The value and measurement of innovation in health technology assessment and its impact on public financing of medicines

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Tesis Doctoral en Ciencias Económicas y Empresariales

Departamento de Economía Aplicada

Programa de Doctorado en Ciencias Económicas y Empresariales

Universidad de Granada

Granada, 2024

UNIVERSIDAD DE GRANADA

Editor: Universidad de Granada. Tesis Doctorales
Autor: Juan Carlos Rejón Parrilla
ISBN: 978-84-1195-297-2
URI: https://hdl.handle.net/10481/92318

Agradecimientos / Acknowledgements

A los primeros que me gustaría dedicar un sincero y eterno agradecimiento es a David Epstein y Jaime Espín, por haberme regalado el lujo de que dirijan mi tesis, y por conseguir que haya sido para mí un placer tan enorme hacerla.

También me gustaría agradecer a Mikel Berdud y a Federico Augustovski que hayan dedicado su tiempo a revisar este documento, y que lo hayan escrutado con ojo crítico y mirada constructiva. Gracias a vuestra generosidad y aportaciones.

A los miembros del tribunal, titulares y suplentes, Jorge Mestre-Ferrandiz, Puerto López, Juan Oliva y Ángeles Sánchez. A todos, gracias por aceptar nuestra invitación a participar en el tribunal de mi tesis. En el momento que escribo estas líneas no sé a ciencia cierta delante de cuáles de vosotros tendré el lujo de celebrar la defensa. Mi agradecimiento va a partes iguales a todos y cada uno de vosotros por no dudar en aceptar nuestra invitación.

To the international members of the thesis tribunal, Dimitra Pantelli and Koonal Shah. Huge thanks to you both for accepting my invitation be part of (or the international reserve member of) my thesis committee, despite the obvious added difficulty of having to travel from afar.

I would also like to thank Sarah Garner for her faith in my work and her support. You made a fascinating part of this journey and part of the research that is contained in this document possible. Thanks for the time I spent with your team in Copenhagen. I thoroughly enjoyed it.

También quiero aprovechar para dedicarles unas palabras de agradecimiento a cada una de las personas que, además de los/as coautores/as de los capítulos que componen la tesis por supuesto, me han regalado algo de su tiempo, escuchándome o leyéndome para aportarme algo. Gracias Marta Trapero, Néboa Zozaya, Joan Costa-Font, Emilio Alegre, Jorge y Pedro Luis Sánchez (¡espero no haberme dejado a nadie!). Y aquí me paro para hacer mención especial a Joan Rovira, que nos hizo sugerencias brillantes a uno de los capítulos, y tristemente falleció el pasado junio de 2022. Parte de esta tesis va dedicada a ti Joan.

Y, por último, a mis seres más queridos. A mis padres, por darme la vida y herramientas para que yo aprenda a vivirla y disfrutarla tantísimo como lo estoy haciendo. A mi hermano, por haber sido siempre un referente y una fuente de inspiración infinita para mí. Y a mi pareja, por ser mejor compañera de lo que yo hubiera podido soñar nunca.

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Resumen Ejecutivo

Introducción

La evidencia desempeña un papel crucial en la toma de decisiones para el acceso a las tecnologías sanitarias. Su evaluación sigue unos procesos que pueden agruparse en una serie de etapas genéricas, como la evaluación regulatoria, la evaluación de tecnologías sanitarias (HTA) y la reevaluación de la evidencia tras el acceso de la tecnología sanitaria al mercado. Esta tesis se centra principalmente en la etapa de HTA, con énfasis en cómo se define y mide la innovación en HTA, y cómo se recompensa en los sistemas de fijación de precios y reembolsos (P&R).

El desarrollo de la cooperación europea en materia de HTA ha tenido una larga trayectoria histórica, que culmina con la reciente aplicación de la nueva regulación europea sobre HTA, que entró en vigor en 2022 y se desarrollará plenamente a través de un largo proceso de aplicación que concluirá en 2030. Ésta nueva regulación tiene como objetivo mejorar la colaboración entre los Estados miembros de la Unión Europea (UE) para la generación de evidencia sobre la eficacia relativa de las tecnologías sanitarias, manteniendo al mismo tiempo la autonomía nacional sobre las decisiones a tomar.

En España, la institucionalización de la HTA comenzó en 1984 con la creación de la 'Comissió Assessora d'Alta Tecnologia Mèdica' por parte del gobierno regional de Cataluña, que evolucionó hasta convertirse en la Agencia Catalana de HTA, fundada en 1996. En esa época se crearon varias entidades de HTA adicionales en España: la unidad vasca de HTA se fundó en 1992 (Osteba), la agencia andaluza en 1996 (AETSA), y en 1994 se creó en el Instituto de Salud Carlos III de Madrid una unidad de HTA (AETS) que nace "para atender las necesidades consultivas del Sistema Nacional de Salud (SNS)". La ETS española alcanzó un hito importante con la creación de la Red Española de Evaluación de Tecnologías Sanitarias (RedETS) en 2012.

El sistema español de HTA tiene dos vías de evaluación diferenciadas: la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) evalúa los medicamentos y la RedETS las tecnologías sanitarias no farmacológicas. La RedETS nació para armonizar las metodologías y procedimientos aplicados a la evaluación de las tecnologías sanitarias no farmacológicas y eliminar potenciales duplicaciones innecesarias de esfuerzos. Sin embargo, la vía establecida para evaluar los medicamentos se enfrenta actualmente a importantes retos ya que la ausencia de una reglamentación legal que lo soporte, impide a la AEMPS evaluar las dimensiones

económicas o de costes sanitarios, de acuerdo con una sentencia judicial emitida a mediados del 2023. Además, los Estados miembros de la UE, entre ellos España, están adaptando sus procedimientos para integrar las pruebas procedentes de la cooperación europea en materia de HTA. La elaboración conjunta de informes de eficacia relativa a escala europea exigirá que los procesos nacionales de HTA se adapten para dar cabida a esta nueva fuente de pruebas, que deberán tener en cuenta en la toma de decisiones a escala nacional. Como consecuencia de esos dos factores que demandan atención inmediata, España está llevando a cabo una reestructuración formal de su sistema de HTA, la cual está siendo articulada a través de un Real Decreto, que salió a consulta pública en octubre de 2023 y se desarrollará al completo a lo largo del 2024.

El cuerpo principal de la tesis se estructura en tres capítulos. El primero establece un proceso para definir la innovación en HTA, centrándose específicamente en el sistema español como ejemplo para ilustrar cómo puede utilizarse dicho proceso para concebir una definición de innovación que encaje bien en un sistema de HTA dado. El segundo capítulo profundiza en cómo podrían definirse y medirse los distintos criterios de P&R en España. También se examinan las perspectivas de los encuestados sobre el peso relativo de cada criterio y la idoneidad de los criterios que actualmente sustentan las decisiones de P&R en España. Por último, el tercer capítulo hace una descripción de la situación de P&R de terapias avanzadas en 20 países. Dado que las terapias avanzadas suelen disponer de una evidencia limitada en el momento de su lanzamiento, este capítulo explora el uso de mecanismos especiales de apoyo a la fijación de precios y decisiones de reembolso, y las estrategias de gestión de riesgos utilizadas por las instituciones que se ocupan de tomar o apoyar estas decisiones. Esta tesis pretende aportar ideas que puedan ser de utilidad en el abordaje de los complejos procesos de HTA proponiendo un proceso para definir la innovación diseñado específicamente para la HTA, proponiendo también posibles abordajes para mejorar la transparencia en la HTA española y analizando estrategias de P&R para los países que financian tecnologías sanitarias emergentes innovadoras y, a menudo, costosas.

Capítulo I. Cómo definir, evaluar y recompensar la innovación en la evaluación de tecnologías sanitarias

Lo que constituye innovación en tecnologías sanitarias puede definirse y medirse de varias maneras y ha sido objeto de numerosas investigaciones y publicaciones. Sin embargo, aunque muchos países la mencionan como criterio para la fijación de precios o el reembolso de tecnologías sanitarias, hay grandes diferencias en la forma de definirla e incorporarla en los

procesos de HTA. En este artículo, exploramos cómo se ha definido la innovación en la literatura en relación con la HTA. También describimos cómo una selección de países europeos con sistemas de HTA bien establecidos tienen en cuenta la innovación en sus marcos de HTA y exploramos las metodologías clave que pueden capturarla como una dimensión de valor en una nueva tecnología sanitaria. Proponemos una forma de llegar a una definición de innovación para las tecnologías sanitarias, e incorporarla a los sistemas de HTA, que encaje sobre la base de otras dimensiones de valor que ya tienen en cuenta en sus sistemas. Utilizamos España como ejemplo ilustrativo, adaptando los parámetros que construyen el concepto de innovación a un sistema específico de HTA recortando de él las nociones de valor que ya se contabilizan. En el caso de España, la noción de innovación podría construirse en torno a los conceptos de "cambio sustancial", "conveniencia", "solidez de la base de evidencia" e "impacto en la I+D futura". Si se plantea usar el concepto de innovación como criterio para apoyar decisiones sobre adopción, fijación de precios y reembolso de tecnologías sanitarias, el concepto debe definirse claramente, y debe hacerse de forma que sea independiente de otras dimensiones de valor ya recogidas en los sistemas de evaluación en los que se vaya a incorporar.

Capítulo II. ¿Cómo deberían tomarse las decisiones sobre el reembolso de los medicamentos? La opinión de los expertos españoles

Aunque los criterios en los que se basan las decisiones de reembolso de medicamentos suelen estar establecidos en la legislación, como ocurre en España, en muchos casos no se proporcionan ni la definición ni los métodos de medición de dichos criterios. Nuestro objetivo es obtener las opiniones de una amplia muestra de expertos españoles, así como la visión general que tienen sobre cómo evaluar cada uno de los criterios que informan las decisiones de fijación de P&R en España. Para hacerlo, distribuimos una encuesta entre una muestra de más de 1,000 expertos de grupos de interés relacionados con la economía de la salud, la evaluación de tecnologías sanitarias y el desarrollo y comercialización de tecnologías sanitarias. Los resultados de nuestra encuesta, a la que respondieron 90 expertos, proporcionan evidencia útil para sugerir herramientas de medición que podrían utilizarse para apoyar la toma de decisiones de P&R en España. También muestran un amplio consenso en varios de los aspectos consultados, incluyendo la necesidad de utilizar un umbral de coste-efectividad explícito en España, y que este umbral sea diferente para diferentes grupos de población/situaciones especiales. Este estudio podría, no sólo servir para informar futuros procesos de reforma en España, sino también servir de inspiración para investigadores y responsables políticos de otros países que se embarquen en procesos similares hacia la implementación de mayores niveles de transparencia, coherencia y solidez en sus sistemas.

Capítulo III. Mecanismos de fijación de precios y reembolso de medicamentos de terapia avanzada en 20 países

Las terapias avanzadas son un grupo de medicamentos que, en algunos casos, encierran un gran potencial para los pacientes que carecen de un enfoque terapéutico actual eficaz, pero también plantean múltiples retos a los pagadores. Aunque existen muchos documentos teóricos sobre las opciones disponibles para apoyar la fijación de precios y reembolso en este campo, la investigación empírica original es muy escasa. El objetivo de este trabajo es ofrecer una revisión internacional exhaustiva de las decisiones regulatorias y de P&R tomadas para todas las terapias avanzadas con autorización de comercialización europea centralizada en marzo de 2022. Para lograr dicho objetivo, distribuimos una encuesta en julio de 2022 a representantes de 46 países. Se recibieron respuestas de 20 de esos 46 representantes de países (43,5%). 14 países reembolsaron al menos una terapia avanzada. Seis países de esta encuesta no reembolsaron ninguna terapia avanzada. Lo que nos permite concluir que el acceso a terapias avanzadas es desigual entre los países incluidos en este estudio. Esto se debe a las diferencias regulatorias, a las decisiones comerciales de los titulares de autorizaciones de comercialización y a las diferencias en los procesos y criterios de evaluación aplicados por los pagadores en los distintos países. Para avanzar hacia una mayor igualdad de acceso será necesaria la cooperación entre países y partes interesadas, por ejemplo, a través de la Plataforma de Nuevos Medicamentos (Novel Medicines Platform) de la Oficina Regional para Europa de la OMS.

Discusión

Aunque la necesidad de apoyar las decisiones sobre acceso a nuevas tecnologías sanitarias en HTA está mayoritariamente aceptada, y su práctica está bien establecida en los países desarrollados, la formulación de políticas basadas en la evidencia va a la zaga. El objetivo de esta tesis es dotar a los responsables de la formulación de políticas sanitarias de herramientas y datos que les permitan elaborarlas utilizando metodologías sólidas y los mejores datos disponibles.

En la tesis, discutimos las conclusiones de los tres capítulos mencionados arriba, e identificamos áreas en las que se debe seguir trabajando, como por ejemplo el desarrollo de una herramienta para medir el grado de innovación. Destacamos la importancia de incorporar la perspectiva de los pacientes en el sistema español de HTA, y la necesidad de una reforma en respuesta al nuevo reglamento de la UE sobre HTA.

En la discusión, hacemos también hincapié en la creciente importancia de diseñar las políticas sanitarias basándose en la evidencia, citando la creación del Comité asesor de la prestación

farmacéutica del SNS en España como un paso positivo en el país. El proceso australiano de reforma de su sistema de HTA se sugiere como modelo a observar para España, enfatizando la importancia de dotar de recursos la generación de evidencia que informe las reformas del sistema. Se destaca también la coexistencia entre la HTA y las guías de práctica clínicas, y se insiste en la necesidad de contar con infraestructuras robustas de apoyo a la toma de decisiones, incluyendo sistemas para integrar la identificación de lagunas en la evidencia, priorizando las más importantes y traduciéndolas en convocatorias de financiación de propuestas para generar proyectos de investigación que cubran dichas lagunas. Se trata de un elemento clave para que los sistemas sanitarios sean equitativos y eficientes, que a menudo se pasa por alto.

En conclusión, la tesis aborda lagunas críticas en la formulación de políticas basadas en evidencia en el contexto de la HTA, proponiendo metodologías, herramientas y recomendaciones para los responsables de diseñarlas. La tesis subraya también la evolución que se está viviendo en el panorama europeo de la HTA, y el imperativo de transparencia en una toma de decisiones que basarse siempre en la mejor evidencia disponible.

Executive Summary

Introduction

Evidence plays a crucial role in decision-making for access to health technologies. Its assessment steps can be grouped into a number of generic stages, including regulatory evaluation, health technology assessment (HTA), and evidence re-assessments post-market access. The focus of this thesis is mainly on the HTA stage, with emphasis on how innovation is defined and measured in HTA, and how it is rewarded in pricing and reimbursement (P&R) systems.

The development of European cooperation in HTA has had a long historical trajectory, culminating in the recent implementation of the new EU HTA regulation, which became effective on 2022 and will be fully unrolled through a long process of implementation that will conclude in 2030. The regulation aims to enhance collaboration among European Union (EU) Member States in generating relative effectiveness evidence for new health technologies while maintaining national appraisal autonomy.

In Spain, the institutionalisation of HTA started in 1984 with the creation of the Advisory Board on High Technology by the regional government of Catalonia, which evolved in into the Catalan Agency for HTA, founded in 1996. A number of additional HTA units were founded around that period: the Basque HTA unit was founded in 1992 (Osteba), the Andalusian agency in 1996 (AETSA), and a national HTA unit was created in 1994 (AETS). Spanish HTA reached an important milestone with the establishment of the Spanish Network for Health Technology Assessment (RedETS) in 2012.

The Spanish HTA system has two distinct evaluative pathways, with the Spanish Agency for Medicines and Health Products (AEMPS) assessing medicines, and RedETS handling non-drug health technologies. RedETS was born to harmonise the methodologies and procedures applied to the assessment of non-drug health technologies, and eliminate any unnecessary duplicative efforts. However, the pathway established to assess medicines is currently facing substantial challenges, since legal restrictions prevent AEMPS from evaluating health economic or cost dimensions, as ruled by a court decision. Additionally, EU Member States, including Spain, are adapting their procedures to integrate evidence from European HTA cooperation. Joint production of relative efficacy reports at European level will require that national HTA processes adapt to accommodate this new source of evidence, which they will be mandated to consider in

national decision-making. Consequently, Spain is undergoing a formal restructuring of its HTA system through a Royal Decree that was out for public consultation in October 2023, and which will be fully developed in 2024.

The main body of the thesis is structured in three chapters. The first one establishes a process for defining innovation in HTA, specifically focusing on the Spanish system as a case example to illustrate how the process can be used to conceive a definition of innovation that fits well within an existing HTA system. The second chapter delves into how the various P&R criteria in Spain could be defined and measured. Respondents' perspectives on the relative weight of each criterion and the adequacy of the criteria list are also examined. Finally, the third chapter investigates the P&R landscape for Advanced Therapy Medicinal Products (ATMPs) in 20 countries. With ATMPs often having limited evidence at launch, the chapter explores the use of special pricing mechanisms and risk management strategies used by institutions dealing with P&R. The thesis seeks to contribute valuable insights to the complex landscape of HTA proposing a process to define innovation for HTA purposes, proposing potential ways of enhancing transparency in Spanish HTA, and analysing P&R strategies for countries financing emerging innovative, and often costly, health technologies.

Chapter I. How innovation can be defined, evaluated and rewarded in Health Technology Assessment

What constitutes innovation in health technologies can be defined and measured in a number of ways and it has been widely researched and published about. However, while many countries mention it as a criterion for pricing or reimbursement of health technologies, countries differ widely in how they define and operationalise it. In this paper, we explore how innovation has been defined in the literature in relation to Health Technology Assessment (HTA). We also describe how a selection of European countries with well-established HTA systems take account of innovation in their frameworks and explore the key methodologies that can capture it as a dimension of value in a new health technology. We propose a way of coming to, and incorporating into HTA systems, a definition of innovation for health technologies that works based on other dimensions of value that they already account for in their systems. We use Spain as an illustrative example, tailoring the items that construct the concept of innovation to a specific HTA system by trimming from it the notions of value that are already accounted for. In the case of Spain, a notion of innovation might be constructed around concepts of `step-change', `convenience', `strength of evidence base' and `impact on future R&D'. If innovation is to be used as operational criteria for adoption, pricing and reimbursement of health technologies, the

concept must be clearly defined, and it must be done in such a way that it is independent from other value dimensions already captured in their systems.

Chapter II. How should medicines reimbursement work? The views of Spanish experts

Although the criteria that support reimbursement decisions for medicines is often set by legislation, as it is the case in Spain, in many cases neither the definition nor the measurement methods for these criteria are provided. Our goal is to elicit the values of a large sample of Spanish experts as well as the general agreement on how to evaluate each one of the criteria that inform pricing and reimbursement (P&R) decisions in Spain. Over 1,000 experts from stakeholder groups involved in health economics, health technology assessment, and health technology development and commercialization were given a survey to complete. The results of our survey, to which 90 experts responded, provide useful evidence to suggest measurement tools that could be used to assist P&R decision-making in Spain. They also show broad consensus on several of the aspects consulted, including the need to use an explicit cost-effectiveness threshold in Spain, and for this threshold to be different for different population groups/special situations. This study could, not only inform further developments in Spain, but also serve as inspiration for researchers and policy makers in other countries embarking in a similar journey towards implementing greater levels of transparency, consistency and robustness in their systems.

Chapter III. Pricing and reimbursement mechanisms for advanced therapy medicinal products in 20 countries

ATMPs are a type of therapies that, in some cases, hold great potential for patients without an effective current therapeutic approach but they also present multiple challenges to payers. While there are many theoretical papers on pricing and reimbursement (P&R) options, original empirical research is very scarce. This paper aims to provide a comprehensive international review of regulatory and P&R decisions taken for all ATMPs with centralized European marketing authorization in March 2022. To achieve such aim, we distributed a survey in July 2022 to representatives of 46 countries. Responses were received from 20 country representatives out of 46 (43.5%). 14 countries reimbursed at least one ATMP. Six countries in this survey reimbursed no ATMPs. Which allows us to conclude that access to ATMPs is uneven across the countries included in this study. This arises from regulatory differences, commercial decisions by marketing authorization holders, and the divergent assessment processes and criteria applied by payers. Moving towards greater equality of access will require cooperation between

countries and stakeholders, for example through the WHO Regional Office for Europe's Novel Medicines Platform.

Discussion

While the need for HTA is mostly accepted, and its practice is well-established throughout developed countries, evidence-informed policymaking lags behind. This thesis aims to equip healthcare policymakers with tools and evidence to shape policies using robust methodologies and the best available evidence.

We discuss the findings of the three chapters outlined above, and identified areas for further work, including for instance the development of a checklist for measuring the degree of innovation. We emphasize the importance of capturing the perspectives of patients in the Spanish HTA system, and the need for reform in response to the new EU regulation on HTA.

The discussion emphasizes the growing importance of evidence-based policy shaping, citing Spain's Advisory Committee for the Reimbursement of the Pharmaceutical Provision as a positive step in the country. The Australian HTA reform process is suggested as a model for Spain, emphasizing the importance of resourcing the generation of evidence to inform reforms of the system. The coexistence of HTA and clinical guidelines is highlighted, and we stress the need for robust decision support infrastructures, including systems to embed the identification of evidence gaps, prioritising the most important ones and translating them into calls for proposals to fund research that fills such gaps. That is a key element of equitable and efficient healthcare systems, and one which is often overlooked.

In conclusion, the thesis addresses critical gaps in evidence-informed policymaking within the context of HTA, proposing methodologies, tools, and recommendations for policymakers. It underscores the evolving landscape of HTA and the imperative for transparent, evidence-based decision-making.

Introduction

Healthcare systems around the world strive to create processes and infrastructures that provide their decision makers with sufficient and appropriate evidence to support their decisions, at the relevant decision-making points, on access to health technologies.

The typical pathway of a health technology since it is developed till it reaches patients comprehends, at a very high level, the following points of assessment of the evidence:

- Regulatory assessment: ensures the health technology is of sufficient quality, safety and efficacy.
- Health Technology Assessment (HTA): assesses the added value of the health technology being assessed compared with the gold standard applied at the time of the assessment. It helps inform pricing negotiations and the decision of whether or not to include the new health technology in the basic benefit package of the health system at hand.
- Re-assessments: often, when on substantial source of uncertainty are identified at the HTA of technologies that are considered promising, HTA bodies offer conditional access subject to the marketing authorization holder producing Post Launch Evidence Generation (PLEG) studies, that inform further re-assessment of the evidence within a pre-defined period of time (often 2-5 years from the first assessment).

The present thesis focuses mainly on the HTA of new health technologies, with emphasis on how innovation is defined and measured in HTA, and how it is rewarded in pricing and reimbursement (P&R) systems.

An Advanced Therapy Medicinal Product (ATMP) is a type of medicine for human use that is based on genes (gene therapy medicines), tissues (tissue-engineered medicines), or cells (somatic-cell therapy medicines) (1). We used ATMPs as an example of a family of therapies with great potential health benefit, but also often high prices and considerable uncertainty, to illustrate how innovation can be rewarded in P&R systems.

1. Background and context: European cooperation on HTA and HTA in Spain

The methods supporting HTA activities are ideally developed ensure the assessments are supported on solid science and robust methodological grounds (2). However, HTA bodies, particularly in Europe, have been widely criticised on several fronts. While observers agree with the principle that rigorous and appropriate assessment is necessary, there are concerns by patients and industry in many countries that the process is too long, and that the multiplicity of organisations each with different criteria are unnecessarily duplicating work and delaying the final decision. Academic authors recommend that there should be a separation and independence between the "assessment" phase (reviewing and presenting the scientific evidence supporting the use of a technology) and the "appraisal" phase capturing decision rules to produce a recommendation that is in nature context specific (3). This thinking has underpinned the recent implementation of the EU regulation on HTA, which aims to centralize and streamline the "relative effectiveness assessment" phase at EU level, while leaving other assessment domains (such as health economics and local implementation) and appraisal as national HTA competencies. Meanwhile, in Spain, it has become clear that there are substantial legal gaps and organizational weaknesses in HTA of medicines (4). The following sections review and contextualize the recent historical background behind these developments. Hence, in Spain alongside other EU countries, there is vigorous debate about how HTA should be reorganised at national level once the European regulation becomes operational (5, 6). Now is, therefore, a highly opportune moment for this doctoral thesis, which it is hoped can inform and contribute to this debate.

1.1 Cooperation on HTA in Europe: A brief historical background

Cooperation in HTA in Europe has been operationalised through a series of projects that were meant to articulate the European collaboration of HTA agencies, generating common methods and procedures that can produce evidence of common interest. European cooperation in HTA rests on the idea that countries can collaborate on areas such as horizon scanning of new and emerging health technologies, early scientific consultations, and the generation of joint assessments, producing evidence on comparative effectiveness of health technologies, but that appraisals will necessarily remain a national competency (7).

The rise of HTA in the European policy agenda experienced an important milestone in 1991, when Health Ministers identified HTA as a key tool to improve the management of scarce healthcare resources (8). Since then, the European Commission funded projects to begin to establish conceptual and methodological grounds fertile for European collaboration, building a common understanding of HTA and flagging the need for information sharing among European countries (EUR-ASESS project (1994–97) (9)), and to describe the European HTA landscape at the time (the HTA Europe project (1997-98) (10)).

This rise became an inflexion point in 2000, when HTA was mentioned for the first time in a policy document from the European Commission, where it was stated that:

"Technological developments in the health field will be a focus for action in the new program. The Commission intends to strengthen health technology assessment structures and mechanisms by supporting collaboration between the agencies involved to refine methodologies, promote joint working, and help disseminate the results of studies effectively" (11).

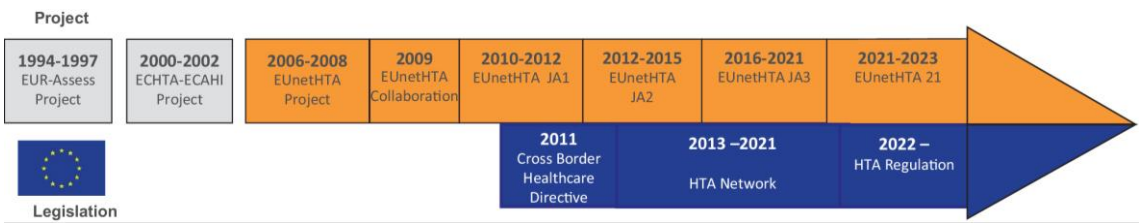
On that same year (2000), the Commission funded a project to explore options to establish a permanent coordination structure for HTA in Europe (the ECHTA/ECAHI project (2000-2002) (12)). After that, the first formal project where European HTA bodies joined forces as part of what would become the future permanent European collaborative network on HTA, was the EUnetHTA project, which lasted 3 years, kicking-off in January 2006 and reaching its end in December 2008 (13). This project, built on the work done by the ECHTA/ECAHI project, took a step further and actually developed a management and governance structure for cooperation on HTA in Europe, and elaborated plans to continue with such cooperation. The HTA agencies involved were so convinced of the value of cooperation at European level, that they funded the activities of the network during 2009 (the EUnetHTA Cooperation) (7). Three subsequent Joint Actions (the EUnetHTA Joint Actions 1 (2010-2012), 2 (2012-2015) and 3 (2016-2021) (14)) were the route the Commission used to give continuity to the activities of the Network.

One of the key methodological documents that guides the work in European joint assessments is the HTA Core Model® (15), developed as part of the above mentioned EUnetHTA project (2006-2008), and tested and refined in the Joint Actions that followed (the latest version available online being the one produced in Joint Action 2 (16)). The broadest version of the Core Model covers aspects relative to the clinical value of the technologies being compared, as well as organisational and other aspects (15). It includes specific questions on the level of innovation of the technology being assessed (the subject of the research done in this thesis), within the

section labelled as *'Is the technology a new, innovative mode of care, an add-on to, or modification of a standard mode of care, or a replacement of a standard mode of care?'* (16): (i) *is the technology an innovation?* and (ii) *Is the technology only partially innovative (i.e. a modification of an existing technology), and in that case, is it possible to specify the degree of innovation the technology may represent?* In the Core Model, there is no further indication around how assessors ought to judge whether the technology is an innovation or not, or how to measure the degree of innovation. This gap is part of the reason that inspired the focus of this thesis.

Once the last one of the EUnetHTA Joint Actions finished, the plans of the European Commission became to create a European regulation that would develop and sustain a permanent structure for HTA cooperation in Europe (17). To bridge the gap between the last Joint Action and the beginning of the transition period into the new regulation, the Commission launched a tender, to fund a limited number of European joint assessments, which were done by a subset of the agencies involved in EUnetHTA, coordinated by the EUnetHTA Secretariat (thereafter self-renamed as EUnetHTA 21 Secretariat) (18).

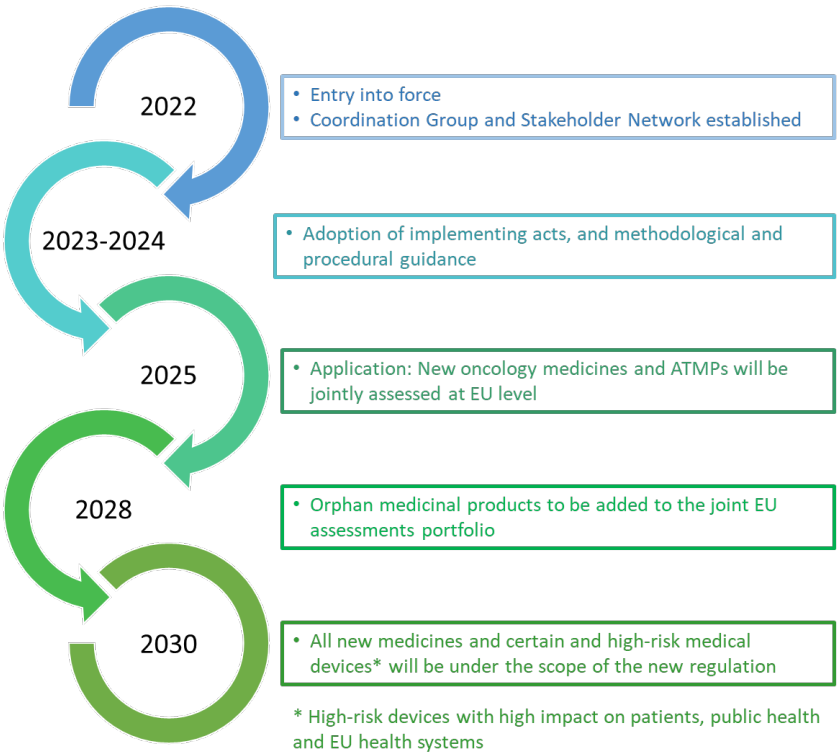
Figure 1 below shows the establishment of a European network for HTA on a timeline



Source: (7)

The new EU regulation on HTA came into force in January 2022, entering a transitionary period whereby it will be fully implemented by 2025 (19). The timelines for its planned implementation span to 2030, including new types of technologies in a staged manner (see figure 2 below for further details).

Figure 2 (below) shows the planned timelines for the development and adoption of the new European regulation on HTA, since the moment it was approved (2022) until its adoption for all new medicines (2030).



Source: Figure built with information published by the European Commission in the Factsheet – Implementing the EU Health Technology Assessment Regulation (20).

The idea behind the new regulation is that EU Member States will collaborate on the generation of evidence of comparative effectiveness for new health technologies, which they will then use in their own national appraisal processes. The intent is to improve the efficiency of HTA activities across Europe, and minimise any unnecessary duplications of efforts. EU HTA bodies will additionally collaborate on several additional fronts, on a voluntary basis, covering the non-clinical aspects of health technology assessments (e.g. economic, ethical, organizational aspects), the collaborative assessment on medical devices, the assessment of health

technologies that are not medicinal products nor medical devices, and activities linked to evidence generation to support HTA (17).

However, the legislative proposal that was the seed for the new regulation, and the implementation of it, are under the critical lens of HTA researchers and other stakeholders (21, 22). Specific aspects of it have been flagged, pointing out unanswered questions that will need addressing as the process unfolds, in fronts like the choice of standard of care, how joint assessments will address situations where there is a lack of randomized clinical studies or where there is a predominance of use of surrogate outcomes, or what the new HTA regulation will contribute to the generation of additional real-world-evidence (19).

As briefly explained above, the evidence generated through the European cooperation on HTA will inform national HTA activities, but it will not replace them. For instance, the appraisal of the evidence, and actual decisions about pricing and reimbursement, will remain national competencies. All of which will ideally lead to optimal resource allocation decisions for all health technologies in each member State within the EU. Hence, a necessary pre-requisite for optimal resource allocation will be that countries base their own HTA activities and their decisions on robust methodologies.

In the next sub-section, we briefly introduce the history of HTA in Spain. The Spanish system will be the subject of part of the research done in this PhD thesis.

