ASCERTAIN

ACCESS2MEDS FRAMEWORK

Version 3.0 – 22 April 2026

FUNDING

Funded by
the European Union

Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the European Health and Digital Executive Agency (HADEA). Neither the European Union nor the granting authority can be held responsible for them. Grant Agreement 101094938.

STATEMENT OF ORIGINALITY

This deliverable contains original unpublished work except where clearly indicated otherwise. Acknowledgement of previously published material and of the work of others has been made through appropriate citation, quotation or both.

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Executive Summary

The ASCERTAIN project addresses a key challenge in European healthcare systems: ensuring equitable, timely, and affordable access to potentially innovative health technologies (pIHTs) while maintaining financial sustainability and incentives for innovation. Despite efforts towards EU-level regulatory harmonisation, significant disparities persist across countries in access to new treatments, driven by differences in pricing, reimbursement systems, and health technology assessment (HTA) practices.

To tackle these challenges, ASCERTAIN develops the ACCESS2MEDS Framework, an integrated approach built around three core areas of healthcare decision-making: pricing, cost-effectiveness and budget impact, and reimbursement. These areas and their interactions provide a structured and transparent way to evaluate pIHTs across their lifecycle and support more balanced decision-making. The framework and its models are grounded in EU legislation and policies, as well as the European health values of universality, equity, access to quality care, and solidarity, while also incorporating financial and environmental sustainability considerations.

The ACCESS2MEDS Framework introduces an innovative access-based pricing (ABP) model, which moves beyond traditional value-based and cost-based approaches. By combining elements such as research and development costs, production costs, therapeutic value, and a sustainable profit margin, the model estimates prices that are both affordable for health systems and sufficient to incentivise innovation. This provides a transparent and policy-relevant starting point for price negotiations.

In the area of cost-effectiveness and budget impact, health technologies are assessed in terms of their value relative to costs and their financial impact on healthcare systems. Through open-source, multi-country models, the framework enables robust evaluation of clinical benefit, cost-effectiveness, and budget impact, while explicitly accounting for uncertainty and differences across national contexts. The framework includes models for three use cases: precision cancer medicines, cell and gene therapies, and next-generation sequencing (NGS) / genomic profiling.

In the area of reimbursement, the ACCESS2MEDS Framework includes a flexible cost-effectiveness threshold (CET) framework, which allows thresholds to reflect societal and patient preferences, and a managed entry agreement (MEA) modelling approach, which enables stakeholders to explore risk-sharing arrangements that address uncertainty in clinical outcomes and financial impact. Together, these tools support more adaptive and transparent reimbursement decisions.

The models across these areas are fully integrated within the ACCESS2MEDS Framework, allowing stakeholders to analyse them both individually and in combination to explore interactions between price, value, affordability, and uncertainty. This integrated approach enables more informed and consistent decision-making, supporting policy strategies that improve patient access while safeguarding healthcare system sustainability.

All models are implemented in an open-source, web-based tool that supports collaboration, shared assessments, and transparent reporting, and is designed for users with different levels of expertise. By combining methodological rigour with practical usability, the ACCESS2MEDS Framework provides a comprehensive and adaptable solution to support evidence-based pricing and reimbursement decisions across Europe, ultimately contributing to more equitable access to innovative healthcare technologies.

GLOSSARY

This section contains a catalogue of key terminology used in this report.

Access (Accessibility): A patient's (or the collective) ability to obtain medical care, including medicinal products and medical devices, and a measure of the proportion of a population that reaches appropriate health services. This term covers geographic access and financial access, as well as the health literacy required to seek healthcare when appropriate.

Access-based price: Price for a medicinal product or medical device estimated with the objective of improving patient access through considering and reconciling the interests of stakeholders (for payers/governments: ensuring affordability for and financial sustainability of a country's healthcare system; for the industry: allowing cost recuperation and an appropriate profit, as well as providing incentives for development of innovative health technologies, and making a product or device available on a market).

Affordability: The extent to which medicinal products, medical devices and other health technologies are available to the people who need them at a price they / their health system can pay.

Budget impact: Budget impact refers to the total costs that pharmaceutical or medical device reimbursement and use entail with respect to one part of the health care system, pharmaceutical care, or to the entire health care system, taking into account the possible reallocation of resources across budgets or sectors of the health care system.

Cell and gene therapy: therapy involving the use of genes and cells to treat disease. Gene therapy is the use of genetic material to treat genetic diseases. This may involve adding a wild type copy of the gene (gene addition) or altering a gene with mutation to the wild type gene (gene editing). The treatment may take place outside of the body (ex vivo) or inside the body (in vivo). To get the gene into the genome inside the cells, modified viruses or other vectors are used. Cell therapy is the use of cells that are taken either from the patient themselves or a donor to treat diseases. Cells used for cell therapy are often stem cells, cells that can mature into different types of specialised cells. Cells used for cell therapy may or may not be genetically altered. It is sometimes easier to remove cells from the body, treat them with gene therapy and then place them back than treating the cells inside the body. This is the case for gene therapy for blood disorders. Gene and cell therapy therefore often go together, which is reflected in the name of our society.

Cost-effectiveness: Value for money. A specific health care treatment is said to be "cost-effective" if it gives a greater health gain than could be achieved by using the same resources in other ways.

Demand-side cost-effectiveness threshold: Demand-side cost-effectiveness thresholds are thresholds which are determined based on an approach that suggests that individuals are best positioned to make decisions about maximizing their own health utility, emphasizing the importance of aligning budget allocation with societal preferences. In this context, CETs are determined by assessing willingness-to-pay through contingent valuation surveys or using the value of statistical life methods.

Economic evaluation: Economic evaluation in healthcare is the analysis of the costs and effects of alternative interventions that may be given to a defined population in order to support decision-making about reimbursement or implementation of the preferred interventions. Both the immediate costs and health effects and their 'downstream' consequences (future events averted) are considered. The output/result of an economic evaluation is an incremental cost-effectiveness ratio, which may be compared with a threshold value (willingness to pay for a unit of health outcome).

European health values: A set of common values that underpin European health systems as stated by the Council of the European Union. These values include universality, access to good quality care, equity, and solidarity.

Health technology: A medicinal product, a medical device or medical and surgical procedures as well as measures for disease prevention, diagnosis or treatment used in healthcare.

Health technology assessment (HTA): Health technology assessment or 'HTA' means a multidisciplinary process that summarises information about the medical, patient and social aspects and the economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased and robust manner.

In vitro diagnostic medical device (IVD): Any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:

a) concerning a physiological or pathological process or state;

b) concerning congenital physical or mental impairments;

c) concerning the predisposition to a medical condition or a disease;

d) to determine the safety and compatibility with potential recipients;

e) to predict treatment response or reactions;

f) to define or monitor therapeutic measures.

Specimen receptacles shall also be deemed to be in vitro diagnostic medical devices.

Innovation: Innovation is the use of new ideas, products or methods where they have not been used before. Innovations are based on the results of new technological developments, new technology combinations, or the use of other knowledge, acquired by the enterprise.

List price: The price that suppliers display as the price at which they are prepared to sell their product and/or regulated by legislation. A list price is quoted and/or indicated in a purchaser's price list, a catalogue, on an internet site, in advertisements, in a national price list/formulary or similar. A list price may differ from the actual transaction price. Depending on the country and/or the product, they may or may not include delivery and installation costs, value-added tax/VAT and other indirect taxes on products, discounts, surcharges and rebates, invoiced service charges and voluntary gratuities.

Managed entry agreements (MEA): An arrangement between a manufacturer and payer/provider that enables access to (coverage/reimbursement of) a health technology subject to specified conditions. These arrangements can use a variety of mechanisms and are usually classified into financial-based agreements, which focus only on the price (reward for manufacturers), through discounts, rebates, or expenditure caps; and performance-based agreements which links the price to health outcomes.

Medical device: Any instrument, apparatus, appliance, software, implant, reagent, material, or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment, or alleviation of disease,

- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,
- investigation, replacement, or modification of the anatomy or of a physiological or pathological process or state,
- providing information by means of in vitro examination of specimens derived from the human body, including organ, blood, and tissue donations,

and which does not achieve its principal intended action by pharmacological, immunological, or metabolic means, in or on the human body, but which may be assisted in its function by such means.

The following products shall also be deemed to be medical devices:

- devices for the control or support of conception
- products specifically intended for the cleaning, disinfection or sterilisation of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point.

Medicinal product: A substance or combination of substances that is intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action.

Modifiers: Modifiers are characteristics that decision makers can use to vary the level of the cost-effectiveness threshold. These characteristics could be related to the intervention, the specific medical condition(s), or the targeted population.

Next-generation sequencing (NGS): A high-throughput method used to determine part of the nucleotide sequence of an individual's genome. This technique utilizes DNA sequencing technologies that are capable of processing multiple DNA sequences in parallel. Also called massively parallel sequencing and NGS.

NGS technologies are used clinically for whole genome sequencing (WGS), whole exome sequencing (WES), gene panel testing and increasingly for single gene testing.

(Potentially) innovative health technology: on-patent health technology whose innovative character, especially based on (added) therapeutic benefit, must still be assessed at the time of marketing authorisation.

Precision cancer medicine (PCM): Precision medicine is the tailoring of medical treatment to the individual characteristics of each patient and his or her disease.

Price: Generally, the price is the amount of money given by the buyer to the seller in exchange for a good or service. For medicinal products, different buyers pay different prices and to different sellers along the supply chain. Therefore, the price type (i.e. the stage in the supply chain to which a price applies) needs to be specified. Common price types include:

- ex-factory price,
- pharmacy purchasing price,
- pharmacy retail price.

In addition, a distinction needs to be made between net (after deduction of discounts) and gross price (usually referred to as "price"). See also "list price" and "net price" in this glossary.

Price determinant: Inputs and parameters linked to a health technology for the calculation of a health technology's price, considered by stakeholders (health technology developer, healthcare payers, policy- and decision-makers, patients, health care professionals, and investors).

Reimbursement / payment / funding: Coverage of the cost of reimbursable medicines or medical devices by a public payer (such as social health insurance / National Health Service).

Supply-side cost-effectiveness threshold: Supply-side cost-effectiveness thresholds are thresholds which are determined based on an approach that suggests that healthcare resource allocation should be guided by the principle of opportunity cost. When resources are reallocated, new investments displace existing services, so the CET should reflect the value of the health benefits forgone by the best alternative use of the resources.

Value of information (VoI) analysis: VoI analysis in economic evaluation assesses the potential benefit of acquiring additional information before making a decision, especially when there is uncertainty in the data. It helps determine whether further research or data collection is worth the cost, by quantifying how much uncertainty impacts the decision-making process and outcomes. VOI analysis aids in prioritizing research investments by identifying where new information could lead to more efficient or effective healthcare decisions

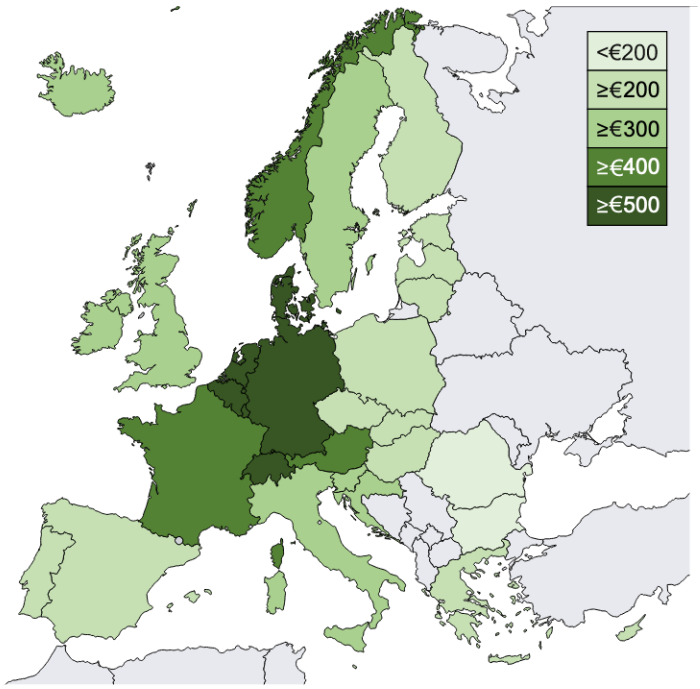
1. Introduction

1.1. Problem Statement

The affordability and accessibility of potentially innovative health technologies (pIHTs) presented a significant challenge for many health care systems. These technologies include pharmaceuticals, advanced medicinal therapy products (ATMPs), such as cell and gene therapies, as well as medical devices (MDs) and in vitro diagnostic (IVD) MDs. Due to their often high costs, these technologies can place substantial pressure on health care budgets [1]. Increasing access to these pIHTs plays an important role in improving equity, survival rates, and quality of life (QoL) for patients. However, considerable disparities exist among European countries, in the speed and extent of access to these technologies following regulatory approval by the European Medicines Agency (EMA) [2–4]. These disparities arise from a complex interaction of economic, institutional, and regulatory factors and health priorities that differ across countries. Many pIHTs are associated with high prices, making them unaffordable for many patients and healthcare systems [2].

