanish guidelines on the subject,[6–8] as well as selected international guidelines primarily from Australia, Canada, the United States, England and Wales, France, and Portugal, with a focus on the latter two.[9,10] Additionally, the CHEERS 2022 statement[11] and the EUnetHTA Guideline[12] were considered. The first draft was reviewed by CAPF members (EA, AC, FL, AO and JPJ) and subsequently shared with a larger group of thirty-one experts, selected for their expertise and significant contributions to the field (their names are listed in the acknowledgments). We received written feedback from all these experts. Although the initial contact list of national experts was longer, no response was received from some of them. CAPF members carefully reviewed all contributions and finalized the document accordingly.

The content of the guideline was developed in several stages, as shown in Figure 1. Initially, each section or dimension was drafted by at least two members of the working group individually, followed by a peer-review of the working group members. Subsequently, the content and final form of the initial draft were determined by the working group. It was agreed to organize the content by clearly separating the definition of the reference case, the recommendations aimed at the authors conducting health economic evaluations and their reviewers, the explanation of each section, and the checklist. Following this, the document underwent a review by the CAPF, the DGF, and external experts. Finally, the CAPF completed the final version to be submitted to the DGF.

The reference case delineates the methods and criteria selected for conducting health economic evaluations of medicines to support decision-making for their public funding or pricing. Table 1 reports a literal English translation of the main technical concepts of the core components of the reference case, aligning conceptual terms with those most commonly used in other international guidelines.

This reference case is accompanied by a checklist that should be utilized to evaluate the methodological quality of a health economic evaluation of medicines in Spain. This checklist can be employed during both the development and review stages of an economic evaluation analysis (see Table A.1 in online Appendix for details).

Practical application and usefulness

This guideline is part of a reform process of the medication evaluation procedure in Spain, proposed by the CAPF.[1] It is specifically designed for the evaluation of medicines, and it comes at a time of transformation in the decision-making system for medicines in the country. Its publication, at the request of the General Directorate of Pharmacy of the Ministry of Health, may be used as a first step for the implementation of explicit methodology for decision-making regarding the funding of medicines.

At a methodological level, this guideline incorporates two elements that have been infrequently included in this type of document. The first is the importance of validating decision models, both internally and externally, and the other is the need to establish a distinct dimension for the re-evaluation of decisions made from this medication evaluation process. Although authors considered that the societal perspective would be appropriate for the analysis, data requirements to use a societal perspective can be challenging, and incorporating the healthcare payer perspective, which includes all healthcare costs associated with the intervention and not just the price of medicines, would constitute a significant achievement. Additionally, the proposed guideline for medicines can be easily adapted to other health products and technologies.

It is important to note that, while the guideline on health economic evaluation represents a first step and provides an initial methodological foundation, it should be complemented by additional guidelines that delves into specific methodological aspects related to economic evaluation. In particular, guidelines on relevant added clinical benefit, efficiency thresholds, clinical and economic uncertainty analysis, and budget impact analysis are required.[1]

In any case, the guidelines, by itself, are merely small pieces in a complex organisational and cultural change in the field of medicine evaluation that has yet to be realised. Analyzing the efficiency of medicines requires commitment, involvement and adequate resourcing from the Ministry of Health.[5] Consequently, a prioritization system should be implemented to ensure the economic evaluation is primarily used for evaluating those medicines that offer a significant additional clinical benefit. In cases where there is no clinical benefit relative to alternatives, or where the additional clinical benefit over comparators is not relevant, a cost-minimization analysis should be conducted.

A health economic evaluation guideline in the context of the incorporation of medicines and health technologies into the service portfolio of the National Health System can have multiple uses and benefits. Its primary purpose is to establish a methodological framework to systematically, transparently, and objectively evaluate the value that these medicines and technologies bring to the health system and patients. It ensures that the limited resources of the health system are used efficiently, provides a clear and consistent framework for evaluating new technologies, promotes efficient innovation, justifies and accounts for health spending to society, and provides a solid basis for negotiating prices and reimbursements with suppliers of medicines and technologies, based on evidence of their economic and clinical value.

In summary, the proposed guideline for economic evaluation of medicines represents an essential tool for health services seeking to optimize the allocation of resources, promoting interventions with the best cost-effectiveness ratio, improving the quality of care, and ensuring the long-term sustainability of the system.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.gaceta.2025.102448.

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Transparency declaration

The corresponding author, on behalf of the other authors guarantee the accuracy, transparency and honesty of the data and information contained in the study, that no relevant information has been omitted and that all discrepancies between authors have been adequately resolved and described.

Authorship contributions

Contributions to this research article were shared among all participating authors. The conceptualization and design of this article were carried out by all authors. The first draft of the paper was written by M. Trapero-Bertrán with help of J. Oliva, but all

authors contributed substantially equally to the final version of the manuscript.

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Conflicts of interest

None.

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