1.2 The Spanish historical background

In Spain, the first initiative to institutionalise the promotion of rational introduction of health technologies in the system dates back to 1984, with the creation of the Advisory Board on High Technology by the regional government of Catalonia, which evolved in into the Catalan Agency for HTA, founded in 1996 (23). The Basque Country established an HTA unit in 1992 (Osteba), the Andalusian government created an agency in 1996 (AETSA), and a national HTA unit was created in 1994 (AETS) (23). To try and address a series of weaknesses identified at the time, the Spanish government created a Working Group on HTA (an Advisory Committee of the Interregional Council of the NHS) (23). Subsequently, similar agencies were created in other regions such as Madrid (UETS-Madrid), Galicia (Avalia-T), Aragon (IACS) and the Canary Islands (SESCS).

In 2012, the creation of the Spanish Network for Health Technology Assessment of the National Health System (RedETS) marked a landmark in the Spanish HTA landscape (24). RedETS includes all public HTA organizations at national and regional levels, and has been working to harmonise the methodologies and procedures they apply to the assessment of non-drug health technologies, with a view on having a common portfolio of HTA production and eliminate any unnecessary duplicative efforts (24).

At the time of writing, Spain is navigating turbulent storms in the field of HTA. The country has two distinct pathways of evaluation for medicines and for medical devices. The assessment of medicines is done by the Spanish Agency for Medicines and Health Products (AEMPS), and RedETS assesses non-drug health technologies. A major weakness of this system was that AEMPS were unable by law to assess health economic or cost dimensions of HTA, which was clearly restated in a court decision that declared the plan to incorporate economic evaluation into HTA reports for medicines illegal (25). This forced the country into a process of re-shaping the national HTA system (5). Nevertheless, before this court ruling, Vida et al. (2020) had already pointed out a long list of aspects, including the issues raised in the afore mentioned court decision, requiring urgent attention to improve a system that they deemed as disorganised (4).

Additionally, EU member countries are being forced to adapt their national HTA procedures to accommodate the evidence that will start being generated through the European cooperation on HTA since 2025. Hence, significant developments are to be expected in the coming years that will re-shape the national HTA landscape.

Part of the changes that are to come will affect the process that will connect the HTAs with pricing and reimbursement decisions for medicines and medical devices. In Spain, the criteria that are meant to support pricing and reimbursement decisions are listed in a law (26, 27):

a) Severity, duration and sequelae of the different pathologies for which they are indicated;
b) Specific needs of certain groups;
c) Therapeutic and social value of the medicine and its incremental clinical benefit, taking into account its cost-effectiveness;
d) Rationalization of public spending on pharmaceuticals and budgetary impact on the National Health System;
e) Availability of medicines or other therapeutic alternatives for the same conditions at a lower price or lower treatment cost;

f) Degree of innovation of the new medicine.

Some of these criteria, such as unmet need and cost-effectiveness, have been conceptualized in the academic literature, including studies commissioned by the Spanish government (28-30). Furthermore, some regional governments have adopted these guides for pharmaceutical HTA (31). However, these have not been translated into use in national HTA or decision-making bodies for medicines in Spain. So far, those criteria have not been defined in the legislation or associated procedural guidance, nor is the method to be used to measure them described in any official methodological document produced by the Ministry of Health (32).

2. Aims

The topic of innovation in HTA (how it is defined and measured in HTA, and how it is rewarded in P&R systems) is the connecting thematic thread that binds together the 3 chapters of this thesis.

In the first chapter, we aimed to answer the question 'how do we define innovation in HTA?'. We propose a process to define the value dimensions that ought to compose the concept for a given system, taking account of the criteria already captured in the decision-making process. We used the Spanish system as a case example, and proposed a definition of the concept 'degree of innovation' that ought to be valid to support pricing and reimbursement decisions in Spain. Previous efforts to propose ways of measuring innovation in Spain, such as the so-called 'Innovometer' (30), did not comply with the 'non-redundancy' requirement (in relation to other items considered in Spain) set out in Diaby and Goeree' framework (33), which described the properties that items need to exhibit to be useful for decision making.

In the second chapter, we aimed to answer the question 'how should we measure each one of the reimbursement criteria that support reimbursement decisions in Spain?'. Given that the degree of innovation is one of the criteria that informs reimbursement in Spain, the question 'how should we measure the degree of innovation' was contained within this chapter, but we covered the wider set of criteria that is listed in Spanish law, including, as well as the degree of innovation, the following: severity, duration and sequelae of the different pathologies for which the new medicine is indicated; specific needs of certain groups; therapeutic and social value of the new medicine and its incremental clinical benefit, taking into account its cost-effectiveness;

rationalization of public spending on pharmaceuticals and budgetary impact on the National Health System; availability of medicines or other therapeutic alternatives for the same conditions at a lower price or lower treatment cost.

A secondary research question we addressed in the second chapter was what relative weight our respondents thought that each criterion should have in the overall decision. We also asked if they deemed the list of criteria adequate, specifically asking if they would add the perspective of patients as an additional criterion.

Whilst the first two chapters of this thesis deal with the definition of pricing and reimbursement criteria, and the methods used to measure them, the third and last chapter explores the instruments used to articulate actual pricing and reimbursement decisions in a selection of countries ('how should we reward developers of health technologies that display high degrees of innovation?'). ATMPs often present a sparse evidence base at launch, which leads to the clinical and economic data that reaches HTA and reimbursement stage often being insufficient for healthcare systems to assess their added therapeutic value with certainty (34, 35) and to negotiate value-based prices (36). Payers handling the difficult task of managing financial risk and uncertain evidence, where it exists, need to embed risk management strategies into their P&R decision making processes, and they often do so through special pricing mechanisms (36-38). In this chapter, we surveyed representatives of institutions dealing with the pricing and reimbursement of medicines in 20 countries, to explore the reimbursement status of a sample of ATMPs, whether they used any special pricing and reimbursement schemes to articulate their decisions, which instruments they used, and more.

Chapter I. How innovation can be defined, evaluated and rewarded in Health Technology Assessment

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DOI: https://doi.org/10.1186/s13561-021-00342-y

1. Background and Introduction

There is a huge industry dedicated exclusively to the discovery and development of new and innovative health technologies. The average research and development (R&D) investment per approved new compound is about UD$1,5 billion (39, 40). In such a competitive industrial environment, it becomes vital to the industry to read any signals public payers may send around what they value and what they do not regard as relevant when it comes to deciding which health technologies to fund and at what price. Health Technology Assessment (HTA) is defined by the World Health Organization (WHO) as the approach used to inform policy and decision-making in health care, especially on how best to allocate limited funds to health interventions and technologies (41). The criteria used to judge what constitutes desirable health interventions and technologies can vary amongst HTA systems depending on their aims and the methodologies picked to reach them.

This paper considers how innovation is defined, evaluated and rewarded in HTA. The term is widely used and encompasses multiple attributes. Most HTA systems evaluate features of innovation that consider the impact of a product from the perspective of current patients (therapeutic benefit, unmet need, safety, administration) or current budget holders (cost), also called the "static" perspective (42). Examples of this approach can be seen in the paper published by de Solà-Morales et al. (43), which looks at how innovation is defined from a current payer's perspective, or also in the work led by Karl Claxton on the cost-effectiveness threshold that defines the opportunity cost of decisions on new technology in terms of the marginal health

displaced in the current NHS (44). HTA systems less frequently explicitly consider the "dynamic" consequences or incentives created by a decision to adopt or not a new technology on the direction of future R&D and ultimately, further innovations. These terms overlap to some extent with the idea of the source of innovation being `pulled by demand' or `pushed by supply' or entrepreneurship (45).

Previous reviews in this topic have explored specific aspects of innovation: from an organizational point of view (46), for medicines (43, 47-49) and for medical devices (45). However, none look at the question in a holistic way to consider how innovation should be included as a criterion for HTA in practice.

Hence, the overall aim of this article is to construct a broad concept of innovation and a process of tailoring it to individual HTA systems that can be useful for healthcare policy makers considering if and how their HTA frameworks capture innovation. To fulfil this aim, we followed three objectives: First, to assess with reference to the literature the theoretical justification for which attributes of innovation ought to be considered in HTA. Second, to assess how HTA bodies in France, Italy, England, Spain and Japan consider these issues in their assessments for adoption or pricing & reimbursement (P&R). Finally, Spain is taken as a case-study to consider how the degree of innovation should and can be strengthened in HTA decisions, and we discuss the relevance of the findings for other HTA systems.

2. Methods

We performed a literature review, using a snowballing search (50). We chose this technique because the literature suggests it is a more effective approach for complex and heterogeneous evidence than more formal protocol-driven searches (51). The steps in a snowball search are: 1) Establish the research question and inclusion and exclusion criteria 2) Identify the start set: a small number of seminal papers or highly cited papers 3) Backward snowballing: Reviewing the reference list of the seminal papers 4) Forward snowballing: Searching for papers that cite the seminal paper.

Our inclusion criteria were that the papers included dealt with the concept of innovation in HTA decisions (adoption, reimbursement or pricing) about all types of health technologies (medicines, devices and diagnostics). We excluded 1) papers where "innovation" was used as a

term to refer exclusively to therapeutic benefit or similar terms, already separately accounted for in HTA; 2) papers did not add anything new on top of the seminal papers; 3) papers that focused on concepts of organizational innovation that are not relevant to HTA adoption or P&R decisions; 4) editorials 5) Regulatory approval criteria and literature that focus exclusively on efficacy, safety and quality. We included papers both in English and Spanish. There was no limitation on the dates when papers were published. One of the authors of this paper made a first selection of included and excluded papers, a second author double checked it and a third author was available to resolve any discrepancies. The search strategy is described in more detail in Annex I.

Not all concepts are eligible or useful for decision making. Diaby and Goeree (33) recommended that items need to exhibit all the following properties: 'value relevance', 'understandability', 'measurability', 'non-redundancy', 'independence' and 'comprehensiveness'. We use this framework as a test for each feature of innovation identified in the literature, seeking to trim these down to a smaller set of items that jointly display these properties, and could potentially be used as criteria in HTA. We then consider methods that could be used to measure or rank health technologies in practice on the basis of the degree of innovation in the chosen countries. In the end, countries choose the criteria that they feel best align and promote their specific aims. Our intention is to identify those criteria that have some theoretical justification and can be measured.

We also assess how HTA bodies in France, Italy, England, Japan and Spain consider innovation in their assessments for adoption, P&R processes. Our choice of countries is based on our judgment of HTA systems that take different stands on whether and how they account for degree of innovation as an independent source of value of new health technologies. We chose a set of countries that allow us to analyse different approaches to HTA to show how innovation can be embedded in different HTA systems for the evaluation and reimbursement of health technologies. Our reasons for including France and England are that they have internationally leading nationally centralized systems that work following high standards of transparency, one rewarding innovativeness as an independent feature (England) whilst the other entangles the concept more with other criteria (France). Japan presents a recently reformed centrally coordinated HTA system, different to the rest of the countries we will be looking into, in that they reward innovative new technologies by applying a premiums system whereby the technologies considered to be innovative receive a premium price beyond the price of the comparator. Italy, whilst having a national agency, is a more fragmented model, with the added

interest of having recently introduced a new method to capture innovation (52). Spain goes one step further in how decentralized it is in its' HTA activities, having several regional agencies as well as national entities, each with parallel competencies. The main interest in this country is that the law includes degree of innovation amongst the criteria that should be used to make P&R decisions for drugs (53), but provides no guidance on how to define or measure this concept. Despite the size of R&D investment having been consistently higher in the US compared with Europe, and the US being the biggest pole of clinical trials worldwide (39), we decided not to include the US because P&R decisions in practice are not consistently based around the HTA evidence produced by leading research institutes such as the Institute for Clinical and Economic Review.

3. Results

3.1 Literature search

The bibliographic search described in Annex I identified 38 papers. From this list, and papers recommended by colleagues and contacts, four seminal papers were chosen (43, 45, 54, 55). Reference lists of these 4 papers were examined and we used Google Scholar to identify the articles that cited the 4 papers. These forward and backward snowball searches identified 523 papers. Adding in the aforementioned 38 papers and eliminating duplicates provided 543 articles to be screened by title. We reviewed abstracts when titles were not enough to decide. From these, we assessed 73 full papers and decided to exclude 15. That left us with the 58 papers that we included in our review and final synthesis. These are briefly summarised in Appendix II.

Figure 1 below shows the flow diagram.

Figure 1. PRISMA flow diagram (56)

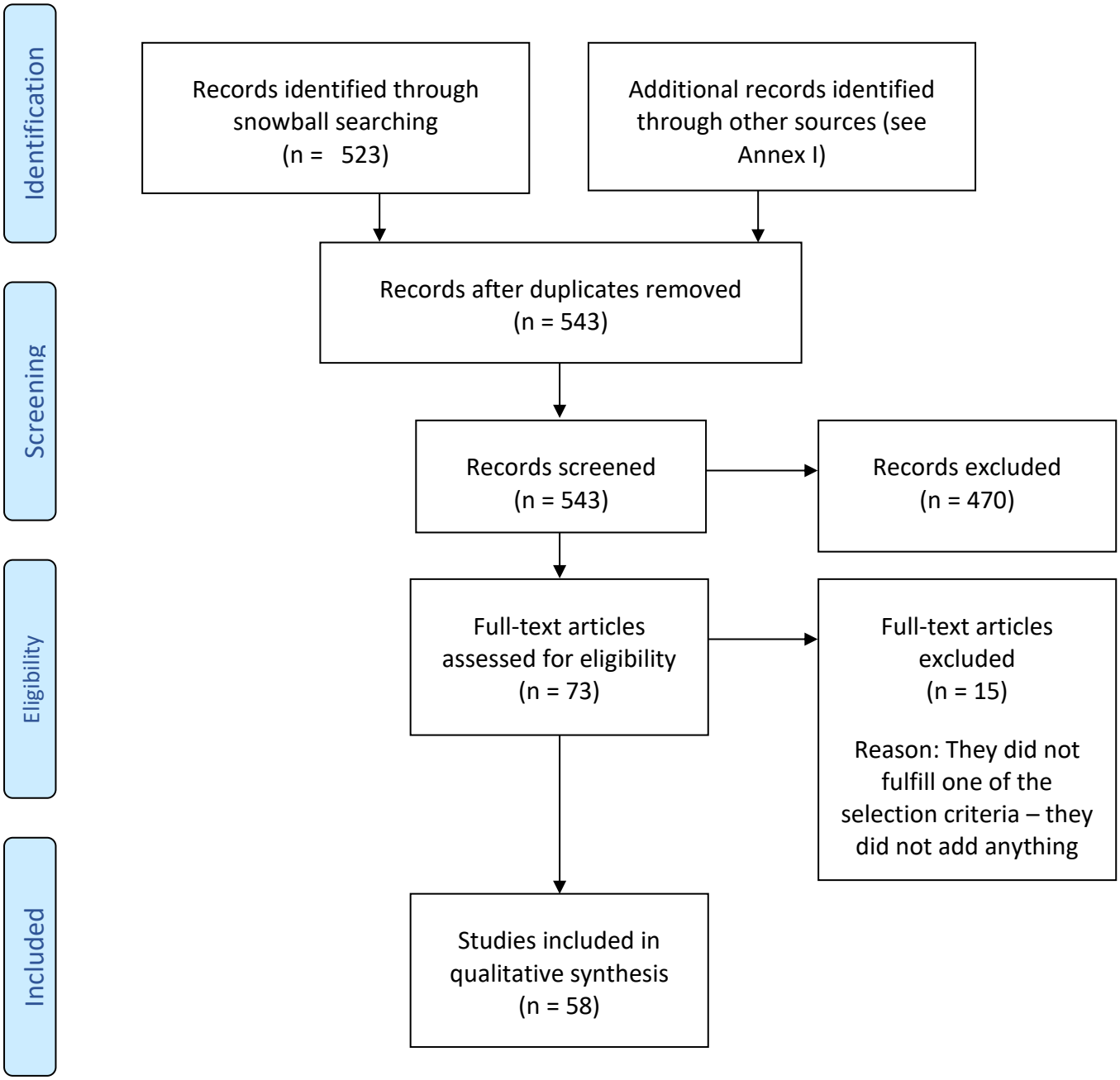

Table 1 summarises the attributes related to innovation that were discussed in the included papers. All of the concepts of innovation discussed in the 58 papers in the literature search were covered in 5 papers: the four seminal papers (43, 45, 54, 55), and one other (57). Hence only these papers are included in Table 1.

For medicines, Solà-Morales et al. (2018) (43) identified 10 dimensions of innovation in the literature which, in order of most to least widely referred to in identified papers, are: therapeutic benefit, novelty (of structure or mechanism of action), availability of existing treatment, unmet need, safety, newness, administration, clinical evidence, cost, and 'other'.

The Advance Value Framework is a Multiple Criteria Decision Analysis (MCDA) framework for medicines proposed by Angelis & Kanavos (2017) (55). They do not phrase a definition for innovation as such, but they do include it as one of the 5 dimensions of value that make up their framework. Their proposed notion of innovation captures the following value items: (a) medicine's mechanism of action, (b) spill-over effects, and (c) patient usefulness (i.e. convenience).

Garrison et al. (2017) (54) include spill-over effects as one of the potential "sources of value" for health technologies. They define it as the knowledge that is produced in the process of coming up and using a particular innovative treatment that spills over to foster other innovations and benefits other patient groups. That is, the adoption of a given product with benefit for a specific group of patients produces what economists refer to as a "knowledge externality", with spillover benefits for others. Garrison also discussed 'real option value'. This is the value to a patient of extending their life for a limited period of time because that opens up the possibility for them to benefit from future medical advances, above and beyond the value that the immediate clinical benefit that the intervention brings to the patient.

Ciani and collaborators (2016) (45) identify three broad dimensions of innovation related to medical devices: (i) the source of innovation (demand or supply driven), (ii) the degree of discontinuity introduced (incremental or breakthrough) and (iii) the impact or consequences of innovation (measurable changes in terms of patients' benefits, quality of the service or costs).

Ciani also discuss the 'learning curve' – the issue around how innovations are incorporated into routine practice, and how that can affect the measured performance of the new intervention over time. The learning curve might apply to all health technologies but it is particularly acute for non-drug health technologies such as medical devices.

Mestre-Ferrandiz et al. (57) advocate for a concept of innovation that is incremental or a matter of degree, as opposed to it being a quality that is either present or not in a health technology. They characterise innovation for pharmaceuticals using 10 attributes grouped under 3 general headings: (A) Health gains, including: (1) tackling a new disease and/or indication; (2) health gains measured in quality of life and/or life duration; (3) faster health improvement; (4) reduced side-effects and/or improved tolerability; (5) reduced negative interactions with other therapies; (6) treating better than current standard of care one or more different patient subpopulations; (B/7) 'Patients' / carers' convenience'; (C) Other societal gains, including cost savings: (8) releasing other healthcare resources; (9) releasing other non-healthcare resources; (10) productivity benefits.

Table 1. Items found in the literature to compose a broad concept of innovation for health technologies

	Solà-Morales et al. (2018)	Angelis & Kanavos (2017)	Ciani et al. (2016)	Garrison et al. (2017)	Mestre-Ferrandiz et al. (2012)
Attributes related to therapeutic added value of technology, compared to relevant comparator					
Therapeutic benefit	✓	✗	✓	✗	✓
Attributes related to step-change					
Breakthrough status	✗	✗	✓	✗	✗
Attributes related to the underlying health condition of the patients & current care					
Availability of existing intervention	✓	✗	✗	✗	✓
Unmet need	✓	✗	✗	✗	✓
Attributes related to safety					
Safety	✓	✗	✓	✗	✓
Attributes related to convenience					
Patient usefulness (i.e. convenience)	✓	✓	✓	✗	✓
Carer usefulness (i.e. convenience)	✗	✗	✗	✗	✓
Administration	✗	✗	✗	✗	✓
Attributes related to economic impact					
Cost or budget impact	✓	✗	✓	✗	✓

	Solà-Morales et al. (2018)	Angelis & Kanavos (2017)	Ciani et al. (2016)	Garrison et al. (2017)	Mestre-Ferrandiz et al. (2012)
Impact on non-healthcare resources and productivity benefits	✗	✗	✗	✗	✓
Attributes related to evidence base					
Strength of clinical evidence	✓	✗	✗	✗	✗
Learning curve	✗	✗	✓	✗	✗
Attributes related to R&D and impact on future innovation pipeline (dynamic effects)					
Novelty	✓	✓	✗	✗	✗
Spill-over effects	✗	✓	✗	✓	✗
Real option value	✗	✗	✗	✓	✗

3.2 How innovation is perceived, measured and rewarded in Spain, France, Italy, England and Japan

Payers and HTA bodies across the world use the `degree of innovation` as a criterion for adoption or P&R, though, in parallel with the academic literature, the meaning of this term is not precisely or consistently defined. Table 2 summarises the stated position of HTA bodies in Spain (Interministerial Medicinal Products Pricing Committee – CIPM & the Spanish Agency of Medicines and Medical Devices – AEMPS), England (National Institute for Health and Care Excellence – NICE), Italy (Agenzia Italiana del Farmaco – AIFA), France (Haute Autorité de Santé – HAS) and Japan (National Institute of Public Health – NIPH). Note that some of these institutions also hold other responsibilities than HTA, such as AIFA, which is also responsible for the regulation of medicines in Italy (52). We classify attributes into 8 dimensions: added therapeutic value, step change, underlying health condition, safety, convenience, economic impact, evidence base, and dynamic impacts that may influence future R&D.

We used the same broad dimensions in Table 1 and 2, though some of the items differ. Table 1 is a summary of how the selected literature defines innovation in HTA. For instance, incremental cost-effectiveness ratio is not present in table 1 because it was not specifically listed in the included papers. Table 2 includes all the items in Table 1, together with the criteria used by the selected HTA bodies to capture innovation in their frameworks. Hence Table 2 shows the degree

of alignment of the criteria used by HTA agencies against each other and compared with the academic literature.

In England the Kennedy report (2009) called for NICE to define innovation and for the Department of Health to regularly update their priorities for innovation in the healthcare sector (58). This would allow stakeholders across the healthcare ecosystem to judge whether new health technologies respond to the declared needs of the system or not. NICE were encouraged to regard innovation as a social value worth pursuing independently for instance from maximizing health outcomes. As a result, NICE established 3 conditions that must be met by health technologies to be classed as innovative (59):

1. The novelty condition: the technology must display "innovative characteristics" or be of an "innovative nature".
2. The substantial benefits condition: the innovative nature of the technology must bring substantial health benefits to the patient, also referred to as a "'step-change' in the management of the condition" (60).
3. The demonstrable and uncounted benefits condition: the substantial benefits brought by the innovative characteristics of the health technology must not already be captured in the incremental cost-effectiveness ratio (ICER) calculation of the technology under scrutiny and they must be "demonstrable and distinctive".

If a health technology is judged to be innovative this might justify recommending a health technology for use in the NHS with an ICER greater than £20,000/Quality Adjusted Life Year (QALY) (59).

In April 2017 AIFA implemented a new system to define and measure drug innovation (52). The new system judges the innovativeness of a new medicine on the basis of three indicators: the level of therapeutic need that the new drug is responding to, the added therapeutic value of the new medicine compared current practice, and the quality of the clinical evidence available to support the claims of benefit of the new intervention (assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (52)). The result can be one of three levels of innovative status: fully innovative, conditionally innovative or non-innovative. The process of reaching a conclusion about the level of innovativeness of a new drug has a deliberative component, whereby the components of the Scientific and Technical Committee (Commissione Tecnico-Scientifica, CTS) assign a level to each one of the 3 indicators of innovativeness, and then discuss the overall level of innovative status appropriate

for each new drug. Depending on the level of innovativeness obtained, a new drug might benefit from access to the so-called innovative drug fund and/or immediate inclusion in regional formularies, avoiding that way any re-assessments at the regional/local level. These forms of assessment coupled with incentives for chosen technologies are meant to accelerate access to therapies deemed as innovative in the Italian healthcare system.

In France, HAS evaluates medicines and other health technologies. It considers innovation as the improvement in expected benefit (IEB) (61), taking account of the improvement in efficacy and/or safety brought by the new technology compared to others available with the same indication. Other dimensions that contribute to define innovation are taken into account in their assessment of actual clinical benefit (ACB). ACB includes the severity of the disease and the 'public health benefit'. Public health benefit includes organizational dimensions, economic outcomes and the impact on the state of health of the population. The ACB is not comparative and it is used to determine if the new technology assessed should be reimbursed or not, while prices are negotiated on the basis of the IEB (62). Secondary criteria for evaluating the degree of innovation include discerning between symptomatic, preventive and curative, and, for medical devices and medical equipment, HAS takes account of how disruptive the new technology is (that 'affect existing technologies in the health field, and that may definitely replace them') in contrast to others that might just be incrementally innovative (that only 'show technological improvement in comparison with other devices') (63). However, there are no mechanisms in place specifically to reward innovations that suppose a disruptive change. There are only access-with-evidence-development schemes for devices that did not show sufficient ACB but were deemed to be of promising innovative value. Additionally, to reward innovative medicines appropriately while still collecting evidence HAS recently published their 'Innovative medicines assessment action plan', which expands the remit of conditional access schemes, reinforcing the use of real-world evidence to monitor medicines that have entered the market with high levels of uncertainty, fast-tracking access to promising therapies amongst other measures to better support innovation, along with other improvements in their processes (64).

In Japan, the Ministry of Health, Labour and Welfare generally reimburses all drugs and devices recommended by the Japanese regulatory agency. Pricing decisions for new health technologies are made by that same ministry but the NIPH, supported by various academic groups, coordinates the review process of the evidence submitted by manufacturers in their reimbursement applications (65). Innovation is rewarded using a premium system, whereby new health technologies considered to be innovative are priced between 5-120% beyond the price

of the comparator. The size of the premium is decided based on the number of the following criteria met by the new technology: (i) new mechanism of action; (ii) higher safety or efficacy; (iii) improvement of treatment for target disease, and; (iv) beneficial presentation (65).

In Spain the criteria that should be taken into account to decide whether a medicine is reimbursed by the National Healthcare System (NHS) are (53): a) severity of the disease; b) the specific needs of certain groups of people; c) the therapeutic and social value of the medicine and incremental clinical benefit taking into account its cost-effectiveness; d) the rational use of public expenditure and the budget impact to the health service; e) the existence of therapeutic alternatives at lower price; and f) the degree of innovation of the medicine. In theory, decisions to include new medicines in the basic package covered by the National Health System, which sit with the CIPM, are made taking into account those criteria. However, the law does not define these terms or regulate how they are to be used, weighted or combined in decision-making. HTA reports also include data on safety and other factors as deemed relevant (66), but these attributes are not specifically mentioned in the P&R legislation. Despite the degree of innovation being amongst the criteria formally required for reimbursement of new medicines in Spain since 2006 (67), there is currently no definition of the concept in the public domain, nor is there a commonly accepted methodology to measure it.

For non-health technologies, the Spanish Network of Agencies for Health Technology Assessment and Services of the National Health System (RedETS) and GuíaSalud coordinate the HTA activities of the regional agencies and units in Spain and their guideline producing activities respectively, working towards the harmonization of methods applied in Spain for the assessment of health technologies and their inclusion in clinical guidelines. There are no official guidelines for how to price or reimburse non-pharmaceutical technologies. However, REdETS has published a 'guideline for the elaboration and adaptation of rapid HTA reports' (68), which outlines the dimensions taken into account also in full HTAs of non-drug health technologies in Spain. That is: safety, efficacy (within this efficacy dimension, there is a sub-section that captures what they refer to as patient satisfaction and acceptability), implementation considerations (economic – budget impact and efficiency of the technology –, organizational, and ethical, social and legal). This suggests that in Spain in practice, broadly speaking, similar criteria are used for medicines and non-drug health technologies, although importantly innovation is not mentioned amongst the criteria considered for non-drug health technologies.

Table 2. Criteria for HTA recommendations in England, Italy, France and Spain

	NICE (England and Wales)	CIPM & AEMPS (Spain) (‡)	AIFA (Italy)	HAS (France)	NIPH (Japan)
	All HTA	Medicines	Medicines	Medicines	All HTA
Attributes related to therapeutic added value of technology, compared to relevant comparator					
Therapeutic benefit	✓	✓	✓ (I)	✓ (I)	✓ (I)
Attributes related to step-change					
Step-change in the management of the condition	✓ (I)	✗	✗	✗	✓ (I)
Disruptiveness	✗	✗	✗	✓	✗
Breakthrough status	✗	✗	✗	✗	✗
Demonstratable and distinctive benefit	✓ (I)	✗	✓ (I)	✗	✗
Attributes related to the underlying health condition of the patients & current care					
Severity of underlying disease	✗	✓	✗	✓ (I)	✗
Impact on the health of the population	✓	✗	✓	✓ (I)	✓
Availability of existing intervention	✓	✓	✓	✓	✓
Unmet need	✓	✓	✓ (I)	✓	✓
Attributes related to safety					
Safety	✓	✓	✓	✓	✓ (I)
Attributes related to convenience					
Administration	✗	✓	✓	✓	✓ (I)
Patient usefulness (i.e. convenience)	✓	✗	✓	✓	✓ (I)
Carer usefulness (i.e. convenience)	✗	✗	✗	✗	✗
Attributes related to economic impact					
Cost or budget impact	✓	✓	✓	✓	✓
Impact on non-healthcare resources and productivity benefits	✗	✗	✗	✗	✗
Incremental cost-effectiveness ratio	✓	✓	✓	C	✓
Attributes related to the evidence base					
Strength of clinical evidence	✓	✗	✓ (I)	✓	✓
Learning curve	✗	✗	✗	✗	✗
Attributes related to R&D and impact on future innovation pipeline (dynamic effects)					
Novelty	✓ (I)	✗	✓	✗	✓

	NICE (England and Wales)	CIPM & AEMPS (Spain) (‡)	AIFA (Italy)	HAS (France)	NIPH (Japan)
Spill-over effects	✗	✗	✗	✗	✗
Real option value	✗	✗	✗	✗	✗
Reference/s	(69, 70)	(32, 66, 70)	(52, 70)	(62, 63, 70)	(65, 71)

Note: (I) refers to whether the criteria is labelled by the HTA agency as an attribute of 'innovation' (C) refers to 'in certain circumstances' (‡) Spain has a criteria labeled 'innovation' but no definition or further guidance is provided.

It is worthwhile highlighting that, besides incentivizing companies to innovate by rewarding them pricing favourably and purchasing the innovations they bring to the market, states do also reward innovative companies with fiscal benefits. For instance, Spain has what they call Profarma, which is a program to stimulate the pharmaceutical sector in Spain incentivizing innovative companies with fiscal incentives. The aim is, mainly, to incentivize companies to invest in Spain, for instance setting up production and/or R&D centers there (72).

4. Discussion

4.1 Attributes of innovation that may be used as criteria for HTA decisions

The countries analysed here can be divided into 2 groups with respect to how they define innovation. France, Japan and Italy use features such as severity, unmet need and therapeutic added value as indicators of the degree of innovation of a health technology, while England, Spain consider the degree of innovation as a separate and additional criterion from others. However, official methodological guidelines in England or Spain do not offer much guidance as to how decision makers should measure innovation, leaving such matters to the discretion of the committee members.

Hence for countries such as Spain that aim to evaluate the degree of innovation as a separate criterion, it is worthwhile to offer some clarity about which attributes of the technology are being measured. This section applies the framework of Diaby and Goeree (33) to whittle down the items identified in the literature review to a set of attributes related to innovation that could be used as criteria for HTA in the countries of interest. Spain is taken as a "case study", though the general approach is meant to be generalisable to other jurisdictions.

A `comprehensive' set of decision-making criteria would encompass all the dimensions listed in Table 2. The legislation in Spain does not mention `step-change', `convenience', `strength of evidence base' or `impact on future R&D' as criteria. This does not mean these items are ignored in HTA in Spain, only that they are not explicitly listed, and so we take these dimensions forward as candidates for inclusion in the category of 'innovation' for Spain. A comprehensive set of criteria would also be applicable to both medicines and other technologies. In some cases this can be achieved by tweaking the definition. For example, novelty refers to new drug structures or mechanisms of action, but it could very well refer to innovative mechanical architectures in the case of a device.

`Value relevance' refers in this context to whether a particular candidate item reflects the preferences of decision-makers with regard to the level of innovation in a product. Decisions makers in each jurisdiction would have to judge whether a given item is relevant and important to the decision problem at hand.

`Non-redundancy' refers to whether criteria are all necessary and do not repeat, double-count or overlap. NICE recognise this by requiring that benefits brought by the innovative characteristics of the health technology must not already be captured in other dimensions. For example, if the novel mode of administration leads to better adherence and hence greater effectiveness, this benefit should not be double-counted both in `added therapeutic value' and in 'patient convenience'. `Independence' requires that the items are mutually exclusive, such that the level of performance in one item does not influence assessments about others.

Decision-makers must have a common understanding of what the criteria aim to measure to achieve precision and legitimacy. The items in Table 2 seem mostly self-explanatory, possibly with the exception of spill-over effects and real-option value. These items are rather abstract and might require explanation for decision-makers.