While countries with larger healthcare budgets and greater purchasing power are generally well equipped to adopt new treatments, delay in access also occurs among high-income countries. Studies have documented significant variation in approval and reimbursement timelines across these countries, underscoring that financial capacity alone does not ensure timely adoption of innovations [3]. Institutional differences, such as the availability and quality of medical care further exacerbate inequities in access. Additionally, regulatory and access processes across the European Union (EU) remain fragmentated. Differences exist among Member States in the organisation and regulation of market access pathways, including variations in regulatory requirements, evidentiary standards, and decision-making processes. These differences are particularly evident in the implementation and methodologies of health technology assessment (HTA). HTA is a multidisciplinary process used to evaluate the value of a health technology at different stages of its lifecycle in order to inform decision-making. While the aim of HTA is to objectively promote equitable, efficient, and high-quality health systems [5], application variability leads to variation in evaluations of clinical benefit and cost-effectiveness, ultimately influencing routine and reimbursed access. Furthermore, pharmaceutical companies often prioritise launching new treatments in larger or more profitable markets first, further delaying access in smaller or lower-income countries [3]. These disparities contradict the principles of the European Pillar of Social Rights, namely the right to timely access to affordable, preventive, and curative care of good quality [6]. Moreover, they are irreconcilable with several European Health Values, including universality, equity, and access to good-quality care [7].

These disparities are even more pronounced in therapeutic areas characterised by rapid innovation and high costs. Oncology provides a clear example: significant progress in targeted therapies and immunotherapies have transformed the therapeutic landscape, leading to improved survival and QoL for many patients. However, access to these advances remains highly unequal across Europe, with substantial regional variations linked to differences in healthcare investment [8]. Spending on cancer care varies markedly across Europe, reflecting persistent inequities in resource allocation and patient outcomes. As per 2018, annual (non-adjusted) per-capita spending on cancer care ranged from €500-600 in countries like Switzerland and Germany to below €50 in several Eastern European nations [9]. Figure 1 shows the per-capita cancer care burden across European countries, adjusted for purchase power parity. These financial disparities are mirrored in clinical outcomes: five-year cancer survival rates are higher in Northern and Western Europe compared to Eastern Europe [10]. These figures underscore the urgent need to address geographic and economic inequalities in cancer care and access to innovation [11].



Europe	€378		
AUT	€440	**ITA**	€348
BEL	€522	**LVA**	€201
BGR	€165	**LTU**	€235
HRV	€366	**LUX**	€510
CYP	€211	**MLT**	€282
CZE	€278	**NLD**	€524
DNK	€516	**NOR**	€406
EST	€250	**POL**	€237
FIN	€277	**PRT**	€256
FRA	€459	**ROU**	€160
DEU	€524	**SVK**	€248
GRC	€229	**SVN**	€362
HUN	€226	**ESP**	€285
ISL	€324	**SWE**	€336
IRL	€356	**CHE**	€578
		GBR	€310

Figure 1: Total costs of cancer care in 2018 in € per capita, adjusted for purchase power parity (source: Hofmarcher et al., The cost of cancer in Europe 2018 (2020). https://doi.org/10.1016/j.ejca.2020.01.011)

Abbreviations: AUT, Austria; BEL, Belgium; BGR, Bulgaria; CHE, Switzerland; CYP, Cyprus; CZE, Czechia; DEU, Germany; DNK, Denmark; ESP, Spain; EST, Estonia; FIN, Finland, FRA, France; GBR, United Kingdom; GRC, Greece; HRV, Croatia; HUN, Hungary; IRL, Ireland; ISL, Iceland; ITA, Italy; LTU, Lithuania; LUX, Luxembourg; LVA, Latvia; MLT, Malta; NLD, Netherlands; NOR, Norway; POL, Poland; PRT, Portugal; ROU, Romania; SVK, Slovakia; SVN, Slovenia; SWE, Sweden.

Addressing these disparities requires comprehensive reforms in pricing and reimbursement mechanisms across the EU. Striking a balance between the high costs of pIHTs, societal willingness to pay, and health systems goals is essential to ensuring equitable access to lifesaving and quality-enhancing treatments with proven benefits for patients across all European countries.

On 16 December 2025, the European Commission proposed a new package of measures to make the EU health sector more innovative, competitive and resilient: a Biotech Act, revised rules for medical devices and a Safe Hearts Plan [12]. The revision related to MDs aims to ensure a high level of patient safety and care, the availability of safe and innovative devices, faster market access, a more competitive EU medical devices sector and support for innovation [13]. For example, criteria for breakthrough devices and orphan devices are introduced. After "designation" by an expert panel, breakthrough devices and orphan devices will be subject to a priority and rolling review. Manufacturers have access to expert panels' advice. Additionally, member States and the Commission may establish regulatory sandboxes to address needs of emerging technologies.

The scope of the Clinical evaluation consultation procedure will be limited to class III implantable devices with the empowerment of the Commission to add other types of devices by delegated act. The performance evaluation consultation procedure will be removed. Instead, the possibility of early advice from expert panels for class Class C and D IVDs will be introduced [14].

1.2. Background: European Regulatory Framework and Policy

1.2.1. European Pharmaceutical Legislation Reform

As an overarching policy strategy, the Pharmaceutical Strategy for Europe (adopted by the European Commission (EC) in November 2020), aims to create "*a future-proof regulatory framework and* [to support] *the industry in promoting research and technologies that reach patients to fulfil their therapeutic needs while addressing market failures*" [15,16]. The Strategy is operationalised most notably through the reform of the general pharmaceutical legislation of the EU, which was proposed by the EC in April 2023, and for which political agreement was reached between the Council and the European Parliament in December 2025. The legislation, which is aimed at medicinal products (MPs) only, constitutes a key element of the regulatory and policy framework at European level regarding pIHTs. The objectives addressed by the proposal include affordable access to safe and effective medicines for patients across Europe, security of supply, an attractive and innovation-friendly environment for research, development, and production, environmentally sustainable pharmaceuticals, and addressing antimicrobial resistance (AMR) [15]. Additionally, the reform inter alia intends to address medicine shortages, accelerate supply chains and market entry, as well as incentivise pharmaceutical innovation within the EU [15]. Additional legislation is being proposed to address the resilience of the EU with respect to critical medicines (through the Critical Medicines Act) and to foster innovation (through the Biotech Act).

Key aspects of the reform of the general pharmaceutical legislation include (but are not limited to) the following:

a. A modular system of incentives with more flexible regulatory protection periods that can be extended based on the fulfilment of specific criteria. Alongside a standard regulatory protection period, extended periods are possible if an MP addressed an unmet medical need (UMN) or - for products with a new active substance - if specified characteristics regarding testing in clinical trials (comparative trials, and trials conducted in Europe), or the market authorisation application (within 90 days after the first authorisation application outside the EU) are met [17,18]. Additionally, accelerated market entry of generic and biosimilar MPs is supported through clarification of the scope of the "Bolar" exemption, allowing manufacturers to conduct activities related to such products during the originator's market protection period [17,18].

b. For orphan medicinal products (OMPs), a subcategory named "breakthrough OMPs" is established for products addressing a disease with no currently available treatment (alternative), and where the use of the OMP results in a clinically relevant reduction in disease morbidity or mortality for the relevant patient population [18]. As per the current legislation proposal version, such products would be subject to an 11-year market exclusivity period [18]. This category replaces the term "high unmet medical need" [19].

c. Transparency requirements regarding clinical trials, declaration of interests in the pharmaceutical industry by experts and rapporteurs, supply chain, and direct public funding received by pharmaceutical companies as a support to research and development (R&D) activities [20,21].

d. Addressing the environmental impact of MPs through environmental sustainability enhancement [14,22]. This involves an obligation of pharmaceutical companies to include an environmental risk assessment in a marketing authorisation application, which must also contain a risk evaluation regarding AMR [17,18].

e. Establishment of **regulatory sandboxes** based on a recommendation by EMA if the development of an MP or product category in compliance with the current regulatory framework is not possible due to the product's/products' characteristics and methods, and if these characteristics and methods positively and distinctively contribute to the product's/products' quality, safety or efficacy [23]. The development and testing of innovative therapies can thus be conducted under direct supervision of the competent authorities [17,18].

f. **Enhancement of security of supply** to address systemic MP shortages and supply challenges. To this end, three approaches are stipulated in the proposed legislation (Chapter X of the proposed Regulation): (i) the establishment of a shortage management framework (especially with regard to critical medicines); (ii) the legal capacity of EMA to conduct inspections of EU interest at pharmaceutical manufacturing sites located outside the EU (including for emergency situations); and (iii) a Joint Audit Programme within EMA to maintain an equivalent and harmonised implementation of the EU legislation on good manufacturing, clinical, and distribution practices, alongside corresponding enforcement activities [21].

In December 2025, the EC proposed the European Biotech Act, a "Regulation to establish measures to strengthen the Union's biotechnology and biomanufacturing sectors" [24]. In response to a weakened competitive position of the EU with regard to clinical research due to fragmentation and the complexity of the EU regulatory framework, Its aim is to create an "enabling environment to make it easier to bring biotechnology products from the laboratory to the factory and then onto the market, while maintaining the highest safety standards for the protection of the population and the environment" [24]. To this end, the proposed regulation seeks to address barriers concerning the development of health biotechnologies in the EU with a focus on small and medium-sized enterprises. This involves a framework for recognising and supporting (high-impact) health biotechnology projects to reduce time-to-market trajectories, and "future-proofing provisions to anticipate the needs of health biotechnologies" [24].

The Critical Medicines Act (CMA) was proposed by the EC in March 2025 and intends to improve the availability, supply and production of critical medicines within the EU [25]. The CMA primarily focuses on critical medicines where supply shortages have been observed, or critical vulnerabilities have been identified (i.e. in many cases off-patent MPs) and is therefore not immediately expected to impact on the key topics of the ASCERTAIN project (innovative health technologies). However, the CMA also foresees the promotion of (cross-border) joint procurement of medicines where individual countries may face access challenges, i.e. OMPs [26].

1.2.2. EU HTA Regulation

Since January 2025, the EU HTA Regulation (Regulation (EU) 2021/2282) has been directly applicable in all EU Member States (MSs). This regulation contains frameworks on the joint clinical assessment (JCA) of MPs undergoing a market authorisation procedure, as well as on joint scientific consultations (JSCs), horizon scanning (identification of emerging health technologies), and voluntary cooperation [27]. An overarching purpose of the EU HTA Regulation and these frameworks is to reduce duplication efforts for national HTA authorities and the industry for the purpose of faster and more efficient value assessments, facilitate business predictability, and ensure the long-term sustainability of HTA cooperation at a European level [4,28]. The relevant provisions in the EU HTA Regulation are complemented by Implementing Regulations on JCAs regarding MPs [29], JCAs regarding medical devices (MDs) and *in vitro* diagnostics (IVDs) [30], on JSCs for MPs [31] and JSCs for certain MDs/IVDs [32], and regarding exchange of information with the EMA [33], as well as on the management of conflicts of interest of experts within joint work [34].

Within a JCA, a new health technology is subjected to a clinical value assessment evaluating its comparative effectiveness and safety against relevant existing treatments. This value assessment is based on one or multiple sets of PICOs which were determined in a scoping procedure at the beginning of the respective JCA trajectory, and reflect the MSs' needs [35]. For MPs, a JCA is performed in parallel to the respective market authorisation procedure; and for certain high-risk medical devices from those which are subject to a scientific opinion by expert panels under EMA coordination [30,35,36]. During the procedure, patient experts, patient organisations, healthcare professionals and other experts should receive the opportunity to provide their input [27,29,30]. Published JCA reports must be given due consideration in the respective national HTA procedures and decision-making processes [27].

JSCs facilitate evidence generation satisfying the evidence requirements of a subsequent JCA process of a given health technology of which clinical studies are still in the planning stage [27,37]. For MPs, JSCs are initiated based on a corresponding request and a briefing package submitted by the health technology developer (HTD). Following a review of the list of issues drawn up by an assessor and co-assessor appointed by the JSC subgroup, a virtual meeting involving the HTD, the JSC subgroup, the assessors, individual experts, and, if in parallel consultation, EMA is held to discuss the list of issues and the proposed development plan regarding the further clinical study trajectory. Subsequently, a JSC outcome document is drafted, and following approval by the HTA Coordination Group, provided to the HTD [38]. For certain high-risk medical devices and class D IVDs, the JSC is conducted in two formats: the HTA Coordination group (HTA CG) JSC and in parallel with the expert panel consultation (the Parallel HTACG/ExP JSC) [14,39]. In both cases and as part of the voluntary cooperation within the scope of the EU HTA Regulation, advice related to the HTA of the health technology in question can be provided as an option. Such advice is then provided in the JSC outcome document [32].

1.2.3. European Innovation Agenda

On 5 July 2022, the European Commission adopted a "New European Innovation Agenda", which aims to position Europe as a leader of the new wave of deep-tech innovation and start-ups [40,41]. The agenda consists of five pillars: (1) Fostering deep tech innovation; (2) creation of innovator networks across Europe; (3) attracting talent; (4) attracting investors; and (5) revamping policies to promote innovation [40,41]. This innovation agenda is relevant for medical devices used in connection with cancer treatments, as they are considered as an example of deep-tech solutions (i.e., technologies based on cutting-edge science and engineering) [42,43]. Additionally, the research-intensive biomedicine sector, which also includes biotechnological product, provides a high level of innovation; this sector is prominently populated by start-up businesses, which heavily rely on investments and long research and development (R&D) trajectories to bring a biotechnological product or medical device to market [44,45].

1.2.4. Health Economic Evaluation of AI-Assisted Medical Devices

AI-assisted medical devices utilise artificial intelligence (AI) and machine learning algorithms to enhance various aspects of healthcare, including diagnostics, treatment planning, patient monitoring in real-time as well as automation of routine tasks. These devices can analyse vast amounts of data quickly and accurately, providing healthcare professionals with potentially valuable insights that could improve patient outcomes and streamline clinical workflows. In oncology, such devices can enable early cancer detection, improve (*in vitro*) diagnostic accuracy, and facilitate targeted and personalised treatment for patients [46–49]. For health economic evaluations of AI-assisted medical devices, their accuracy regarding analyses, prognoses and diagnoses are central in assessing clinical effectiveness and patient safety [50]. Such evidence should be applicable to the target patient group, especially when they are un- or underrepresented in training datasets, which may induce bias into AI-assisted medical devices and their trials [51]. Additionally, careful consideration should be given to data privacy and

security, quality of training data, the integration of AI-assisted
medical devices into clinical workflows and practice, changes in organisational practice due to their involvement in clinical practice, as well as regulatory implications and ethical considerations [52].

Several national and regional HTA bodies (England & Wales, Catalonia, France, Finland) have begun to develop frameworks to address the complexities of HTA procedures involving digital health technologies, which includes AI-assisted medical devices. These frameworks focus on information-related issues regarding AI functionality, training data quality, further aspects related to the deployed algorithm, data risk management, support costs, algorithm bias, privacy and liability, human oversight, implementation in daily routine,monitoring, re-evaluation and updates [53–58].

1.2.5. European Database on Medical Devices

Established on the basis of the EU Medical Devices Regulation (Regulation (EU) 2017/745) and the Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices, the European Database on Medical Devices (EUDAMED) is an IT system that aims to improve transparency by providing better access to up-to-date and reliable information for the public and healthcare professionals, while also fostering stronger coordination among EU MSs [59–61]. EUDAMED consists of six modules: an actor (ACT) module, a unique device identification (UDI)/device module, a notified bodies and certificates module, a market surveillance module, a post-market surveillance and vigilance module, and a clinical investigations/performance studies module [62]. The database's development and implementation have been progressing gradually, with some modules being currently available for voluntary use (actor registration, UDI/device registration, and notified bodies and certificates). The system is expected to be fully operational by 2027, with mandatory use for manufacturers planned by the second quarter of that year [63].

1.3. Objective of the ASCERTAIN Project

The ASCERTAIN project ("*Affordability and Sustainability improvements through new pricing, Cost-Effectiveness and Reimbursement models to Appraise INnovative health technologies*") operates within a rapidly evolving European HTA and regulatory landscape. While the European Network for Health Technology Assessment (EUnetHTA), established in 2006, strengthened cooperation among national HTA bodies, its voluntary structure and differing approaches limited harmonization [64]. To overcome these challenges, the EU adopted the Health Technology Assessment Regulation (EU 2021/2282), fully applicable from January 2025, establishing joint clinical assessments, aligned evidence requirements, and a more consistent framework across Member States [27].

ASCERTAIN builds on this shift by developing integrated pricing, cost-effectiveness, and reimbursement approaches, together with policy-support tools adaptable to diverse national systems, whether countries apply cost-per-quality-adjusted life year (QALY) thresholds or follow alternative decision models. These methods can enhance evidence generation, transparency, and budget management while supporting structured assessment where formal HTA is limited. Running from December 2022 to November 2026 (Grant Agreement No. 101094938), the project promotes value-based and equitable access to pIHTs across Europe.

The overall goal of the ASCERTAIN project is to facilitate accelerated patient access to pIHTs across the EU. To achieve this, it will develop a comprehensive policy support tool (the "ACCESS2MEDS Toolbox") encompassing i) pricing models tailored to medicinal products and medical devices, ii) dynamic HTA models for life-cycle-based (cost-)effectiveness and budget impact assessments, as well as iii) models for reimbursement and cost-effectiveness thresholds. To this end, research within this project involves the development, testing, and quality-check of

these models based on three use cases (UCs), namely precision
cancer medicines, cell and gene therapies (CGTs), and next-generation sequencing (NGS) IVD medical devices.

Figure 2 provides a visualisation of the ASCERTAIN project; this includes a description of the research and development activities performed during the project trajectory, as well as a depiction of the relevant workflows.

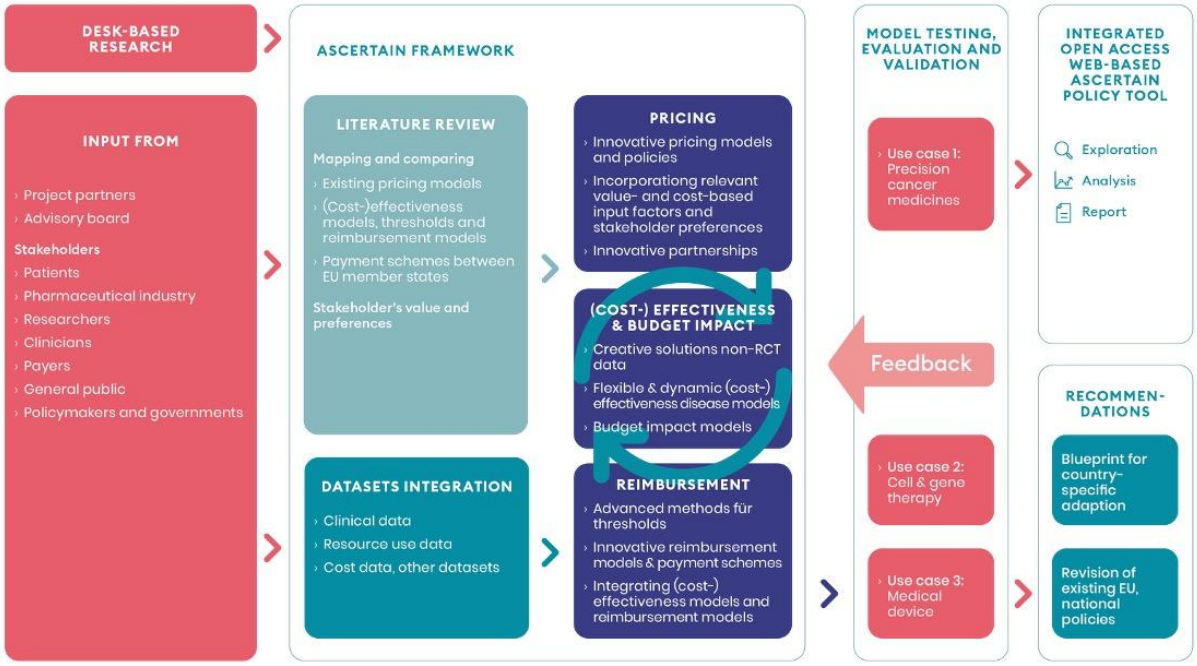


Figure 2: Overview of the ASCERTAIN project

1.4. Objective of the ACCESS2MEDS Framework

In view of the described objectives of the ASCERTAIN project (see section 1.3.), the ACCESS2MEDS Framework is positioned to serve as a fundamental conceptual and value-related basis for the models developed within the project, as well as for the ACCESS2MEDS Toolbox containing these models. It aims to incorporate a set of core values underpinning all models that (i) are aligned with the ASCERTAIN's overarching goal of improving patient access to pIHTs; (ii) are aligned with the objectives and priorities of the relevant European regulatory framework and policies with regard to pIHTs; and (iii) underpin the objectives and the design of all models developed within ASCERTAIN. In this context, an additional purpose of the ACCESS2MEDS Framework is to make the overarching characteristics shared by all models developed within ASCERTAIN explicit. This incorporation supports the objective of providing a structured approach to balancing affordability, incentivisation of innovation, and sustainability in healthcare decision-making. Additionally, the links between the core characteristics of the models and the core values of the ACCESS2MEDS Framework are explicitly described.

To address current challenges in pricing and reimbursement of pIHTs (e.g., uncertainty, variable methodological standards across EU MSs), the ACCESS2MEDS Framework further integrates evidence from both scoping literature reviews and structured stakeholder engagement. The latter in particular forms a crucial part of the Framework, as it helps reduce uncertainties concerning pricing and reimbursement, while creating a more predictable environment for payers and health technology developers. By supporting transparent, evidence-based decision-making and

balancing clinical, economic, and societal priorities in a flexible manner, the Framework aims to offer benefits across healthcare ecosystems at national and European level.

1.5. Structure of this Document

This document is structured as follows: Section 2 contains a description of the core values incorporated into the ACCESS2MEDS Framework, which inform the underlying characteristics of the models developed within ASCERTAIN. Section 3 outlines the fundamental and overarching characteristics and features of the models developed within the ASCERTAIN project. This also includes a general description of how these models can interact with each other within the ACCESS2MEDS Toolbox environment ("cross-model interactions"). Section 4 provides more detailed deliberations about the conceptualisation and key characteristics regarding the individual models (pricing, cost-effectiveness and budget impact, cost-effectiveness threshold and threshold modifiers, reimbursement). Where applicable, model characteristics specific to the individual UCs are described. Section 5 is dedicated to the ACCESS2MEDS Toolbox, containing a description of its purpose and its technical implementation. Finally, Section 6 incorporates a discussion of the ACCESS2MEDS Framework, which *inter alia* includes an outlook into future iterations of the Framework and the further development of the models.

2. Core Values

2.1. European Health Values

Across different countries in the EU, there exist substantial differences in access to medicinal products and medical devices, as well as large differences in patient outcomes [2–4]. These differences may be partially attributable to equity-related issues regarding patient access. Given the transnational nature of this issue, a potential resolution with the purpose of improving patient access to pIHTs should be grounded in values that apply at a European level.

The Charter of Fundamental Rights of the European Union (CFR) establishes in its article 35 that "[e]veryone has the right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices." Moreover, this provision stipulates that the EU's policies and activities must ensure "a high level of human health protection in [their] definition and implementation" [65]. Hence, access to health care for everyone is a fundamental human right. The second part of article 35 CFR is also reflected in article 168.1 Treaty on the Functioning of the European Union (TFEU), indicating that at a European level, healthcare policy is underpinned by a human rights approach [66]. However, based on article 168.7 TFEU, the jurisdiction and primary responsibility for health protection and healthcare systems continues to lie with the MSs [67].

Despite the limited legislative jurisdiction, the EU has developed fundamental strategies and policies that are based on the human rights approach as stipulated in the mentioned provisions of the CFR and the TFEU. A centrepiece in this regard is the catalogue of European Health Values. These values constitute fundamental principles for action on health, were taken from the Council Conclusions on Common Values and Principles in European Union Health Systems, and subsequently formulated in the White Paper "Together for Health: A Strategic Approach for the EU 2008-2013" by the European Commission [68].

The European Health Values are the following [7,69]:

Universality: This value stipulates that no one should be barred from access to healthcare. Healthcare services are available to all individuals in a given population, without any discrimination or exclusion. It implies that everyone, regardless of their socioeconomic status, age, gender, ethnicity, or any other characteristic, has equal access to essential healthcare services. Universality aims to ensure that no one is left behind and that healthcare is a fundamental right in all EU MSs. This health value explicitly and directly aligns with the wording of article 35 CFR.

Access to good quality care: Health systems should strive to provide good quality care. This is achieved through the obligation to continuous training of healthcare staff based on clearly defined national standards and ensuring that staff have access to advice about best practice in quality, stimulating innovation and spreading good practice, developing systems to ensure good clinical governance, and through monitoring in the health system. This also relates to the principle of (patient) safety.

Equity: Equity in healthcare focuses on fairness and justice in the distribution of healthcare resources and services. Under this value, it is recognised that individuals have different needs and circumstances, and therefore, equal access to healthcare may not necessarily result in equal outcomes or health status. Equity seeks to address these disparities and provide individuals with an equal opportunity to achieve their optimal health outcomes. It involves distributing healthcare resources according to need, with an emphasis on reducing health inequalities and addressing the social determinants of health. Patients should therefore receive equal access *according to their need*, regardless of ethnicity, gender, age, social status, or ability to pay.

Solidarity: This value is closely linked to the financial arrangement of national health systems and the need to ensure accessibility to all. Solidarity requires countries to ensure that the cost of health and care services are fairly allocated to ability to pay, and that services are available to all according to their respective individual needs. As a value, it underpins initiatives promoting equitable access to healthcare, cross-border collaboration, and collective responses to health challenges, ultimately fostering a more cohesive and inclusive European healthcare system. Solidarity can thus be considered a core value that applies not only within an individual MS, but also at a transnational level across MSs.

Although the European Health Values were developed nearly twenty years ago, these values are still relevant today. They provide a moral and ethical compass for shaping healthcare policies, systems, and practices that prioritise the well-being of individuals and communities in a constantly evolving healthcare landscape. Given their alignment with the overall objective of the ASCERTAIN project and the ACCESS2MEDS Framework, these values take a fundamental position with regard to the development, objectives, purpose, and characteristics of the individual models developed within ASCERTAIN.