'Measurement' of each item does not have to be necessarily quantitative, but must be sufficiently rigourous and reproducible to avoid bias and achieve a reasonable degree of precision. Decision makers in HTA already have tools for measuring some of the items that might constitute a criterion of innovation. Where products promise a `step-change', regulators (e.g. the Food & Drug Administration (FDA) in the United States, or European Medicines Agency (EMA) in Europe) may enable priority designation policies and accelerated access pathways, for devices (73), therapies generally (74, 75) and for specific cases such as gene therapies (76). The strength of the evidence base is commonly assessed by applying a hierarchy of evidence (77)

and where relevant might also capture uncertainties related to the learning curve (78). There are a variety of instruments and outcome measures for patient convenience, though these are not comprehensive or easily transferable between patient groups or technology types. There is some theoretical work on how real option value might be measured, though it has yet to be validated in practice (79). Spill-over would be challenging to measure as an HTA criterion.

4.2 Towards a concept of innovation in Spain

The concept of innovation in healthcare has been widely described and discussed in the literature. However, rarely has it been done thinking about how different countries could go about defining a concept that fits with their HTA systems, to then be able to measure it and incorporate it in their methods guides and their assessments of different types of health technologies. It has been argued in the past that, although there might be distinct features of innovation worth rewarding distinctively, it would only be advisable to do so if innovation can be defined clearly and distinctively enough from other value dimensions already accounted for in the system, and if sustainable ways of rewarding innovativeness can be devised (80). In this paper, the use of a case study allows us to point to how this concept might be tailored to a particular HTA system.

Our findings suggest that the following dimensions might be candidates for a criterion of innovation, at least in the context of HTA in Spain: `step-change', `convenience', `strength of evidence base' and `impact on future R&D'. Of these, the concepts of step-change and strength of evidence base appear to be most straightforward to measure using existing instruments and procedures. However, in the context of innovative technologies, they are in some instances not entirely mutually exclusive. For `step-change', regulators have designations such as 'breakthrough', and 'fast-track' that indicate serious conditions with a potential for significant improvement or unmet need, but at the same time high uncertainty. The evidence base may be undeveloped or weak, leading regulators to require further evidence collection as a condition of approval. HTA decision makers may also wish to stipulate further evidentiary or conditional reimbursement conditions for adoption into national health systems. The relevance of items such as `convenience' or `novel mode of administration' depends on context, though it is important to avoid double counting benefits and to apply such criteria consistently across different indications and interventions. Undoubtedly the most abstract and difficult to measure are items related to the interaction between current adoption decisions and the direction of

future R&D. Novelty *per-se* might be seen as a necessary but not sufficient condition for recognising a technology as innovative, apart from specific circumstances such as an option for patients who are contra-indicated for existing interventions. Real-option value also would only be applicable in very specific circumstances, where patients need to buy time until they can take advantage of another new therapy just on the horizon. Scientific spillover effects are quite abstract and diffuse. R&D investment is a global enterprise influenced by a multitude of factors, and HTA decision-making procedures in individual countries and individual indications may have only a marginal impact, if any. However, there may be specific contexts where scientific advance is propelled forward by synergistic achievements in related areas, such as gene or cell therapies, and this might be usefully recognised at national level.

A change in HTA criteria requires transparency, robustness and an integrative process that gives the opportunity to different stakeholders to present their perspectives (81). MCDA could and has been used to measure the degree of innovation (55, 82-89), to weight the different items to produce an overall innovation score and/or weight the importance of innovation relative to other value dimensions. However, it can be a complex method, data hungry and challenging to use routinely adhering to good practice guidelines (90), particularly by smaller HTA bodies, though the challenges are not insurmountable. A more pragmatic approach could be the use of a checklist, which is something that has already been done for other purposes in HTA (91).

Research into the extent to which innovation is actually captured and used in practice in decision making in HTA suggests that it is indeed taken into account in decision making, and in fact it is referred to by NICE with a high frequency relative to other criteria in their appraisal documents (92). However, it does not rank between the most relevant criteria for most decision makers from across the World (93). An interesting step further would be to explore the societal (i.e. public's) preferences for innovation (94) in any country considering its inclusion in their HTA systems.

5. Conclusions

If innovation is to be used as operational criteria for adoption and P&R of health technologies, the concept must be clearly defined, and it ought to be independent from other value dimensions already captured in HTA systems. We acknowledge that, in the present paper, we have only superficially touched upon these ways of enabling innovation in health technology assessment, and further research would be to work with decision makers to produce a practical framework.

List of abbreviations

Actual Clinical Benefit – ACB

Agenzia Italiana del Farmaco – AIFA

Commissione Tecnico-Scientifica – CTS

European Medicines Agency – EMA

Food & Drug Administration – FDA

Grading of Recommendations Assessment, Development and Evaluation – GRADE

Haute Autorité de Santé – HAS

Health Technology Assessment – HTA

Improvement in Expected Benefit – IEB

Incremental Cost-Effectiveness Ratio – ICER

Interministerial Medicinal Products Pricing Committee – CIPM

Multiple Criteria Decision Analysis – MCDA

National Healthcare System – NHS

National Institute for Health and Care Excellence – NICE

National Institute of Public Health – NIPH

Pricing & Reimbursement – P&R

Quality Adjusted Life Year – QALY

Research and Development – R&D

Spanish Agency of Medicines and Medical Devices – AEMPS

Spanish Network of Agencies for Health Technology Assessment and Services of the National Health System – RedETS

World Health Organization – WHO

Chapter I – Annex I. Search Strategy

To search for relevant literature we used Medline (Ovid) and Google Scholar using free search terms including innovation or Invention or improvement, assessing or defining or measuring or value or degree or technological innovation, Industry or Discovery or Investigation or Design or Evaluation or cost or approval drug, cost or 'cost benefit analysis' or 'health care costs', assessment technology and MESH terms including Innovation or "Diffusion of Innovation" or Inventions, Cost-Benefit Analysis, Biomedical Technology or Technology, Pharmaceutical, Technology Assessment, Biomedical. These search terms were combined using Boolean terms and proximity operators. These searches allowed us to identify the 4 seminal papers that form the basis of our snowballing search. If, whilst searching for those 4 seminal papers, we found papers we found relevant for our review but that did not quite meet our requirements to become one of our seminal papers, we included them in the review as a standard reference. We also run manual secondary searches within the lists of references of the included papers to identify additional relevant studies, performing the snowballing search technique described in the methods section of this paper. We limited the search to publications in Spanish or English. We imposed no limitations to the date of publication of the manuscripts. We selected and included additional publications for this review on the basis of our expertise in the field of health technology assessment, and in particular in the topic of innovation related to health policy. We also added additional relevant records to our search through recommendations of colleagues and through contacts within our networks with expertise in the topic under study in this paper, as suggested by Greenhalgh & Peacock (2015) in their paper (see reference 13 in the main body of our paper).

Chapter I – Annex II. Brief summaries of included papers

Nr.	Reference	Brief Summary
1	Mestre-Ferrandiz J, Sussex J, Towse A. The R&D cost of a new medicine. London: Office of Health Economics; 2012.	This publication reviews research published over the last three decades on the cost of R&D for a successful new medicine, and explores the major factors that are leading to higher R&D costs.
2	DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. J Health Econ. 2016;47:20-33. doi:10.1016/j.jhealeco.2016.01.012.	This study presents the research and development costs of 106 randomly selected new drugs obtained from a survey of 10 pharmaceutical firms. They used these data to estimate the average pre-tax cost of new drug and biologics development.
3	World Health Organization. Health Technology Assessment. [Internet] Geneva WHO; [2021] [cited 2021 3 jan]; Available from: https://www.who.int/health-technology-assessment/about/en/.	WHO website page defining Health Technology Assessment (HTA).
4	Claxton K. OFT, VBP: QED? Health Econ. 2007;16:545-58. doi:10.1002/hec.1249.	Critique examining the theoretical underpinnings of the report by the British Office of Fair Trading on the UK pharmaceutical price regulation scheme (PPRS) published in 2007.
5	de Solà-Morales O, Cunningham D, Flume M, Overton PM, Shalet N, Capri S. Defining innovation with respect to new medicines: a systematic review from a payer perspective. Int J Technol Assess Health Care. 2018;34:224-40. doi:10.1017/s0266462318000259.	Systematic literature review investigating how innovation is defined with respect to new medicines and assessing the extent to which published definitions incorporate the impact of new medicines on healthcare costs.

Nr.	Reference	Brief Summary
6	Claxton K, Martin S, Soares M, Rice N, Spackman E, Hinde S, et al. Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. Health Technol Assess. 2015;19:1-503, v-vi. doi:10.3310/hta19140.	This paper presents the conceptual and methodological framework that builds the cost-effectiveness threshold used by NICE, and presents a best estimate of the threshold for policy purposes.
7	Ciani O, Armeni P, Boscolo PR, Cavazza M, Jommi C, Tarricone R. De innovatione: The concept of innovation for medical technologies and its implications for healthcare policy-making. Health Policy Technol. 2016;5:47-64. doi:10.1016/j.hlpt.2015.10.005.	This systematic literature review of the academic literature aims to summarise acceptable definitions of innovation in relation to medical devices.
8	Ilinca S, Hamer S, Botje D, Espin J, Veloso Mendes R, Müller J, et al. All You need to know about innovation in healthcare: The best 10 reads. Int J Healthc Manag. 2012;5:193-202. doi:10.1179/2047971912y.0000000018.	Study presenting the results of a Delphi panel conducted to identify and select the 10 most relevant and informative scientific writings, which can add significantly to the knowledge of managers by offering an introduction in the academic discussion on the topic of innovation in healthcare.
9	Juárez Castelló CA, Antoñanzas Villar F, Pinillos García MO. Innovación en medicamentos: efectos para el" cliente" público y cambios legislativos recientes. In: Ayala Calvo JC, Universidad de la Rioja, Grupo de Investigación Fedra, editors. Conocimiento, innovación y emprendedores : camino al futuro.	This paper presents an analysis of the R&D process of medicines in the context of the degree and types of innovation they bring by. Additionally, the authors review the main economic aspects of the 2006 Act of Guarantees and Rational Use of the Medicine and the Sanitary Products in Spain.

Nr.	Reference	Brief Summary
	Logroño: Universidad de la Rioja; [2007]. p. 1466-81.	
10	Motola D, De Ponti F, Rossi P, Martini N, Montanaro N. Therapeutic innovation in the European Union: analysis of the drugs approved by the EMEA between 1995 and 2003. Br J Clin Pharmacol. 2005;59:475-8. doi:10.1111/j.1365-2125.2004.02320.x.	The authors review the list of drugs approved by the EMEA between January 1995 through the first 6 months of 2003, and assign to them scores for therapeutic innovation assigned through a consensus process classifying them into one of three degrees of innovation: 'A' (important), 'B' (moderate) and 'C' (modest).
11	Moreno SG, Ray JA. The value of innovation under value-based pricing. J Mark Access Health Policy. 2016;4. doi:10.3402/jmahp.v4.30754.	In this paper, the authors outline the limitations of the conventional cost-effectiveness analysis approach, while proposing an alternative method of evaluation that, they argue, captures the value of innovation more accurately.
12	Badampudi D, Wohlin C, Petersen K. Experiences from Using Snowballing and Database Searches in Systematic Literature Studies. Proceedings 19th International Conference on Evaluation and Assessment in Software Engineering (EASE 2015), Nanjing, China; 2015: ACM Press; 2015.	This study evaluates the efficiency and reliability of snowballing search techniques when used as a search strategy in literature studies. They also compare the performance of snowballing searches with database searches.
13	Greenhalgh T, Peacock R. Effectiveness and efficiency of search methods in systematic reviews of complex evidence: audit of primary sources. Bmj. 2005;331(7524):1064-5. Greenhalgh T, Peacock R. Effectiveness and efficiency of search methods in	This paper is a review of reviews, aimed at describing where papers come from in systematic reviews of complex evidence. The authors assess whether formal protocol-driven search strategies are sufficient to respond complex policy questions, or if other searching techniques may perform better.

Nr.	Reference	Brief Summary
	systematic reviews of complex evidence: audit of primary sources. Bmj. 2005;331(7524):1064-5. doi:10.1136/bmj.38636.593461.68.	
14	Diaby V, Goeree R. How to use multi-criteria decision analysis methods for reimbursement decision-making in healthcare: a step-by-step guide. Expert Rev Pharmacoecon Outcomes Res. 2014;14:81-99. doi:10.1586/14737167.2014.859525.	This article presents the main MCDA decision support methods (elementary methods, value-based measurement models, goal programming models and outranking models) using a case study approach. The authors provide a step-by-step guide on how to use MCDA methods for reimbursement decision-making in healthcare.
15	Fortinguerra F, Tafuri G, Trotta F, Addis A. Using GRADE methodology to assess innovation of new medicinal products in Italy. Br J Clin Pharmacol. 2020;86:93-105. doi:10.1111/bcp.14138.	The aim of this study is to describe the new model that the Italian Medicine Agency (AIFA) presented in April 2017 to grant any new medicinal product with an innovative designation.
16	Real Decreto Legislativo 1/2015 de 24 de julio. Ley de garantías y uso racional de los medicamentos y productos sanitarios., Boleín Oficial del Estado, nº 177, (25-07-2015).	Legislative Royal Decree, published in July 2015, whereby a series of previous legislative measures are consolidated into one law of guarantees and rational use of medicines and health products.
17	Garrison LP, Jr., Kamal-Bahl S, Towse A. Toward a Broader Concept of Value: Identifying and Defining Elements for an Expanded Cost-Effectiveness Analysis. Value Health. 2017;20:213-16. doi:10.1016/j.jval.2016.12.005.	This paper identifies and defines potentially useful expansions to traditional cost-effectiveness analysis as often used in health technology assessment. The authors propose a an expanded framework, incorporating a wider range of elements of value to health technology assessment.
18	Angelis A, Kanavos P. Multiple Criteria Decision Analysis (MCDA) for evaluating new medicines in Health Technology Assessment and beyond:	This study proposes a Multiple Criteria Decision Analysis (MCDA) methodological process for the assessment of medicines, eliciting 5 key domains of value and structuring them into a generic

Nr.	Reference	Brief Summary
	The Advance Value Framework. Soc Sci Med. 2017;188:137-56. doi:10.1016/j.socscimed.2017.06.024.	value tree. The combination of these MCDA modelling techniques for the elicitation and construction of value preferences across a generic value tree provides a new value framework (Advance Value Framework) enabling the comprehensive measurement of value in a structured and transparent way.
19	Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535. doi:10.1136/bmj.b2535.	In 1996, an international group developed the QUOROM Statement (Quality Of Reporting Of Meta-analyses), which focused on the reporting of meta-analyses of randomized controlled trials. This paper summarises a revision of these guidelines, renamed PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses), updated to address several conceptual and practical advances in the science of systematic reviews.
20	Mestre-Ferrandiz J, Mordoh A, Sussex J. The many faces of innovation. A report for the ABPI by the Office of Health Economics. London: Association of the British Pharmaceutical Industry; 2012.	The objective of this report is to aid understanding of the nature of innovation in the pharmaceutical industry. To do so, they do a review of the literature on the economics of innovation and present a series of case studies of several therapy areas to demonstrate pharmaceutical innovation in practice showing cases where there were major advances in treatments bringing by innovation to the market.
21	Kennedy I. Appraising the Value of Innovation and Other Benefits: A Short Study for NICE. [Internet] London: NICE; 2009 [cited 2021 23 feb]; Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/Research-	This report is a result of NICE commissioning a study to respond to the following questions: (i) Are there any benefits (or values) which NICE should take into account in its technology appraisals which it currently does not capture?; (ii) is innovation as a benefit properly taken account of?; (iii) to the extent that innovation

Nr.	Reference	Brief Summary
	and-development/Kennedy-study-final-report.pdf.	and other benefits should be taken into account, how should NICE do so?
22	Charlton V, Rid A. Innovation as a value in healthcare priority-setting: the UK experience. Soc Justice Res. 2019;32:208-38. doi:10.1007/s11211-019-00333-9.	The authors use UK's NICE as an example to examine how efforts to promote healthcare innovation in the priority-setting process can play part in the inevitable trade-offs between maximising health and promoting health equity. They nalyse under what conditions NICE recommends funding technologies of an "innovative nature", even when these technologies do not satisfy NICE's cost-effectiveness criteria.
23	National Institute for Health and Care Excellence. Single technology appraisal: User guide for company evidence submission template. [Internet] London: NICE; 2015 [cited 2021 18 feb]; Available from: https://www.nice.org.uk/process/pmg24/resources/single-technology-appraisal-user-guide-for-company-evidence-submission-template-pdf-72286715419333.	This is the user guide for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. It explains what information NICE requires and the format in which it should be presented.
24	Haute Autorité de Santé. Annual report 2005. [Internet] Saint-Denis La Plaine: HAS; 2005 [cited 2021 1 jan]; Available from: https://www.has-sante.fr/upload/docs/application/pdf/ra_gb_has_2005.pdf.	This annual report presents the activities carried out by HAS in 2005 and looks ahead into the future plans of the agency.
25	Haute Autorité de Santé. Pricing & Reimbursement of drugs and HTA policies in France. Saint-Denis La	This is a presentation outlining the reimbursement and pricing system for drugs in place in France, describing the aspects of value of

Nr.	Reference	Brief Summary
	Plaine: HAS; 2014 [cited 2021 2 jun]; Available from: https://www.has-sante.fr/upload/docs/application/pdf/2014-03/pricing_reimbursement_of_drugs_and_hta_policies_in_france.pdf.	a drug considered by HAS and how those are incorporated in a system to make reimbursement and pricing decisions. It also describes more procedural aspects of the system.
26	Dubromel A, Geffroy L, Aulagner G, Dussart C. Assessment and diffusion of medical innovations in France: an overview. J Mark Access Health Policy. 2018;6:1458575. doi:10.1080/20016689.2018.1458575.	This article provides an overview of the assessment and diffusion of medical innovation in France. The authors also discuss key opportunities and challenges of medical innovation assessment and diffusion in France.
27	Haute Autorité de Santé. Innovative medicines assessment action plan [Internet] Saint-Denis La Plaine: HAS; 2020 [cited 2021 22 feb]; Available from: https://www.has-sante.fr/upload/docs/application/pdf/2020-03/innovative_medicine_action_plan_27.01.20.pdf.	This report presents HAS' 2020 action plan for innovative therapies, describing their plans to respond to an environment where increasingly drugs reach HTA agencies with evidence that presents numerous unresolved uncertainties, most notably in cases of short clinical development often seen for small patient sample sizes.
28	Ministerio de Sanidad Servicios Sociales e Igualdad. Propuesta de colaboración para la elaboración de los informes de posicionamiento terapéutico de los medicamentos. [Internet] Madrid: AEMPS; 2013 [cited 2021 19 feb]; Available from: https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/propuesta-colaboracion-	This document sets the foundations for a collaborative process to produce the therapeutic positioning reports for medicines in Spain. It describes the procedure and agents involved in the production of these reports, and it also describes the phases in which the reports will be generated.

Nr.	Reference	Brief Summary
	informes-posicionamiento-terapeutico.pdf.	
29	Ley 29/2006, de 26 de julio. Ley de garantías y uso racional de los medicamentos y productos sanitarios, Boleín Oficial del Estado, nº 178, (27-07-2006) (2006).	Law for the rational use of medicines and health products, published in 2006, which regulates the reimbursement and financing mechanisms for these products in Spain.
30	Puñal-Riobóo J, Baños Álvarez E, Varela Lema L, Castillo Muñoz MA, Atienza Merino G, Ubago Pérez R, et al. Guía para la elaboración y adaptación de informes rápidos de evaluación de tecnologías sanitarias. Madrid. Santiago de Compostela: Red Española de Agencias de Evaluación de Tecnologías Sanitarias y Prestaciones del SNS. Agencia Gallega para la Gestión del Conocimiento en Salud. Unidad de Asesoramiento Científico-técnico, Avalia-t; 2016.	Methodological document describing the methodology used by the Spanish Network of Health Technology Assessment Agencies in their assessments. The Network seeks a unified and coordinated approach to the production of HTAs of medical devices in Spain.
31	National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. [Internet] London: NICE; 2013 [cited 2021 19 feb]; Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781.	This document provides an overview of the principles and methods of health technology assessment and appraisal within the NICE technology appraisal process.
32	Angelis A, Lange A, Kanavos P. Using health technology assessment to assess the value of new medicines:	In this paper, the authors study the practices, processes and policies of value-assessment for new medicines across eight European countries

Nr.	Reference	Brief Summary
	results of a systematic review and expert consultation across eight European countries. Eur J Health Econ. 2018;19:123-52. doi:10.1007/s10198-017-0871-0.	and the role of HTA beyond economic evaluation and clinical benefit assessment. The countries under study in this article are France, Germany, England, Sweden, Italy, Netherlands, Poland and Spain.
33	Epstein D, Espín J. Evaluation of new medicines in Spain and comparison with other European countries. Gac Sanit. 2020;34:133-40. doi:10.1016/j.gaceta.2019.02.009.	The authors of this study compare the use of HTA as a tool to support pricing and reimbursement (P&R) of new medicines in Spain with its use in England, Sweden, France and Germany.
34	Kamae I, Thwaites R, Hamada A, Fernandez JL. Health technology assessment in Japan: a work in progress. Journal of medical economics. 2020;23(4):317-22. doi:10.1080/13696998.2020.1716775.	This paper provides an update on recent HTA developments in Japan and key challenges still to be addressed, reporting the results of a review of publications and commentaries since April 2019, together with views from a group of experts on key issues to be addressed.
35	Shiroiwa T, Fukuda T, Ikeda S, Takura T. New decision-making processes for the pricing of health technologies in Japan: The FY 2016/2017 pilot phase for the introduction of economic evaluations. Health Policy. 2017;121(8):836-41. doi:10.1016/j.healthpol.2017.06.001.	In this paper, the authors provide an overview of relevant discussions and the process of trial implementation of the reformed Japanese system after a brief explanation of the Japanese system of pricing drugs and medical devices.
36	Ministerio de Industria Comercio y Turismo. PROFARMA (2017-2020): Fomento de la competitividad en la Industria Farmacéutica. [Internet] Madrid: Ministerio de Industria, Comercio y Turismo; 2017 [cited 2021 16 feb]; Available from:	This is the webpage within the Spanish Ministry of Industry describing PROFARMA, a government lead programme aiming to incentivise the pharmaceutical sector to invest in Spain. To do so, they empower pharmaceutical companies to invest in new production plants in the country, invest in new manufacturing technologies and

Nr.	Reference	Brief Summary
	https://www.mincotur.gob.es/PortalAyudas/profarma/Descripcion/Paginas/objetivos.aspx	facilities in Spain. Their incentives are mainly fiscal.
37	Food and Drug Administration. Breakthrough Devices Program. [Internet] Silver Spring: FDA; 2021 [cited 2021 22 jan]; Available from: https://www.fda.gov/medical-devices/how-study-and-market-your-device/breakthrough-devices-program.	FDA webpage presenting their breakthrough devices program. It is a is a voluntary program for certain medical devices and device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. It replaces their earlier Expedited Access Pathway and Priority Review for medical devices.
38	Food and Drug Administration. Breakthrough Therapy. [Internet] Silver Spring: FDA; 2018 [cited 2021 24 jan]; Available from: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy.	FDA webpage presenting their breakthrough therapy program, which is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).
39	Baird LG, Banken R, Eichler HG, Kristensen FB, Lee DK, Lim JC, et al. Accelerated access to innovative medicines for patients in need. Clin Pharmacol Ther. 2014;96:559-71. doi:10.1038/clpt.2014.145.	This paper describes the specific approaches that have been taken in four economically developed regions to the design and implementation of early-access pathways or initiatives, reviews their success rates, and suggests possible new directions.
40	Yitong Wang TQ, Shuyao Liang, Claude Dussart. Regulatory Pathways in Europe, the United States, and Japan and Health Technology Assessments for Gene Therapies. Value & Outcomes Spotlight. 2020;6:37-41.	This article given reviews the marketing-authorization pathways for cell and gene therapies in the European Union (EU), the United States, and Japan. Furthermore, the authors compared the regulatory and reimbursement status of gene therapies in the United States and 5 European countries: France, the United

Nr.	Reference	Brief Summary
		Kingdom (England and Scotland), Germany, Italy, and Spain.
41	Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924-6. doi:10.1136/bmj.39489.470347.AD.	This paper explores the advantages of the GRADE system, which is increasingly being adopted by organisations all over the world, to help reduce inconsistencies in how guideline developers worldwide rate the quality of evidence and the strength of recommendations.
42	Ramsay CR, Grant AM, Wallace SA, Garthwaite PH, Monk AF, Russell IT. Assessment of the learning curve in health technologies. A systematic review. Int J Technol Assess Health Care. 2000;16:1095-108. doi:10.1017/s0266462300103149.	The authors of this work reviewed and appraised the methods by which the issue of the learning curve has been addressed during health technology assessment in the past.
43	Thornton Snider J, Romley JA, Vogt WB, Philipson TJ. The Option Value of Innovation. Forum Health Econ Policy. 2012;15. doi:10.1515/1558-9544.1306.	This paper defines the term “option value” of innovation in health technologies, explain how to calculate it in a variety of standard cost effectiveness analysis contexts and provide a proof-of-concept using the example of the drug tamoxifen.
44	Ferner RE, Hughes DA, Aronson JK. NICE and new: appraising innovation. BMJ. 2010;340:b5493. doi:10.1136/bmj.b5493.	In this article the authors consider how innovativeness might be defined in health care, and how NICE and other organisations analysing health technologies might allow it to influence appraisal decisions.
45	National Institute for Health and Care Excellence. NICE’s methods of technology evaluation - presenting a case for change. [Internet] London: NICE; 2020 [cited 2021 27 jan]; Available from:	Webpage within NICE’s website announcing the launch, on the 6 November 2020, of a public consultation on proposals for changes to the methods it uses to develop its guidance on medicines, medical devices and diagnostics.

Nr.	Reference	Brief Summary
	https://www.nice.org.uk/news/article/nice-s-methods-of-technology-evaluation-presenting-a-case-for-change.	
46	Angelis A. Evaluating the Benefits of New Drugs in Health Technology Assessment Using Multiple Criteria Decision Analysis: A Case Study on Metastatic Prostate Cancer With the Dental and Pharmaceuticals Benefits Agency (TLV) in Sweden. MDM Policy & Practice. 2018;3:2381468318796218. doi:10.1177/2381468318796218.	The aim of this paper is to test in practice the Advance Value Framework, an MCDA methodological framework for HTA, in a proof-of-concept case study with decision makers from the Dental and Pharmaceuticals Benefits Agency (TLV) in Sweden.
47	Angelis A, Linch M, Montibeller G, Molina-Lopez T, Zawada A, Orzel K, et al. Multiple Criteria Decision Analysis for HTA across four EU Member States: Piloting the Advance Value Framework. Soc Sci Med. 2020;246:112595. doi:10.1016/j.socscimed.2019.112595.	This article presents the application of the Advance Value Framework (AVF), an MCDA methodology for HTA based on multi-attribute value theory, through a series of case studies with decision-makers in four countries (Sweden (TLV), Andalusia/Spain (AETSA), Poland (AOTMiT) and Belgium (INAMI-RIZIV)), to explore its feasibility and compare decision-makers' value preferences and results.
48	Angelis A, Thursz M, Ratziu V, O'Brien A, Serfaty L, Canbay A, et al. Early Health Technology Assessment during Nonalcoholic Steatohepatitis Drug Development: A Two-Round, Cross-Country, Multicriteria Decision Analysis. Med Decis Making. 2020;40:830-45. doi:10.1177/0272989x20940672.	The aim of this paper was to investigate the use of multicriteria decision analysis (MCDA) to support decision making during drug development while considering payer and health technology assessment (HTA) value concerns, by applying the Advance Value Framework in nonalcoholic steatohepatitis (NASH) and testing for the consistency of the results.

Nr.	Reference	Brief Summary
49	Baran-Kooiker A, Czech M, Kooiker C. Multi-Criteria Decision Analysis (MCDA) Models in Health Technology Assessment of Orphan Drugs-a Systematic Literature Review. Next Steps in Methodology Development? Front Public Health. 2018;6:287. doi:10.3389/fpubh.2018.00287.	This work provides an overview of the current state of the art and latest developments in the area of MCDA in HTA for orphan drugs, to review existing models, their characteristics, as well as to identify opportunities for further refinement.
50	Angelis A, Montibeller G, Hochhauser D, Kanavos P. Multiple criteria decision analysis in the context of health technology assessment: a simulation exercise on metastatic colorectal cancer with multiple stakeholders in the English setting. BMC Med Inform Decis Mak. 2017;17:149. doi:10.1186/s12911-017-0524-3.	This project tests in practice the Advance Value Framework (AVF), MCDA methodological framework, through a proof-of-concept case study in metastatic colorectal cancer engaging multiple stakeholders within the English setting.
51	Hsu JC, Lin JY, Lin PC, Lee YC. Comprehensive value assessment of drugs using a multi-criteria decision analysis: An example of targeted therapies for metastatic colorectal cancer treatment. PLoS One. 2019;14:e0225938. doi:10.1371/journal.pone.0225938.	This study paper presents a decision-making model with multiple criteria for appraisal and reimbursement to compare the attitudes of different stakeholders toward various dimensions and criteria and to evaluate the five targeted therapies (bevacizumab, cetuximab, panitumumab, aflibercept, and regorafenib) for metastatic colorectal cancer.
52	Jakab I, Németh B, Elezbawy B, Karadayı MA, Tozan H, Aydın S, et al. Potential Criteria for Frameworks to Support the Evaluation of Innovative Medicines in Upper Middle-Income Countries-A Systematic Literature	Systematic review aiming to facilitate the development of future MCDA frameworks, by proposing a set of criteria focusing on the purchasing decisions of single-source innovative pharmaceuticals in upper middle-income countries.

Nr.	Reference	Brief Summary
	Review on Value Frameworks and Multi-Criteria Decision Analyses. Front Pharmacol. 2020;11:1203-. doi:10.3389/fphar.2020.01203.	
53	Thokala P, Duenas A. Multiple criteria decision analysis for health technology assessment. Value Health. 2012;15:1172-81. doi:10.1016/j.jval.2012.06.015.	This article analyses the possible application of MCDA approaches in health technology assessment and describes their relative advantages and disadvantages.
54	Phillips LD. Best Practice for MCDA in Healthcare. In: Marsh K., Goetghebeur M., Thokala P., Baltussen R, editors. Multi-Criteria Decision Analysis to Support Healthcare Decisions. Cham, Switzerland: Springer; 2017. p. 311-29.	Book chapter that presents the theoretical underpinnings of decision theory extending it to accommodate multiple criteria for evaluating the values of alternative courses of action, to then present an eight-step framework for constructing an MCDA model used to formulate best practice principles.
55	Hailey D. Toward transparency in health technology assessment: a checklist for HTA reports. Int J Technol Assess Health Care. 2003;19:1-7. doi:10.1017/s0266462303000011.	This paper presents an initiative of the International Network of Agencies for Health Technology Assessment (INAHTA) that developed a checklist for assessment reports as a means of improving transparency and consistency in HTA.
56	de Folter J, Trusheim M, Jonsson P, Garner S. Decision-components of NICE's technology appraisals assessment framework. Int J Technol Assess Health Care. 2018;34:163-71. doi:10.1017/s0266462318000090.	The authors present a novel application of text analysis that characterizes NICE's Technology Appraisals in the context of the newer assessment frameworks and they present the results in a visual way. They identify a hierarchical set of decision factors considered in the assessments, and determine the frequency of recurrence of decision factors.
57	Tanios N, Wagner M, Tony M, Baltussen R, van Til J, Rindress D, et	This study gathers qualitative and quantitative data on criteria considered by healthcare

Nr.	Reference	Brief Summary
	al. Which criteria are considered in healthcare decisions? Insights from an international survey of policy and clinical decision makers. Int J Technol Assess Health Care. 2013;29:456-65. doi:10.1017/s0266462313000573.	decision makers from 23 countries in five continents.
58	Linley WG, Hughes DA. Societal views on NICE, cancer drugs fund and value-based pricing criteria for prioritising medicines: a cross-sectional survey of 4118 adults in Great Britain. Health Econ. 2013;22:948-64. doi:10.1002/hec.2872.	This paper explores societal preferences for criteria such as those used by the National Institute for Health and Clinical Excellence (NICE) for accepting higher incremental cost-effectiveness ratios for some medicines over others, or to implement policies such as the Cancer Drugs fund and the attempt made to introduce the so-called value based pricing scheme in England. To do so, they conducted a choice-based experiment in 4118 UK adults via web-based surveys.

Chapter II. How should medicines reimbursement work? The views of Spanish experts

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1. Introduction

Countries around the world face similar questions when it comes to shaping their pricing and reimbursement (P&R) systems. Amongst other concerns, they need to resolve conundrums such as 'What criteria should we take into account to inform our P&R decisions?' 'What methodologies should we apply to measuring compliance with those criteria?'. In countries like England and Wales, their health technology assessment (HTA) system is set in such way that HTA recommendations come with a funding mandate (the National Health System must fund technologies recommended by their HTA agency) (95). Hence, one only needs to look at their HTA methods and processes manuals to find out how they have answered the questions above. However, in other systems the answer is less self evident.