2.2. SUSTAINABILITY

As the concept of sustainability has increasingly emerged as a key topic in health policy at a national, but also at a European level [5,73,74], it is also taken into account in the ACCESS2MEDS Framework.In the context of ASCERTAIN's core values, the term "sustainability" is subject to ambiguity. In the following, the definitions of the term in the relevant contexts are briefly outlined.

A common understanding of this term in connection with health systems concerns their financial sustainability. In the context of healthcare, it refers to "the presence of an imbalance between the obligations that a health system has in respect of entitlements and instituted rights on the one hand, and its ability to meet those obligations on a continuing basis on the other" [70,71]. In view of most health systems' budgets being based on government funding, healthcare expenditures are often linked to concerns and considerations in policy-making, especially with regard to addressing increasing cost pressures [72].

On the other hand, the aspect of environmental sustainability addresses the healthcare sector's responsibility for a substantial share of global greenhouse gas emissions. In this context, the literature has discussed three main principles: reduction of healthcare demand through disease prevention, appropriate healthcare provision (i.e., avoidance of unnecessary testing and treatments), and minimising greenhouse gas emissions associated with (necessary) healthcare provision [73,74].

In the following subsections, both aspects and their relevance for the ACCESS2MEDS Framework are discussed in more detail.

2.2.1. FINANCIAL SUSTAINABILITY

Public expenditure on healthcare and long-term care absorbs a significant and growing share of economic resources, with most EU MS being expected to face strong and increasing expenditure pressures on their health systems over the next few decades [75]. As launch prices of innovative health technologies have been reaching record highs, their reimbursement has increased the financial pressure on healthcare systems [76]. In addition, healthcare spending related to medical devices constitutes a considerable part of annual healthcare expenditures, ranging from 5% to 12% across European countries [77]. As new diseases and health challenges continually emerge, and diseases requiring treatments that are life-saving or life-prolonging and are often subject to long treatment trajectories (especially in the field of oncology), new health technologies that aim to meet these requirements have successfully been developed [78–80]. However, research and development into new medicinal products and such products' subsequent market entry has

increasingly shifted from breakthrough treatments ("blockbusters") to treatments that target small indications ("nichebusters"), with market authorisation to expensive products being granted based on uncertain evidence [81–83]. Moreover, the advancement of scientific knowledge has contributed to a demographic shift characterised by an ageing population in all EU MSs.

Considering this paradigm, the escalation of healthcare expenditures coupled with finite resources underscores the critical importance of considering sustainability and cost-effectiveness to ensure that healthcare systems can continue to provide high-value quality care without compromising future generations' access to healthcare. The European health values help guide responses to these changes, ensuring that healthcare systems remain adaptable, effective, and patient-centred. Consequently, the ACCESS2MEDS Framework collates the European health values with these developments. In this context, the Framework includes core principles relating to financial sustainability on the one hand, and environmental sustainability on the other.

As sustainability has increasingly emerged as a key topic in health policy at a national, but also at a European level [4,84,85], it is also taken into account in the ACCESS2MEDS Framework. In this respect, sustainability relates to both financial and environmental sustainability.

The fiscal sustainability of health systems is currently a pressing policy concern due to two key factors: (a) challenging initial fiscal positions and (b) projected future increases in healthcare and long-term care spending. While investing in healthcare and long-term care can lead to improved health outcomes, the escalating costs can also restrict the availability of resources for other public policy domains [75]. The European Commission (EC) has acknowledged a need to increase efforts to lessen the growth of expenditure in healthcare and long-term care; this calls for targeting reforms with the highest potential to improve value for money of the relevant services provided [75]. Sustainable financing of healthcare systems involve efficient financing mechanisms ensuring the long-term viability of healthcare services.

Key aspects of sustainable financing involve adequate and equitable funding, as well as efficient resource allocation. The application of HTA to inform healthcare decision-making, well-designed policy planning involving stakeholders and stakeholder collaboration, as well as cross-country collaborations regarding pricing and reimbursement negotiations can support these objectives [86,87].

2.2.2. Environmental Sustainability

Environmental sustainability is defined as a "condition of balance, resilience, and interconnectedness that allows human society to satisfy its needs while neither exceeding the capacity of its supporting ecosystems to continue to regenerate the services necessary to meet those needs nor by our actions diminishing biological diversity" [88]. In the context of healthcare systems, environmental sustainability as part of a trade-off with the performance of core health system functions might face difficulties in finding acceptance. Hence, win-win solutions should be sought whereby environmental sustainability actions reinforce health system functions [89]. However, the environmental impact of pIHTs should be weighed against their health-related benefits when it comes to their financing ("environment-focused evaluation") [90].

As the healthcare sector was estimated to be responsible for 4.4% of greenhouse gas emissions worldwide (2017) and causing between 1% and 5% of global environmental impacts on a global level as well as more than 5% on a national level in several countries [91,92], general policies such as the European Green Deal are being implemented [93]. Actions targeting transformations into low-carbon, more sustainable health systems have been observed at international level, but also at national/regional level (United Kingdom, Canada) [94–96]. However, approaches to address environmental consequences with regard to healthcare service provision, MPs and MDs are

complicated by different regulations in different sectors as well as flawed alignment between regulations and environmental objectives [97].

A new aim in the strategic approach by the EU in 2019 consists of reducing the significant risks of pharmaceutical residues in the environment [98]. MSs are encouraged to promote environmentally friendly practices in healthcare facilities, measure and reduce the carbon footprint of healthcare systems, and integrate environmental considerations into health policies and strategies. This strategy highlights the value of environmental sustainability with regard to new health technologies, and the need to seek simultaneous improvements in both human and environmental well-being. The desirable consequence of this would consist of healthcare products and services facilitating the improvement, maintenance and/or restoration of human health, while minimising negative impacts on the environment, and leveraging opportunities to restore and improve the environment to the benefit of the health and well-being of current and future generations [89].

2.3. The ACCESS2MEDS Framework in the Context of the Core Values

In defining the conceptual fundament and value base underpinning the objectives of the models developed within ASCERTAIN, the ACCESS2MEDS Framework draws on the European Health Values while embedding financial and environmental sustainability as essential principles for resilient healthcare systems [99]. Functioning as fundamental guidance, the core values inform the development, objectives, and application of adaptable models, as well as the ACCESS2MEDS web tool (see sections 4 and 5), which support consistent, transparent, and evidence-based decision-making [100].

While investments in prevention and health promotion also contribute to curbing future healthcare expenditures [101,102], such aspects lie outside the scope of ASCERTAIN. Therefore, core values linked to these aspects are not included in the ACCESS2MEDS Framework nor considered for the respective models.

3. Fundamental and Overarching Characteristics and Features of the ASCERTAIN Models

3.1. Key Concepts of Model Characteristics

3.1.1. Purpose

The key purpose of the models developed within ASCERTAIN is to advance improved patient access across diverse health system contexts. To this end, the core characteristics featured in the models include an alignment regarding this common objective, and consistency with the core values (see section 2). Moreover, to facilitate application across health systems in Europe and their individual characteristics, they are adaptable to local and regional needs. Overall, the design of the models conforms to the objective of supporting scalable, sustainable, and context-sensitive implementation.

In addition, to ensure practical relevance and to facilitate implementation and application, stakeholders play a crucial role in informing the model development and validation processes (see section 3.1.2. for more details). Moreover, all models and the model application environment are developed and implemented exclusively using open-source software (see section 3.1.3. for more details).

3.1.2. Stakeholder Involvement

As mentioned above (section 1.3), a key objective of the ASCERTAIN project is to facilitate accelerated patient access to health technologies. In this context, the improvement of access relies on relevant experiences in pricing and reimbursement practice. Such experiences help provide an encompassing perspective of the advantages and shortcomings of existing models and approaches in this regard. To effectively evaluate pricing and reimbursement models for health technologies, information must be retrieved from a variety of stakeholders, including patients, healthcare providers, policymakers, payers and pharmaceutical companies. In view of the aim to provide models fit for all European countries, stakeholders should be involved from all European regions. Considering that access to new health technologies is especially challenging in Central and Eastern European countries, which are subject to relatively more constrained healthcare budgets and delays due to launch strategies [8,103], the involvement of stakeholders located in such countries is all the more important.

Hence, the elicitation of stakeholder views and preferences forms a fundamental pillar for the models developed within ASCERTAIN. Elicitation methods such as interviews, surveys and focus groups have been employed to determine the relevance and the operationalisation of parameters relevant to the respective models. Moreover, stakeholders of all relevant groups (patients, clinicians, industry, consultancy, HTA agencies and payers) are involved in the validation procedures for all models. The purpose of this is to ensure the models' fitness for practice to inform negotiations and decision-making regarding the pricing and reimbursement of newly authorised health technologies. This continuous stakeholder input serves to improve the user-friendliness of the models.

3.1.3. Use of Open-Source Technology

Concerning the model development and implementation, the ACCESS2MEDS Framework adopts an open-source policy to promote transparency, collaboration, and shared ownership across stakeholders. This ensures open access to the models and the associated application environment developed within ASCERTAIN. Additionally, the open-source nature of the models and its application environment encourages continuous improvement and maintenance,

facilitates knowledge exchange, and supports adaptation to diverse health system contexts. This approach lowers barriers to adoption, enables collective learning, and strengthens the framework's capacity to evolve in response to emerging needs and evidence.

All ASCERTAIN models are implemented in R using open-source R packages. RStudio is used as a development environment. The models are exposed as containerised API services implemented in R using Plumber and are orchestrated by the ASCERTAIN web tool, which is itself deployed using Docker. The full toolchain relies exclusively on open-source components and does not require proprietary software to operate.

3.1.4. Intended Interactions with Health Policy

The ASCERTAIN framework is designed to interact constructively with existing and emerging health policies by providing an evidence-informed, adaptable reference model rather than a prescriptive solution. It aims to support policymakers by informing policy design, implementation, and evaluation processes, while remaining responsive to national and regional priorities. Through alignment with core health system values and stakeholder engagement, the framework seeks to complement policy objectives, support coherence across initiatives, and contribute to sustained improvements in patient access.

3.2. Cross-Model Interactions

3.2.1. Purpose

The implementation of the models developed within ASCERTAIN is designed to integrate insights from access-based pricing, cost-effectiveness, budget impact, and reimbursement models to inform more balanced, evidence-driven decision-making. By linking these complementary perspectives, the ACCESS2MEDS Framework supports holistic evaluation of interventions, ensures alignment between financial sustainability and patient access goals, and enables policymakers and stakeholders to identify trade-offs and optimise outcomes across multiple dimensions of healthcare delivery.

To facilitate this holistic evaluation, the implementation of the models developed within ASCERTAIN places an emphasis on points of interaction between models. These cross-model interactions provide the user of the models and the ACCESS2MEDS web tool with a high level of flexibility and the possibility to explore a multitude of scenarios informed by the corresponding relevant models to inform pricing and reimbursement negotiations, and healthcare decision-making, respectively. Hence, the user has full control over the number and types of models they intend to use, which facilitates an improved overview regarding a health technology's characteristics relevant for healthcare decision-making.

3.2.2. Types of Interactions between Models

The cross-model interactions can materialise in multiple ways. For instance, such an interaction consists of the output of a specific model ("Model A") being used as an input for another model ("Model B"). As part of the application of the models and the ACCESS2MEDS web tool, the outcome of such an interaction, expressed by the change of Model B's output, can be explored by means of a scenario analysis. Another example is that an input parameter relevant for Model A can also be used as an input parameter in Model B. This can be of particular importance when consistency of model inputs is crucial; for example, if both models are used either in conjunction or to facilitate a comparison of outcomes under both models.

The consistent implementation of these cross-model interactions plays a vital role for the ACCESS2MEDS web tool, as it allows for the models to be considered as components of a

dynamic and multi-layered entity to inform healthcare decision-making, rather than a set of individual models that can only be used in isolation. This structured exchange ensures consistency, enhances the robustness of analyses, and allows stakeholders to explore the combined impact of financial, clinical, and access considerations when making strategic decisions.

4. Description of the Individual Models

4.1. Pricing Model

4.1.1. Rationale and Purpose

As innovative health technologies increasingly enter the market at unprecedented prices and pressure on public budgets is tightening, health systems in Europe and elsewhere face a key challenge in ensuring timely patient access to innovation. Empirical evidence shows major increases in prices for newly authorised medicines over the past 15 years [104,105]. A negative consequence of these developments is increasingly inequitable access to new medicines [4]. When they provide meaningful therapeutic benefits, health technologies can contribute to a healthier population. However, in order to enable widespread access to such meaningfully innovative products, they must be priced so that health systems can afford to use them and maintain their long-term financial sustainability. Hence, as has been recognised by stakeholders involved in healthcare, affordability plays a key role in ensuring access to potentially innovative health technologies [2,106–111]. The development of a pricing model concerning potentially innovative medicinal products as well as guiding principles for the pricing of newly authorised medical devices in the field of next-generation sequencing diagnostics is guided by the purpose of addressing the policy challenge of how to reconcile affordable and timely patient access to new medicinal products with incentives for continuous innovation.