In Spain for instance, pricing and reimbursement decisions, which are the responsibility of the Interministerial Commission on Drug and Health Product Prices (CIPM), should be made considering 6 criteria (26, 27):

a) Severity, duration and sequelae of the different pathologies for which they are indicated;

b) Specific needs of certain groups;
c) Therapeutic and social value of the medicine and its incremental clinical benefit, taking into account its cost-effectiveness;
d) Rationalization of public spending on pharmaceuticals and budgetary impact on the National Health System;
e) Availability of medicines or other therapeutic alternatives for the same conditions at a lower price or lower treatment cost;
f) Degree of innovation of the new medicine.

However, although the law came into effect in 2005, there is still a lack of regulatory development to define and measure the criteria outlined above. This has led to concerns of methodological incoherence in the evidence, and that decisions lack transparency, predictiblity and consistency (4, 96). In other words, in Spain the first question listed above (what criteria should support P&R decisions) has been answered, but the second (how should we measure them) has not.

Moveover, in the Spanish case, their own Advisory Committee for the Reimbursement of the Pharmaceutical Provision recommended greater transparency and robustness (96, 97). Principles of good practice for HTA recommend criteria and instruments that facilitate a broad focus and promote fair and transparent decisions (98, 99). Additionally, countries in the European Union (EU) will need to adapt to the new european regulation on HTA, to accommodate their national systems to the new context (100). Hence, the present moment is favourable for exploring the level of consensus in the expert community around the options that could be used to define and measure the criteria listed in the law for medicines financing decision-making in Spain. This could, not only inform further developments in Spain, but it could also serve as inspiration for other countries embarking on a similar journey towards implementing greater levels of transparency, consistency and robustness in their systems.

Some previous papers have covered similar ground. A group of publications have reviewed the actual criteria that support decisions in a number of countries. Research on the Bulgarian reimbursement system analysed what criteria were being used to support reimbursement decisions in Bulgaria, and what criteria should be used in the views of a range of stakeholders (101). A study focusing on the French system provides empirical research of the criteria that drive positive reimbursement decisions in France, where medicines deemed to gave an insufficent “medical service rendered” (MSR) by the French Medicines Agency are excluded from coverage by the National Health Service (102). Furthermore, researchers have examined the

Irish system, extracting information from both published and grey literature, including HTA reports, to identify the criteria that have impacted reimbursement decisions in Ireland (103). In an additional paper, a focus panel of 5 experts was convened to share their opinions on the criteria that should be used to determine reimbursement decisions for medicines in Slovenia. Their views, elicited using a focus panel approach, were compared with the actual criteria used in the country (104). Other authors have surveyed the views of stakeholders or experts about the criteria for P&R in Spain focusing on specific case studies (105) or gathering views about the P&R process without specificifically focusing on how to measure these criteria (106).

Additional research efforts have focused on analysing and further unveiling specific reimbursement criteria. For instance, one publication explored the attributes that might define the degree of innovation and how a selection of countries approach their incorporation in decision making (107). A comparative study analysed the role of disease severity and how it is operationalized in reimbursement decisions for medicines in Belgium, France, the Netherlands and Sweden (108). A Dutch project analysed the use of budget impact as a criterion to support reimbursement decisions for medicines in the Netherlands, and the rationale and legitimacy for considering this criterion in rationing decisions (109).

This paper presents the results of a survey distributed to a group of experts involved or with an interest in the evaluation of medicines in Spain at different levels. The survey inquired about the optimal ways of measuring the criteria specified in Spanish law that ought to support reimbursement decisions. We also sought input on the weighting of these criteria in reimbursement decisions, their appropriateness for informing such decisions, and the potential inclusion of additional criteria to the existing list. Specifically, we explored the potential appropriateness of adding the experience of patients to this list of criteria.

With this paper, our ambition is to contribute to the field of health technology assessment and health policy by generating empirical evidence of the views of a broad sample of experts with knowledge of the Spanish pricing and reimbursement system, covering the key stakeholder groups involved in it, on on the range of issues described above. To our knowledge, no previous research has elicited the views of experts on how to measure the reimbursement criteria listed in Spanish law. We believe this research could be useful beyond the Spanish context, potentially serving as inspiration to researchers and policy makers in countries that might be facing similar challenges.

The paper is organised as follows. The next section outlines the data we have obtained and the methods we used to obtain it and analyse it. In the following section we present the results obtained. And finally, we put these results into context in the discussion section and formulate brief conclusions and recommendations in the very last section of the paper.

2. Data and methods

2.1 Data

We distributed a survey (see Annexes and for the original survey in Spanish – Annex I – and a translation of it into English – Annex II) members of scientific, professional, academic and industry organizations who currently participate in the HTA process at national or regional level in Spain, who have indepth knowledge of it. We do not know if these individuals themselves participate (this information is confidential) but are likely to be colleagues of people who do, or to have a professional interest and opinion about the HTA process. The main reason why we targetted specialists in the topic was that to answer the questionnaire they needed to be familiarised with the contents of course, and in healthcare there is an information asymetry between the general public and specialised professionals, arising from the highly specialised nature of knowledge in this field (110).

The target respondents were:

- Spanish Association of Health Economics (AES): an association of professionals working in the field of health economics and HTA. Most members are academics. This group provides comments on national HTA reports.
- Technicians and senior officials of the 8 agencies that make up the Spanish Network of Health Technology Assessment Agencies (RedETS): This network mainly focuses on HTA of medical devices.
- The GENESIS group: a group created within the Spanish Society of Hospital pharmacist, entailing hospital pharmacists with an interest in HTA for hospital decision making purposes, created to coordinate and harmonise practices across Spanish hospitals, and to further develop the guidance supporting their evaluations.

- Spanish Agency of Medicines and Health Products (AEMPS): the national regulatory body which produces therapeutic positioning reports (a form of HTA) on new medicines.
- Farmaindustria (the Spanish Pharmaceutical Industry Association): a trade body representing producers of patented medicines.
- Spanish chapter of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR): a society including industry, academia and consulting firms.
- Technical analysts and advisors to the Spanish Ministry of Health.

The survey was designed by the authors of this paper. We drafted a first version, which we circulated to 4 reknowned experts to pilot it and refine it, including two health economists, one hospital pharmacist and a director-level staff member of an umbrella industry association. We used the online software Tally (https://tally.so/) to construct the survey (see Annex I for the original survey in Spanish and Annex II for a translation in English). We drafted an email that included an invitation letter and a link to the survey. In order to maximise participation, we made use of contacts in each interest group to distribute the survey. We distributed the survey to members of the AES community using their mailing list. To reach staff members of the RedETS, we asked the directors of the agencies to forward the email to the targeted staff in the Network. We used a member of the GENESIS group to make the survey available to hospital pharmacists. We distributed the survey to AEMPS staff via one of their directors. The members of the Spanish Chapter of ISPOR received the survey via one of the Board Members of their Chapter. One of the co-authors of the paper (DE) was holding a role as advisor to the Spanish Ministry of health whilst this research was being performed. He distributed the survey to technical staff and advisors to the Ministry involved in areas relevant to the assessment and pricing and reimbursement processes for medicines in the Ministry. We distributed the survey to members of the Spanish Farmaindustria through one of the members of their Board.

We circulated the survey on the 9 May 2022, giving initally 2 weeks to respond (until the 23 May at 23:59 pm). We sent 2 reminders between the 9 May and the 23 May. Where specific stakeholder groups requested it, we offered one extra week to respond to the survey.

The survey was designed and distributed in Spanish. We present a full original version of the survey in Annex I, accompanied by a translation of it into English in Annex II.

The survey has an initial section surveying respondents about the stakeholder group they belong to, their years of professional experience and their level of seniority within their organisations.

Then, it includes questions to investigate the preferred instrument/s for respondents to measure each one of the criteria used to support reimbursement decisions for new medicines in Spain, as explained in the introduction. Each one of the questions contained in within these sections, had an option labelled as 'Others' where respondents had a free text section, to express views not captured in any of the options offered in the survey. For instance, if they thought the criterion they were being asked about best ways to measure it should not be taken into account in decision making, they could write it there. Or they could also suggest alternative ways of measuring that criterion not listed by us in the survey. We then asked a question asking respondents to weight each one of the criteria, from 0 to 100, taking into account that all weights should add up to 100. We also asked if respondents believed the criteria listed in the law are appropriate, and if they thought any additional criteria should be taken into account. Fnally, we asked if they thought the patient perspective should be added to the list of criteria considered in Spain to make reimbursement decisions for new medicines.

2.2 Methods

Most questions in our survey allow for multiple responses, but some only allow one response, depending on whether we thought the responses were mutually exclusive or if decisions could be informed by alternative ways of measuring the same criteria. In Annex IV we reported a table showing where responders opted for one single answer or if they chose multiple ones.

To analyze whether the respondents' characteristics might be associated with the responses, logistic regressions were fitted to each question following the form of equation 1:

$$y = \beta_1 institution + \beta_2 experience + \beta_3 position,$$

Where y represents whether the respondent chooses an option or not in a given question, and the categorical independent variables indicate the institution where the respondent works, the years of experience in the field, and the position of the respondent. We detail all our analyses of differences in responses amongst stakeholder groups in Annex V, and also describe more briefly below, in our results section.

3. Results

We structure this section in subsections, resembling the structure followed in our survey. First, before getting into the detail of each question and the exact percentages of responders that chose each option, we present a brief general overview of the preferred ways of measuring each one of the criteria addressed in our survey. Then, we move on to present a short summary of the characteristics of the sample of respondents, to then go on to describe in detail the responses they gave to the questions in the survey (the survey is fully disclosed in Annex I, in it's original version in Spanish, and also translated into English), including the exact percentages that chose each option and also descriptions of the answers they entered as free text.

3.1 The sample

We distributed the survey via interest groups and professional societies, with collectively about over 1,000 members. We received 90 responses.

The highest proportion of responders belonged to one of the HTA bodies that compose the RedETS (23 (26%)). The second group most represented amongst respondents is governmental entities (15 (17%)), including but not limited to the Spanish Ministry of Health (e.g., some of the members of AES could work for their regional departments of health and would fall under this category). The third most represented group in our survey were researchers (13 (14%)), closely followed by industry representatives (13%). Other groups included staff from regulatory agencies (10 (11%)), hospital pharmacists (10 (11%)) and consultants (7 (8%)). Most (72(80%)) had 8 or more years experience.

3.2. General Overview of preferred measurement instruments

Table 1 classifies responses in ranges of percentages of respondents who chose each one of the options we listed in the survey (all responses to all questions in the survey are tabulated in Annex III).

Table 1. Preferred ways of measuring each criterion (N=90)

	0% – 25%	**26% - 50%**	**51% - 75%**	**76% - 100%**
Severity*	Disease specific severity instrument (19 (21%)) Other (2 (2%))	DALY (40 (44%))	QALY (61 (68%)) Clinical units (61 (68%))	/
Specific groups*	Other (5 (6%))	Paediatric population (42 (47%)) End of life (32 (36%))	Rare diseases (64 (71%))	Unmet need (82 (91%))
Therapeutic value*	Other (0 (0%))	Clinical units (44 (49%)) Clinical benefit index – French approach (SMR) (44 (49%))	/	QALY (72 (80%))
Cost-effectiveness*	Other (6 (7%))	/	ICER (60 (67%))	ICUR (70 (78%))
Threshold (yes/no)	No (6 (7%))	/	/	Yes (84 (93%))

	0% – 25%	26% - 50%	51% - 75%	76% - 100%
Threshold (explicit/implicit)	Implicit (14 (16%))	/	/	Explicit (70 (78%))
Threshold (special situations: yes/no)	No (10 (11%))	/	/	Yes (74 (82%))
Social value*	Other (4 (4%))	Impact of industry on the local/national economy (25 (28%))	/	QoL informal carers (73 (81%)) Productivity (87 (97%))
Budget impact	Pharmaceutical spending, 3-5 years horizon (3 (3%)) Other (9 (10%))	/	/	Total expenditure, 3-5 years horizon (78 (87%))
Therapeutic* alternatives	ATC4 (11 (12%)) Other (8 (9%))	ATC5 (34 (38%))	Therapeutic equivalent (59 (66%))	/
Degree of innovation*	Other (9 (10%))	MCDA (32 (36%))	Checklist (49 (54%))	/

*Respondents were able to choose one or more options in the survey

3.3. Severity, duration and sequelae of the different pathologies for which they are indicated

To measure the severity, duration and sequelae of the different pathologies for which a new medicine is indicated, we offered respondents 5 options, allowing them to mark multiple ones (i.e., meaning that they believe more than one way of measuring this should be used to inform decisions). The most voted options, both voted by 61 (68%) respondents, were: The Quality Adjusted Life-Year (QALY), and the use of clinical markers of severity, durationand sequelae.

The binary outcome regression found that industry staff were less likely to choose the QALY while academics were less likely to prefer clinical markers (see Table A1 in Annex V).

3.4. Specific needs of certain groups

Spanish legislation requires that the specific needs of certain groups are taken into account in reimbursement decisions in Spain, without naming particular groups or needs. We consulted our respondents about four groups: those with unmet medical needs, rare diseases, paediatric populations, and those at the end of life. Each of these situations has been addresssed by European Pharmaceutical Regulation (100) or HTA bodies in other countries (111-115). Multiple responses were allowed. The first group we listed in our survey was populations with a condition for which there is no satisfactory therapeutic alternative, following the European Commission's definition of unmet medical need (116). In Spain this group has been defined as population living with a serious pathology for which there is a therapeutic gap (117). 82 (91%) respondents thought this group deserved special consideration when it came to reimbursement decisions for new medicines. Orphan medicines (as per the European Medicines Agency (EMA) definition (118)), or medicines indicated for ultra-rare diseases (113, 119), do also deserve special consideration according to 64 (71%) of our respondents. Just about less than half (42 (47%)) of our respondents were of the view that pediatric populations (112, 120) also deserve special consideration. The care given to patients facing the end of their lifes was also deemed to deserve special consideration by a smaller group of respondents (32 (36%)) (121).

5 (6%) of respondents used the free text box to express views not captured by any of the options offered in our survey. One of the respondents suggested in this section that any special consideration of any specific group should be based on empirical evidence of societal

preferences, such as the large cross-sectional survey done by Linley & Hughes (2012) to elicit the views of the public around some of the special consideration NICE gave to specific groups at that time (94). Another expert suggested that situations where specific groups could be left in situations of social exclusion or other kinds of discrimination deserve particular attention. A different respondent suggested that the healthcare budget should simply follow burden of disease (measured in DALYs). A respondent indicated a view not captured amongst the options we offered to respondents, which was not to give special consideration to any of the groups we outlined in our survey. And finally, an expert suggested that we consider the possibility of incorporating equity concerns in cost-effectiveness analysis, using the distributional cost-effectiveness analysis approach, which allows incorporating equity-relevant social considerations (such as, socioeconomic status, ethnicity or location) and disease characteristics (like severity of illness, rarity or disability) to the economic evaluation (122).

Attending to the choices based on the respondents' characteristics, we found that academics were less likely to think that orphan designation deserves special consideration (see Table A2 in Annex V).

3.5. Therapeutic and social value of the medicine and its incremental clinical benefit, taking into account its cost-effectiveness

The therapeutic value of a new medicine and its cost-effectiveness can be measured in different ways, and also the social value of a medicine has different ways of being measured. Hence, we formulated different questions to cover each one of these domains.

To measure the therapeutic value or the incremental clinical benefit of a new medicine we proposed a number of approaches, allowing multiple responses in our survey. The most voted one was the use of the QALY as a measure of therapeutic value (72 (80%)). The second and third options received the same amounts of votes (44 (49%)). The second option was to measure added clinical benefit using clinical variables specific to the pathology being treated, and the third option was to translate clinical criteria into a common barometer for comparison across all pathologies (similar to the French approach to quantifying clinical value (SMR) and clinical added value (ASMR) (62, 123)).

To measure the cost-effectiveness of the new therapy (compared to the standard of care) we gave two options, again allowing multiple responses, with most respondents tagging the incremental cost-utility ratio (ICUR) as their preferred approach (70 (78%)) with the incremental cost-effectiveness ratio (ICER) as a close follower (60 (67%)). 4 (4%) respondents used the 'Other' free-text box to express alternative views of to add to their responses.

A cost-effectiveness threshold (CET) is a decision rule based on ICERs or ICURs (in the case of cost-utility thresholds (CUT)) that distinguishes treatments that can be considered efficient use of resources from those that are not (124). Hence, we asked in our survey if respondents thought a CUT was needed in Spain. A vast majority of respondents did deem it necessary (84 (93%)). Out of that 93% that deemed a threshold necessary, most preferred an explicit threshold (70 (78%)) over an implicit one (14 (16%)) (125). Within this group of respondents, there was also a high level of consensus around the need to apply differential thresholds in particular situations or to particular population groups, with 74 (82% of the total sample) of them agreeing that it would be appropriate to do so.

The legislation also mentions the "social value" of a medicine. We asked respondents to vote on proposed ways of measuring the social value, allowing them again to tag multiple responses if they thought that more than one way of measuring it should be accepted. The option deemed as an appropriate measure of the social value of a new medicine by the vast majority of respondents in our survey was the improvement in productivity, or in allowing earlier return to work, brought by the new therapy not only to the patient/s being treated, but also to those informally taking care of them (87 (97%)). A metric that also received a high number of votes was a measure of the improvement in the quality of life of informal carers, in parallel with the amelioration of those they are caring for (i.e., the patient receiving the new therapy) (73 (81%)). The option that attracted the least votes from respondents (25 (28%)) was the consideration of the potential economic impact that the pharmaceutical company producing the new medicine could have on aspects of the national economy such as employment in the country, such as generating jobs for qualified personnel, and on other wider economic benefits (e.g. competitiveness, value added, etc.) (126).

Four additional respondents (4%) opted for the 'Other' option, either to just highlight that they think other options would be best (without specifying which those should be), expressing alternative views to the ones offered in the pre-entered options, or complementing their responses using the free-text box.

3.6. Rationalization of public spending on pharmaceuticals and budgetary impact on the National Health System

Budget impact analysis (BIA) is a measure of the impact that the introduction of a new technology has on the budget of a healthcare system. A 3-5 year time horizon is usually recommended (31, 127). We asked whether budget impact analysis should take the perspective of the pharmaceutical sector or the healthcare sector, because several Spanish HTA reports have only measured pharmaceutical costs. 87% of respondents believed that BIA should measure all healthcare costs.

Staff of regulatory agencies was more likely to choose the option where only the medicine's acquisition costs are considered when carrying out a budget impact analysis (see Table A7 in Annex V).

Nine respondents (10%) used the 'Others' option to express views not captured by any of the options offered in our survey. A respondent highlighted the need to scan the horizon for the specific medicine at hand, extending the time horizon up to the point of patent expiry if necessary, or up to timepoints when there would be any other kind of relevant landmark in terms of budget impact. A few respondents argued that time horizons longer than 5 years would be more appropriate.

3.7. Availability of medicines or other therapeutic alternatives for the same conditions at a lower price or lower treatment cost

Spanish pharmaceutical law requires that decision makers take into account in the P&R of a new medicine whether there is a therapeutic alternative at lower cost than the new medicine. The idea being that, in situations when a new medicine is requesting reimbursement at a given price and there is an equivalent alternative on the market, the healthcare system will never pay more for the new medicine. This raises the question of what is meant by an "equivalent alternative". To measure this the concepts of therapeutic equivalence (128) or the World Health Organisation groups based on Anatomical, Therapeutic and Chemical Classification (ATC) at level 5 (chemical substance) or level 4 (chemical subgroup) were proposed (the ATC is a coding system for medicines according to their pharmacological effect, therapeutic indications and chemical structure, divided into five levels: the first level (ATC1) is the most general and the fifth level

(ATC5) the most detailed - it designates the specific active substance or pharmacological association) (129, 130). Multiple responses were allowed.

Respondents working in regulatory agencies were less likely to choose the ATC group 5 (see table A8 in Annex V).

Eight additional respondents (9%) used the 'Others' option to express views not captured by any of the options offered in our survey. A responder suggested that the concept of equivalence is not appropriate here because it may include off-label uses. Another suggestion was to avoid using, in reimbursement decisions, instruments that have not been designed for such purpose since that could lead to unintended errrors, such as neglecting potential differences in the pharmacodinamic and pharmacocinetic properties of a new galenic formulation.

3.8. Degree of innovation of the new medicine

In this category, multiple responses were not allowed, since we understood that applying more than one of the options we offered to measure the degree of innovation would incur in redundancy in practice, and it would not offer substantially enough additional information to support decisions to justify the duplicative effort. The most voted option was using a checklist to measure the degree of innovation (49 (54%)). In this option, we offered the example of the checklist developed by the International Network of Agencies for Health Technology Assessment (INAHTA) to support the development of HTA reports (91), and clarified that such an instrument to purposedly measure the degree of innovation for HTA purposes would need to be the subject of further research. Multi-criteria decision analysis (MCDA) was the alternative we offered, and received less votes (32 (36%)).

Nine additional respondents (10%) used the 'Others' option to express views not captured by any of the options offered in our survey.

3.9. Relative weights of criteria

We asked respondents to indicate the weight (from 0 to 100) that they think each criterion should have in the funding decisions for medicines in Spain, asking them to ensure that the sum of the scores given sums up to 100. The average weight of all responses for each criterion can be seen in Table 3 (below).

Table 3. Relative weights of reimbursement criteria (descriptions of criteria simplified for brevity)

Criterion	Average Weight from all responses
Severity	21
Specific populations / needs	13
Therapeutic and social value, incremental benefit and cost-effectiveness	26
Budget impact	16
Availability of an equivalent alternative	14
Degree of innovation	10

3.10. Are we addressing all relevant criteria?

We asked participants in our survey if they think the criteria listed in the law to support rembursement decisions for medicines in Spain are adequate, to which more than half of respondents responded negatively (50 (56%)) and the rest responded afirmatively (40 (44%)). We then asked if respondents thought any criteria should be added to the current list, to which a wide majority said yes (69 (77%)) and the rest said no (21 (23%)). And we ended this part of the survey asking respondents if they thought the perspective of patients should be considered as an additional criterion, with which most agreed (67 (74%)) and the rest did not (23 (26%)).

Respondents working in consulting firms and academic institutions were less likely to consider that the current criteria were adequate (see Table A.10 in Annex V).

4. Discussion

The results of this survey show that the majority of respondents, for the majority of questions, agreed around a number of ways of measuring the criteria listed to support reimbursement decisions for new medicines in Spain (all responses had at least one option picked by more than 50% of respondents), and the weighting exersice we did gave us a good idea of the relative weight that experts give to each criterion in such decisions. Additional questions shed light on the actual appropriateness of the criteria too, as well as on the potential suitability of adding specific ones to the list.

The majority (more than half) of the experts surveyed are of the opinion that the criteria used to support decision-making on reimbursement of medicines in Spain are not adequate, and a large majority (over three quarters of them) are of the opinion that additional criteria should be added. In particular, the survey referred to the need to add the patients' perspective as an additional criterion to those listed in the law in order to support reimbursement decisions for medicines in Spain in an appropriate manner, which is in line with ongoing reforms in Spain aiming to incorporate representatives of patient groups into decision making processes (131).

The criteria weighting exercise we carried out among the respondents shows that, for them, the most important criteria when deciding whether or not a new medicine should be reimbursed is its therapeutic and social value and its incremental clinical benefit, taking into account its cost-effectiveness, as well as the severity, duration and sequelae of the different pathologies for which it is indicated, both with weightings of more than 20 out of 100.

To measure severity, the approaches voted by more than half of our respondents were using clinical units and the QALY. Neighbouring HTA systems do engage in more complex approaches to give additional weight to quality of life gains in people living with more severe health conditions. One way of defining severity is the use of the absolute QALY shortfall (the number of QALYs an individual can expect to lose in years to come as as result of ligiving with a given condition) (132) and the proportional QALY shortfall (proportion of future QALYs someone can experct to lose as a result of living with a given condition, taking their total remaining life expectancy as the total possible maximum if lived in full quality of life) (133). For instance, in England, NICE recently introduced a new severity-modifier that allows committees to weight QALYs more when gained in patients with more severe diseases (134). In Norway, severity is formally captured through the absolute shortfall approach (135, 136), which estimates the

number of future QALYs that someone living with a condition is expected to lose as a result of it, under current care conditions, and consequently for more severe conditions Norways accepts higher cost-effectiveness ratios (135). In the Netherlands, they introduced the proportional shortfall (a measure of severity) as an equity approach combining aspects of fair innings (advocates that everyone is entitled to a 'fair' span of life oe health, weighting QALY gains more in younger persons and less in relatively older ones) and prospective health (expected life expectancy regardless of how much one has lived so far) (137). Despite these guidelines, a recent study exploring the priority setting criteria cited by Dutch appraisal committee reports showed that severity of illness was not referenced at all in Dutch HTA reports between 2013 and 2016 (138).

The characteristics of the disease can also have bearings on how decision makers treat reimbursement decisions in particular circumstances. Decision makers across Europe have given particular consideration to groups of patients such as those close to the end of their life. NICE introduced the end-of-life criteria in 2009, allowing treatments at the end of life to be funded with ICERs over the regular threshold (111), though replaced it with the severity modifier in 2022 (139)). Patients living with rare diseases do also constitute a group that has been regarded with particular attention by European payers, as analyses of the European pricing landscape have shown suggesting that European payers tend to pay premium prices for orphan medicines (140, 141)). A similar situation has been observed with patients living with diseases that pose an unmet medical need, with countries like Norway and Sweden presenting a willingness to pay that depends on the level of unmet need amongst other factors (142). The new european pharmaceutical regulation adds a layer of potential rewards to manufacturers, since it does include the provision of extensions of market exclusivity (which should translate into increased rates for return) for orphan and paediatric medicinal products and those responding to unmet needs (100). National decision makers should take into account the incentives provided by the new european pharmaceutical regulation when considering whether these products should also qualify for premium prices in National Health Systems .

Furthermore, the specific needs of particular patient groups can only be captured if the right methods to do so are implemented, and embedded in an HTA model that can accommodate special consideration for these patient groups and translate these criteria into decisions. For instance, if the Spanish society expressed a willingness to give a special consideration to health gains in patients with very severe disease, one way to do so would be to weight QALY gains

under those circumstances more than in other scenarios, as recommended in England, Netherlands and Norway (143).

One way of capturing the needs of particular patient groups is to apply different thresholds for given populations. Payers across the biggest medicines markets in Europe appear to offer price premiums to medicines for rare diseases (140). However, Patricia Danzon (2018) (144) recommended not to implement a higher threshold or premium price for orphan medicines. Instead, her suggestion was to dedicate future research to studying whether a higher value-based threshold could be granted for a subset of orphan indications which fulfil conditions of disproportionately high R&D costs per patient and can follow a limitation of indication expansions. The case of people living with rare diseases or needing to be treated with orphan medicines is complex, because if the condition is severe aguably the therapy is being rewarded twice once through the severity premium described above and again for rarity. Additionally, a recent paper suggested caution when considering giving special treatment to the pricing and reimbursement of orphan medicines due to: the increasing number of orphan indications; the highly profitable nature of the orphan medicines market this shift suggests; the growing number of indications of medicines that do have at least one orphan indication, and; the potential negative impact on non-orphan indications an overly stark shift of R&D towards orphan indications could cause (144).

An additional group of patients that, in our survey, a moderate number of respondents deemed as deserving special treatment in financing decisions in Spain were paediatric populations. It has been recognised that the clinical development and the assessment of technologies aimed at treating children present distinct challenges (112, 120). One such challenge is the difficulty in measuring quality of life in children, with one paper arguing that this difficulty could penalise paediatric populations in utilitarian systems that assume QALY gains to be equal across a population if the quality of the evidence is indeed poorer or scarcer than in adults (145). Petrou (2010), for instance, suggested that society may value health gains in children more than in adults (146). The new european pharmaceutical legislation does include rewards for manufacturers of medicinal products for children, in the form of supplementary market exclusivity extensions, amongst others (100).

Moreover, in our survey, people living with a disease that was considered to have an unmet health need was clearly deemed to be deserving of prioritisation. Unmet need, as per the definition provided in article 83 of the new european pharmaceutical legislation (100), has been an area that has received considerable attention in European health policy. The EMA established

the priority medicines scheme (PRIME) in March 2016 to expedite the development and approval of promising products aimed at treating diseases with high unmet medical need (147). By June 2018, the EMA had awarded PRIME status to 39 therapies (148). The new european pharmaceutical legislation contemplates rewarding manufacturer of medicinal products addressing unmet medical needs with the application of accelerated assessment mechanisms and the prolongation of data protection and subsequently of market exclusivity (100).

A concern in the HTA community about this kind of scheme is the potential spillover effect it may have on the evidence presented to them, for instance due to a proliferation of positive regulatory decisions based on surrogate endpoints (as a result of the introduction of "expedicted" regulatory pathways), which are often not good predictors of the outcomes that matter to patients most, namely quality and length of life (149). Medicines approved on the basis of surrogate endpoints and other major uncertainties in the clinical evidence (lack of comparator arm, short follow up, etc.) often enter regulatory conditional approval schemes (149). One way through which reimbursement decisions have given continuity to this kind of regulatory decisions has been to devise managed entry agreements (also known as coverage with evidence development) to enable the generation of the necessary evidence to inform a full HTA, and make a final reimbursement decision (150). In Spain, VALTERMED (Spanish accronym for Information System to determine the Therapeutic Value of High Health and Economic Impact Medicines for the NHS in Real Clinical Practice) was created recently as a registry system articulated through a web-based tool to collect real-world data, and is being used to inform outcomes-based agreements for the funding to cover costly new therapies (151) and reduce the associated uncertainty (152). However, so far, little has been published about the results obtained from this real-world data collection and this should be priortised.

In our survey, an overwhelming majority of respondents would prefer that a CUT was officially adopted in Spain to support reimbursement decisions, and they would prefer this threshold to be explicit rather than implicit. A threshold for Spain has been estimated to be in the range of 22,000€ and 25,000€ per QALY (28). The use of a CUT expressed as a "cost-per-QALY" implies that health benefits must be measured using the QALY, which is something that has not yet been established in the Spanish system (97). Furthermore, the adoption of economic evaluation to inform reimbursement decisions in Spain is still an ongoing process, but one that is yet far from being a systematic reality (96). Since 2021, therapeutic positioning reports (IPTs) have started to include economic evidence , but not all of them do and the quality of the evidence they include is inconsistent (4). Besides defining the methods that should be applied to developing

appropriate evidence, it is pivotal to understand how evidence on the efficiency of investments in health technologies might inform reimbursement decisions. The decision rule used in countries like England is defined in the methods guides, and publicly available, and given that recommendations made by NICE come with a funding mandate the methods that inform their assessments are automatically those that inform reimbursement decisions in England. In the Spanish context, academic work (commissioned by the Spanish Ministry of Health) has estimated a supply-side CUT (28), and published methods for economic evaluations have been available for some time (29, 153). Nevertheless, other Ministry of Health procedural guidance seems to recommend different methods (154), and currently economic evaluation is missing in the majority of HTA reports used to support P&R in Spain (96).

The value of a new medicine to society might, in some cases, go beyond what an incremental cost-effectiveness ratio would capture. To take into account such dimension of value of a new medicine, there was very broad support among respondents to our survey around two such benefits: (1) the benefit that the treatment generates among patients' relatives and other informal caregivers by improving their quality of life in parallel with the improvement of the living conditions of the patients they care for, and; (2) the benefit that the treatment generates among patients' relatives and other informal caregivers by improving their quality of life in parallel with the improvement of the living conditions of the patients they care for, enabling an improvement in productivity generated by the treatment, as patients (and their informal carers) in addition to benefiting from an improvement in health due to the use of the medication, are sometimes able to return to work earlier or in conditions more favourable to their productivity than without the new therapy. In Sweden for instance (amongst other countries), the way they approach capturing benefits of new medines that go beyond direct health benefits to the patients treated, is adopting a societal perspective in the economic evaluations they use to inform P&R decisions (155, 156).

The budget impact to the system was one of the criteria analysed in our survey. The options we offered as potential ways to capture the budget impact were very straight forward approaches to analysing the actual costs involved in implementing a new intervention. However, on top of measuring the actual economic impact of incorporating a new technology in the system, there are ways of embedding the budget impact in the reimbursement decision making process that are relevant to consider. For instance, in England NICE introduced the so called budget impact test in 2017, whereby NICE estimates the budget impact of all recommended medicines over the first 3 years of introduction in the system, and if the result is over the £20 million mark,

pricing negociations between the NHS and the sponsor are triggered (157). Other countries such as Australia, Belgium, Ireland, France, Poland, Brazil, and Canada, also have official guidelines outlining the principles and methods that should underpin budget impact analysis in their systems, as well as the decision rules that might gravitate around them (158). Further elaboration of how budget impact is calculated and used to inform financing decisions for medicines in Spain would match the Spanish system with international comparable healthcare systems.