An approach that appropriately addresses this challenge is not adequately provided by existing pricing models. In particular, pricing approaches that are rooted in value-based pricing (VBP) on the basis of the costs of existing treatments are only likely to result in higher prices in the future for two reasons. As prices are commonly anchored in the prices of existing treatments, and new innovative health technologies claim advantages in therapeutic benefit over those, VBP based on existing treatments yield a pattern of increasing prices over time [112–115]. As another approach for defining “fair” prices for medicinal products, cost-based pricing (CBP) anchors the price to expenses required for producing and making it available to patients, as well as a profit margin. However, this approach appears irreconcilable with the interests of stakeholder groups: while payers, healthcare professionals, and patients advocate for the viability of CBP, and investors have highlighted the relevance of cost components for their own decision-making, representatives of the pharmaceutical industry oppose this approach. However, to strike a balance between the required sustainability for the company on one hand and for the healthcare system on the other, the allocation of a profit sufficient for the company to ensure continuation of their business is necessary. This necessity is irrespective of the product’s value-related characteristics, as well as security of supply, and limited to what is affordable for the health system. A comparative overview of the CBP and VBP approaches is shown in Table 1.

Table 1: Comparative overview of CBP and VBP regarding their strengths and shortcomings

Pricing approach	**Cost-based/cost-plus pricing**	**Value-based pricing**
Key characteristics	- Anchors price to expenses required for production and availability to patients, and profit margin	- Price is based on value provided by the health technology, informed by a value assessment
Advantages	- anchors price to costs for the manufacturer and risks taken in bringing a new product to market - costs feature in return and profit considerations	- Widely considered as a beneficial and efficient approach to pricing
Shortcomings	- Opposed by some stakeholders due to (a) transparency concerns and (b) concerns regarding lack of incentive for efficient R&D	- does not address affordability issue given ever-increasing cost of standard care - lack of agreement on what constitutes value - often uncertainty in clinical evidence

Abbreviation: R&D, research and development.

Moreover, VBP typically results in prices set according to the value of the respective first indication for which a new product is authorised. This is likely to be a narrow indication with an unmet medical need, providing scope for claiming a high price compared to (unsatisfactory) existing treatments [116]. As pricing policies in most countries impose uniform prices across indications, differences in (added) value of an MP for different indications are not appropriately reflected in a (uniform) price, often established based on the first indication for which market authorisation was received [117].

Against this background, the purpose of the pricing model for medicinal products is to estimate a price that enables access, i.e. a price that allows health systems to make innovative medicinal products available to patients while providing the required incentives to companies for developing and producing these products. This model output is considered to be an **access-based price (ABP)**.

4.1.2. Characteristics of the Access-Based Pricing Model

The access-based pricing model follows the following set of principles:

- **Reflection of the core values of the ACCESS2MEDS Framework** (see section 2);
- **Stakeholder view incorporation** (see section 3.1.2): based on the acknowledgement of different interests by stakeholders in relation to the pricing of health technologies, different stakeholder views are considered for the implementation of the pricing model;
- **Practical relevance** ensured by reflecting and reconciling decision-making practices regarding pricing by relevant stakeholders;
- **Flexibility** regarding the use of price determinants as model inputs: in addition to essential price determinants required for model operability, users can freely select additional further optional determinants relevant to their respective decision-making processes;
- **Dynamic/iterative pricing implementation**: to reflect price revision practices applied in several European countries [113,115,118–121], the pricing model allows for recurring/iterative use.
- **Open-source development and implementation** (see section 3.1.3).

Based on these principles and on the described rationale, the access-based pricing model combines cost and value determinants to calculate a European ABP for newly launched medicinal products under patent. At its core, the model incorporates four components (see Figure 3).

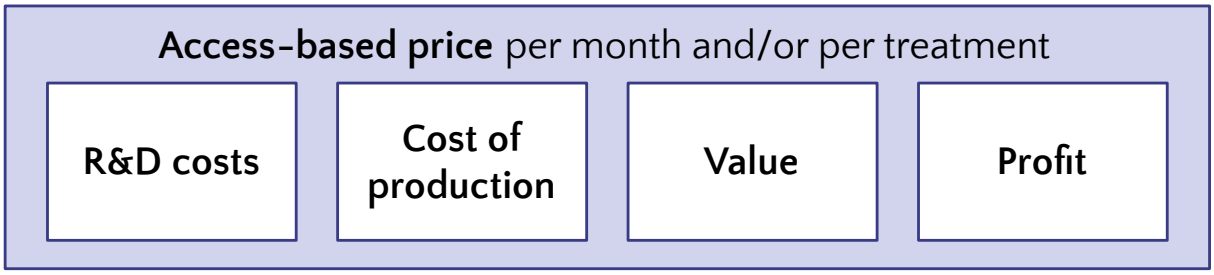


Figure 3: Graphical representation of the pricing model components

"R&D costs" concern the cost of bringing future innovation to the market; "cost of production" involves the operational cost of manufacturing the MP of interest. "Value" incorporates different value-related aspects inherent to the product that the user may want to see reflected in a price in the form of a reward for innovation, and is directly linked to R&D costs; finally, "Profit" represents the minimum profit over operational costs.

The ASCERTAIN access-based pricing model is intended to provide a transparent starting point for price negotiations within existing national or regional pricing and reimbursement systems. The access-based pricing model therefore intends to complement (rather than replace) existing systems. It is therefore possible to use the access-based pricing model in a value-based reimbursement framework informing the cost-effective use of resources. An access-based price (ABP) below the cost-effectiveness threshold may trigger further discussion with the market authorisation holder on affordability of the proposed price, while an ABP above the threshold for cost-effective use of resources in that health system may either result in a reduced price after negotiations which allows the product to be reimbursed (i.e. the pharmaceutical company reduces their price to launch their product on the market in question), in a negative reimbursement decision (i.e. the price at which the company can be reasonably expected to launch the product is higher than what is considered a cost-effective use of resources in that health system), or in a discussion on the cost-effectiveness threshold value (especially in systems were thresholds are only used implicitly).

4.2. Cost-Effectiveness and Budget Impact Models

4.2.1. Overarching Purpose (Applicable to All Use Cases)

The introduction of pIHTs for small patient cohorts imposes several challenges for the current framework for the evaluation of clinical and cost-effectiveness. The first challenge concerns the identification of the incremental health outcome, by estimating a comparator when data is collected in a non-randomised setting. The need for developing methods for using real world evidence (including registry data) has been addressed by EMA and the European Network of Health Technology Assessment (EUnetHTA). The second challenge lies in accounting for uncertainty both for input parameters (response, duration of response, survival and treatment duration) and decision uncertainty (the likelihood of a new treatment being cost-effective), when sample sizes are very small [122]. To better facilitate more personalised analyses, fully utilizing combinations of available data sources will improve granularity of findings. The new EU HTA Regulation establishes a JCA framework regarding health technologies in the EU starting with oncologic drugs and advanced therapy medicinal products (see section 1.2.2). However, the Member States' competence and responsibility to draw their own conclusions on the overall clinical added value and to make their own decisions on pricing and reimbursement on their own responsibility remains unaffected [27,67,123].

In ASCERTAIN, open-access global simulation models will be developed for three use cases: Precision cancer medicine, gene and cell therapy (using chimeric antigen receptor [CAR] T-cell therapies as a representative example) and medical devices (using next-generation sequencing

(NGS) IVDs as an example). Open access global simulation models create a more equitable, efficient, and resilient scientific ecosystem. In the development of the three global models, a quality assurance framework (building blocks in Figure 4) followed by the cost-effectiveness and budget impact models for use cases 1 to 3 follows has been developed and implemented. The quality assurance framework is based on published recommendations and guidelines for validation, such as (ISPOR/SMDM) guidelines for transparency and validation [124–126]. In addition, the coding framework and structure follows the standard of the DARTH coding group [127]. It is anticipated that most users have limited experience with cost-effectiveness models in general, and will therefore use the functionality to use provided default parameters and adjust them according to their own needs. These users are referred to as level 2 users. More experienced level 1 users will be able to access the R scripts from the repository.

For use cases 1 and 2, we have developed a core model with a standardised coding structure that is applied for precision cancer medicine and cell and gene therapy. The core model is a partitioned survival model, estimating cost-effectiveness and budget impact. The model for use case 3 is based on a decision three model. The following subsections describe the rationale and distinct characteristics of the use-case-based models in further detail.

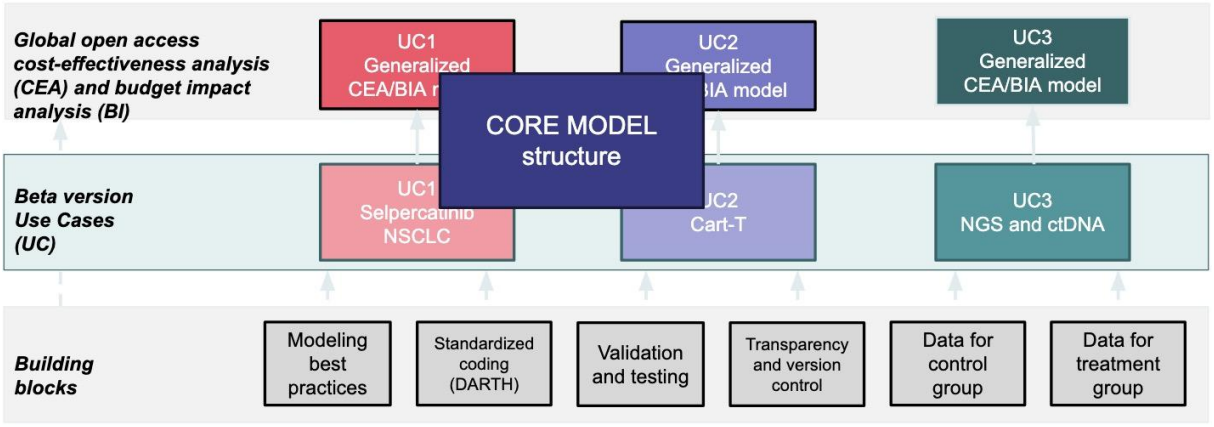


Figure 4: Schematic representation of the cost-effectiveness models' structure
Abbreviations: CRC, colorectal cancer; DARTH, decision analysis in R for Health Technologies; CAR-T, chimeric antigen receptors T-cells; NGS, next generation sequencing; NSCLC, non-small cell lung cancer

4.2.2. Use Case 1 (Precision Cancer Medicines)

Clinical trials of new drugs and technologies play a critical role in reimbursement decisions of new interventions. In oncology, phase II trials primarily evaluate the efficacy and safety of a new anticancer agent [128]; while phase III trials, often conducted as a randomised controlled trial (RCT), provide evidence on the comparative efficacy of a new treatment against existing alternative(s). During the latest decades, there has been a shift towards accelerated clinical approvals and conditional marketing authorizations, leading to the rise of early-phase trials with uncontrolled study designs, i.e., single-arm trials (SATs) [129–131]. It is particularly challenging to generate robust comparative evidence for interventions targeting small patient populations due to limited patient availability, reduced statistical power, and difficulties in recruiting sufficiently large and representative study cohorts. Although considered the gold standard, RCT trials are notably time-consuming, expensive, and may involve treatment crossover, which can further complicate comparative clinical outcomes, such as overall survival [132].

For use case 1, we develop a cost-effectiveness analyses, using different sources of evidence (i.e., published clinical evidence) to estimate the long-term health and economic consequences of selpercatinib versus pembrolizumab plus pemetrexed and platinum-based chemotherapy for advanced RET fusion-positive non-small cell lung cancer patients. The model development is

based on the core model, but further developed to account for
specific characteristics of use case 1 and country specific settings. The model development follows the quality assurance framework and is being compared between use cases.

Evidence for selpercatinib was first based on data from a single arm phase II trial, but with evidence from a phase III RCT data published several years later. This setup provides an opportunity to evaluate and compare phase II data with external controls with data from RCT. In many cases this is not an option, and the decision has to be based on phase II data only. Additionally, This use case facilitates the evaluation of a managed entry agreement (MEA) (WP6).

For use case 1, the global model will include results for Norway, Netherlands, UK, Lithuania and Croatia. For each country we will account for differences in discount rates, input parameters for costs, perspective (healthcare or societal), price of the treatment and prevalence of the disease.

4.2.3. Use Case 2 (Cell and Gene Therapies: CAR-T cell therapy)

CAR T-cell therapies have shown great therapeutic benefit as treatments for haematological malignancies, as they significantly improve survival for patients and show potential for cure [133,134]. However, their high costs and uncertainty regarding long-term effects complicate reimbursement decision-making [135,136]. Moreover, transparency of health economic models and transferability of economic evaluation (EE) results are hampered by methodological differences and the application of proprietary software (e.g., Microsoft Excel®) [137,138]. While existing EE frameworks are adapted to the clinical characteristics of CAR T-cell therapies (e.g., one-time treatment and specific follow-up trajectory; development of statistical survival extrapolation methods to account for the treatments' curative prospects), they are often developed for and applied within a single jurisdiction. Therefore, for use case 2 within ASCERTAIN, a key objective is to develop a transparent multi-country framework using CAR T-cell therapy as a test case, with the goal of enhancing transferability and exploring methodological approaches for the robust evaluation of CAR T-cell and other cell and gene therapies.

To support more comparable, transparent, and efficient economic evaluations across jurisdictions, a use-case-tailored adjustment to the core model is developed, enabling reuse, replication, and systematic adaptation of models and fostering more coordinated HTA processes. This framework is informed by a comparative methodological review of national EE guidelines conducted across eight European countries (Bulgaria, England and Wales, France, Germany, Italy, the Netherlands, Norway, and Spain) [139–147]. This review concerned key EE elements, identified based on established methodological and reporting checklists [148–153](REF) and refined through expert consultation, including analytic framework and perspective, time horizon, model structure and assumptions, costing approaches, outcomes and utilities, discounting, uncertainty and sensitivity analyses, validation, expert involvement, and budget impact analysis. Based on this structured comparison, the modelling framework distinguishes core methodological components from country-specific requirements. This approach supports standardisation through consistent model structures and coding while enabling transparent and systematic adaptation to jurisdiction-specific methodological requirements.

This modelling framework forms the core of an open-source partitioned survival model to estimate the cost-effectiveness and budget impact of CAR T-cell therapies across the same eight European countries. The foundational model structure is designed to be adaptable to country-specific requirements, including analytic perspective, discount rates, and background mortality, while maintaining structure- and code-based standardisation. Furthermore, the model incorporated both general and country-specific sensitivity and scenario analyses to assess parameter and structural uncertainty.

4.2.4. Use Case 3 (Next-Generation Sequencing / Genomic Profiling)

New cancer medicines approved by the EMA are increasingly targeted to genomic characteristics of individual patients' tumours, and require molecular diagnostics to identify patients for these treatments [154]. Testing technologies based on next-generation sequencing, which allow for high-throughput and parallel analysis of many different genomic biomarkers, are therefore becoming a highly relevant tool to implement potentially innovative targeted treatments in clinical practice and ensure that patients can benefit from these treatments [155]. The access to molecular diagnostics, and in particular next-generation sequencing (NGS) tests in oncology, however, differs considerably across Europe [155,156]. Costs for next-generation sequencing tests have historically been going down [157], but high costs still represent an important barrier to implementation in clinical practice. Further, NGS tests require an extensive infrastructure with laboratory equipment, testing platforms, analytical pipelines and highly-skilled healthcare professionals for analysis and interpretation of genomic data, which explains why organizational barriers are another important challenge for patient access to NGS tests [158]. Finally, there are many methodological challenges related to the economic evaluation of NGS tests [159], especially due to their potential to inform treatment beyond a clear companion diagnostic-targeted treatment and scarcity of clear clinical evidence on the clinical utility of NGS in oncology. It is therefore not surprising that NGS tests are frequently underassessed and that no standardised evaluation practices for NGS exists among HTA bodies [160].

As previously described for the ASCERTAIN pricing model [100], the complexity of NGS tests requires a different approach to the development of both pricing and cost-effectiveness models for this use case. As analysing the consequences of NGS tests on quality-adjusted life years is too complex to be represented in an easily accessible global cost-effectiveness model, the primary focus of this model is on diagnostic outcomes and costs up to the treatment decision. The model allows to compare various testing strategies based on an intervention and a comparator technology for genomic profiling, i.e., an NGS technology compared to any other technology for molecular diagnostics such as single-gene immunohistochemistry tests, or targeted NGS panels. The model facilitates such analysis for any group of cancer patients eligible for therapy informed by genomic profiling. Consequently, the perspective of this model is a healthcare (provider) perspective.

Given the scarcity of previous health technology assessments, one key target group of this model are hospital/laboratory/clinical decision-makers and national payers/HTA bodies

- to obtain a high-level overview of the characteristics of different genomic diagnostics,
- get insights into early cost-effectiveness comparisons of different genomic diagnostics and,
- explore data needs for potential future, more detailed analysis.

The default parameters are supposed to introduce standardised tutorial cases for genomic diagnostics, based on previously conducted and published economic evaluations of NGS tests. For more advanced users the functionality of uploading their own parameter file is planned to conduct an early comparison of the cost-effectiveness of different genomic diagnostics by specifying their own input parameters (level 1 users). This function is also intended for other other researchers (level 1 users) who want to use the model as a potential starting point for economic evaluation of genomic profiling.

4.3. Cost-Effectiveness Threshold and Threshold Modifier Model

4.3.1 Rationale and Purpose

Reimbursement decision-making is based on the assessment of available alternatives against predefined criteria. These criteria vary across countries, reflecting differences in healthcare system structures, policy priorities, and available resources. Among these, cost-effectiveness is one of the most commonly applied criteria, as it allows decision-makers to assess whether an intervention delivers sufficient health benefits relative to its costs. Countries that incorporate cost-effectiveness into reimbursement decisions typically operationalise this assessment through the implicit or explicit use of a cost-effectiveness threshold (CET).

The CET represents the maximum acceptable incremental cost-effectiveness ratio (ICER) for reimbursement. The ICER itself is a valuable estimate, as it reflects the efficiency with which an intervention generates additional health outcomes compared to existing alternatives. However, theoretically, comparing the ICER to the CET indicates whether a new intervention is considered more efficient (ICER below the threshold) or less efficient (ICER above the threshold) in producing health gains than interventions currently funded within the healthcare system [161,162]. Robust evaluation of pIHTs supports the effective management of healthcare innovation while balancing accessibility and affordability [163].

To determine the CET there are two main theoretical approaches: the demand-side and supply side approach. The demand-side approach is grounded in welfare economics and emphasises the importance of societal preferences in healthcare decision-making. It assumes that the value of health gains should be determined by what individuals are willing to pay for them, regardless of existing budget constraints [164,165]. In contrast, the supply-side approach focuses on the efficient allocation of limited healthcare resources. Rather than relying on societal willingness to pay, it argues that thresholds should reflect health opportunity costs, the health benefits that are foregone when resources are diverted from existing interventions to fund new ones. From this perspective, societal preferences are considered less relevant for setting thresholds, as healthcare budgets are fixed and difficult to adjust [164–168].

Alongside these theoretical approaches, two more practical methods have been described for estimating CETs. One widely used approach links the threshold to a country's GDP per capita, typically suggesting a threshold in the range of one to three times GDP per capita per QALY gained [169]. Another method, proposed by Pichon-Riviere et al., estimates thresholds using per capita health expenditure in combination with life expectancy (or healthy life expectancy), thereby more directly linking healthcare spending to expected health outcomes [170].

However, in practice, no "gold standard" exists for determining CETs. Considerable variation remains in how CETs are established, and those applied in practice often do not align with their theoretical foundations. Substantial variation persists across countries in both the methods used to estimate CETs and the values ultimately applied, and these often diverge from their stated theoretical foundations [171]. While some jurisdictions formally endorse a supply-side or demand-side rationale, the thresholds used in decision-making are frequently shaped by political, institutional, and pragmatic considerations. As a result, CETs may reflect compromises between economic theory, budgetary realities, and broader policy objectives rather than a strictly defined conceptual approach. For example, England and Wales generally adopt a supply-side perspective when approaching their cost-effectiveness threshold and have recently increased the applied range to £25,000–£35,000 per health gain [172]. However, empirical

estimates of health opportunity costs indicate that the threshold
consistent with this perspective would be considerably lower, approximately £12,936 estimated by Claxton et al. in 2015 [173].

Moreover, establishing CETs strictly on a theoretical basis requires substantial analytical effort, as well as extensive data and/ or research. Limited reproducibility further constrains these approaches, reducing their practicality and making real-world implementation challenging. As a result, many countries rely instead on GDP per capita–based thresholds as a pragmatic alternative. However, this approach has generated considerable controversy. Critics argue that GDP-based thresholds lack a clear conceptual link to healthcare budgets, system efficiency, technical capacity, and societal preferences or values. Despite these limitations, the simplicity, transparency, and ease of adoption of GDP-based thresholds continue to make them attractive to policymakers, particularly in settings with limited capacity [173–176].

CETs are often differentiated through the application of modifiers. These modifiers capture additional elements of value beyond QALYs and are intended to ensure that value-for-money assessments align more closely with broader health system objectives and societal preferences. Such elements typically reflect patient and public values as well as country-specific policy priorities, and commonly include considerations such as disease severity, rarity, and unmet medical need [177,178]. In practice, modifiers may be operationalised either through explicit adjustments to CET levels or through the application of differential weights to QALYs. Although an increasing number of jurisdictions are incorporating modifiers into their reimbursement frameworks, the underlying rationale for these adjustments is frequently insufficiently specified and often lacks robust empirical justification.

ASCERTAIN does not aim to establish a single "gold standard" for CET determination; rather, it seeks to support the ongoing debate on how thresholds should be defined, acknowledging that each approach has its own advantages, limitations, and context-specific relevance. Furthermore, ASCERTAIN contributes to the use of modifiers by proposing a framework of a flexible threshold that can be adapted to public and patient preferences, thereby allowing threshold values to better reflect real-world values.

4.3.2. ASCERTAIN Flexible Threshold Framework

The ASCERTAIN flexible threshold framework is designed to support more context-sensitive reimbursement decision-making by allowing the CET to adapt to the value profile of individual IHTs. Rather than relying on a fixed threshold, the framework provides a structured and transparent mechanism for adjusting a reference CET based on empirically derived public and patient preferences.

By explicitly incorporating additional value considerations into threshold setting, the framework enables decision-makers to differentiate between interventions based on characteristics that extend beyond cost-effectiveness alone. At the same time, calibration and constraint mechanisms are integrated to ensure that any adjustments remain policy-feasible and consistent with underlying health opportunity costs. In this way, the framework complements existing threshold-setting practices while improving transparency, consistency, and empirical justification in the application of modifiers.

Operationally, the framework consists of four core components:

- Reference CET: Unadjusted cost-effectiveness threshold that serves as the baseline for all subsequent adjustments.

- Preference weights: Quantify the relative importance assigned to specific decision criteria and jointly determine the direction and magnitude of threshold adjustments.
- Modifier constraints: Define the minimum and maximum bounds within which the threshold may vary and specify the responsiveness of the adjustment.
- Calibration factor: Anchors the adjusted threshold to the reference level by correcting for the average effect of the preference weights, thereby preventing systematic drift.

4.3.2.1. Reference CET

The reference CET represents the unadjusted threshold that serves as the starting point for the CET framework and forms the basis for all subsequent adjustments. Any threshold value may be specified as the reference, allowing the CET framework to be applied across diverse healthcare systems and policy environments. Importantly, this ensures that the CET framework can accommodate existing national thresholds without requiring them to be redefined.

For countries in which a CET has already been formally established, the CET framework does not seek to replace or modify the existing benchmark. Instead, it builds upon the reference CET to enable value-based adjustments that reflect additional decision criteria. In settings where no formal CET exists, a reference value may be selected using available estimation approaches. The most pragmatic and readily implementable options include thresholds based on GDP per capita and the method proposed by Pichon-Riviere et al., which combines per-capita healthcare expenditure with life expectancy [170].

Although these approaches provide only approximations and may not fully reflect true health opportunity costs, they offer a clearly defined and transparent starting point. Using such reference values within the CET framework allows decision-makers to explicitly assess how societal preferences influence the resulting CET.

4.3.2.2. Preference weights

Preference weights represent the relative importance assigned to different characteristics of health interventions and constitute the primary driver of threshold adjustment within the CET framework. These weights are derived from coefficients estimated in a multi-country discrete choice experiment (DCE). The DCE elicits trade-offs across key decision criteria, including disease severity, rarity, unmet medical need, treatment effectiveness, uncertainty surrounding effectiveness, budget impact, and environmental impact.

Importantly, not all criteria included in the DCE are intended to function as threshold modifiers, and the CET framework does not prescribe which attributes must be applied. Instead, users retain flexibility to include or exclude specific criteria based on their policy context, institutional setting, and decision requirements.

4.3.2.3. Modifier constraints

Modifier constraints define the extent to which the cost-effectiveness threshold may be adjusted in response to preference weights. While the CET framework is designed to allow thresholds to reflect societal values, unconstrained adjustments could lead to implausibly large deviations from the reference CET. Establishing explicit limits therefore ensures that flexibility is balanced with stability.

These constraints specify the minimum and maximum range within which the threshold may vary and determine the responsiveness of the adjustment to the combined effect of the

preference weights. Constraint parameters can be set by the user, allowing adaptation to national policy priorities while preventing extreme threshold shifts and preserving meaningful differentiation across interventions.

4.3.2.4. Calibration factor

When applied without correction, preference weights are likely to result in predominantly upward adjustments of the CET. This reflects the structure of DCEs, which typically estimate preferences relative to less preferred baseline levels, leading to largely positive coefficients. A systematic upward shift in the threshold would be inconsistent with underlying health opportunity costs and could undermine the efficient allocation of healthcare resources.

To address this, the framework incorporates a calibration factor that corrects for the average effect of the preference weights before adjustments are applied. By accounting for this tendency, calibration anchors the adjusted threshold to the reference CET and prevents unintended upward drift, ensuring that value-based flexibility does not compromise system-level efficiency.