Using therapeutic equivalence (128) to substantiate P&R decisions received the highest number of votes in our survey (59 (66%)). There is a long history of literature about how to prove therapeutic equivalence (128, 159-164). In Spain, a group of hospital pharmacist that has been developing a methodological base and guidance to underpin evaluations of pharmaceutical products to inform decisions in Spanish Hospital Pharmacies (by their Spanish accronym, GENESIS), has published research on the appropriate use of this concept to inform decisions to position two therapies as interchangeable equivalents (165). At an international level, the notion of therapeutic equivalence has also underpinned programmes whereby the cheapest available equivalent sets the bar for that given indication, implying that if higher prices do not buy any extra effectiveness or avoid adverse events then that extra cost is not subsidised (this are referred to reference medicines programmes) (166). In countries like Australia, programmes of these characteristics, based on therapeutic equivalence, have shown positive economic results for their healthcare systems and suggest being useful tools to steer disinvestment in their systems (167). The concept of equivalence might include non-authorised uses of a therapy (off-label), and this would need to be taken into account by the relevant health authority. A concern in the industry is that therapeutic equivalence might leave out aspects of the value of a new medicine, such as those that a new galenic formulation might carry, but it is important to keep in mind that therapeutic equivalence is only used to measure one specific dimension of value of a medicine, and other dimensions (such as the degree of innovation) might capture additional sources of benefit (such as convenience of administration). The ATC groups 5 and 4 received less attention from respondents (34 (38%) and 11 (12%) respectively). Indeed, the WHO does not recommend using the ATC system for P&R decisions (168). This shows that combining clinical and economic considerations to inform P&R decisions is a complex task, and if not done based on robust measurements and decision rules, it could easily lead to inconsistent decisions.

The degree of innovation, considered independently from other criteria that already inform reimbursement decisions, is a complex concept to define, articulate in decision making systems

and measure. Previous research approached this issue and came up with a conceptual construct that could inform such decisions in Spain, considering what other criteria are listed as relevant in our system (107), and came up with a definition of degree of innovation that includes: step-change, convenience; strength of evidence base taking into account the degree of uncertainty associated with the evidence (among other factors); impact on future R&D (i.e., how the research that went into developing the technology at hand might enable future innovations). To our knowledge, the only institution that defines the degree of innovation independently from other concepts that traditionally have informed reimbursement decisions, such as therapeutic value, cost-effectiveness or whether they respond to an unmet medical need, is NICE (in Spain the degree of innovation is only listed, not defined) (169). The deffinition of degree of innovation is made in the context of how it can inform their decision making, establishing 3 conditions to class a new medicine as innovative (59, 107): (i) the technology must display "innovative characteristics" or be of an "innovative nature"; (ii) the innovative nature of the technology must bring substantial health benefits to the patient, also referred to as a "'step-change' in the management of the condition"; (iii) the substantial benefits brought by the innovative characteristics of the health technology must not already be captured in the ICER calculation of the technology under scrutiny and they must be "demonstrable and distinctive". Providing a clear deifinition of what is understood by degree of innovation in the context of reimbursement decisions in Spain, and how to measure it, would add robustness and transparency to the process.

Furthermore, the preferred way of measuring the degree of innovation of a new medicine according to the responses we received to our survey, was the use of a purposedly designed checklist, focusing specifically on the dimensions of value that construct the concept of degree of innovation. However, such instrument does not yet to our knowledge exist. Hence, developing it with the aim of it being used to inform reimhursement decisions for new medicines in Spain should be the subect of further research. The alternative we offered in our survey as a methodology that could be use to measuring the degree of innovation is the MCDA approach. There is plenty of literature about this methodology and its potential use to support decision making in healthcare, and it is said to be a tool that could add consistency and transparency to the HTA process (89), but it has also attracted criticism. Some argue that it is overly mechanistic (170), whilst others highlight the potential of this approach but still see plenty of scope for methods development if it is to achieve its full potential in practice (171). The respondents to our survey preferred the more pragmatic option of using a checklist.

Additional areas for further research were highlighted in the free text boxes by responders to the survey. One, raised to our attention the need to incorporate equity concerns in cost-effectiveness analysis, using the distributional cost-effectiveness analysis approach (122). This is in line with an approach suggested by Vallejo-Torres in a recent paper proposing a broader cost-effectivness analysis framework that captures equity considerations too, amongst other additional dimensions (172). Another respondent argued that surveying experts to elicit their preferences for aspects related to the level of priority specific population groups may deserve was insufficient, and that societal preferences should instead be elicited to inform such policies, replicating exersices of that kind that have informed policy choices in other jurisdictions (94).

Finally, the analysis by Vida et al. (2023), calling for a deep rethink of how the evaluation of medicines is structured in Spain and signposting flaws in the system (4), has gained momentum, since some of their observations are echoed in a court ruling that overrides recent reforms and strikes the recently created Pharmaceutical Evaluation Network (REvalMed) (173). This suggests that a wider organisational rethink, beyond specifying measument instruments for P&R criteria, seems to be overdue in Spain, and raises the question of whether a new structure like REvalMed is needed, or rather empowering existing ones.

The key issues we have dealt with in this paper and the main recommendations arising from it are summarised in table 4 (below).

Table 4. Key issues and recommendations

To guide economic evaluations, we recommend the use of the QALY, and the use of an explicit cost-utility threshold that can vary to give particular consideration to specific patient groups or therapies, such as those responding to previously unmet medical needs. However, in Spain, the actual relevance of economic evaluation in decision making needs to be stated, clearly positioning it in the decision making process, defining whether the system will do de-novo models or review submitted ones, and investing in the necessary specialised staff to implement change.
A straight forward way of measuring budget impact would be capturing all costs relevant to the healthcare system within a 3-5 years horizon. However, further elaboration of how budget impact is calculated and used to inform financing decisions for medicines in Spain would match the Spanish system with international comparable healthcare systems.

To decide whether there is a therapeutic alternative available at a lower cost to the system, the concept of therapeutic alternative should be applied in combination with economic evidence.

Providing a clear deifinition of what is understoon by degree of innovation in the context of reimbursement decisions in Spain, and guiding on how to measure it, would add robustness and transparency to the process. Further research could focus on developing a purpose made checklist to measuring the degree of innovation of new health technologies to inform P&R decisions.

We would recommend capturing the patients' perspective as an additional criterion in a systematic and robust manner to support reimbursement decisions for medicines in Spain.

A large study to elicit the preferences of the Spanish society around which groups deserve particular consideration in medicines financing decisions would be very useful to inform policy making in this area. Always keeping in mind that the specific needs of particular patient groups can only be captured if the right methods to do so are implemented, and embedded in an HTA model that can accommodate special consideration for these patient groups and translate these criteria into decisions (e.g., through QALY weighting).

Duplication should be avoided when rewarding specific dimensions of value of health technologices (e.g., adding price premiums to a therapy twice – once for rarity and once for severity). National decision makers should take into account the incentives provided by the new european pharmaceutical regulation when considering whether these products should also qualify for premium prices in National Health Systems.

Managed entry agreements can be useful to mitigate the financial risk of reimbursing costly therapies that are approved subject to high levels of uncertainty around their long-term efficacy. However, there is a gap around their efficacy. Further research should focus on evaluating how these schemes, and the real-world-data collection requirements associated with them, perform in practice to meet pre-defined goals.

5. Conclusions

Although the results of this survey do not provide all the keys to publish measurement instruments or criteria that more clearly define each of the criteria on which decisions on reimbursement of new medicines in Spain are based, we firmly believe that the opinion of the community of experts in health economics and health technology assessment in Spain can shed some light to guide the development of a more detailed methodological framework in the future, questioning not only how to define and measure each of the criteria currently used, but even the desirability of updating the relevant criteria. Ideally, transparency should be an essential quality characterising both the decision-making processes on reimbursement of new medicines in Spain, and the processes through which the methodologies that support these decisions are defined, embedding them in a solid infrastructure able to support robust, consistent and equitable decision-making in the country and its regions.

Chapter II – ANNEX I. Original version of the Survey (in Spanish)

Marque el tipo de institución que mejor se ajuste a la institución para la que usted trabaja:

- ☐ Agencia de evaluación de tecnologías sanitarias
- ☐ Agencia reguladora
- ☐ Entidad gubernamental (ya sea de un gobierno regional o del gobierno nacional)
- ☐ Institución académica o de investigación
- ☐ Consultora
- ☐ Industria
- ☐ Otro/a

Indique la franja de años de experiencia profesional que mejor se ajusten a su perfil (años haciendo el doctorado se contabilizarían como experiencia profesional):

- ☐ 1-3 años
- ☐ 3-5 años
- ☐ 5-8 años
- ☐ 8 años o más

Marque el tipo de perfil que mejor se ajuste a su puesto:

- ☐ Director, coordinador o responsable de área, unidad, departamento o equivalente
- ☐ Personal técnico, profesor o investigador
- ☐ Personal de gestión o similar
- ☐ Otro/a

Por favor, marque la opción que, en su opinión, sería más adecuada para medir cada una de las categorías indicadas para los medicamentos sobre los que se va a decidir su inclusión o no en el paquete básico de prestaciones del SNS:

A) GRAVEDAD, DURACIÓN Y SECUELAS DE LAS DISTINTAS PATOLOGÍAS PARA LAS QUE RESULTEN INDICADOS

Por favor, marque aquellas opciones que considere apropiadas y compatibles para medir gravedad, duración y secuelas de las distintas patologías para las que está indicado un nuevo medicamento sobre el que hay que tomar una decisión de inclusión en el paquete básico del SNS (en caso de considerar que este parámetro no debería ser tenido en cuenta en las decisiones de financiación de los medicamentos en España, por favor marque la casilla 'Otro' y explique su posición en el casillero de texto libre):

- El AcutePhysiology And Chronic Health Evaluation (APACHE) II (174, 175), que mide gravedad en pacientes en cuidados intensivos, u otros instrumentos similares específicos de áreas terapéuticas concretas (el que sea relevante para el medicamento sobre el cual se va a decidir su inclusión o no en el paquete básico de prestaciones del SNS), acompañado de una medida temporal de duración
- Los 'años de vida ajustados por discapacidad' (AVAD, o DALY por sus siglas en inglés) (176)
- El Año de Vida Ajustado por Calidad (AVAC) (177)
- Marcadores clínicos de gravedad y secuelas, o un número de unidades de medida clínica de eficacia específica a la patología que tenga significado clínico, añadiéndoles una medida temporal de duración (Ejemplos: los índices de letalidad y de morbi-mortalidad son medidas ampliamente aceptadas de la gravedad de una enfermedad; otros indicadores útiles son la frecuencia de eventos graves que cursan con hospitalización o visitas a urgencias).
- Otro – por favor indique sólo el instrumento de medida de gravedad, duración y secuelas de una enfermedad que le parezca más apropiado (sólo uno) (Texto libre)

B) NECESIDADES ESPECÍFICAS DE CIERTOS COLECTIVOS

Existen grupos poblacionales que, debido a sus características o a las de la enfermedad que padecen, son tenidos en cuenta de manera específica dentro de las decisiones de financiación de medicamentos en España. De los grupos poblacionales que listamos abajo, marque todos los que crea que merecen consideración especial en dichas decisiones en España (en caso de considerar que este parámetro no debería ser tenido en cuenta en las decisiones de financiación de los medicamentos en España, por favor marque la casilla 'Otro' y explique su posición en el casillero de texto libre):

- Poblaciones con una afección para la que no existe una alternativa terapéutica satisfactoria, siguiendo la definición de la Comisión Europea de necesidad médica no cubierta (178) o también situaciones en las que existe laguna terapéutica en patología grave, lo que implica ausencia de alternativas eficaces de tratamiento, tal y como se define en el plan para la consolidación de los informes de posicionamiento terapéutico de los medicamentos en el sistema nacional de salud (117).
- Los medicamentos huérfanos (179), siguiendo la definición de la EMA[1], o para enfermedades ultra-raras.
- La población pediátrica (180).
- Pacientes enfrentándose al final de sus vidas (94)
- Otro – por favor ponga sólo el grupo poblacional que le parezca más apropiado tener en cuenta (sólo uno) (Texto libre)

C) VALOR TERAPÉUTICO Y SOCIAL DEL MEDICAMENTO Y BENEFICIO CLÍNICO INCREMENTAL DEL MISMO TENIENDO EN CUENTA SU RELACIÓN COSTE-EFECTIVIDAD

El valor terapéutico de un medicamento y su coste-efectividad se puede medir de diversas maneras, y el valor social del mismo tiene maneras de medirse diferentes. Por tanto, le presentaremos primero alternativas para medir: (1) valor terapéutico; (2) coste-efectividad, y; (3) valor social.

(1) Por favor, de los siguientes instrumentos para medir el valor terapéutico o beneficio clínico incremental de los medicamentos marque las opciones que le parezcan apropiadas (marque más de una opción si cree que múltiples parámetros podrían informar mejor la decisión que uno sólo – en caso de considerar que esta dimensión de valor no debería ser tenida en cuenta en las decisiones de financiación de los medicamentos en España, por favor marque la casilla 'Otro' y explique su posición en el casillero de texto libre):

- El Año de Vida Ajustado por Calidad (AVAC) (177).

[1] Definición de la EMA de medicamento huérfano: https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview

- El impacto de la nueva estrategia en las variables clínicas específicas a la patología que se está tratando o alguna otra medida clínica de eficacia específica a la patología.
- Una medida de beneficio real de la nueva terapia basada en una combinación de criterios clínicos, que se acaban traduciendo en un índice (al estilo del sistema francés (62)).
- Otro – por favor pon sólo el instrumento de medida de valor terapéutico que te parezca más apropiado (sólo uno) (Texto libre)

(2) Por favor, de los siguientes instrumentos para medir la relación coste-efectividad de los medicamentos marque las opciones que le parezcan apropiadas (en caso de considerar que este parámetro no debería ser tenido en cuenta en las decisiones de financiación de los medicamentos en España, por favor marque la casilla 'Otro' y explique su posición en el casillero de texto libre):

- La ratio de Coste-Utilidad Incremental (RCUI, o ICUR por sus siglas en inglés) usando medidas de utilidad como el AVAC
- La ratio de Coste-Efectividad Incremental (RCEI, o ICER por sus siglas en inglés) usando medidas de efectividad clínica (una/s variable/s concreta/s de medida clínica de eficacia específica a la patología, que tenga significado clínico)
- Otro – por favor ponga sólo el instrumento que le parezca más apropiado para medir la relación de coste-efectividad de una nueva terapia (sólo uno) (Texto libre)

Para poder apoyar decisiones de financiación de medicamentos en una ratio de coste-efectividad y/o de coste-utilidad, es necesario tener una referencia de qué se considera uso eficiente de recursos en el sistema:

- ¿Cree que hace falta un umbral de coste-utilidad en España? Si / No
- Si cree que hace falta un umbral, marque la opción que le parezca más apropiada:
  - Un umbral explícito (descrito y especificado en los manuales metodológicos que enmarcan la actividad de evaluación de tecnologías sanitarias en un país)
  - Un umbral implícito (no oficialmente especificado, deducido de publicaciones en revistas especializadas y de informes publicados)
- ¿Cree que debe haber diferentes umbrales para diferentes grupos poblacionales / situaciones especiales? Si / No

(3) Los medicamentos, además de tener un valor terapéutico directo en salud para los pacientes para los que están indicados, aportan un beneficio para la sociedad en conjunto a varios niveles (126), que se puede medir (marque todas las opciones que le parezcan relevantes – en caso de considerar que este parámetro no debería ser tenido en cuenta en las decisiones de financiación de los medicamentos en España, por favor marque la casilla 'Otro' y explique su posición en el casillero de texto libre):

- ☐ Los familiares y otros cuidadores informales de los pacientes ven mejorada su calidad de vida en paralelo a la mejora de las condiciones de vida de los pacientes a los que cuidan.
- ☐ Los pacientes (y sus cuidadores informales) además de beneficiarse de una mejora en salud a causa del uso del medicamento, en ocasiones pueden volver a trabajar antes o en condiciones más favorables a su productividad que sin la nueva terapia.
- ☐ La empresa farmacéutica que produce el nuevo medicamento es posible que genere un impacto económico considerable, en el empleo del país generando gran cantidad de empleo de calidad para personal cualificado y en otros aspectos de la economía (como por ejemplo la competitividad, el valor añadido que genera, etc.) (126)
- ☐ Otro – por favor ponga sólo una manera de medir el valor social del medicamento que no hayamos listado en las opciones anteriores (Texto libre)

D) RACIONALIZACIÓN DEL GASTO PÚBLICO DESTINADO A PRESTACIÓN FARMACÉUTICA E IMPACTO PRESUPUESTARIO EN EL SISTEMA NACIONAL DE SALUD

El análisis de impacto presupuestario es la medida estándar para reflejar el impacto que la incorporación de una nueva tecnología tiene en el presupuesto de un sistema sanitario, y existen guías metodológicas que describen cómo hacerlo adecuadamente (31). Sin embargo, la legislación no entra a describir la manera en que mide el impacto presupuestario de nuevos medicamentos para apoyar sus decisiones de financiación. Por favor, marque sólo la casilla que describa mejor los costes que le parezcan relevantes para un análisis de impacto presupuestario. En caso de opinar que habría otra manera más adecuada de medir el impacto presupuestario o si considera que este parámetro no debería ser tenido en cuenta en las decisiones de financiación de los medicamentos en España, por favor marque la casilla 'Otro' y explique su posición en el casillero de texto libre:

- El impacto presupuestario solo tiene que tener en cuenta los gastos en la terapia farmacéutica nueva y actual en un horizonte temporal de 3 a 5 años
- El impacto presupuestario debe tener en cuenta todos los costes sanitarios (administración de la terapia, efectos adversos, etc.) en un horizonte temporal de 3 a 5 años
- Otro – por favor ponga sólo el instrumento de medida de impacto presupuestario, diferente al ya mencionado arriba, que le parezca más apropiado (sólo uno) (Texto libre)

E) EXISTENCIA DE MEDICAMENTOS U OTRAS ALTERNATIVAS TERAPÉUTICAS PARA LAS MISMAS AFECCIONES A MENOR PRECIO O INFERIOR COSTE DE TRATAMIENTO

Mediante este criterio se tiene en cuenta si existe una alternativa terapéutica de eficacia similar o superior y a menor coste que el nuevo medicamento. Para medir esto, se pueden utilizar los conceptos de equivalencia terapéutica o los grupos ATC5 (La clasificación Anatómica, Terapéutica y Química (ATC) es un sistema de codificación de los medicamentos, según su efecto farmacológico, sus indicaciones terapéuticas y su estructura química. Se divide en cinco niveles: el primer nivel (ATC1) es el más general y el quinto nivel (ATC5) el más detallado – designa el principio activo específico o asociación farmacológica (129)). A alternativas equivalentes, nunca se paga más. Si conoce otra manera más apropiada de medir esto, propóngala más abajo (en caso de considerar que este parámetro no debería ser tenido en cuenta en las decisiones de financiación de los medicamentos en España, por favor marque la casilla 'Otro' y explique su posición en el casillero de texto libre):

- Concepto de alternativa terapéutica equivalente
- Grupos ATC4
- Grupos ATC5
- Otro – por favor ponga sólo el instrumento, diferente a los mencionados arriba, que le parezca más apropiado (sólo uno) (Texto libe)

F) GRADO DE INNOVACIÓN DEL MEDICAMENTO

Para los propósitos de esta encuesta utilizaremos la definición de grado de innovación basada en las dimensiones de valor que componen el concepto identificadas en una investigación previa (107). Esto es: salto cualitativo en su indicación (`step-change'), conveniencia (`convenience'),

robustez de la evidencia (`strength of evidence base') teniendo en cuenta el grado de incertidumbre asociado a la evidencia (entre otros factores), impacto en futura I+D (`impact on future R&D').

Ahora, ¿con que tipo de instrumento cree que debería medirse el grado de innovación para apoyar la toma de decisiones de financiación de medicamentos en España tal y como describe la ley? Por favor, marque sólo el instrumento que, bajo su punto de vista, sea más apropiado (en caso de considerar que este parámetro no debería ser tenido en cuenta en las decisiones de financiación de los medicamentos en España, por favor marque la casilla 'Otro' y explique su posición en el casillero de texto libre):

- Un instrumento tipo 'checklist' (actualmente sólo conocemos el 'checklist' de INAHTA (91) que se aplica a la evaluación de tecnologías sanitarias en general – nosotros propondremos un 'checklist' específico para medir el grado de innovación, como parte de este proyecto).
- Como parte de un Análisis de Decisiones Multicriterio (MCDA por sus siglas en inglés), como uno de los dominios de valor medidos y capturados (como, por ejemplo, en el Advance Value Framework desarrollado y publicado por Angelis & Kanavos (2017) (55) o el 'innovómetro' propuesto por Zaragozá-García & Cuéllar (2017) (30), teniendo en cuenta que varios de los parámetros ya medidos en epígrafes anteriores serían contabilizados por duplicado si usásemos el 'innovómetro' ya que éste captura parámetros como el valor terapéutico por ejemplo).
- Otro – por favor pon sólo el instrumento de medida de grado de innovación, distinto a los mencionados arriba, que te parezca más apropiado (sólo uno) (Texto libe)

PONDERACIÓN DE CADA CRITERIO

Por favor, indique el peso (de 0 a 100) que usted crea que debería tener cada criterio en las decisiones de financiación de medicamentos en España. Por favor, tenga en cuenta que la suma de las puntuaciones otorgadas debe ser 100.

a) Gravedad, duración y secuelas de las distintas patologías para las que resulten indicados;
b) Necesidades específicas de ciertos colectivos;

c) Valor terapéutico y social del medicamento y beneficio clínico incremental del mismo teniendo en cuenta su relación coste-efectividad;
d) Racionalización del gasto público destinado a prestación farmacéutica e impacto presupuestario en el Sistema Nacional de Salud;
e) Existencia de medicamentos u otras alternativas terapéuticas para las mismas afecciones a menor precio o inferior coste de tratamiento;
f) Grado de innovación del medicamento.

IDONEIDAD DE LOS CRITERIOS LISTADOS EN LA LEY PARA APOYAR DECISIONES DE FINANCIACIÓN DE MEDICAMENTOS EN ESPAÑA

Por favor, responda sí o no a la siguiente pregunta:

¿Cree que los criterios listados en la ley para apoyar la toma de decisiones sobre financiación de medicamentos en España son los adecuados?

- ☐ Si
- ☐ No

¿Cree que habría que añadir algún criterio a los listados en la ley para apoyar la toma de decisiones sobre financiación de medicamentos en España de manera idónea?

- ☐ Si
- ☐ No

En la lista de criterios utilizados en España para apoyar este tipo de decisiones, observamos una diferencia respecto a otros marcos de apoyo a la toma de decisiones de nuestro entorno. Esto es, la consideración específica de la perspectiva de los pacientes. Por favor, responda sí o no a la siguiente pregunta:

¿Cree que habría que añadir la perspectiva de los pacientes como un criterio adicional a los listados en la ley para apoyar la toma de decisiones sobre financiación de medicamentos en España de manera idónea?

- ☐ Si
- ☐ No

Chapter II – ANNEX II. Translated version of the Survey (into English)

Tick the type of institution that best fits the institution you work for:

- ☐ Health Technology Assessment Agency
- ☐ Regulatory Agency
- ☐ Governmental entity (either regional government or national government)
- ☐ Academic or research institution
- ☐ Consultant
- ☐ Industry
- ☐ Other

Please indicate the range of years of professional experience that best fits your profile (years of doctoral studies would count as professional experience):

- ☐ 1-3 years
- ☐ 3-5 years
- ☐ 5-8 years
- ☐ 8 years or more

Tick the type of profile that best suits your position:

- ☐ Director, coordinator or head of area, unit, department or equivalent
- ☐ Technical staff, teachers or researchers
- ☐ Management staff or similar
- ☐ Other

Please tick the option that, in your opinion, would be most appropriate to measure each of the categories indicated for the medicines for which a decision on their inclusion or non-inclusion in the basic package of benefits of the NHS is to be taken:

A) SEVERITY, DURATION AND SEQUELAE OF THE VARIOUS PATHOLOGIES FOR WHICH THEY ARE INDICATED

Please tick those options that you consider appropriate and compatible for measuring severity, duration and sequelae of the different pathologies for which a new medicine for which a decision on inclusion in the basic package of the NHS is indicated (in case you consider that this parameter should not be considered in the funding decisions for medicines in Spain, please tick the box 'Other' and explain your position in the free text box):

- ☐ The Acute Physiology And Chronic Health Evaluation (APACHE) II (174, 175), which measures severity in intensive care patients, or other similar instruments specific to particular therapeutic areas (whichever is relevant to the medicine for which inclusion or non-inclusion in the basic NHS benefits package is to be decided), accompanied by a temporal measure of duration
- ☐ Disability-adjusted life years (DALYs) (176).
- ☐ Quality Adjusted Life Year (QALY) (177).
- ☐ Clinical markers of severity and sequelae, or a number of clinical units of measure of pathology-specific efficacy that have clinical significance, with the addition of a temporal measure of duration (Examples: case fatality and morbidity-mortality rates are widely accepted measures of disease severity; other useful indicators are the frequency of serious events leading to hospitalisation or emergency department visits).
- ☐ Other - please indicate only the instrument for measuring severity, duration and sequelae of
- ☐ a disease that seems most appropriate to you (only one) (Free Text)

B) SPECIFIC NEEDS OF CERTAIN GROUPS

There are population groups that, due to their characteristics or those of the disease they suffer from, are specifically taken into account in decisions on the financing of medicines in Spain. Of the population groups listed below, please tick all those that you believe deserve special consideration in such decisions in Spain (if you consider that this parameter should not be taken into account in decisions on the financing of medicines in Spain, please tick the 'Other' box and explain your position in the free text box):

- ☐ Populations with a condition for which there is no satisfactory therapeutic alternative, following the European Commission's definition of unmet medical need (178) or also situations where there is a therapeutic gap in serious

pathology, implying an absence of effective treatment alternatives, as defined in the plan for the consolidation of therapeutic positioning reports of medicinal products in the national health system (117).

- ☐ Orphan medicine (179), as defined by the EMA[2], or for ultra-rare diseases.
- ☐ The paediatric population (180)
- ☐ Patients facing the end of their lives (94)
- ☐ Other - please put only the population group you think it is most appropriate to take into account (only one) (Free text)

C) THERAPEUTIC AND SOCIAL VALUE OF THE MEDICINE AND ITS INCREMENTAL CLINICAL BENEFIT, TAKING INTO ACCOUNT ITS COST-EFFECTIVENESS

The therapeutic value of a medicine and its cost-effectiveness can be measured in different ways, and the social value of a medicine has different ways of being measured. Therefore, we will first present alternatives for measuring: (1) therapeutic value; (2) cost-effectiveness, and; (3) social value.

(1) Please tick the options that seem appropriate from the following instruments for measuring the therapeutic value or incremental clinical benefit of medicines (tick more than one option if you think that multiple parameters would better inform the decision than just one - if you consider that this value dimension should not be taken into account in funding decisions for medicines in Spain, please tick the 'Other' box and explain your position in the free text box):

- ☐ Quality Adjusted Life Year (QALY) (177).
- ☐ The impact of the new strategy on clinical variables specific to the pathology being treated or some other clinical measure of efficacy specific to the pathology.
- ☐ A measure of real benefit of the new therapy based on a combination of clinical criteria, eventually translated into an index (in the style of the French system (62)).

[2] EMA definition of orphan medicine: https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview

- ☐ Other - please put only the instrument of measurement of therapeutic value that seems most appropriate to you (only one) (Free text)

(2) Please tick the appropriate options from the following instruments to measure the cost-effectiveness of medicines (in case you consider that this parameter should not be taken into account in funding decisions for medicines in Spain, please tick the box 'Other' and explain your position in the free text box):

- ☐ Incremental Cost to Utility Ratio (RCUI, or ICUR) using utility measures such as QALY
- ☐ The Incremental Cost-Effectiveness Ratio (ICER) using clinical effectiveness measures (a concrete, clinically meaningful, pathology-specific clinical effectiveness variable(s)).
- ☐ Other - please put only the instrument you think is most appropriate to measure the cost-effectiveness of a new therapy (only one) (Free text)

In order to support medicines financing decisions on a cost-effectiveness and/or cost-utility ratio, it is necessary to have a benchmark of what is considered efficient use of resources in the system:

- Do you think there is a need for a cost-utility threshold in Spain? Yes / No
- If you think a threshold is needed, please tick the option that seems most appropriate:
  - ☐ An explicit threshold (described and specified in the methodological manuals that frame the health technology assessment activity in a country)
  - ☐ An implicit threshold (not officially specified, deduced from publications in peer-reviewed journals and published reports).
- Do you think there should be different thresholds for different population groups / special situations? Yes / No

(3) Medicines, in addition to having a direct therapeutic health value for the patients for whom they are indicated, bring a benefit to society as a whole at various levels (126), which can be measured (tick all options that seem relevant to you - in case you consider that this parameter should not be taken into account in funding decisions on medicines in Spain, please tick the box 'Other' and explain your position in the free text box):

- Family members and other informal caregivers of patients see their quality of life improve in parallel with the improvement of the living conditions of the patients they care for.
- Patients (and their informal caregivers) in addition to benefiting from improved health due to the use of the medicine, are sometimes able to return to work earlier or in conditions more favourable to their productivity than without the new therapy.
- The pharmaceutical company producing the new medicine is likely to have a considerable economic impact, on employment in the country by generating a large number of quality jobs for qualified personnel and on other aspects of the economy (e.g. competitiveness, value added, etc.) (126).
- Other - please put only one way of measuring the social value of the medicine that we have not listed in the above options (Free text)

D) RATIONALISATION OF PUBLIC EXPENDITURE ON PHARMACEUTICALS AND THE BUDGETARY IMPACT ON THE NATIONAL HEALTH SYSTEM

Budget impact analysis is the standard measure to reflect the impact that the introduction of a new technology has on the budget of a healthcare system, and methodological guidelines exist that describe how to do this adequately (31). However, the legislation does not go into describing how it measures the budgetary impact of new medicines to support its funding decisions. Please tick only the box that best describes the costs that seem relevant for a budget impact analysis. In case you are of the opinion that there would be another more appropriate way to measure budget impact or if you consider that this parameter should not be taken into account in funding decisions for medicines in Spain, please tick the box 'Other' and explain your position in the free text box:

- The budgetary impact only has to take into account expenditure on new and current pharmaceutical therapy over a time horizon of 3 to 5 years.
- The budgetary impact should take into account all healthcare costs (administration of therapy, adverse effects, etc.) over a time horizon of 3-5 years.
- Other - please put only the budgetary impact measurement instrument, other than the one mentioned above, which seems most appropriate to you (only one) (Free text)

E) AVAILABILITY OF MEDICINES OR OTHER THERAPEUTIC ALTERNATIVES FOR THE SAME CONDITIONS AT A LOWER PRICE OR LOWER COST OF TREATMENT

This criterion takes into account whether there is a therapeutic alternative with similar or superior efficacy and at lower cost than the new medicine. To measure this, the concepts of therapeutic equivalence or ATC groups can be used5 (The Anatomical, Therapeutic and Chemical Classification (ATC) is a coding system for medicines according to their pharmacological effect, therapeutic indications and chemical structure. It is divided into five levels: the first level (ATC1) is the most general and the fifth level (ATC5) the most detailed - it designates the specific active substance or pharmacological association (129)). For equivalent alternatives, you never pay more. If you know of another more appropriate way to measure this, please propose it below (in case you consider that this parameter should not be taken into account in funding decisions for medicines in Spain, please tick the box 'Other' and explain your position in the free text box):

- ☐ Concept of equivalent therapeutic alternative
- ☐ ATC4 groups
- ☐ ATC5 groups
- ☐ Other - please put only the instrument, other than those mentioned above, that seems most appropriate to you (only one) (Free text)

F) DEGREE OF INNOVATION OF THE MEDICINAL PRODUCT

For the purposes of this survey we will use the definition of degree of innovation based on the value dimensions that make up the concept identified in previous research (107). That is: qualitative leap in its indication (`step-change'), convenience (`convenience'), robustness of evidence (`strength of evidence base') taking into account the degree of uncertainty associated with the evidence (among other factors), impact on future R&D (`impact on future R&D').

Now, what kind of instrument do you think should be used to measure the degree of innovation to support the decision making on the financing of medicines in Spain as described in the law? Please tick only the instrument that, in your view, is most appropriate (in case you consider that this parameter should not be taken into account in funding decisions for medicines in Spain, please tick the box 'Other' and explain your position in the free text box):

- A checklist instrument (currently we are only aware of the INAHTA checklist [16] which applies to health technology assessment in general - we will propose a specific checklist to measure the degree of innovation as part of this project).
- As part of a Multi-Criteria Decision Analysis (MCDA), as one of the value domains measured and captured (as, for example, in the Advance Value Framework developed and published by Angelis & Kanavos (2017) (55) or the 'innovometer' proposed by Zaragozá-García & Cuéllar (2017) (30), taking into account that several of the parameters already measured in previous headings would be double-counted if we were to use the 'innovometer' as it captures parameters such as the therapeutic value domains measured in previous headings.
- Other - please put only the instrument for measuring the degree of innovation, other than those mentioned above, that seems most appropriate to you (only one) (Free Text)

WEIGHTING OF EACH CRITERION

Please indicate the weight (from 0 to 100) that you think each criterion should have in the funding decisions for medicines in Spain. Please note that the sum of the scores given should be 100.

a) Severity, duration and sequelae of the different pathologies for which they are indicated;
b) Specific needs of certain groups;
c) Therapeutic and social value of the medicinal product and incremental clinical benefit of the medicinal product taking into account its cost-effectiveness;
d) Rationalisation of public expenditure on pharmaceuticals and the budgetary impact on the

   National Health System;

e) Availability of medicines or other therapeutic alternatives for the same conditions at a lower price or lower cost of treatment;
f) Degree of innovation of the medicinal product.

SUITABILITY OF THE CRITERIA LISTED IN THE LAW TO SUPPORT FUNDING DECISIONS FOR MEDICINES IN SPAIN

Please answer yes or no to the following question:

Do you think that the criteria listed in the law to support decision-making on the financing of medicines in Spain are adequate?

- ☐ Yes
- ☐ No

Do you think that any criteria should be added to those listed in the law to support decision-making on medicines funding in Spain in an appropriate manner?

- ☐ Yes
- ☐ No

In the list of criteria used in Spain to support this type of decision, we observe a difference with respect to other decision support frameworks in our environment. This is the specific consideration of the patients' perspective. Please answer yes or no to the following question:

Do you think that the patients' perspective should be added as an additional criterion to those listed in the law to support decision-making on medicines funding in Spain in an appropriate way?

- ☐ Yes
- ☐ No

Chapter II – ANNEX III. All responses to all questions in the survey

Criteria / Question	Measurement option	Respondents N (%) that picked it
Severity, duration and sequelae	Severity instrument	19 (21%)
	DALYs	40 (44%)
	QALYs	61 (68%)
	Clinical units	61 (68%)
	Other	2 (2%)
Groups with specific needs	End of life	32 (36%)
	Paediatric population	42 (47%)
	Rare diseases	64 (71%)
	Unmet need	82 (91%)
	Other	5 (6%)
Therapeutic value	Clinical units	44 (49%)
	Benefit index (French approach)	44 (49%)
	QALYs	72 (80%)
	Other	0 (0%)
Incremental Cost-effectiveness	ICER	60 (67%)
	ICUR	70 (78%)
	Other	4 (4%)
Cost-Utility Threshold (yes / no)	No	6 (7%)
	Yes	84 (93%)
Threshold (explicit / implicit)	Implicit	14 (16%)
	Explicit	70 (78%)
Threshold (different in special situations: yes / no)	No	10 (11%)
	Yes	74 (82%)
Social value	Impact on economy	25 (28%)
	QoL informal carers	73 (81%)
	Productivity	87 (97%)
	Other	4 (4%)

Criteria / Question	Measurement option	Respondents N (%) that picked it
Rationalization of public spending (budget impact)	Pharmaceutical spending, 3-5 years horizon	3 (3%)
	Total expenditure, 3-5 years horizon	78 (87%)
	Other	9 (10%)
Availability of therapeutic alternatives	ATC4	11 (12%)
	ATC5	34 (38%)
	Therapeutic equivalent	59 (66%)
	Other	8 (9%)
Degree of innovation	MCDA	32 (36%)
	Checklist	49 (54%)
	Other	9 (10%)
Are we addressing all relevant criteria?	Yes	44%
	No	56%
Should any criteria be added to the current list?	No	23%
	Yes	77%
Do you think the perspective of patients should be an additional criterion?	No	26%
	Yes	74%

Note: *The relative weights are presented on a different table, in the body of the paper. They are presented as means, based on a total of 88 correctly formulated responses (2 did not sum up to 100). It was a weighting exercise, not a matter of picking options. Hence, percentages are not relevant.*

Chapter II – ANNEX IV. Respondents who chose multiple answers (N=90)

Criteria / Question	Number of options chosen by respondent	Number of respondents	% of respondents
Severity, duration and sequelae	1	35	39
	2	21	23
	3	24	27
	4	8	9
	Other/none	2	2
Groups with specific needs	1	15	17
	2	20	22
	3	35	39
	4	15	17
	Other/none	5	6
Therapeutic value	1	34	38
	2	42	47
	3	14	16
	Other/none	0	0
Incremental Cost-effectiveness	1	46	51
	2	42	47
	Other/none	2	2
Social value	1	11	12
	2	57	63
	3	20	22
	Other/none	2	2
Rationalization of public spending	1	81	90
	Other/none	9	10
Availability of therapeutic alternatives	1	62	69
	2	18	20
	3	2	2

Criteria / Question	Number of options chosen by respondent	Number of respondents	% of respondents
	Other/none	8	9
Degree of innovation	1	81	90
	Other/none	9	10

Note: we rounded up where decimals were .5 or higher and down when they were .49 or lower. This may have caused that, in some instances, total percentages were 101 or 99 instead of 100; questions about the threshold only had one possible answer, and the option to tick the 'Other' free text box was not offered, so we did not include those in this table.

Chapter II – ANNEX V. LOGISTIC REGRESSIONS

Table A1. Measurement of severity, duration and sequelae

	(1) Acute Physiology	(2) DALY	(3) QALY	(4) Clinical markers
HTA agencies	0 (.)	0 (.)	0 (.)	0 (.)
Regulatory agencies	-0.121 (0.888)	-0.749 (0.352)	-1.303 (0.130)	0.729 (0.443)
Consulting firms	-0.507 (0.698)	-0.407 (0.684)	-0.771 (0.565)	1.188 (0.351)
Government Institution	-0.0164 (0.985)	-1.163 (0.154)	-1.613 (0.055)	-0.605 (0.442)
Industry	-0.403 (0.683)	-0.419 (0.615)	**-2.125*** **(0.022)**	1.633 (0.177)
Academic institution	-0.242 (0.778)	-1.270 (0.112)	0.248 (0.800)	**-2.065*** **(0.016)**
Other	-1.051 (0.385)	-0.651 (0.454)	-1.345 (0.164)	-0.604 (0.496)
1-3 years	0 (.)	0 (.)	0 (.)	0 (.)
3-5 years	0.611 (0.663)	0.746 (0.569)	-0.597 (0.687)	-0.454 (0.610)
5-8 years	0 (.)	0 (.)	-0.512 (0.750)	-0.248 (0.809)
8 years or more	0.328 (0.794)	-0.198 (0.861)	-0.705 (0.594)	0 (.)
Management/direction position	0 (.)	0 (.)	0 (.)	0 (.)
Other	0 (.)	0 (.)	-0.925 (0.570)	0 (.)
Administrative	0 (.)	0 (.)	0 (.)	0 (.)
Technicians, professors, researchers	0.519 (0.402)	-0.614 (0.250)	**-1.657**** **(0.008)**	0.512 (0.366)
Constant	-1.613 (0.232)	0.893 (0.454)	3.268* (0.025)	0.604 (0.369)
Observations	83	83	90	84
Pseudo R^2	0.033	0.059	0.142	0.172

Table A2. Necessities of certain specific patient groups

	(1) No therapeutic alternative	(2) Orphan medicines	(3) Pediatric population	(4) End of life
HTA agencies	0 (.)	0 (.)	0 (.)	0 (.)
Regulatory agencies	1.805 (0.186)	-0.207 (0.818)	1.715 (0.067)	-0.162 (0.846)
Consulting firms	0 (.)	-0.867 (0.439)	-0.639 (0.545)	-1.248 (0.242)
Government Institution	0 (.)	-1.029 (0.220)	-0.751 (0.372)	-1.847 (0.057)
Industry	0.330 (0.742)	-0.0406 (0.968)	1.089 (0.197)	1.150 (0.192)
Academic institution	1.072 (0.312)	**-1.637*** **(0.049)**	-0.493 (0.536)	-1.004 (0.251)
Other	0 (.)	-0.887 (0.352)	0.810 (0.351)	-0.197 (0.826)
1-3 years	0 (.)	0 (.)	0 (.)	0 (.)
3-5 years	-0.560 (0.669)	-0.971 (0.237)	1.717 (0.239)	-0.169 (0.845)
5-8 years	0 (.)	-0.679 (0.516)	-0.890 (0.605)	0.830 (0.427)
8 years or more	0 (.)	0 (.)	0.359 (0.777)	0 (.)
Management/direction position	0 (.)	0 (.)	0 (.)	0 (.)
Other	0 (.)	0 (.)	-0.0474 (0.977)	-1.223 (0.496)
Administrative	0 (.)	0 (.)	0 (.)	0 (.)
Technicians, professors, researchers	-0.0806 (0.920)	-0.441 (0.422)	-0.301 (0.586)	**-1.130*** **(0.046)**
Constant	0.729 (0.359)	1.784* (0.017)	-0.637 (0.627)	0.331 (0.617)
Observations	44	84	90	86
Pseudo R^2	0.057	0.067	0.157	0.148

Table A3. Clinical and social value

	(1) V_AVAC	(2) V_clin	(3) V_comb
HTA agencies	0 (.)	0 (.)	0 (.)
Regulatory agencies	-1.503 (0.098)	0.631 (0.424)	0.517 (0.515)
Consulting firms	0 (.)	-0.432 (0.658)	-0.634 (0.522)
Government Institution	-0.908 (0.360)	0.380 (0.602)	-0.494 (0.529)
Industry	-1.171 (0.231)	0.496 (0.545)	0.351 (0.673)
Academic institution	-0.172 (0.868)	-0.851 (0.273)	-0.552 (0.471)
Other	-0.409 (0.722)	0.140 (0.868)	-0.339 (0.693)
1-3 years	0 (.)	0 (.)	0 (.)
3-5 years	-1.058 (0.203)	0.756 (0.586)	-0.153 (0.903)
5-8 years	0.679 (0.632)	0.584 (0.696)	0 (.)
8 years or more	0 (.)	1.207 (0.332)	-0.303 (0.785)
Management/direction position	0 (.)	0 (.)	0 (.)
Other	-1.648 (0.334)	0 (.)	0 (.)
Administrative	0 (.)	0 (.)	0 (.)
Technicians, professors, researchers	-0.192 (0.753)	-0.138 (0.784)	-0.526 (0.313)
Constant	2.099* (0.014)	-1.062 (0.413)	0.648 (0.579)
Observations	79	88	83
Pseudo R^2	0.084	0.051	0.035

Table A4. Instruments to measure cost-effectiveness

	(1) C_ICUR	(2) C_ICER
HTA agencies	0 (.)	0 (.)
Regulatory agencies	**-3.052**** **(0.004)**	0.444 (0.640)
Consulting firms	0 (.)	-1.281 (0.209)
Government Institution	**-2.296*** **(0.028)**	-0.702 (0.367)
Industry	-1.508 (0.186)	0.485 (0.621)
Academic institution	-1.458 (0.178)	-0.566 (0.476)
Other	-0.0793 (0.960)	-0.329 (0.719)
1-3 years	0 (.)	0 (.)
3-5 years	-0.357 (0.823)	0.982 (0.463)
5-8 years	1.705 (0.396)	-1.289 (0.399)
8 years or more	0.719 (0.622)	0.885 (0.435)
Management/direction position	0 (.)	0 (.)
Other	-2.694 (0.146)	0 (.)
Administrative	0 (.)	0 (.)
Technicians, professors, researchers	-0.396 (0.533)	0.0649 (0.906)
Constant	2.275 (0.143)	0.108 (0.927)
Observations	83	88
Pseudo R^2	0.188	0.090

Table A5. Thresholds

	(1) Threshold?	(2) Explicit	(3) Implicit	(4) Exceptions
HTA agencies	0	0	0	0
	(.)	(.)	(.)	(.)
Regulatory agencies	-1.944	**-2.990****	2.234	-0.129
	(0.125)	**(0.003)**	(0.068)	(0.900)
Consulting firms	0	-0.0675	0.460	-0.0695
	(.)	(0.962)	(0.768)	(0.960)
Government Institution	0	0	0	0
	(.)	(.)	(.)	(.)
Industry	-1.084	-0.412	0.138	0
	(0.495)	(0.716)	(0.927)	(.)
Academic institution	-0.638	-1.486	1.769	-1.429
	(0.673)	(0.122)	(0.143)	(0.104)
Other	-1.243	-0.674	1.224	-0.863
	(0.432)	(0.552)	(0.358)	(0.387)
1-3 years	0	0	0	0
	(.)	(.)	(.)	(.)
3-5 years	-0.859	0.175	-0.808	1.508
	(0.410)	(0.857)	(0.511)	(0.377)
5-8 years	0	-1.269	1.916	-0.200
	(.)	(0.382)	(0.236)	(0.909)
8 years or more	0	0	0	0.519
	(.)	(.)	(.)	(0.711)
Management/direction position	0	0	0	0
	(.)	(.)	(.)	(.)
Other	0	0	0	0
	(.)	(.)	(.)	(.)
Administrative	0	0	0	0
	(.)	(.)	(.)	(.)
Technicians, professors, researchers	-0.839	0.156	-0.552	-0.649
	(0.382)	(0.809)	(0.422)	(0.354)
Constant	3.763**	1.859*	-2.252*	1.342
	(0.008)	(0.039)	(0.046)	(0.341)
Observations	61	71	71	63
Pseudo R^2	0.103	0.166	0.112	0.080

Table A6. Social value

	(1) Family impact	(2) Patient impact	(3) Industry impact
HTA agencies	0 (.)	0 (.)	0 (.)
Regulatory agencies	-2.356 (0.084)	-0.351 (0.809)	-0.452 (0.637)
Consulting firms	0 (.)	0 (.)	0.522 (0.623)
Government Institution	**-3.159* (0.015)**	0 (.)	-0.865 (0.414)
Industry	-1.169 (0.469)	0 (.)	0.293 (0.755)
Academic institution	**-2.686* (0.045)**	0.458 (0.761)	0.401 (0.644)
Other	-1.479 (0.361)	0 (.)	0 (.)
1-3 years	0 (.)	0 (.)	0 (.)
3-5 years	-0.731 (0.476)	-0.914 (0.531)	**1.834* (0.039)**
5-8 years	-1.734 (0.218)	0 (.)	0 (.)
8 years or more	0 (.)	0 (.)	0 (.)
Management/direction position	0 (.)	0 (.)	0 (.)
Other	0 (.)	0 (.)	0 (.)
Administrative	0 (.)	0 (.)	0 (.)
Technicians, professors, researchers	-0.0000992 (1.000)	0.379 (0.734)	**-1.603* (0.021)**
Constant	3.559** (0.006)	1.925 (0.092)	-0.235 (0.751)
Observations	77	33	70
Pseudo R^2	0.164	0.044	0.145

Table A7. Rationalization of public spending

	(1) P_farm	(2) P_san
HTA agencies	0 (.)	0 (.)
Regulatory agencies	1.577 (0.239)	**-2.477*** **(0.025)**
Consulting firms	0 (.)	-3.147 (0.084)
Government Institution	0 (.)	-0.808 (0.576)
Industry	0 (.)	-1.064 (0.465)
Academic institution	0 (.)	-0.0481 (0.972)
Other	0 (.)	-1.843 (0.156)
1-3 years	0 (.)	0 (.)
3-5 years	0.241 (0.863)	-0.899 (0.382)
5-8 years	0 (.)	0 (.)
8 years or more	0 (.)	0 (.)
Management/direction position	0 (.)	0 (.)
Other	0 (.)	0 (.)
Administrative	0 (.)	0 (.)
Technicians, professors, researchers	0 (.)	**-2.879*** **(0.012)**
Constant	-2.564* (0.026)	4.939*** (0.001)
Observations	20	79
Pseudo R^2	0.089	0.262

Table A8. Availability of other medicines and therapeutic alternatives

	(1) A_equ	(2) A_atc4	(3) A_atc5
HTA agencies	0 (.)	0 (.)	0 (.)
Regulatory agencies	-0.208 (0.802)	-0.301 (0.812)	**-2.486*** **(0.033)**
Consulting firms	-1.820 (0.091)	1.232 (0.419)	-0.442 (0.659)
Government Institution	-0.0603 (0.943)	0.436 (0.686)	-0.552 (0.457)
Industry	-1.163 (0.171)	0.484 (0.685)	0.0289 (0.972)
Academic institution	-0.181 (0.819)	-0.398 (0.754)	-0.431 (0.570)
Other	1.978 (0.145)	-0.292 (0.839)	0 (.)
1-3 years	0 (.)	0 (.)	0 (.)
3-5 years	1.044 (0.237)	-0.159 (0.896)	0.321 (0.825)
5-8 years	2.046 (0.190)	0.851 (0.458)	1.766 (0.241)
8 years or more	0 (.)	0 (.)	1.512 (0.230)
Management/direction position	0 (.)	0 (.)	0 (.)
Other	-2.334 (0.210)	2.503 (0.189)	0 (.)
Administrative	0 (.)	0 (.)	0 (.)
Technicians, professors, researchers	-0.592 (0.293)	1.410 (0.114)	0.383 (0.501)
Constant	0.903 (0.184)	-3.024** (0.005)	-1.358 (0.301)
Observations	86	86	79
Pseudo R^2	0.132	0.094	0.102

Table A9. Innovation

	(1) I_chec	(2) I_mcda
HTA agencies	0 (.)	0 (.)
Regulatory agencies	-0.983 (0.235)	0.0191 (0.980)
Consulting firms	0.378 (0.701)	-0.209 (0.832)
Government Institution	0.770 (0.323)	-0.580 (0.456)
Industry	0.611 (0.459)	-0.426 (0.607)
Academic institution	-0.140 (0.851)	-0.605 (0.439)
Other	-0.195 (0.819)	-1.061 (0.269)
1-3 years	0 (.)	0 (.)
3-5 years	-0.872 (0.530)	0.792 (0.567)
5-8 years	0.240 (0.883)	-0.316 (0.846)
8 years or more	-0.887 (0.480)	0.625 (0.618)
Management/direction position	0 (.)	0 (.)
Other	0 (.)	0 (.)
Administrative	0 (.)	0 (.)
Technicians, professors, researchers	0.138 (0.788)	-0.266 (0.612)
Constant	0.796 (0.537)	-0.704 (0.587)
Observations	88	88
Pseudo R^2	0.063	0.028

Table A10. Adequacy of criteria

	(1) Criterios_adec_a	(2) Criterios_adicional	(3) Criterio_paciente
HTA agencies	0 (.)	0 (.)	0 (.)
Regulatory agencies	-0.447 (0.614)	0.887 (0.338)	-0.259 (0.750)
Consulting firms	**-2.566*** **(0.023)**	0 (.)	0 (.)
Government Institution	-1.160 (0.179)	0.968 (0.251)	-0.201 (0.806)
Industry	-1.649 (0.070)	0.374 (0.671)	1.335 (0.264)
Academic institution	**-2.669**** **(0.004)**	1.136 (0.219)	-0.707 (0.363)
Other	-2.252* (0.020)	0.136 (0.879)	-0.201 (0.824)
1-3 years	0 (.)	0 (.)	0 (.)
3-5 years	-1.692 (0.053)	-0.0797 (0.956)	0.0406 (0.961)
5-8 years	0.420 (0.733)	-1.765 (0.248)	0.651 (0.587)
8 years or more	0 (.)	-0.414 (0.745)	0 (.)
Management/direction position	0 (.)	0 (.)	0 (.)
Other	0 (.)	0 (.)	0 (.)
Administrative	0 (.)	0 (.)	0 (.)
Technicians, professors, researchers	-0.209 (0.704)	-0.127 (0.824)	-0.461 (0.400)
Constant	1.650* (0.029)	1.029 (0.436)	1.108 (0.102)
Observations	84	81	77
Pseudo R^2	0.153	0.060	0.058

p-values in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Chapter III. Pricing and reimbursement mechanisms for advanced therapy medicinal products in 20 countries

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DOI: https://doi.org/10.3389/fphar.2023.1199500

1. Introduction

Advanced Therapy Medicinal Products (ATMPs) are medicines for human use that are based on genes, tissues or cells (1). Some of these therapies hold great potential for patients without an effective current therapeutic approach (181, 182). Development is rapid in this area. By October 2022, 19 ATMPs had received full, conditional or exceptional marketing authorization (MA) in the European Union (EU) (183).The Food and Drugs Administration (FDA) forecasts that by 2025 they will approve between 10 and 20 cell and gene therapies every year (184). However, the individual companies choose whether to submit products for regulation, to the FDA or to other regulatory bodies in other regions, as well as for registration and reimbursement in particular countries. For example, whilst a product may have a central marketing authorization, the companies can then decide when and where to launch or file for reimbursement.

The generation of evidence in therapeutic areas where there is an unmet medical need can be challenging (185). The PRIority MEdicines (PRIME) scheme was developed by the European

Medicines Agency (EMA) to enhance technical support for the development of medicines that target an unmet medical need. Many ATMPs target unmet needs. Almost half (45%) of PRIME designations (183) – combining medicines that were once granted PRIME designation but that are no longer in the scheme and therapies that are in the scheme at the time of writing – were ATMPs (186) (Annex I). Furthermore, ATMPs, up to now, have almost all been designated as orphan drugs for rare diseases (14 out of the 19 approved by the EMA).

In order to facilitate early access for patients, where a product addresses an unmet need, regulators can give a conditional MA on the basis of early data, providing certain conditions are met including the provision of further evidence (187). However, this often means that MA holders then file for reimbursement with insufficient evidence to support the claim of cost-effectiveness (187), particularly in the long-term. As these medicines are often priced highly this creates high financial and clinical uncertainty and risk for payers. Outcomes-based (or pay-for-performance (P4P)) arrangements offer instruments that can mitigate financial risk, limit the patient population and generate further evidence. Qualitative research suggests that some experts view P4P schemes as potential enablers for MA holders to meet many of their strategic goals (188). Early access allows sales to be initiated sooner in the product life cycle, allowing earlier returns on capital.

Whilst regulatory policies are being adopted in Europe to facilitate the accelerated approval of ATMPs (189), the complexities of the existing pathways are often seen as a barrier by therapy developers (190). However, if marketing authorization is successfully obtained, gaining access to a market where there was previously unmet need can set up the product as the market leader, develop economies of scale, and potentially establish it as the new standard of care ("first-mover advantage"). Furthermore, sales can be made without changing the "official" price of the product in that country (i.e., the net price of a therapy in a country does not need to be the same as its list price (191)), which is advantageous for the MA holder in countries that adopt external reference pricing. Whilst that can be attractive to manufacturers, it can raise questions about equity in access (192).

The way ATMPs are administered has relevance for decision making both from clinical and reimbursement perspectives. Unlike most medicines, which can be withdrawn if no response is achieved, gene therapies are one-off treatments. Out of the 15 indications (13 ATMPs) in our sample, 14 are intended for single administration (Annex I). Due to the early and often sparse evidence base at launch, the clinical and economic data that reaches Health Technology Assessment (HTA) and reimbursement stage can be insufficient for healthcare systems to assess

their added therapeutic value with certainty (34, 35) and to negotiate value-based prices (36). The difficulty of demonstrating value to payers, very small fragmented markets, and manufacturing and logistical difficulties have been cited as reasons for the withdrawal of some ATMPs from the market in Europe (183).

Payers handling the difficult task of managing financial risk and uncertain evidence, where it exists, need to embed risk management strategies into their pricing and reimbursement (P&R) decision making processes, and they often do so through special pricing mechanisms (36-38). While there are many theoretical papers on P&R options (38, 193-195), original empirical research is very scarce. The Organization for Economic Co-operation and Development (OECD) conducted a survey of experts on the use of managed entry agreements (MEA) in 12 countries (188) but did not deal with specific therapies. A few papers describe country experiences of P&R arrangements (37, 196-198). This paper aims to provide a comprehensive international review of regulatory and P&R decisions taken for all ATMPs with European marketing approval in March 2022. We consider regulatory approval, reimbursement status, use of special P&R arrangements (type and aims) and arrangements for further evidence collection and re-assessments.

2. Methods

A survey was distributed in July 2022 to 46 countries (see Annex II) through the Pharmaceutical Pricing and Reimbursement Information (PPRI) Network, a unique collaboration of pharmaceutical P&R authorities with 50 members from national competent bodies (mostly European) and international institutions. The PPRI enables members to exchange information and data on P&R decisions and policies (199, 200).

By March 2022, 13 ATMP had received European central MA via the EMA. 2 of them have 2 licensed indications with European central MA (Annex I), making for a total of 15 therapy-indication pairs. All were included in our survey.

Data collection sheets were pre-filled with information from the literature review or previous PPRI Network enquiries where available. Respondents were allowed approximately 3 weeks to respond, with one reminder, and were contacted again to clarify responses that were unclear. The survey included questions about the regulatory approval status in the country (not all operated through the European centralized MA procedure), reimbursement status, the reasons

for not reimbursing in case the ATMP is not reimbursed, whether any special arrangements are in place to finance the therapy (such as coverage with evidence development, discounts or rebates– see Annex III for definitions), the main purpose of special arrangements (for example, control expenditure, share risk), whether information on the scheme is publicly available, how further evidence is to be collected (if any), whether reassessment of the evidence, coverage or price is planned, and any other further information respondents may want to provide. The survey and responses were all in English (the questions asked in the survey are transcribed in Annex IV). We reviewed targeted peer reviewed and grey literature to contrast the answers to our survey, and to contextualize them. A draft of this manuscript was circulated amongst responders to ensure we captured their responses accurately. Our focus was on national policies. Within some countries, the manufacturer can negotiate contracts with individual social health insurance bodies, regional health authorities, hospitals, or the private healthcare sector, including P4P schemes. We indicate the cases where our respondent had knowledge of these decentralized agreements, but there may be other similar cases which we were not informed about. We provide a narrative description of results for each country, and consider common themes and suggest policy recommendations in the discussion. The data are anonymized in accordance with the World Health Organization's (WHO) Framework for Engagement with non-State actors so as not to confer any endorsement of a specific non-State actor's name, brand or product.

3. Results

Responses were received from 20 countries out of 46 (43.5%) (Annex II). 6 of those countries (Armenia, Australia, Brazil, Canada, Israel and Türkiye) do not operate through the European MA procedure (See Annex V). Differences in regulatory status in these countries compared to the EMA, for the ATMPs under study, were observed in 44 instances. The regulatory status in Türkiye, where none of the ATMPs had received regulatory approval at the time of the survey (see Table 1 and Annex V for further details), showed the starkest difference compared to their status with regards to the European centralized regulatory system. Armenia, Brazil, Bulgaria, Iceland, Malta and Türkiye did not reimburse any ATMP (Table 1). Malta and Iceland do operate through the European centralized regulatory system, but had not received applications for reimbursement for any ATMPs. To overcome this situation, the government of Malta has an agreement for hematology patients in need of an ATMP to be treated in the United Kingdom. In

Brazil, ATMP12 is under assessment and pending a reimbursement decision, for ATMP5 the price has been appealed and ATMP7 was rejected for reimbursement based on the budget impact. Bulgaria, supporting their decision by HTAs in some cases, decided not to fund any of the ATMPs in the list. Armenia gave no reasons for the lack of reimbursement for all ATMPs included in our study, hence we excluded this country from Table 1.

14 countries reimbursed at least one ATMP (Table 2). Austria and Israel provided no information about P&R schemes. ATMP13 was withdrawn by the manufacturer from Europe. Hence, we did not include it in Table 2.

4 of the ATMPs included in our study were chimeric antigen receptors (CAR) T-cells medicines (CAR-Ts) (ATMPs 1, 5, 10 and 11). Previous research in a smaller sample of countries (Germany, Italy, Spain, France and United Kingdom) and ATMPs (11 included, of which 2 were CAR-Ts) found that the CAR-Ts they included in their study were being reimbursed in the countries they observed (198). Our results show wide variation in access across countries for CAR-Ts, with ATMP1 being reimbursed in 2 countries (France and Germany), ATMP5 (indication 5) in 13 countries, ATMP5 (indication 6) in 11 countries, ATMP10 in 4 countries (Israel, France, Germany and Italy), ATMP11 (both for I12 and I13) in the same 11 countries. We observed no systematic differences in reimbursement status (Table 1) or P&R arrangement used for reimbursement (Table 2) between CAR-Ts and other types of ATMPs.

3.1 Australia

In Australia, the purpose of all special arrangements used to finance ATMPs was to share risks. These agreements were always associated to the collection of further evidence. The Pharmaceutical Benefits Advisory Committee (PBAC) does provide advice on the nature of the patient registry that is most suitable in each case (i.e., a disease-based one or therapy-based ones), as well as the minimum data to be collected. For instance, for both indications of ATMP11 and ATMP5, they recommend the Australian Bone Marrow Transplant Recipient Registry, for ATMP7 they recommended including data from Australian patients in the Novartis international registry, and for ATMP12 they noted that a disease-based registry would be suitable, instead of therapy-based registries. For all therapies the manufacturer would be responsible for providing any new data to the HTA committee, which would re-assess the new evidence. The periods for

reassessment varied between 2 years from commencement of public financing for both indications of ATMP11 and ATMP5, 3 years for ATMP7 and 5 years for ATMP12.

The special pricing and reimbursement arrangements used for ATMPs were confidential. However, the PBAC does publish its recommendation. For ATMP11, ATMP7 and ATMP12, the PBAC recommended a P4P risk sharing arrangement combined with a confidential discount. For ATMP5, they recommended a P4P.

3.2 Canada

In Canada the regulatory authority (Health Products and Food Branch (HPFB) of Health Canada) can issue a Notice of Compliance (NOC), which corresponds to an MA, or a NOC with conditions, corresponding to a Conditional MA. Special agreements to finance medicines are confidential. They may involve simple discounts (e.g. first dollar rebates), incremental rebates in the event an annual threshold is exceeded, and other forms of risk-sharing arrangements. There are special arrangements in place for all 3 ATMPs being reimbursed (ATMP5, ATMP11 and ATMP12). Whether the agreements are linked to the collection of further evidence is also confidential. For therapies that are indeed being subject to the collection of further evidence as part of managed access schemes, such evidence would be meant to inform the clinical and cost-effectiveness parameters of a reassessment (HTA). The institutions responsible for the collection and analysis of this further evidence are the pan-Canadian Pharmaceutical Alliance (pCPA) and/or provincial and territorial drug plans. In Canada, any drug that is reimbursed in the public healthcare system could be eligible for a proactive or reactive reassessment (201).

3.3 Israel

Israel applies special pricing and reimbursement agreements for both indications of both ATMP11 and ATMP5, ATMP2, ATMP7, ATMP10 and ATMP12. However, information about the arrangements is either confidential, not publicly available or not known to the respondents of our survey. In all cases, the schemes are subjects of the collection of further evidence, which is to be collected and analyzed by the Ministry of Health of Israel, although no further information about this is publicly available.

3.4 Czechia

In the Czechia, the national HTA body only makes assessments of drugs for outpatient settings. ATMP2 and ATMP3 have been recommended in this context. ATMP2 is subject to a special confidential reimbursement arrangement to control expenditure. ATMP3 is reimbursed without any special arrangement. The HTA body does not assess therapies for in-hospital settings, and have no record of their use. Reimbursement in the hospital settings is theoretically possible for all products within the scope of our study and lies within the competency of health insurance companies and hospitals.

3.5 Denmark

Denmark reimburses 4 ATMPs: ATMP3, ATMP7, ATMP12 and ATMP5 (only its indication for B-cell acute lymphoblastic leukemia). ATMP7 is financed by a P4P model in yearly instalments conditioned on continuing clinical response, with data collected by the national procurement agency and healthcare providers (202). The main aim was to control expenditure.

3.6 France

France reimburses most ATMPs (Table 1), with confidential price discounts. The information about whether or not the reimbursement arrangements include mandatory evidence collection is confidential. If such data collection was mandated, the responsibility for collecting this information would fall under the Technical Agency for Information on Hospitalization (AITH), and the health ministry would be responsible for analyzing the data. Health technology re-assessment of ATMP11 (both indications), ATMP5 (both indications) and ATMP10 are planned for mid-2023, and in 2024 for ATMP2 and ATMP7. In each case the price can be revised during the entire life cycle of the product. If the HTA assessment indicates that the therapy provides major added clinical value, France has a system to inject additional funding to cover the costs of ATMPs administered in hospitals, on top of the existing diagnosis related group (DRG) fee

(198). Eligibility for inclusion in this "add-on list" is based on the cost of the product compared with the tariff applied to the DRG (cost>30% of the tariff). As a result, for ATMP5 and ATMP11, an additional 15,000€ was added in France on top of the DRG fee (198). ATMP3 and ATMP1 were assessed as providing minor added clinical value and no added clinical value respectively, compared with existing alternatives, and so hospitals can use these therapies but receive no additional DRG-funding from the national health insurance system for doing so.

3.7 Germany

All ATMPs in this study were being reimbursed in Germany (203), except for 2 (i.e., ATMP9 and ATMP13), which had been taken off the market by the company (204). In the German market, all new therapies used to be reimbursed at a price freely set by the company during the first year, after which manufacturers negotiate the price of their product with the social insurance providers (205). In November 2022, a policy reform (namely the GKV-Finanzstabilisierungsgesetz or SHI Financial Stabilization Act) shortened the period of free pricing to 6 months (206). In a regular benefit assessment, a drug would only be able to command a premium price if the evidence established a "major" or "substantial" added benefit. The law makes an exception for orphan drugs. Added benefit is "assumed" for orphan drugs as soon as they get European central MA if the total expenditure is less than €50 million per year (203). Hence in these cases the drugs are reimbursed at premium prices. This has proved controversial (207) and concerns have been raised about the spill-over effect on the prices of orphan drugs throughout international markets, since prices of medicines in Germany weigh heavily in the baskets used to estimate reference prices in other countries (208, 209). Diverse local MEAs and P4P schemes have been negotiated between the manufacturer and local payers in Germany (210). At the end of 2019 routine practice data collection was required binding the manufacturer to set up a patient registry and to submit results yearly (211, 212). In Germany, there are no special arrangements at national level to finance ATMPs (as stated in Table 2), but social health insurers negotiate outcomes-based rebates with manufacturers (37, 198).