4.4. Reimbursement Models

4.4.1 Rationale and Purpose

Reimbursement decision-making for IHTs requires balancing uncertainty, requiring trade-offs between clinical benefits, financial sustainability, and societal values. At market entry, strong evidence on real-world effectiveness, long-term outcomes, and budget impact is inherently limited, leading to decision uncertainty [179,180]. Although randomised controlled trials provide evidence on clinical performance, uncertainty often remains regarding long-term outcomes and the generalisability of trial results to routine clinical practice. In addition, considerable financial uncertainty persists at market entry, as budget impact analyses and economic evaluations rely on assumptions and projections that are themselves subject to uncertainty [181,182].

To address these challenges, managed entry agreements (MEAs) can be used as policy instruments to support reimbursement decision-making under uncertainty. MEAs are contractual arrangements between healthcare payers and health technology developers that enable market access and reimbursement under predefined conditions. These agreements may specify payment levels, covered cost components, and the timing of payments, and are widely used as pragmatic tools to manage and share risk at the time of market entry [183]. By allowing reimbursement decisions to be made despite residual clinical and financial uncertainty, MEAs have the potential to support innovation, improve patient access to IHTs, and enhance financial sustainability by increasing the predictability of healthcare expenditures [183–185].

MEAs are commonly classified into two broad categories: finance-based and outcome-based agreements (Table 2). Finance-based MEAs rely exclusively on financial mechanisms, such as discounts, expenditure caps, or price–volume arrangements, and primarily aim to mitigate financial uncertainty [186,187]. In contrast, outcome-based MEAs link reimbursement to the achievement of predefined clinical outcomes in real-world practice, thereby directly addressing uncertainty related to clinical effectiveness [186]. In both cases, a share of the financial or clinical risk associated with the adoption of new health technologies is transferred from the healthcare payer to the health technology developer [182,184,188].

Table 2: Managed entry agreement types

Financial- based agreements		Outcome-based agreements	
· Simple discount: confidential price reduction from list price · Expenditure caps: HTD covers costs beyond spending limit · Price-volume agreements: Price decreases when volume thresholds are exceeded		· Pay-by-performance: Payment linked to achieved patient outcomes. · Coverage with Evidence Development (CED): Temporary coverage while collecting additional effectiveness evidence. · Conditional Treatment Continuation (CTC): Reimbursement continues only for responding patients.	
Advantages	**Limitations**	**Advantages**	**Limitations**
· Simple to implement · High budget predictability · Low administrative burden · Low transaction costs	· Do not address clinical uncertainty · No additional evidence generation · Weak link to treatment value · Limited transparency	· Address clinical uncertainty · Align payment with real-world value · Generate effectiveness evidence	· Operationally complex · Outcome attribution can be difficult · High data and monitoring requirements · Delayed financial predictability

Table: Overview of financial-based and outcome-based Managed Entry Agreements, including key characteristics, advantages, and limitations [184,188–195].
Abbreviation: HTD, health technology developer.

Despite the conceptual appeal of MEAs, selecting and designing appropriate agreements remain challenging for decision-makers, as finance-based and outcome-based arrangements each present distinct advantages and limitations. The anticipated impact, feasibility, and trade-offs associated with alternative agreement structures are often uncertain prior to implementation. Structured, model-based ex-ante analyses that explore the expected performance of alternative designs therefore represent a promising approach to strengthening MEAs as policy instruments for managing clinical and financial uncertainty.

ASCERTAIN adopts a more integrated, lifecycle-oriented approach to economic decision-making by operationalising MEAs within a unified ex ante modelling MEA framework. Rather than treating MEAs as purely contractual instruments, this MEA framework translates their core economic mechanisms into model assumptions that directly affect costs, outcomes, and decision uncertainty. By enabling alternative MEA designs to be explicitly specified, implemented, and compared under identical clinical assumptions prior to real-world adoption, ASCERTAIN allows their expected impact on cost-effectiveness, budget impact, and financial risk to be assessed ex ante. This approach supports more informed agreement design and enhances the transparency, consistency, and adaptability of reimbursement decision-making across the health technology lifecycle.

4.4.2. ASCERTAIN Managed Entry AGreements

Building on the rationale outlined above, ASCERTAIN operationalises MEAs within a unified ex ante modelling MEA framework that enables alternative agreement designs to be explicitly specified in terms of their key economic parameters, implemented within the model, and compared under identical clinical assumptions prior to real-world adoption. Rather than replicating contractual details or legal arrangements, the MEA framework focuses on translating the core economic mechanisms of MEAs into model assumptions that directly influence costs and decision uncertainty. By embedding these mechanisms within cost-effectiveness and budget impact models, ASCERTAIN allows the expected consequences of alternative MEA designs to be assessed in terms of incremental cost-effectiveness ratios, budget impact, and the distribution of financial risk.

The ASCERTAIN MEA framework distinguishes between financial-based and outcome-based agreements, while additionally incorporating value of information methods to assess and manage decision uncertainty within a unified modelling structure.

Financial-based MEAs are modelled in ASCERTAIN by modifying the list price of the technology according to predefined contractual rules. The MEA framework supports a range of commonly used financial arrangements, including simple discounts, fixed rebates, expenditure caps, and price–volume agreements.

Simple discount agreements are represented as proportional or absolute reductions from list prices and can be specified at different levels, including per unit, per patient, or as a fixed total rebate over a defined period. Expenditure caps and price–volume agreements are modelled using threshold-based mechanisms, whereby spending, treatment volume, or the number of treated patients exceeding a predefined limit triggers rebates or reduced prices for the excess share.

Although financial agreements differ in their contractual basis, within the ASCERTAIN MEA framework they are reduced to a common set of underlying components that allow them to be operationalised within a single modelling structure. Specifically, each agreement is represented by: (i) the relevant threshold, (ii) the basis on which the threshold is assessed (spending-, unit-, or patient-based), and (iii) the rebate or net price applied beyond the threshold. This harmonised representation enables systematic comparison of alternative financial-based MEA designs in terms of their effects on budget impact, effective net prices, and cost-effectiveness outcomes.

While financial-based agreements primarily address financial uncertainty, the ASCERTAIN MEA framework is designed to be extensible to outcome-based MEAs that link reimbursement to clinical outcomes. Within the ASCERTAIN MEA framework, outcome-based agreements are decomposed into their core components and operationalised within the same unified modelling structure as financial-based agreements. Outcome-based agreements are operationalised using simple endpoints, such as overall survival (OS) or progression-free survival (PFS), assessed at predefined time points. By default, the proportion of patients achieving these outcomes is derived from the randomised controlled trial evidence underpinning the cost-effectiveness model, although alternative user-defined values can be specified to reflect real-world assumptions.

Reimbursement rules (thresholds) are applied conditional on whether patients meet the outcome criteria at each assessment point, with the model explicitly determining, for each simulated patient, whether the outcome threshold is achieved. Based on this, different payment rules are applied, such as assigning different net prices, rebates, or continuation decisions to responders and non-responders. At the population level, this results in an effective net unit price that reflects the proportion of patients achieving the specified outcomes and the corresponding payment structure. This approach supports the modelling of pay-for-performance and conditional

treatment continuation agreements, including designs with multiple outcome assessment time points, by applying sequential outcome-based adjustments within the model.

Outcome-based MEAs are implemented using the same structural principles as financial-based agreements, enabling consistent ex ante comparison of their effects on costs, cost-effectiveness, and decision uncertainty.

To further characterise decision uncertainty associated with the reimbursement of pIHTs, ASCERTAIN incorporates value of information (VOI) analysis alongside standard cost-effectiveness and budget impact assessments. VOI methods quantify the expected value of reducing uncertainty in model parameters, thereby identifying whether additional evidence collection is likely to improve decision-making and whether the benefits of further research outweigh its costs.

This functionality directly supports the assessment of coverage with evidence development (CED) arrangements, in which temporary reimbursement is granted while additional evidence on outcomes, utilisation, or effectiveness is collected after market entry. By evaluating the expected reduction in decision uncertainty under alternative evidence-generation scenarios, ASCERTAIN enables ex ante assessment of whether CED represents a preferable strategy compared with immediate full reimbursement or rejection.

Crucially, the reimbursement model adopts a lifecycle-oriented approach to economic decision-making by embedding VOI analysis, MEA design, and evidence generation within a single analytical framework. The same model structure used at the initial reimbursement decision can be updated as post-launch evidence becomes available, supporting consistent reassessment of cost-effectiveness, budget impact, and residual uncertainty over time. This approach addresses well-recognised practical and methodological challenges in translating new evidence into updated economic evaluations and strengthens the role of MEAs as policy instruments for managing uncertainty across the technology lifecycle.

5. ACCESS2MEDS WEB TOOL

5.1. PURPOSE OF THE WEBTOOL

The ASCERTAIN web-based tool serves as the central interface through which stakeholders can explore and apply the ASCERTAIN Framework and its underlying health-economic, pricing, and reimbursement models. The tool operationalises the methodological foundations and translates them into an accessible, structured and transparent workflow for policy assessment. It supports decision-makers, HTA bodies, payers, clinicians, researchers, and patient representatives by providing a coherent environment that guides users from model selection to interpretation, sharing and further use of results.

The purpose of the tool is to support evidence-informed policy decisions under conditions of uncertainty, evolving evidence, and heterogeneous national contexts. To achieve this, it offers an integrated assessment workflow: users begin by defining an assessment (either using a single model or a full multi-model analysis), are guided through model recommendations based on user preferences, and are assisted through the parameterisation and execution of the selected models. Interactive guidance elements help users understand how specific models relate to each other, what types of evidence are required, and how model outputs feed into

subsequent analyses. By structuring the assessment as a series of clearly defined stages—selection, configuration, execution, review, and sharing—the tool helps embed consistency, transparency, and methodological alignment within and across assessments.

The tool is designed for different levels of expertise. Users with policy or clinical backgrounds can rely on default values, pre-filled parameters, recommendations and explanatory notes, whereas analysts can make use of more fine-grained configuration options, CSV import mechanisms, and the possibility to re-run or iteratively adjust models. Template values and model-specific defaults, including cross-model consistent inputs and use-case-specific parameter presets, reduce the technical burden and ensure methodological coherence.

A key function of the tool is to support collaboration and shared assessments. Authenticated users can invite co-users, assign roles, and jointly work on a shared assessment. If users operate without an account, the tool remains accessible but clearly indicates that progress will not be saved and warns users before they close a session.

The tool also supports dissemination and further policy work. Users can export model results, download structured output tables, or generate shareable URLs for controlled access to assessment results. These features enable decision-makers to incorporate ASCERTAIN outputs into policy reports, payer negotiations, or clinical discussions. Throughout all functions, the tool remains aligned with the ASCERTAIN values of transparency, reproducibility, stakeholder involvement, and accessibility, while adhering to strict GDPR and data governance principles.

5.2. Technical Implementation

The technical implementation of the ASCERTAIN web-based tool is based on a modular and layered architecture that ensures reliability, scalability and methodological transparency. All components rely exclusively on open-source and licence-free technologies, which supports long-term accessibility, auditability and collaborative development across the consortium and external stakeholders.

At the infrastructure level, the tool operates on a lightweight Kubernetes distribution (k3s) that manages containerised services. This orchestration layer provides automated scaling, service discovery and continuous health monitoring. It allows several model computations to run at the same time, which is essential for scenario exploration and multi-model analyses. Kubernetes also ensures that the computational environment remains stable under varying workloads while supporting smooth updates and deployment processes.

The Compute API Layer provides the execution environment for all ASCERTAIN models. Each model is implemented in R and exposed through Plumber-based REST interfaces. The models run in isolated compute containers that are coordinated through Valve, a Rust-based process handler designed to support efficient multi-process execution. This design enables users to create several model instances within a single assessment and to re-run models with adjusted parameters without interference between processes. It also ensures reproducibility and a clear separation between application logic and computational tasks.

The Application Layer is implemented in Python using Flask. It processes user interactions, prepares model inputs, validates parameters and coordinates the execution of one or several models. This layer also handles authentication, assessment management, collaborative editing, user roles and session-specific behaviours such as warnings before closing a page or prompts to log in when attempting to save work. Built-in validation routines ensure that parameter

values follow the constraints defined during model development and that shared inputs remain consistent across models.

Parameter management is handled by a dedicated subsystem. It offers predefined default values, use-case-specific presets and shared inputs that facilitate cross-model consistency. The subsystem also generates downloadable CSV templates that users can edit offline. Users may upload these templates or provide their own CSV files containing technical data such as mortality tables or cost information. CSV files uploaded by authenticated users are stored only within the corresponding assessment and remain accessible exclusively to that user and to collaborators invited into the same assessment. The uploaded data contains no personal or patient-level information and is not shared across assessments or reused elsewhere. All files are checked for completeness and internal consistency before being passed to the compute services.

The Presentation Layer uses server-rendered Jinja2 templates delivered through Flask together with interactive JavaScript components. It guides users through all stages of the workflow, including the start page, the model selection assistant, parameter configuration, model execution and the results interface. Tooltips, contextual information boxes and dedicated explanation elements support users in understanding the role of each model and the meaning of parameters and outputs. The interface is structured to remain intuitive for first-time users while offering sufficient flexibility for experienced analysts.

Security and data protection considerations are integrated into all layers of the architecture. Authentication, role-based authorisation, secure session handling and audit logging follow the requirements defined in the project's data-protection framework. The system stores no clinical or patient-related information. The only personal data processed are user account details such as name and email address, which are required solely for authentication and collaborative features. These data are not used in any analytical process and remain restricted to their intended purpose. In addition, uploaded CSV files do not contain any personal or patient-level information and consist exclusively of technical data relevant for model execution, such as mortality tables or cost parameters. CSV files remain confined to the specific assessment of the authenticated user and are never shared or made accessible across different assessments or users.