3.8 Greece

Greece applies confidential special arrangements to finance ATMP11 (indications 12 and 13) and ATMP5 (indications 5 and 6), ATMP12 and ATMP7. The main aim of the special arrangements is to control expenditure. For ATMP11 and ATMP5 there is a budget cap (there may be additional, confidential, components), with additional data collection over 2 years, followed by a planned reassessment and renegotiation.

3.9 Italy

At the time of writing, Italy had decided to reimburse 8 of the ATMPs included in our study, for 10 different indications. To reimburse them, Italy uses a range of types of P&R arrangements (see table 2). Most of the arrangements in place to finance ATMPs in Italy are P4P payment models, paid in instalments (upon result), linked to individual patient data, and applying a confidential discount. Although the size of the discount is kept confidential, information about the P&R arrangement applied is made publicly available in Italy. ATMP7 is reimbursed applying a budget cap, and outcomes are followed through the Italian regulator's (AIFA) registry (linking prescriptions and payments/rebates to clinical outcomes (213)). For ATMP10 and ATMP6, the arrangement is similar but a simple discount was applied instead of a budget cap.

All ATMPs reimbursed in Italy are subject to the collection of further evidence collected by AIFA registries. The technological architecture of the registries is resourced by companies but governed by AIFA (214). This evidence is subsequently used to reassess the value of the therapy, which usually occurs after two years from the agreement signature or in case of extension of indication. Some of these ATMPs were assigned the so called AIFA innovativeness recognition (i.e., ATMP3, ATMP7, ATMP10, ATMP6 and ATMP12), which entitles them to being financed in Italy through a special innovative drug fund, plus becoming immediately available in regional formularies, and exempt from the usual pay-back mechanism (215).

3.10 Netherlands (Kingdom of the)

The special arrangements to finance ATMPs are confidential in nature, but in general terms, they were implemented to improve cost-effectiveness and to control expenditures. Only 2 of the special arrangements in place to finance ATMPs in the Netherlands (Kingdom of the) were

organized centrally by the government (ATMP7 and ATMP12). The rest were arranged by insurance providers. ATMP11 was re-evaluated based on 3-year survival data and budget impact, which resulted in a confidential discount of the price of at least 5%. The Netherlands (Kingdom of the) is also a member of the BENELUXA Initiative, which recently published an HTA jointly produced between Belgium, Ireland and Netherlands (Kingdom of the) for ATMP6 (216), resulting in a recommendation not to reimburse unless cost effectiveness can be improved relative to existing treatment. The countries that constitute the initiative have not yet entered in joint negotiations to reach reimbursement terms for this product (216).

3.11 Slovenia

Slovenia applies special arrangements for the reimbursement of ATMP5 (indication 5 and 6), ATMP2 and ATMP12. The main purpose of these financing schemes is to control expenditures, and they achieved this through confidential discounts. None of these schemes are associated with the collection of further evidence.

3.12 Spain

In Spain, the special arrangements to finance ATMPs aimed to share risk and to control expenditure. In most cases this comprised a P4P scheme, combined with restrictions in the eligible patient populations. ATMP7 and ATMP12 were financed with P4P schemes combined with expenditure cap and a price-volume agreement respectively. All of them involved the collection of further evidence, which was in all cases operationalized through a national registry operated by the health ministry (Sistema de Información para determinar el VALor TERapéutico de MEDicamentos, which stands for Information System to determine the Therapeutic Value of Medicines, or VALTERMED) (197). VALTERMED's data collection protocols are made publicly available at the website of the Spanish Ministry of Health (both in Spanish and in English). Each decentralized region in Spain has a monitoring committee responsible for data collection and quality. Data analysis and re-assessment will be conducted by the health ministry "when sufficient data become available", and some provisional data have been published (217).

3.13 Sweden

In Sweden, the county councils are responsible for in-patient care, which includes ATMPs. A committee called the New Therapies Council supports county councils, enabling the equality of the system. Also, upon request of the regions, the national HTA agency can perform an assessment of the health economic evidence. This level of fragmentation makes it difficult to access information about what financing schemes are in place in Sweden for ATMPs and how they are operationalized. Nevertheless, county councils do publish information about which therapies have a managed entry agreement in place, and the dates associated with reassessment.

Considering the above, although limited in scope, we do have some information about the reimbursement status of ATMPs in Sweden and how it has been operationalized. ATMP11 (indications 12 and 13), ATMP5 (indication 5 only) and ATMP12 are financed through special arrangements. For ATMP11 (indications 12 and 13), a rebate may be required conditional on further evidence collection through the European Society for Blood and Marrow Transplantation (EBMT) patient register and quality local registers. The same registry is used to collect further evidence for ATMP5, but there is no further detail available around the financing arrangement. For ATMP12, the agreement consists of a confidential discount, and the collection of further evidence, operationalized through the national quality register for neuromuscular diseases (NMiS). ATMP7 is the only ATMP reimbursed in Sweden for which there is no public report of a special financing arrangement being in place.

4. Discussion

Six countries in this survey reimbursed no ATMPs due to a variety of reasons, including regulatory and reimbursement decisions made by the regulators, the payers or the companies themselves (see table 1 for further details). Where a particular ATMP was financed, there was considerable variability across countries in the types of P&R arrangements used (see table 2 for further details). For instance, ATMP5 and ATMP11 were reimbursed using at least 6 different formulas comprising combinations of P4P, discounts, expenditure caps and restrictions on the patient population. No countries used subscription models or more exotic financial instruments

(models and instruments that are further described in Annex III and discussed in the academic literature (218)).

There was considerable variation in the type of P4P schemes for ATMPs in our sample. We identified areas where examples of best practice can be helpful for schemes to achieve their objectives. These included the provision of clear objectives, sharing of information between different departments of the health system, availability of information about the parameters of the agreement (or even whether one exists), and clarity about when, how or by whom the data will be analyzed and re-assessed. Improvement in these areas is a prerequisite that enables the necessary alignment between key stakeholders, including industry and health system actors, for these kinds of schemes to successfully fulfil their purpose, but the necessary human resources and expertise needs to be invested by all involved parties into reaching excellence and productive cross-stakeholder collaboration (219).

P4P databases in our sample were usually set up using either existing disease registries or purpose-build stand-alone platforms. None of the responses received indicated that routine healthcare administrative databases were used. This may be because, for example, such platforms do not collect the appropriate diagnosis, treatment or outcome variables. The new regulation on European cooperation on HTA does not have any provision for collaboration on post-launch evidence generation (PLEG) (220). This would have enabled the development of common protocols and standards (221, 222). The requirement for busy clinicians to manually input (or re-input) P4P data in stand-alone platforms can mean that data is often omitted or duplicated (36, 37, 195, 196, 223, 224). European cooperation on this area should not only be limited to the actual collection of data, but also on developing capacity in countries, and a further understanding, and guiding countries around the methods to quantify the costs and the benefits of risk-sharing, and of the implementation of the different types of schemes available to articulate it (225).

At a European level, data sharing across jurisdictions may be essential to leverage the benefits of further evidence generation, especially for ultra-rare diseases (196). The role of the European Commission in incentivizing or enforcing the collection of further evidence after conditional centralized marketing authorizations are granted is controversial. Furthermore, research has raised concerns about the delays in the delivery and flaws in the design of post-marketing studies under these schemes, both in Europe and the United States (226). The EU has initiated a flagship program to share reports and analyses of regulatory healthcare data (Data Analysis and Real-World Interrogation Network, DARWIN) (227). However, perhaps the absence of a

central European HTA process and payment mechanism explains that no similar EU-wide initiative addresses the sharing of data that might help address uncertainties at this level, which is a national competency. Furthermore, national governments are responsible for primary data quality. Databases require financial investment (228) and the expertise and leadership to make sure the data is relevant and of sufficient quality (218). P4P arrangements can be associated with increased burden to those administering them, while rebates, discounts, price caps and price-volume arrangements can be managed with relatively straightforward contracts and routine administrative healthcare information systems (36). The research undertaken for this paper indicates that there is scope for further European collaboration exploring strategies for countries to build capacity to administer and/or share the burden of the more complex P&R options and increase transparency.

At a country level, the United Kingdom (England) created the Innovative Medicines Fund to ensure fast, provisional access to promising but uncertain treatments, particularly ATMPs, while further evidence is generated (229) and control over budget impact is maintained. The aim of this fund is to provide the system with a route to provide access to selected therapies deemed particularly promising whilst facilitating the collection of further evidence likely to mitigate initial decision uncertainties to avoid the potential opportunity costs associated with these costly therapies (230). The fine details around how this fund is operationalized, particularly around (but not limited to) providing finer definitions of entry requirements such as what is considered to be a promising treatment, or what is deemed to be a 'step-change in treatment', and other operational aspects such as what provisions will be put in place for therapies that fail to prove their added value and/or being appropriate use of limited public resources, will determine its success (230). Other countries, such as Italy (231) and Canada (232, 233), have developed similar frameworks. Dedicated funds such as these are intended to prevent innovative but uncertain high-cost medicines from displacing other cost-effective interventions while further evidence is generated. However, these siloed funds fragment the pharmaceutical budget and need to be carefully managed and combined with other policies to ensure spending in pharmaceuticals remain affordable and efficient (234). An alternative approach is applied in Australia, where the PBAC has recommended existing disease registries for P4P monitoring. The advantage in principle of disease registries over intervention registries is the potential to estimate comparative effectiveness, subject to appropriate adjustment for confounding by indication (235). Countries without a defined strategy to fund and manage the collection of further evidence in the context of managed entry agreements might tend to seek simpler P&R

agreements with MA holders (such as straight discounts), not because that is the most suitable option to meet their needs in a given P&R decision, but for practicality.

In the sample of responses received, information about the price or the P&R arrangement used to fund a therapy tended to be confidential in nature. While a degree of confidentiality can facilitate negotiation (236), ethically there is a case for enabling reporting of clinical evidence that is accrued using public money under the access schemes (237, 238). The World Health Assembly Resolution 72.8 calls for more transparency across a number of areas including prices in other countries, costs of research and patent expiry (239). More transparency across these areas, including MEA schemes, would facilitate P&R decisions and potentially improve access for patients (240-242).

There appears to be considerable variation across regulatory body outcomes. For example, Türkiye has not approved any ATMP and other regulatory bodies have yet to assess all the products. The individual companies choose whether to submit products for regulation and registration in particular countries. For example, whilst a product may have a central European authorization the companies can then decide when and where to launch or file for reimbursement. Our survey shows that the variability of access is in part due to choices made by regulatory and reimbursement authorities, and in part due to commercial decisions by companies about regulatory and reimbursement submissions.

The new European regulation on HTA will help shape the landscape for ATMPs in the EU, since it stipulates that from 2025 onwards, ATMPs will be required to undergo joint clinical assessments, with the potential of significantly mitigating current differences between national comparative effectiveness assessments (243, 244). However, launching and filing for reimbursement and funding decisions will remain at a national level so the overall impact is difficult to assess at this stage. Furthermore, an additional factor that can lead to fragmentation of the EU market is related to the complex manufacturing, logistics and clinical protocols that commercial ATMPs can require (183) and the threat for these costs, or others like the need to translate packaging into each member's official language, to make smaller countries less commercially attractive for manufacturers, particularly for rare diseases.

The results of our study highlight considerable variation in the approaches used by individual countries to provide access to ATMPs and the scope for voluntary collaborations to overcome some of the existing barriers, particularly for smaller countries. For example, some of the options available to them include joint P&R negotiations for new medicines for demand pooling (to

increase the volume), collaboration on the administration of ATMPs (through joint treatment centers), or cross-country collaboration on real-world-evidence generation (243). There are a number of good examples of collaboration in the European region: FINOSE (Finland, Norway, Sweden), BENELUXA or the Valletta Declaration, or bilateral arrangements such as those between Malta and the United Kingdom (i.e., Malta has an agreement for hematology patients in need of an ATMP to be treated in the United Kingdom, as presented at the beginning of the results section).

The development of detailed treatment protocols (including all associated costs), and clear communication of it to stakeholders, would facilitate cross-border collaboration enabling international multidisciplinary care teams to build on existing infrastructures such as the European Reference Networks (ERNs) to deliver care and to collect evidence, which would provide a European instrument to collaborate towards mitigating uncertainties (243). The view of patient representatives is that, although pooled procurement of ATMPs has not yet been extensively explored, it should be considered more widely (245). Options suggested to boost cross-border collaboration in Europe to enhance access to ATMPs include innovative solutions that are yet to be tried, such as providing care through regional expert treatment centers (243).

As the evidence we present in this paper shows, many products are not submitted for reimbursement in individual countries with priority being given to larger markets. Members of the European Federation of Pharmaceutical Industries and Associations (EFPIA) have committed to “file for pricing and reimbursement in all EU countries as soon as possible and no later than 2 years from the central EU market authorization, provided that local systems allow it” (246). The Pharmaceutical Strategy for Europe notes that many developers of ATMPs benefit from financial or other incentives during the development phases and the EC is exploring “conditionality” of those push incentives to support broader access and increase competition (242). However these proposals have sparked significant debate and reactions from stakeholders, including representatives of the Commission (247), hospital pharmacists representatives (248), the European pharmaceutical industry (249) and academic researchers (250) amongst others. There is considerable variation in ability to pay across the European Region. Therefore, in order to support equitable access across smaller and lower income countries, more explicit consideration of pricing principles will be required, ensuring that any use of external reference pricing is appropriate and mechanisms to preventing arbitrage are in place (251).

Our survey has only included “commercial” ATMPs, developed by private MA holders. There are also now several so-called “academic” ATMPs (252-254), developed by non-profits (255) or

public-private collaborations (256) under hospital exemption regulations (253, 257). In some cases the manufacturer is preparing for centralized MA (255). The potential role of academic ATMPs has been highlighted as a potential route to creating a generic market for this kind of therapies, however multiple barriers prevent this from happening (258). It remains to be seen how regulation, pricing and competitiveness of academic ATMPs will compare with commercial ones (258, 259).

4.1 Strengths and limitations of this study

This paper has described the P&R landscape in 2022 for 15 ATMPs in 20 countries, a much larger sample of products and countries than other articles (37, 197, 198). There may of course be other arrangements in other countries. The countries were mainly high-income, with two upper middle-income. More research is needed on P&R arrangements in low- and middle- income countries (260), and in smaller countries too (focusing for instance in the countries included in the WHO led Small Countries Initiative – a network of 11 European countries with 2 million or less inhabitants, out of which 3 were included in our survey). The survey was in English, which was not the first language of most respondents. We attempted to clarify and classify common terms with respondents across diverse language and institutional settings. The survey was directed at national authorities for P&R. To greater or lesser extent, decision making may be decentralized, as in Sweden, Germany and Spain.

5. Conclusions and recommendations

In this section, and in table 3, we have summarized the key areas for further development and the recommendations associated to each.

The work undertaken has demonstrated that there is wide variation in access to ATMPs between the countries surveyed. Furthermore, that this variation has a number of reasons including regulatory differences, commercial decisions by MA holders, and the divergent assessment processes and criteria applied by payers. Moving towards greater equality of access will require cooperation between countries and stakeholders, together with relevant international actors such as the WHO Regional Office for Europe's Access to Novel Medicines Platform.

There is also considerable cross-country variation in how P4P schemes are used for a particular ATMP. This imposes transaction costs on healthcare systems and MA holders, and limits opportunity for data sharing. In line with WHA 72.8, greater transparency, particularly where public funding has been used, will enable dialogue about the schemes in use, and the development of common protocols, terminology and standards for data collection, will lower costs and generate better quality evidence, ultimately with benefits for patients.

The inclusion of post-launch evidence generation in the new European regulation on cooperation in HTA could formalize arrangements. A specific proposal along these lines was made by EURORDIS, which suggested the co-creation, with multi-stakeholder input, of a data strategy for the European Reference Networks (ERNs) to progress towards the common implementation of a European data infrastructure, building on the existing infrastructure of the Networks (261).

Demand pooling and pooled procurement of ATMPs has not yet been frequently used, should be considered more widely (245) and could facilitate evaluation, evidence generation, pricing and ultimately access in all countries due to the stronger negotiating position they would acquire, but particularly in small countries (243).

There have been several examples of non-profit development of “academic” ATMPs. Careful evaluation of these initiatives should be undertaken, considering the legal and regulatory framework, accounting methods for estimating costs, incentives, P&R pathways for these kinds of products and the implications for competition with commercial medicines.

In the mid-term, more investment in enhancing HTA and (other) infrastructures to support P&R processes (be it through a strong European HTA infrastructure supporting the new regulation, and/or enhancing resources deployed nationally), accompanied by coordinated efforts to further develop the necessary expertise, would highly benefit decision makers dealing with complex P&R decisions for ATMPs.

Acknowledgements

The authors acknowledge the support of the Pharmaceutical Pricing and Reimbursement (PPRI) network whose members provided data for this research. The PPRI network is an informal

collaboration of competent pharmaceutical pricing and reimbursement authorities of 50 mostly European countries as well as European and international institutions. The aim of this network is to facilitate information exchange on pharmaceutical policy issues between public officials, supported by scientific evidence. The authors are also grateful to the PPRI Secretariat affiliated to the Pharmacoeconomics Department at Gesundheit Österreich GmbH (Austrian National Public Health Institute) for granting access to the network. The views expressed in the publication are those of the authors.

Chapter III – Tables

Table 1. Reimbursement status and reasons for not financing ATMPs

		Reimbursement status and reasons for not financing per country												
		Countries with national MA only					*Countries that operate through the European MA procedure*							
Countries		*Australia*	*Canada*	*Israel*	*Brazil*	*Türkiye*	*Austria*	*Bulgaria*	*Czechia*	*Denmark*	*France*	*Germany*	*Greece*
ATMP	*Indication*													
ATMP1	***MM(I1)***	NRA	O	NRA	NRA	NRA	NRD	NSR	NSR[a]	O	R[c]	R	NSR
ATMP2	***AFCDP(I2)***	NRA	NRA	R	NRA	NRA	R	NSR	R[a]	NRD	R	R	NRD
ATMP3	***RDCC(I3)***	NRA	NRA	NRA	NRA	NRA	NRD	NSR	R[a]	R	R[c]	R	NSR
ATMP4	***MNRBS(I4)***	NRA	NRA	NRA	NRA	NRA	NRD	NSR	NSR[a]	O	NSR	R	NSR
ATMP5	***BCALL(I5)***	R	R	R	O	NRA	R	NSR	NSR[a]	R	R	R	R
ATMP5	***DLBCL(I6)***	R	R	R	O	NRA	R	NSR	NSR[a]	NRD	R	R	R
ATMP6	***ML(I7)***	NRA	NRA	NRA	NRA	NRA	NRD	NSR	NSR[a]	R	O	R	NSR
ATMP7	***HRD(I8)***	R	O	R	NRD	NRA	R	NSR	NSR[a]	R	R	R	R
ATMP8	***KCR(I9)***	NRA	NRA	NRA	NRA	NRA	NRD	NSR	NSR[a]	O	NRD	R	NSR
ATMP9	***SCIDTADD (I10)***	NRA	NRA	NRA	NRA	NRA	NRD	NSR	NSR[a]	O	NSR	NRA[d]	NSR
ATMP10	***MCL(I11)***	O	O	R	NRA	NRA	NRD	NSR	NSR[a]	O	R	R	O
ATMP11	***DLBCL(I12)***	R	R	R	NRA	NRA	R	NSR	NSR[a]	NRD[b] / O[b]	R	R	R
ATMP11	***PML(I13)***	R	R	R	NRA	NRA	R	NSR	NSR[a]	O	R	R	R
ATMP12	***SMA(I14)***	R	R	R	O	NRA	R	O	NSR[a]	R	O	R	R
ATMP13 [e]	***BT(I15)***	NRA	NRA	NRA	NRA	NRA	NRD	NSR	NSR[a]	NRA	NRA	NRA	NRA

Legend: See Annex VI for indication abbreviations; MA = Marketing authorization; NRA = No regulatory approval or withdrawn at the request of the manufacturer; NRD = Negative reimbursement decision or reason for not reimbursement not reported in response to our survey; NSR = No submission received for public reimbursement; O = Ongoing (includes awaiting or ongoing health technology assessment, or assessment done but no reimbursement decision made); R = Reimbursed.

Note: [a] In the Czechia, the SÚKL (State Institute for Drug Control – the institution tasked with supporting the regulation of prices and reimbursements for pharmaceuticals) does not participate in price-setting or reimbursement in the in-hospital setting. They do however do so for out-patient therapies (see Results for Czechia). [b] In Denmark, ATMP11 for DLBCL has been assessed and not recommended for third line treatment, and an application for assessment for second line treatment has been put forward (assessment yet to be done); [c] In France, ATMP1 and ATMP3 are reimbursed, but the reimbursement payment to the hospital is no greater than that for standard care. [d] ATMP9 was withdrawn by the manufacturer in Germany; [e] ATMP13 was withdrawn by the manufacturer from Europe. Armenia did not give reasons for non-reimbursement and is not included in Table 1.

(continues below)

(continuation of table 1)

		Reimbursement status and reasons for not financing per country						
		Countries that operate through the European MA procedure						
Countries		***Iceland***	***Italy***	***Malta***	***Netherlands (Kingdom of the)***	***Slovenia***	***Spain***	***Sweden***
ATMP	***Indication***							
ATMP1	***MM(I1)***	NSR	O	NSR	O	NSR	O	O
ATMP2	***AFCDP(I2)***	NSR	NRD	NSR	R	R	R	NRD
ATMP3	***RDCC(I3)***	NSR	R	NSR	R	NSR	NRD	NRD
ATMP4	***MNRBS(I4)***	NSR	NSR	NSR	R	NSR	NRD	NRD
ATMP5	***BCALL(I5)***	NSR	R	NSR	R	R	R	R
ATMP5	***DLBCL(I6)***	NSR	R	NSR	R	R	R	NRD
ATMP6	***ML(I7)***	NSR	R	NSR	O	NSR	O	O
ATMP7	***HRD(I8)***	NSR	R	NSR	R	NSR	R	R
ATMP8	***KCR(I9)***	NSR	NRD	NSR	R	NSR	NSR	NRD
ATMP9	***SCIDTADD(I10)***	NSR	R	NSR	R	NSR	NSR	O
ATMP10	***MCL(I11)***	NSR	R	NSR	O	NSR	NRD	NRD
ATMP11	***DLBCL(I12)***	NSR	R	NSR	R	NSR	R	R
ATMP11	***PML(I13)***	NSR	R	NSR	R	NSR	R	R
ATMP12	***SMA(I14)***	NSR	R	NSR	R	R	R	R
ATMP13	***BT(I15)***	NSR	NRA	NSR	NRA	NRA	NRA	NRA

Legend: See Annex VI for indication abbreviations; MA = Marketing authorization; NRA = No regulatory approval or withdrawn at the request of the manufacturer; NRD = Negative reimbursement decision or reason for not reimbursement not reported in response to our survey; NSR = No submission received for public reimbursement; O = Ongoing (includes ongoing assessment, assessment not yet done and assessment done but no reimbursement decision made); R = Reimbursed.

Table 2. P&R arrangements, negotiated at national level between manufacturers and official national institutions, for reimbursed ATMPs in 12 countries

		Types of MEAs used to finance ATMPs and purpose in 12 countries											
		Countries with national MA only				*Countries that operate through the European MA procedure*							
Countries		*Australia*		*Canada*		*Czechia*		*Denmark*		*France*		*Germany*	
ATMP	*Indication*	*MEA*	*Purpose*	*MEA*	*Purpose*	*MEA*	*Purpose*	*MEA*	*Purpose*	*MEA*	*Purpose*	*MEA*	*Purpose*
ATMP1	*MM*	NR	/	NR	/	NR	/	NR	/	NR	/	R	/
ATMP2	*AFCDP*	NR	/	NR	/	D	CE	NR	/	D	CE	D	NA
ATMP3	*RDCC*	NR	/	NR	/	R	/	R	/	NR	/	R	/
ATMP4	*MNRBS*	NR	/	NR	/	NR	/	NR	/	NR	/	R	/
ATMP5	*BCALL*	P4P	SR	C	CE; SR*	NR	/	R	/	D	CE	CED; P4P; D	NA
ATMP5	*DLBCL*	P4P	SR	C	CE; SR*	NR	/	NR	/	D	CE	CED; P4P; D	NA
ATMP6	*ML*	NR	/	NR	/	NR	/	R*	/	NR	/	R	/
ATMP7	*HRD*	D; P4P	SR	NR	/	NR	/	P4Pi	CE	D	CE	CED; D	NA
ATMP8	*KCR*	NR	/	NR	/	NR	/	NR	/	NR	/	R	/
ATMP9	*SCIDTADD*	NR	/	NR	/	NR	/	NR	/	NR	/	NR	/
ATMP10	*MCL*	RNI	RNI	NR	/	NR	/	NR	/	D	CE	R	/
ATMP11	*DLBCL*	P4P; D	SR	C	CE; SR*	NR	/	NR	/	D	CE	CED; P4P; D	NA
ATMP11	*PML*	P4P; D	SR	C	CE; SR*	NR	/	NR	/	D	CE	CED; P4P; D	NA
ATMP12	*SMA*	P4P; D	SR	C	CE; SR*	NR	/	R	/	NR	/	P4Pi	NA

Legend: See Annex VI for indication abbreviations; C = Confidential; CE = Control Expenditure; CED = Coverage with Evidence Development; D = Discount; MA = Marketing authorization; NA = information Not Available; NR = Not Reimbursed; P4P = Pay-for-performance; P4Pi = P4P in instalments; R = Reimbursed without using any special arrangements; RNI = Reimbursement decision published but Not yet Implemented; SR = Share Risk.

* Note: the nature of agreements in Canada is confidential. They may involve simple discounts (e.g. first dollar rebates), incremental rebates in the event an annual threshold is exceeded, and other forms of risk-sharing arrangements; ATMP6 is reimbursed by the Danish healthcare system, but it is not delivered in Denmark. Hence, the Danish Medicines Council (DMC) – the institution responsible for assessing the clinical value of new medicines and new indications in Denmark – will not assess this treatment.

(continues below)

(continuation of table 2)

		Types of MEAs used to finance ATMPs and purpose in 12 countries											
		Countries that operate through the European MA procedure											
Countries		*Greece*		*Italy*		*Netherlands (Kingdom of the)*		*Slovenia*		*Spain*		*Sweden*	
ATMP	*Indication*	*MEA*	*Purpose*	*MEA*	*Purpose*	*MEA*	*Purpose*	*MEA*	*Purpose*	*MEA*	*Purpose*	*MEA*	*Purpose*
ATMP1	*MM*	NR	/	NR	/	NR	/	NR	/	NR	/	NR	/
ATMP2	*AFCDP*	NR	/	NR	/	NA	C*	D	CE	P4P; RPP	CE; SR	NA	NA
ATMP3	*RDCC*	NR	/	P4P; D	NA	NA	C*	NR	/	NR	/	NR	/
ATMP4	*MNRBS*	NR	/	NR	/	NA	C*	NR	/	NR	/	NR	/
ATMP5	*BCALL*	C	CE	P4Pi; D	NA	C	C*	D	CE	P4P; RPP	CE; SR	NR	/
ATMP5	*DLBCL*	C	CE	P4Pi; D	NA	C	C*	D	CE	P4P; RPP	CE; SR	NA	NA
ATMP6	*ML*	NR	/	D; MR	NA	NR	/	NR	/	NR	/	NR	/
ATMP7	*HRD*	C	CE	EC; MR	NA	C	C*	NR	/	P4P; EC	CE; SR	NA	NA
ATMP8	*KCR*	NR	/	NR	/	NA	C*	NR	/	NR	/	NR	/
ATMP9	*SCIDTADD*	NR	/	P4PIPP; D	NA	NA	C*	NR	/	NR	/	NR	/
ATMP10	*MCL*	NR	/	MR; D	NA	NR	/	NR	/	NR	/	NR	/
ATMP11	*DLBCL*	C	CE	P4Pi; D	NA	C	C*	NR	/	P4P; RPP	CE; SR	RB	/
ATMP11	*PML*	C	CE	P4Pi; D	NA	C	C*	NR	/	P4P; RPP	CE; SR	RB	/
ATMP12	*SMA*	C	CE	P4P	NA	C	C*	D	CE	P4P; P-V	CE; SR	D	NA

Legend: See Annex VI for indication abbreviations; C = Confidential; CE = Control Expenditure; D = Discount; EC = Expenditure Cap; MA = Marketing authorization; MR = Monitored by Registry; NA = information Not Available; NR = Not Reimbursed; P-V = Price-volume arrangement; P4P = Pay-for-performance; P4Pi = P4P in instalments; P4PIPP = P4P Linked to Individual Patient Data; RB = Rebate; RPP = Restricted Patient Population; SR = Share Risk.

* Note: in general, the key aims of any MEAs used in Netherlands (Kingdom of the), as reported by the Dutch responder to our survey, are to improve cost-effectiveness and control expenditure.

Austria and Israel are not included Table 2 because they provided no information on MEAs on confidentiality grounds.

Table 3. Key areas for further development and associated recommendations

Key challenges	Recommendations
There is no co-ordination mechanism for RWE to be collected to meet the needs of regulators, HTA agencies and payer organisations purposes	(i) A pan-European approach could be considered for post-launch evidence generation, for example enabled through the new European regulation on cooperation in HTA, in coordination with the implementation of the European data infrastructure and research networks., (ii) More investment and cooperation on capacity building around the implementation of risk sharing schemes and the design and administration of the data collection protocols associated to them, should also be considered
There is considerable variation between countries in the reporting of clinical evidence that has been in part funded with public resources under managed entry schemes. Different countries approach the generation of further evidence under these schemes differently.	The World Health Assembly Resolution 72.8 calls for more transparency, across a number of areas, including prices and managed entry schemes. Greater transparency and fluid communication about the schemes in use, and common practices and requirements for data collection, will generate better quality evidence at lower costs, ultimately benefiting patients.
There is heterogeneity in regulatory and P&R status of ATMPs across countries. Our survey shows that the variability of access is in part due to choices made by regulatory and reimbursement authorities, and in part due to commercial decisions by companies about regulatory and reimbursement submissions	(i) The new European regulation on HTA will provide more homogeneity in the relative effectiveness evidence used to support national HTA processes. Further cross-country collaboration in the economic evaluation and even in joint procurement of ATMPs could further reduce variability in access, particularly for products with an immature evidence base. (ii) Further developing HTA and (other) infrastructures to support P&R processes (investing in European HTA infrastructures to sustain the new regulation, and/or increasing national investments), in parallel with coordinated action to building up the necessary expertise, would highly benefit decision makers dealing with complex P&R decisions for ATMPs. (iii) Fulfilling EFPIA's commitment for MA holders to file for P&R in all countries within 2 years from central European Union MA would be a great further step toward reducing variabilities in access although not all companies/countries have the capacity to support this.
The regulatory environment in Europe is moving towards providing greater support for the development of ATMPs by academic and non-for-profit institutions, but it remains to be seen how the regulatory requirements (under the hospital exemption), pricing and competitiveness of academic ATMPs will compare with commercial ones	Careful evaluation of the regulatory and P&R environments for academic ATMPs, and the implications for competition with commercial medicines, should be undertaken, to ensure safe and effective academic ATMPs that respond to unmet needs are developed, and that they are met with established P&R pathways
Demand pooling and joint purchasing has barely been explored for ATMPs	Such approaches could facilitate evaluation, evidence generation, pricing and ultimately access due to the stronger negotiating position countries would acquire. Collaboration could go from joint assessments and/or negotiations, going as far as exploring options for joint European treatment centres. These solutions could particularly benefit smaller countries
Overarching recommendation: Moving towards greater equality of access will require cooperation between countries and stakeholders, and there is infrastructure and mechanisms that could facilitate this such as the WHO Regional Office for Europe's Access to Novel Medicines Platform.	