Continuous Integration and Deployment workflows are implemented through GitLab. Automated build pipelines, testing routines and deployment processes ensure reliable version control and consistent behaviour across development, test and production environments. Containerised service definitions allow reproducible deployment and facilitate maintenance of the system as components evolve.

The overall architecture is designed for extensibility. New models developed during the project can be integrated as independent compute services without major modifications to existing components. The user interface can be expanded to incorporate additional assessment types, analytical tools or collaboration features. This modular structure ensures that the ASCERTAIN tool can evolve in a sustainable manner and remain robust beyond the duration of the project.

5.3. User Journey and Workflow

The user journey within the ASCERTAIN web-based tool is designed as a structured, transparent, and guided workflow that supports diverse user groups—from policy stakeholders to analysts—in completing assessments efficiently and consistently. The workflow follows a sequence of clearly defined stages that reflect how users interact with the underlying ASCERTAIN Framework and models, ensuring alignment between methodological requirements, evidence needs, and the resulting policy insights.

1. Entry and Initial Navigation

Users begin at the start page, which introduces the purpose of the tool and provides access to either create a new assessment or continue working on an existing one (if authenticated). Informational elements, including tooltips and model-explanation components, ensure that users understand the scope and purpose of the available model types. Unauthenticated users are informed that their session will not be saved and receive warnings if they attempt to close the page before completing their work.

2. Assessment Setup and Model Selection

The workflow continues with the model selection assistant, which supports users in identifying suitable models based on their policy context, preferences, and evidence availability. Users may choose:

- a single-model assessment, or
- a multi-model analysis, where several ASCERTAIN models are executed together.

The assistant highlights model characteristics, required input data, and methodological fit. Based on user answers, the system generates model recommendations while allowing full manual override. Users may review model descriptions, links to methodological documentation, and implications of selecting specific models. Model recommendations are based on a rule-based selection logic (not machine learning), ensuring transparent and predictable results.

3. Parameter Configuration and Data Input

Once models are selected, users proceed to a structured parameter configuration workflow. The tool guides users through model-/country-specific and cross-model parameter inputs, enriched with:

- predefined default values,
- use-case-specific presets,
- guidance elements explaining each parameter,
- validation warnings for inconsistencies or missing data.

Users may optionally download preformatted CSV templates, edit them offline, and upload them back into the tool. Any uploaded CSV data is used exclusively within the specific assessment and is discarded afterward. Non-editable fields ensure cross-model consistency and adherence to methodological constraints.

4. Model Execution and Monitoring

After configuration, users trigger model execution. The tool handles all orchestration of R-based models via parallel compute processes. Progress indicators provide transparency during execution. Users may:

- run a model once,
- create multiple variants for scenario comparisons,
- adjust parameters and re-run models iteratively.

All executions are logged within the session (or persistently for authenticated users), allowing reproducibility and structured iteration.

5. Results Exploration and Interpretation

Once model runs are completed, users are directed to the results section. This interface provides:

- structured outputs such as tables, charts, and model-specific visualisations,
- comparative views for multi-model assessments,
- contextual explanations supporting interpretation,
- access to export functions (CSV, images, copy-ready tables).

Model outputs are framed within the ASCERTAIN Framework concepts, enabling decision-makers to understand uncertainty, cost-effectiveness implications, and potential policy outcomes.

6. Collaboration, Sharing, and Reporting

For authenticated users, the workflow supports collaboration and dissemination:

- inviting co-users to view or edit the assessment,
- assigning roles (editor, viewer),
- generating shareable URLs with controlled access,
- exporting assessment results for reporting.

These features support iterative co-creation, peer review, and integration of ASCERTAIN outputs into broader decision-making contexts.

7. Session Conclusion and Next Steps

The user journey ends with either closing the assessment or generating further scenarios. Unauthenticated users are reminded that data will not be saved. Authenticated users may archive the assessment or return later for additional analysis.

6. Discussion

6.1. Summary of Findings

This report highlights how the ASCERTAIN framework's integrated models, access-based pricing, cost-effectiveness, budget impact, and reimbursement, interact to provide a comprehensive understanding of healthcare interventions. Key findings show that coordinated use of these models enhances decision-making by aligning pricing, value, affordability, and policy considerations. The framework's adaptability and stakeholder-informed design ensure that results are context-sensitive, actionable, and support improvements in patient access while maintaining financial and operational feasibility.

From Section 2 onwards, this report further examines how the different components of the ASCERTAIN framework contribute to the project's objectives and to improved patient access. In particular, the analysis focuses on three key elements: the framework's core values, the analytical models, and the supporting web-based tool.

The consideration of core values provides the conceptual foundation for the ASCERTAIN framework. These values guide the design and application of the analytical models and ensure alignment with the project's objective of improving equitable and sustainable patient access. By explicitly incorporating principles such as transparency, fairness, efficiency, and stakeholder relevance, the framework supports decision-making that takes into account both economic evidence and broader health system priorities. This approach helps ensure that pricing, reimbursement, and access decisions reflect not only value and affordability but also policy objectives and societal considerations.

The analytical models constitute the methodological basis of the framework. At a general level, the models capture key dimensions that influence patient access to healthcare interventions,

including value, affordability, pricing, and reimbursement conditions. Their combined application allows for the analysis of interactions between these dimensions and supports a more comprehensive assessment of policy options. At a more specific level, individual models address distinct components of the decision-making process. Cost-effectiveness models assess the value of healthcare interventions relative to existing alternatives. Budget impact models analyse the financial implications of adoption for healthcare systems. Access-based pricing models explore pricing strategies that align product prices with value and health system affordability. Reimbursement-related analyses examine the policy and system conditions that determine whether interventions become available to patients in practice. Together, these models provide complementary insights that support balanced decisions between value, affordability, and access. The integrated use of these models enables a structured assessment of trade-offs between pricing, value, and budgetary constraints. This integrated perspective supports decision-makers in identifying strategies that can improve patient access while maintaining the sustainability of healthcare systems.

The ASCERTAIN web-based tool facilitates the practical application of the framework. The tool integrates the different models within a single digital environment and allows users to explore scenarios, input data, and analyse the implications of alternative assumptions. By providing a user-friendly interface, the tool improves the accessibility and usability of the framework for policymakers, health technology assessment bodies, researchers, and other stakeholders. In addition, the web tool enhances transparency by clearly documenting model inputs, assumptions, and outputs. It also supports stakeholder engagement by enabling users to test alternative scenarios and better understand the implications of different policy choices. Through these functions, the tool strengthens the framework's role as a decision-support instrument.

Overall, the combination of clearly defined core values, integrated analytical models, and a practical implementation tool enables the ASCERTAIN framework to support more informed and transparent decision-making. By linking value assessment, pricing considerations, affordability analysis, and reimbursement conditions, the framework contributes to the development of policies that improve patient access to healthcare innovations while maintaining the sustainability of healthcare systems.

6.2. Limitations & Knowledge Gaps

While the framework provides a robust, integrated approach to analysing pIHTs, several limitations and knowledge gaps remain. Data availability and quality may vary across regions, which can affect the accuracy and comparability of model outputs. In addition, certain model assumptions may not fully capture local healthcare dynamics or rapidly evolving policy environments. Although interactions between the different models are structured within the framework, they may not fully reflect complex real-world trade-offs or unintended systemic effects. Addressing these gaps through ongoing data collection, validation, and stakeholder engagement will be important to further strengthen the framework' and support its long-term applicability.

With regard to the application of the core values, one limitation concerns the operationalisation of normative principles within analytical models. While values such as transparency, fairness, and efficiency guide the overall design of the framework, translating these principles into measurable indicators or decision criteria can be challenging. Differences in stakeholder perspectives and national policy priorities may also influence how these values are interpreted and weighted in practice. As a result, the application of core values may vary across contexts, potentially affecting the consistency of the framework's outputs. Further methodological work

may therefore be required to refine how these values are systematically incorporated into analytical processes and decision-making.

Limitations and knowledge gaps also arise in relation to the analytical models themselves. At a general level, the models depend on assumptions, parameter estimates, and data inputs that may not always be available or comparable across healthcare systems. Variations in clinical practice, epidemiology, healthcare costs, and reimbursement mechanisms can affect the transferability of model results between settings. In addition, the integration of multiple models introduces methodological challenges, particularly in ensuring consistency of assumptions and avoiding the propagation of uncertainty across model components.

At a more specific level, each model may face particular constraints related to data availability, methodological choices, or contextual relevance. Cost-effectiveness analyses may be limited by uncertainties in clinical evidence or long-term outcome projections. Budget impact analyses depend on assumptions regarding uptake rates, patient populations, and health system capacity, which may change over time. Access-based pricing models rely on assumptions about value assessment frameworks and market dynamics that can vary substantially between countries. Similarly, analyses related to reimbursement and access conditions may be influenced by institutional and regulatory factors that are difficult to capture fully in quantitative models. These limitations highlight the importance of interpreting model outputs as decision-support inputs rather than definitive predictions.

Finally, some limitations relate to the technical implementation of the ASCERTAIN web-based tool. While the tool aims to enhance accessibility and transparency, its functionality depends on the quality and completeness of the data provided by users. Differences in user expertise may also influence how models are applied and how results are interpreted. In addition, integrating multiple models within a single digital platform presents technical challenges related to interoperability, maintenance, and updating of model components as new data and methodologies become available. Ensuring that the tool remains adaptable, user-friendly, and compatible with evolving analytical approaches will therefore require ongoing technical development and user feedback.

Overall, these limitations and knowledge gaps do not diminish the value of the ASCERTAIN framework but highlight areas where further research, methodological refinement, and stakeholder collaboration can strengthen its robustness and practical relevance. Continued validation, data improvement, and iterative development will be important to ensure that the framework remains responsive to the evolving needs of healthcare decision-makers and contributes effectively to improving patient access to healthcare innovations.

6.3. Conclusion & Next Steps

The ASCERTAIN framework demonstrates the value of integrating multiple analytical perspectives to support evidence-informed healthcare decision-making. By combining access-based pricing, cost-effectiveness analysis, budget impact assessment, reimbursement considerations, and cost-effectiveness thresholds within a single structured framework, the approach enables a more comprehensive assessment of healthcare interventions than would be possible through individual models applied in isolation. The coordinated use of these components allows decision-makers to consider the relationships between value, affordability, pricing strategies, and policy conditions, thereby supporting more balanced and transparent decisions regarding patient access to pIHTs.

An important strength of the framework lies in its integrated and stakeholder-informed design. The interaction between models allows for the exploration of how changes in pricing, reimbursement conditions, or health system constraints may influence both the value and the financial feasibility of introducing new interventions. In addition, the incorporation of core values

and stakeholder perspectives helps ensure that the analytical outputs remain relevant to policy priorities and health system objectives. Together with the supporting web-based tool, the framework provides a practical environment in which different scenarios and assumptions can be explored in a transparent and accessible manner.

Through this integrated approach, the ASCERTAIN framework contributes to improving the evidence base for decisions related to pricing, reimbursement, and patient access. By explicitly linking value assessment with affordability and policy considerations, it supports strategies that aim to improve patient access while maintaining the financial sustainability of healthcare systems. At the same time, the framework is designed to be adaptable to different healthcare contexts, recognising the diversity of institutional arrangements, policy priorities, and data availability across countries and health systems.

Looking ahead, several next steps will be important to further strengthen the framework and support its broader application. First, continued refinement and validation of the models will be necessary as new evidence and data become available. Updating model parameters and assumptions will help ensure that analyses remain robust and reflective of evolving clinical evidence, healthcare costs, and policy environments. Additional validation exercises across different settings may also support the assessment of model transferability and improve confidence in the framework's outputs.

Second, further engagement with stakeholders, including policymakers, health technology assessment bodies, healthcare providers, industry representatives, and patient organisations, will be essential. Expanding stakeholder participation can provide valuable insights into how the framework can best support real-world decision-making processes and ensure that the models and tools remain aligned with user needs and policy priorities. Such engagement may also support the identification of additional use cases and opportunities for practical implementation.

Third, ongoing development of the technical infrastructure, including the ASCERTAIN web-based tool, will be important to enhance usability, transparency, and accessibility. Improvements may include the integration of additional data sources, expanded scenario analysis capabilities, and user support features that facilitate interpretation of results. Maintaining flexibility within the technical architecture will also allow the framework to evolve alongside methodological advances and emerging healthcare challenges.

Finally, future work may explore opportunities to extend the framework to additional types of healthcare technologies or policy questions. This could include adapting the models to emerging areas such as innovative therapies, personalised medicine, or new payment and reimbursement models. Strengthening the framework's adaptability will help ensure that it remains relevant in rapidly evolving healthcare environments.

Overall, the ASCERTAIN framework provides a structured and integrated approach to analysing healthcare interventions and their implications for pricing, reimbursement, and patient access. Continued methodological refinement, stakeholder collaboration, and technical development will be key to maximising its long-term value as a decision-support framework for health systems seeking to balance innovation, access, and sustainability.

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