Chapter III – ANNEX I. EMA regulatory categories applied to ATMPs and whether given in a single administration

ATMP	Indication	PRIME (unmet need)	Orphan	Intended for single administration?	Marketing authorization (MA) in European Union	Date of MA by the European Medicines Agency
ATMP1	MM	Yes	Yes	Yes	Conditional MA	18/08/2021
ATMP2	AFCDP	No	Yes	Yes	Additional monitoring	23/03/2018
ATMP3	RDCC	No	Yes	Yes	Conditional MA	17/02/2015
ATMP4	MNRBS	No	No	No	Standard MA	16/12/2015
ATMP5	BCALL	Yes	Yes	Yes	Additional monitoring	22/08/2018
ATMP5	DLBCL	No	Yes	Yes	Additional monitoring	22/08/2018
ATMP6	ML	No	Yes	Yes	Additional monitoring	17/12/2020
ATMP7	HRD	No	Yes	Yes	Additional monitoring	22/11/2018
ATMP8	KCR	No	No	Yes	Standard MA	10/07/2017
ATMP9	SCIDTADD	No	Yes	Yes	Additional monitoring	26/05/2016
ATMP10	MCL	Yes	Yes	Yes	Conditional MA	14/12/2020
ATMP11	DLBCL	Yes	Yes	Yes	Additional monitoring	23/08/2018
ATMP11	PML	No	Yes	Yes	Additional monitoring	23/08/2018
ATMP12	SMA	Yes	Yes	Yes	Conditional MA	18/05/2020
ATMP13	BT	Yes	Yes	Yes	Conditional MA	29/05/2019

Legend: See Annex VI for indication abbreviations. The data are anonymized in accordance with the World Health Organization's (WHO) Framework for Engagement with non-State actors so as not to confer any endorsement of a specific non-State actor's name, brand or product (See Data Availability statement in the manuscript).

Note: in some cases, the ATMP can be intended for a single administration but allow repetition of treatment if the physician considers it necessary.

Chapter III – ANNEX II. List of the 46 countries of origin of PPRI Network members we contacted for our survey, which ones responded and which ones did not respond

List of countries of origin of members of the PPRI Network that received the survey (a total of 46)

Albania, Armenia, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Croatia, Cyprus, Czechia, Denmark, Egypt, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Kosovo[3], Latvia, Lithuania, Malta, Netherlands (Kingdom of the), North Macedonia, Norway, Portugal, Republic of Korea, Republic of Moldova, Republic of Serbia, Romania, Saudi Arabia, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, Türkiye, Ukraine and United Kingdom.

List of countries of origin of members of the PPRI Network that responded to the survey (a total of 20)

Outside the EMA regulatory jurisdiction: Armenia, Australia, Brazil, Canada, Israel and Türkiye.

Within the EMA regulatory jurisdiction: Austria, Bulgaria, Czechia, Denmark, France, Germany, Greece, Iceland, Italy, Malta, Netherlands (Kingdom of the), Slovenia, Spain, Sweden.

List of countries of origin of members of the PPRI Network that did not respond to the survey (a total of 26)

Albania, Belgium, Croatia, Cyprus, Egypt, Estonia, Finland, Hungary, Ireland, Kosovo, Latvia, Lithuania, North Macedonia, Norway, Portugal, Republic of Korea, Republic of Moldova, Republic of Serbia, Romania, Saudi Arabia, Singapore, Slovakia, Switzerland, Ukraine and the United Kingdom.

Note: due to human error, there were 5 discrepancies between the countries of origin of members of the PPRI Network and those we invited to respond to our survey at the time when we distributed the survey. Experts from Luxembourg, Kazakhstan, Kyrgyzstan and South Africa were members of the PPRI Network but they did not receive an invitation to participate in our survey, and there were no Russian members within the PPRI Network, yet one was invited to participate (but did not do so).

[3] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

Chapter III – ANNEX III. Taxonomy of Pricing and Reimbursement options

Type of P&R arrangement	Purpose	Counterparties involved	Country experience/s or example	Reference/s
Financial agreements	***Agreements based on financial aspects, independent of health outcomes achieved***	***NA***	***NA***	***(36)***
Bundle payment, episode of care	A single payment to cover all the care a patient with a condition may need. Aim: to incentivise organisations to control costs, without sacrificing quality, thereby increasing efficiency.	Payers/Insurers (public or private), Service providers	United States	(36, 262)
Rebate	Payment that is refunded by the manufacturer to the payer if a set of pre-agreed conditions occur. Aim: to lower costs.	Payers/Insurers, Manufacturers	Switzerland	(36, 263, 264)
Discounts	Price reductions (often confidential). Aim: cost containment measure.	Payers/Insurers, Manufacturers	Selection of 25 European countries	(36, 265)
Price caps and volume caps	Aim: to control prices or total expenditure on a given medicine. They can be implemented on a patient level (capping the yearly price or the number of yearly courses reimbursed) or at a population level (limiting the volume of product to be sold yearly – the manufacturer reimburses the full cost or a fraction)	Payers/Insurers, Manufacturers	Republic of Korea	(36, 266)
Price-volume agreements	The price of the product is adjusted based on volumes sold – the percentage of reduction is pre-agreed. Aim: to reduce prices.	Payers/Insurers, Manufacturers	Denmark, France, Italy, Lithuania, Spain	(36, 267-270)
Lump-sum or subscription model	Agreement between the payer and the manufacturer to make treatment available for a fixed amount over a period of time. The payment is often spread over such period. Aim: to reduce financial uncertainty, prevent high-upfront costs or facilitate access to large populations.	Payers/Insurers, Manufacturers	Australia, United States	(271-274)

Type of P&R arrangement	Purpose	Counterparties involved	Country experience/s or example	Reference/s
Cost-plus price	Price set according to development and production costs producing a pre-agreed amount fixing the revenues. Proposed for orphan drugs that are not cost-effective, but discouraged by WHO. Aim: cost containment.	Manufacturers, Payers	Sweden, Japan	(36, 275-277)
Drug mortgages, healthcare loans / Credits	Can be offered to payers or patients. Aim: to spread the cost of treatment.	Manufacturers, Payers or Patients	Spain	(36, 278, 279)
Reinsurance risk pool	Multiple payers share risk through a reinsurance risk pool. Aim: to ensure single payers from risks around high costs of treatment. It helps prevent cherry picking in systems with multiple (private) insurers	(Multiple) Payers/Insurers	United States	(36, 280)
National silo funds	National funds dedicated to a particular disease or disease area. Aim: to secure funding for the condition/s or type/s of therapy(ies) covered, and can aim to optimise outcomes within a therapeutic area.	Payer/Insurer (national or regional in public systems), Service Provider/s, Manufacturers, can involve (or be managed by) the HTA body	Italy, United Kingdom (England)	(36, 229, 231, 234)
Special international fund raising	International taxes on specific transactions. Aim: to finance provision of medicines (e.g., the airline ticket levy first implemented by France), pooling of donor aid to create a predictable demand, and waiving debt when the lender country negotiates commitments by the LMIC receiving the loan to dedicate the money saved into the provision of a medical service.	Payer, Other sectors of Government, International Fund (donor aid), third party country that acts as a lender or waiver of debt	France	(36, 281)
Intellectual property-based payment	Includes prizes for patents, either to buy the patent and control production and distribution, or	Payer, Manufacturer, Regulator	European Union	(36, 194, 282)

Type of P&R arrangement	Purpose	Counterparties involved	Country experience/s or example	Reference/s
	extensions of market exclusivity as a reward for innovation in an area of unmet need (as it happens with the orphan drug designation in the European Union). Aim: incentivize innovation in a priority area.			
Tiered pricing	It consists of setting different prices for the same product in different countries, according to their income levels. Aim: to facilitate access in LMICs.	Payers, Manufacturers, International Organisations (e.g., United Nations Children's Fund (UNICEF))	Africa, India	(283)
Health outcomes-based agreements	***Agreements based on the performance of the new therapy***		***NA***	***(36)***
Pay-for-performance (P4P)	Price or revenue are linked to the performance of the medicine. Aim: incentivise access to medicines that perform highly in clinical practice, share risk, and control budget impact.	Payer, Manufacturer, National Health Service	Bulgaria, France, Germany, Italy, Poland, Romania, Spain, United Kingdom	(36, 37, 188, 197, 284-286)
Indication-specific pricing	Links the price to the performance of the medicine in each indication. Aim: prevent companies from focusing on high-performing indications to maintain a high price.	Payer, Manufacturers	Italy	(36, 287)
Rebate risk sharing	The share of co-payment decreases as patients complete cycles of treatment. Aim: incentivise adherence.	Payers/Insurers, Manufacturers, Patients	United States	(36, 288)
Limit pricing approach	Includes payment for outcomes, where performance targets that are not met entail price reductions. That is, the limit price represents a threshold that, if exceeded, involves a net increase in healthcare expenditures (similar to	Payer, Manufacturers, HTA bodies	United States	(36, 289)

Type of P&R arrangement	Purpose	Counterparties involved	Country experience/s or example	Reference/s
	the NICE threshold). Aim: maximise health outcomes per monetary unit invested.			
Annuity payments	Spread the cost of the medicine over a longer period of time (than high upfront payments) when pre-agreed clinical endpoints are met. Aim: manage large upfront costs and share risk.	Payers, Manufacturers	United Kingdom (England), Italy	(36, 37, 290)
Coverage with evidence development (CED)	Conditional reimbursement subject to collection of further evidence in clinical practice, with a reassessment within a pre-agreed timeframe before a final reimbursement and pricing decision is made. Aim: reduce large initial uncertainties and share risk.	Payers, Manufacturers, Service Provider/s	France, Germany, Netherlands (Kingdom of the), Sweden, Switzerland, United Kingdom	(36, 37, 291, 292)
Healthcoin	***A new tradable currency to finance breakthrough medicines. It is exchangeable for fiat currency. Used to compensate for patients transitioning from a private insurer into the public system, when the first had paid before for instance for a curative therapy. Aim: to incentivise private payers to invest in breakthrough therapies.***	***Payer/s (public), Insurers (private)***	***United States***	***(36, 293)***

Chapter III – ANNEX IV. Survey questions

We have transcribed the questions we included in the survey into this annex. The questions included were:

- Is this ATMP financed or reimbursed in your health system?
- If not financed, please give reasons
- Is it financed under special arrangements (managed entry agreement (MEA), patient access scheme (PAS) or other)?
- What is the main purpose of the MEA (e.g. control expenditure, generate further evidence, share risk, other)?
- What type of MEA (confidential discount, volume or expenditure cap, free initial treatment, payment by results, other)?
- Is information on the MEA publicly available?
- Where can the information be found? (link)
- Is the MEA linked to the collection of further evidence?
- What is the nature of the data collected for the MEA and what database/s are used?
- Who is responsible for collecting this information (manufacturer, HTA agency, health ministry, other)?
- Who is responsible for analysing this information (manufacturer, HTA agency, health ministry, other)?
- Is the reassessment of the evidence, coverage or price planned? Please describe the conditions and timelines (e.g., yearly, once after 3 years maximum, etc.)?
- Optional: any further information?

Chapter III – ANNEX V. Medicine regulators, HTA agencies and competent authorities of included countries

	Medicines regulator	**HTA agency**
Armenia	Scientific Centre of Drug and Medical Technology Expertise (SCDMTE)	No use of HTA for pricing and/or reimbursement decisions (218)
Australia	Therapeutic Goods Administration	Pharmaceutical Benefits Advisory Committee
Brazil	Brazilian Health Regulatory Agency (Anvisa)	National Committee for Technology Incorporation (CONITEC)
Canada	Health Products and Food Branch (HPFB) of Health Canada	Canada's Drug and Health Technology Agency (CADTH)
Israel	Pharmaceutical Division, within the Israeli Ministry of Health	Israeli Center for Technology Assessment in Health Care (ICTAHC)
Türkiye	Turkish Medicines and Medical Devices Agency (TMMDA) (294)	Health Services General Directorate - Research, Development and Health Technology Evaluation Department within the Turkish Ministry of Health (294)
Austria	EMA	Austrian Institute for Health Technology Assessment (AIHTA)
Bulgaria	EMA	National Centre for Public Health and Analyses (NCPHA)
Czechia	EMA	the State Institute for Drug Control – SÚKL is its acronym in Czech
Denmark	EMA	Danish Medicines Council
France	EMA	Haute Autorité de santé, or HAS
Germany	EMA	Institute for Quality and Efficiency in Health Care (IQWiG) – usually commissioned by the GBA

		(Federal Joint Committee or Gemeinsamer Bundesausschuss)
Greece	EMA	HTA and reimbursement committee for medicinal products for human use within the National Organization for Medicines (EOF) (295)
Iceland	EMA	The Icelandic Medicine Pricing and Reimbursement Committee (IMPRC) (296)
Malta	EMA	Health Technology Assessment (HTA) Unit within the Health System's Directorate for Pharmaceutical Affairs (DPA) (297)
Netherlands (Kingdom of the)	EMA	National Health Care Institute (ZIN)
Slovenia	EMA	Agency for Medicinal Products and Medical Devices (JAZMP)
Spain	EMA	Interministerial Committee for Pricing and Reimbursement
Sweden	EMA	Dental and Pharmaceutical Benefits Board (TLV)

Chapter III – ANNEX VI. Glossary of therapies and indications

ATMP	***Indication***	***Abbreviation used in our manuscript***
ATMP1	Multiple myeloma	MM or indication 1 (I1)
ATMP2	Anal fistulas in Crohn's disease patients	AFCDP or indication 2 (I2)
ATMP3	Replacement of damaged corneal cells	RDCC or indication 3 (I3)
ATMP4	Melanoma not removable by surgery	MNRBS or indication 4 (I4)
ATMP5	B-cell acute lymphoblastic leukemia	BCALL or indication 5 (I5)
ATMP5	Diffuse large B-cell lymphoma	DLBCL or indication 6 (I6)
ATMP6	Metachromatic leukodystrophy	ML or indication 7 (I7)
ATMP7	Hereditary retinal dystrophy	HRD or indication 8 (I8)
ATMP8	Knee cartilage repair	KCR or indication 9 (I9)
ATMP9	Severe combined immunodeficiency due to adenosine deaminase deficiency	SCIDTADD or indication 10 (I10)
ATMP10	Mantle cell lymphoma	MCL or indication 11 (I11)
ATMP11	Diffuse large B-cell lymphoma	DLBCL or indication 12 (I12)
ATMP11	Primary mediastinal lymphoma	PML or indication 13 (I13)
ATMP12	Spinal muscular atrophy	SMA or indication 14 (I14)
ATMP13	Beta thalassaemia	BT or indication 15 (I15)

Discussion

HTA is well established as the basis for decision making around the pricing & reimbursement of new health technologies, and their positioning in care pathways, in modern health systems. However, not all the concepts, criteria and methodologies required for shaping the policies that underpin HTA infrastructures and processes are well-defined. In other words, attention tends to focus on the levels of transparency and the methods underpinning decisions about individual health technologies, but not enough attention is paid to the processes of reshaping the overall HTA systems. This thesis intends to provide tools and evidence for healthcare policy makers to shape the policies they implement based on defined methodologies and the best available evidence.

Defining the concepts used in policy making is essential, since it sets a common ground for all players involved in the field where such policy will be applied. In Chapter I, we propose a process that could be used by any country aiming to incorporate or define the degree of innovation within their HTA systems (107). We start by building a broad notion of degree of innovation, composed by a wide set of constructs. Then, we propose "cleaning" the concept by filtering it against the criteria that is already being captured in the HTA system at hand. Meaning that, for instance, if clinical value is already being evaluated, it would not be captured within the 'degree of innovation' criterion, to avoid double counting. At the end of the process, the result is a concept of degree of innovation that has been tailored to your HTA system, avoiding any risk of double counting whilst ensuring all relevant dimensions of the concept are being accounted for.

Looking into what has been done in this space, we observed that NICE is the only HTA body that, to our knowledge, has defined the degree of innovation as a distinct feature to other sources of value, to encourage the pursuit of it as a distinct desirable feature in health technologies, establishing three conditions for classifying health technologies as innovative (59): displaying innovative characteristics or having an 'innovative nature', providing substantial health benefits or a "'step-change' in the management of the condition" (60), and having demonstrable benefits not captured in cost-effectiveness calculations. To reward technologies they deem to be innovative, NICE may recommend them for use in the NHS with cost-effectiveness ratios exceeding £20,000/QALY (59).

We applied the process described above to the Spanish System, resulting in a concept composed of constructs of 'step-change', 'convenience', 'strength of evidence base' and 'impact on future research & development' (107). Each one of the constructs we used to define the concept of degree of innovation (when tailored to the Spanish system) can be further defined. We described the concept of 'convenience' as a construct of three attributes: patient usefulness (43, 45, 55, 57), carer usefulness (57), administration (57). New health

technologies, both medicines and other technologies, are often introduced and approved despite high degrees of uncertainty, and this trend has been increasing in recent years as new products are being brought to market earlier and without conducting large, pragmatically designed, randomised controlled trials (226, 298). Hence, for new technologies, the 'strength of evidence base' is widely considered to be a challenge for HTA bodies, but the approach applied to assessing this uncertainty varies from informal qualitative consideration and deliberation, to more structured approaches. For instance, in Italy a recent reform has introduced the use of the GRADE methodology to measure the quality of the clinical evidence available to support the claims of benefit of new interventions to, , along with the level of unmet need addressed and the added therapeutic value, judge the level of innovativeness of new interventions in Italy (52). The level of 'impact on future research & development' has been described as the knowledge that is produced in the process of coming up and using a particular innovative treatment, whereby the research that goes into developing such treatment can spill-over to favour future innovations (54). Further work remains to conceptualize and measure each one of these constructs.

In Chapter II we present how, to try and explore what might be the optimal instrument to measure each of the criteria used to support pricing and reimbursement decisions in Spain, we carried-out a survey amongst 90 experts from a wide range of stakeholder groups, including the pharmaceutical industry, the national regulatory agency, regional HTA bodies, academia, governmental institutions and consulting companies. An interesting finding of this study is the broad consensus around the questions we asked in relation to the efficiency criterion, the optimal way of measuring budget impact, or the population groups deserving particular consideration. To measure the budget impact, total expenditure applying a 3-5 years horizon was the preferred approach by almost 90% of respondents (78 (87%)). Focusing on the efficiency criterion, preferences of respondents to our survey were that the therapeutic half of the efficiency equation is measured using the QALY (80%), that the level of efficiency of investments in new health technologies is measured through the ICUR (78%), that Spain should apply a threshold to guide their decisions (93%), that such threshold ought to be explicit rather than implicit (78%), and that it should offer enough flexibility to give special consideration to particular patient groups or situations (82%). When it came to specifying which population groups deserve special consideration, well above half of respondents thought patents living with rare diseases (64 (71%) and patients with unmet medical needs (82 (91%)) do deserve particular attention in pricing and reimbursement decisions.

We also asked in our survey what relative weights respondents would attach to each one of the criteria, and whether they agreed with the list of criteria or if they thought it should be revised. Interestingly, we found that

more than half of our sample (56%) thought the list is not appropriate, and 74% of them thought the perspective of patients should be included. These insights could inform future developments in Spain, if Spanish policy makers were to revisit the criteria used to support reimbursement decisions and give guidance on how they ought to be measured. Furthermore, an obvious further step towards increasing the level of transparency of decisions would be to publish, not only the actual decisions, but also explanations of the rationale supporting them, substantiating them on the best available evidence.

Part of the survey focused specifically on asking how respondents believe the 'degree of innovation' of health technologies ought to be measured. We found that the tool that has most backing amongst the expert community in Spain to measure the 'degree of innovation' would be a purpose-made checklist. Such checklist would need to contain questions targeted at measuring each one of the constructs mentioned above (i.e., 'step-change', 'convenience', 'strength of evidence base' and 'impact on future research & development'). If such a checklist was to be developed, Spanish healthcare policy makers would have a well-defined concept of degree of innovation, tailored to fit nicely with their current decision-making criteria, and an instrument designed to measure it.

Although Multi-Criteria Decision Analysis (MCDA) was not deemed as the preferred option to measure the 'degree of innovation' in our survey (only 32 respondents (36%) opted for it), there is a whole body of research exploring how it could be useful in HTA. MCDA can be useful to make a more explicit presentation of the criteria supporting decisions, their relative weights, also in some cases translating a qualitative estimation of the measure of a given criterion into a quantitative measure of it, and applying a structured process to reaching recommendations (299). Frameworks like EVIDEM (300, 301) or the Advance Value Framework (55) are examples of MCDA frameworks that have been developed for HTA and piloted to test their applicability in practice. Both of them have been piloted, field-tested or tailored to a Spanish context (83, 302, 303) and to other settings (83, 86, 304, 305). However, the verdict tends to be that, whilst it is a technique that holds great potential in its application to HTA, more work is needed (170, 171, 306, 307).

Finally, Chapter III explores how new therapies are financed by countries, through the example of ATMPs, describing the reimbursement landscape for this group of therapies in 20 countries (308). We observed wide variability in access to these therapies across countries. In some countries, the reason behind ATMPs not being available was that companies had not obtained the necessary regulatory approval (we do not know if they had applied for it or not) or had not applied for pricing and reimbursement. In cases where at least one ATMP was being reimbursed, we observed some degree of variability in the types of P&R arrangements being applied.

This study allowed us to formulate recommendations ranging from a pan-European approach to post-launch evidence generation, to exploring options for demand pooling, joint purchasing or even joint procurement (see Chapter III – Table 3 for more details). One of the aspects we highlight as an area for further development is the need for investment and cooperation on capacity building around the implementation of risk sharing schemes and the design and administration of the data collection protocols associated to them, which would be likely to particularly benefit smaller countries, with less resources dedicated to decision support-oriented institutions. An initiative worth following is the newly established WHO Regional Office for Europe's Access to Novel Medicines Platform, which will be ideally placed to facilitate cooperation between countries and stakeholders. To summarise, Chapter III dives into to how countries handle uncertainty, applying in some cases P&R arrangements that aim to mitigate financial and/or clinical uncertainties. This links nicely with our Chapter I, where we define the concept of degree of innovation through a combination constructs, including the strength of evidence (or, in other words, the level of uncertainty around the evidence base).

In addition to the areas for further work mentioned above, throughout the development of this thesis we have identified some concrete areas where further research would be needed. One is the development of a checklist to help measure the concept of degree of innovation we defined in out firs paper (309), tailored to the Spanish system. Furthermore, our research on the criteria that support P&R decisions in Spain allowed us to realize that, in Spain, HTA and P&R policies are purely based on the values of the policy makers that design them, but evidence from Belgium shows that policy makers' values are not always a good reflection of societal values (310). In fact, we elicited the values of a group of experts by asking them to assign a relative weight to a list of criteria that are meant to inform P&R decisions in Spain. However, to our knowledge, no survey has been administered to a representative sample of the Spanish population, eliciting their values with respect to key questions informing HTA policies in the country. Performing such a survey would provide useful evidence to Spanish policymakers about the values and preferences of Spanish society about key conundrums that would need to be resolved if they were to develop a system that truly captures the preferences of the society they ought to represent, as for instance Linley et al. (2013) did to inform an attempt to implement Value-Based Pricing in the United Kingdom (94).

The question of how the values of society are (or are not) captured in an HTA system, bring us to considering also how the perspectives of different stakeholders are (or are not) incorporated in HTA processes. The most obvious stakeholder group in healthcare are patients. An interesting commentary by Wale et al (2021) highlights how both patients and the public are important stakeholders in HTA, but also how their level of engagement is still low (311). One of the findings we extracted from our survey on criteria for P&R in Spain,

whereby a large number of the experts surveyed (67 (74%)) expressed their preference for the inclusion of the perspective of patients as an additional criterion. An option for Spain to enhance the participation of patients and the public without performing extensive research would be piloting initiatives similar to NICE's Citizens Council (312), with a view on incorporating such practices in routine practices in the country. A complementary approach would be to try and systematically capture research on the views, preferences and experiences of patients, and incorporate such evidence in decision-making processes (313). The view of patients and of other stakeholders can be incorporated into HTA through their participation in committees, which often hold the responsibility of formulating recommendations based on the evidence presented to them through deliberation (314). To help HTA bodies considering to incorporate, or further systematize the way they incorporate deliberative processes in their practices, a joint HTAi/ISPOR[4] task force published a good practices report in 2022 (315). Pinilla-Dominguez & Pinilla-Dominguez (2023) analysed the level of implementation of deliberative processes in HTA for medicines in Spain concluding that, although the level of transparency in HTA for medicines in Spain has improved, to enhance the legitimacy of the process more could be done to progress in stakeholder involvement, and the implementation of deliberative frameworks need further attention (316).

A look into the near future of HTA in the EU shows a landscape that will experience important changes. The new EU regulation on HTA means that, by 2030, all new health technologies with a regulatory approval will be subject to joint clinical assessment performed collaboratively by European HTA bodies. Countries will be mandated to make use of such evidence in their national HTA procedures, but they are free to perform additional assessments where needed, for instance using locally collected real-world evidence or other evidence of interest that might not be included in the European report. To adapt to this new landscape, many European countries (if not all, to some extent at least) will have to adapt their HTA systems to accommodate joint European assessments into their national processes. In the case of Spain, this comes at a time when reform was needed anyways, as a consequence of the court ruling that declared null and void the plan that made it mandatory to include evidence of cost-effectiveness in therapeutic positioning reports, which are meant to inform pricing & reimbursement decisions (317). To legally establish a way of incorporating appropriate economic evidence to inform assessments of new technologies, as well as P&R decisions, and also to adapt a system in dire need of reform to the new European regulation on HTA, the Spanish Ministry of Health has published a consultation on a forthcoming Royal Decree to regulate the evaluation of health

[4] Health Technology Assessment International (HTAi) is a global, non-profit organization dedicated to promoting the importance and use of HTA; The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) is a global professional society for health economics and outcomes research (HEOR).

technologies in the country (5). The new EU HTA regulation will apply from 12 January 2025. Hence, to be ready for it, Spain will need to publish the shape and form of a new and reformed HTA system in 2024.

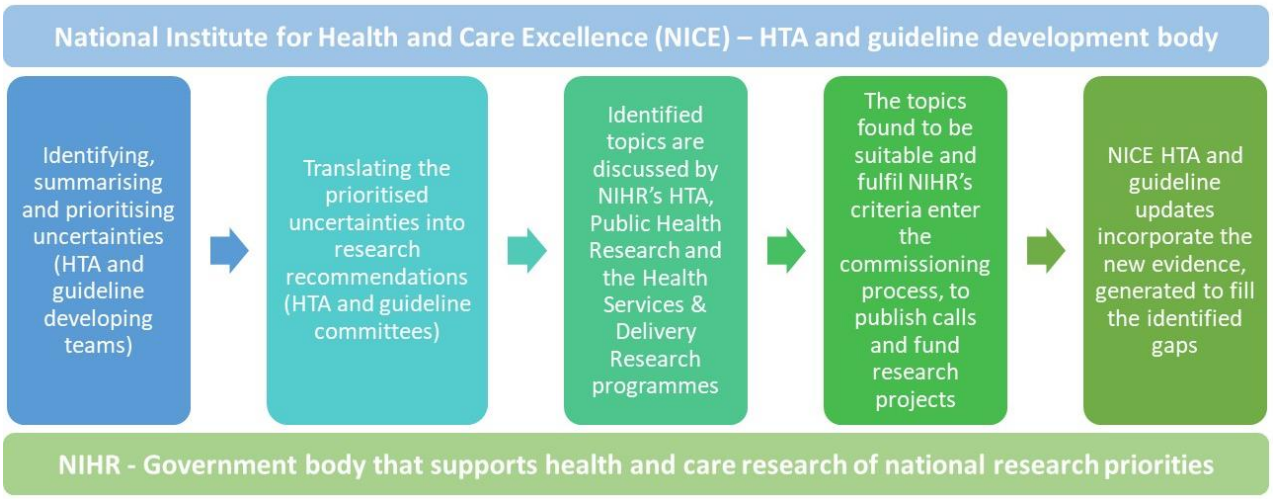
We start this discussion by stating that although nearly all countries conduct HTA, there is wide variability in the scientific rigour of the concepts, criteria and methodologies underpinning that endeavour. Although this is only my perception, and the level of permeability of the policy making sphere to evidence varies widely across European countries, I am convinced that there is ample scope for progress in this field in most European countries. In Spain, the creation of the Advisory Committee for the Reimbursement of the Pharmaceutical Provision meant a step in the correct direction. The Committee is composed of 7 reputed experts in Health Economics, Hospital Pharmacy and other areas of health services policy. They make their recommendations publicly available, opening them up to public scrutiny. The forthcoming reform that the Spanish HTA system is forced to undergo is an opportunity to show that Spain is indeed truly committed to transparent and evidence-based policy making in HTA.

An interesting process of reform of an HTA system that is happening in parallel to the Spanish one is the reform process that is underway in Australia. As part of a process overseen by a Reference Committee composed of 7 experts, the Australian Department of Health and Aged Care will run two rounds of consultation, followed by the commission of seven papers to three different HTA research groups, all of which will inform the contents and final shape of the HTA reform (318, 319). The example set by the Australian Government should, in my view, serve as inspiration for those in charge of reforming the system in Spain, particularly when it comes to appropriately resourcing the generation of tailor-made evidence that will inform the reform process. Arguably, the amount of public resources that go into financing health technologies largely justify making a comparably negligible investment in gathering the best available evidence to inform reforms of HTA systems.

It is also important to remark that an HTA system lives in coexistence with other forms of evidence synthesis that support the practice of evidence-based medicines in a country, such as clinical guidelines. Both HTAs and clinical guidelines can be pivotal in identifying key sources of uncertainty and, if the right bridges are built between the right parts of the innovation system, they can channel public funding into the development of the necessary evidence to fill the identified gaps (320). This potential role for HTA and guideline development, whilst it might easily be overlooked when shaping a national system, it is essential to ensuring that the right evidence is available to HTA and guideline developers when it comes to updating their outputs, and most importantly, it is key to ensuring that the best possible evidence is available to practitioners and patients when they need to make important and often challenging care decisions. Figures 1 and 2 below show the process

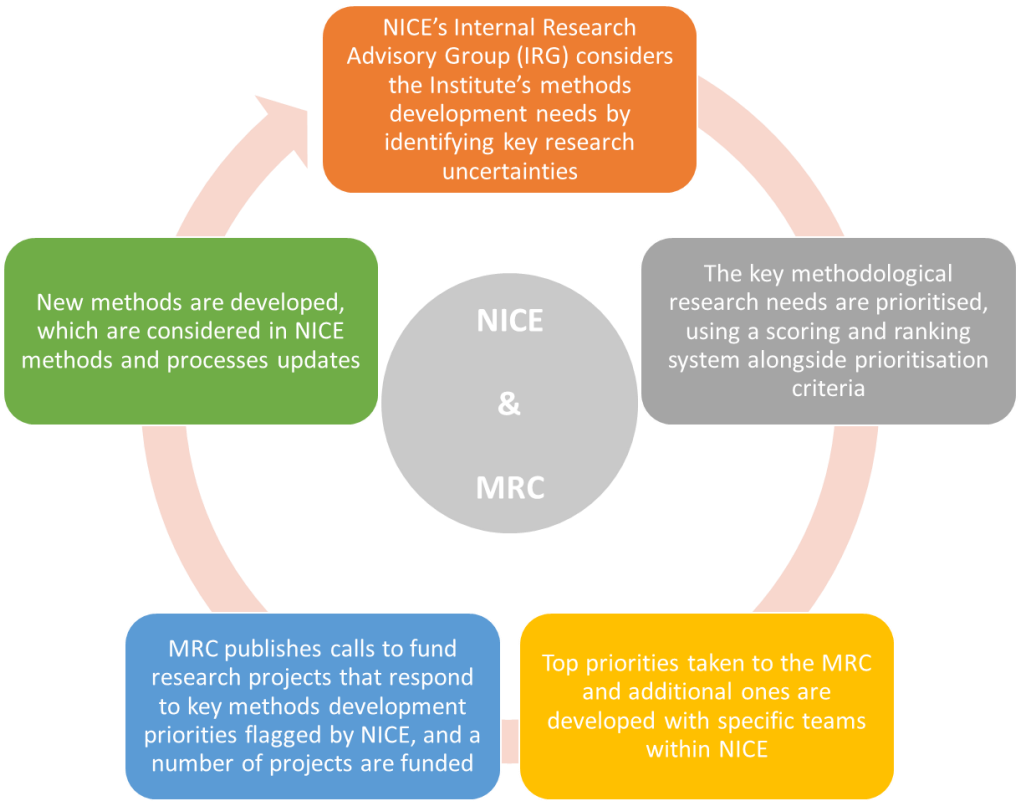
followed by NICE and the National Institute for Health Research (NIHR), and the Medical Research Council (MRC) to identify, prioritise and commission research topics to respond to knowledge gaps.

Figure 1. Identification of evidence gaps and prioritisation of research recommendations by NICE and NIHR



Source: Figure based on information published in Sharma et al. (2018) (320)

Figure 2. Process of identifying methodological research priorities at NICE and relationship with MRC



Source: Figure based on information published in Sharma et al. (2018) (320)

And finally, one essential aspect any healthcare system should carefully consider when shaping their policies, is how HTA recommendations lead to access to medicines. The option of making HTA recommendations binding has been put in practice both for medicines and for medical devices in different countries (3, 321). However, a health technology being included in a national basic-benefit package is no guarantee of it being available to patients across the country. Hence, it is important that policy makers also enable strong guideline development infrastructures, and ensure procurement systems are fit for purpose too, and able to seek innovative solutions when they encounter new challenges in providing the right care to patients across their countries.

Decision support infrastructures ought to be developed and sufficiently resourced to ensure that healthcare systems are ideally placed to diagnose disease on a timely manner, and provide care that is of sufficient quality to all citizens when they need it, whilst ensuring access to it follows principles of equity and efficiency.

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