
IMPACT HTA
Improved methods
and actionable tools
for enhancing HTA

Consortium Membership

Leading Partner:

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Contents

Key Achievements

WP2

HTA staff will now be able to undertake quick, robust cost-effectiveness evaluations using local data. The Discretely Integrated Condition-Event (DICE) simulation model and all the open-source materials that support it are freely available for download at dice.impact-hta.eu. DICE models are easily modified for local adaptation and this flexibility enables sharing models across agencies and from one appraisal to the next in a given therapeutic area.

WP3

WP4

The first European common database of health and social care unit costs in nine countries is now available. The European Healthcare and Social Cost Database (EU HCSCD) is easily accessible and can be used to feed into health-economic evaluations carried out by transferring economic evaluation analyses and models across countries. It not only saves researchers' time in searching costs, but also allows cross-country comparisons and provides an understanding of the variation in costs within and across countries. The database is publicly available on the IMPACT HTA website.

WP5

HTA institutions need to take into consideration the differences between patient health state preferences and the general population preferences as the choice of value set might lead to different decisions in the context of HTA. For national contexts where patient preferences are favoured, it is feasible to combine patient preferences and national general population-based value sets. Patient preferences which show the dimensions of health-related quality of life (HRQoL) that patients consider important can be used for treatment decisions in clinical settings and in organising health care processes. Value sets derived from the generic youth-specific EQ-5D-Y can be used in economic evaluations, particularly cost utility analyses, of paediatric treatments, in the countries in which they were developed (Germany, Slovenia and Spain).

WP6

The lack of randomised data continues to be a challenge in HTA because of the substantial scope for uncertainty about the effectiveness of new health technologies, including potentially exaggerated treatment effects. IMPACT HTA has developed a set of evidence-based recommendations for the use of non-randomised studies to estimate treatment effects in HTA, including the need to justify the use for a non-randomised study, to prospectively plan such studies. Such studies should consider possible biases and how to address them and should transparently report the methods used. HTA systems need to be strengthened to allow effective appraisal of non-randomised evidence.

WP7

Recognising that the relative value of a health care technology spans across a multi-dimensional domain going beyond the classical concept of "economic efficiency" as measured by incremental cost effectiveness ratios (ICERs), two distinct contributions are made in developing and testing the IMPACT HTA Value Framework: first, a model of the parameters associated with HTA coverage recommendations has been developed and tested empirically, encompassing product- and country-specific variables, regulatory variables, critical clinical and economic evidence parameters, the role of evidence uncertainties and the importance of social value judgements. Second, informed by primary and secondary evidence, the IMPACT HTA Value Framework captures the value concerns of decision-makers and other stakeholder groups within a common framework to evaluate new medicines within the context of HTA, reflecting on what is important for HTA agency decision-makers and the broader stakeholder community.

WP8

Implementation of HTA recommendations can be challenging and the anticipated improvement in outcome might not be achieved. Hospital performance is multi-faceted and multiple hospital contextual factors can affect the ways in which health technologies are adopted. With a focus on medical devices, two toolkits were developed: the first assesses the overall hospital performance; and the second provides a methodology to assess how contextual factors affect the full implementation of a technology. The toolkits are supported by a decision model, which identifies the technologies with the same efficacy and safety but which are more subject to clinical variation and assesses different interventions with the goal of improving the performance and efficiency of healthcare delivery.

WP9

Alongside the cost of a medical intervention, the fiscal impact of productivity losses provides an additional dimension characterising the value for money of the intervention. This approach is based on the concept that an individual contributes to society and this contribution should be considered in assessing a new technology and that governments should invest in new medical technologies to increase the population's health and thereby enhance productivity. There is a strong recommendation that fiscal impact should not be used to inform rationing policies or perform cross-group comparisons among different socio-economic categories as it can lead to discrimination against the elderly and low-income subgroups.

WP10

A new appraisal framework for rare disease treatments (RDTs) was created that ensures a fair, lenient, flexible and consistent appraisal, beyond clinical and cost effectiveness in an effort to overcome the associated challenges, notably the small number of patients (which can make clinical trials challenging) and the high cost of the technology. The framework is supported by recommendations and guidance for the appropriate use of Patient-Reported Outcomes (PROs) and Outcomes-Based Managed Entry Agreements (OBMEA) with RDTs. The Appraisal Framework can be used by individual health systems in the EU (which currently use different processes described in country vignettes and beyond, or for collaborative HTA initiatives and proposes ways of collaborating, such as an international repository for OBMEA plans and reports.

WP11

Decremental cost-effective interventions imply cost-savings at the price of a reduction in efficacy compared to usual care. Some of these interventions have been found to be highly effective but are much less studied compared to interventions implying both higher costs and efficacy gains. A Discrete Choice Experiment was designed to investigate under which conditions policy-makers (or participants acting as such) might be willing to adopt decremental cost-effective interventions. A "decision-tree" based on the results of the Discrete Choice Experiment is delivered together with a Political Economy Report that addresses the broader economic, ethical and political aspects associated with the assessment and adoption of decremental cost-effective interventions. These outputs provide policy-makers with guidance on whether and under what circumstances to adopt potentially decremental cost-effective interventions.

IMPACT HTA: Context and Objectives

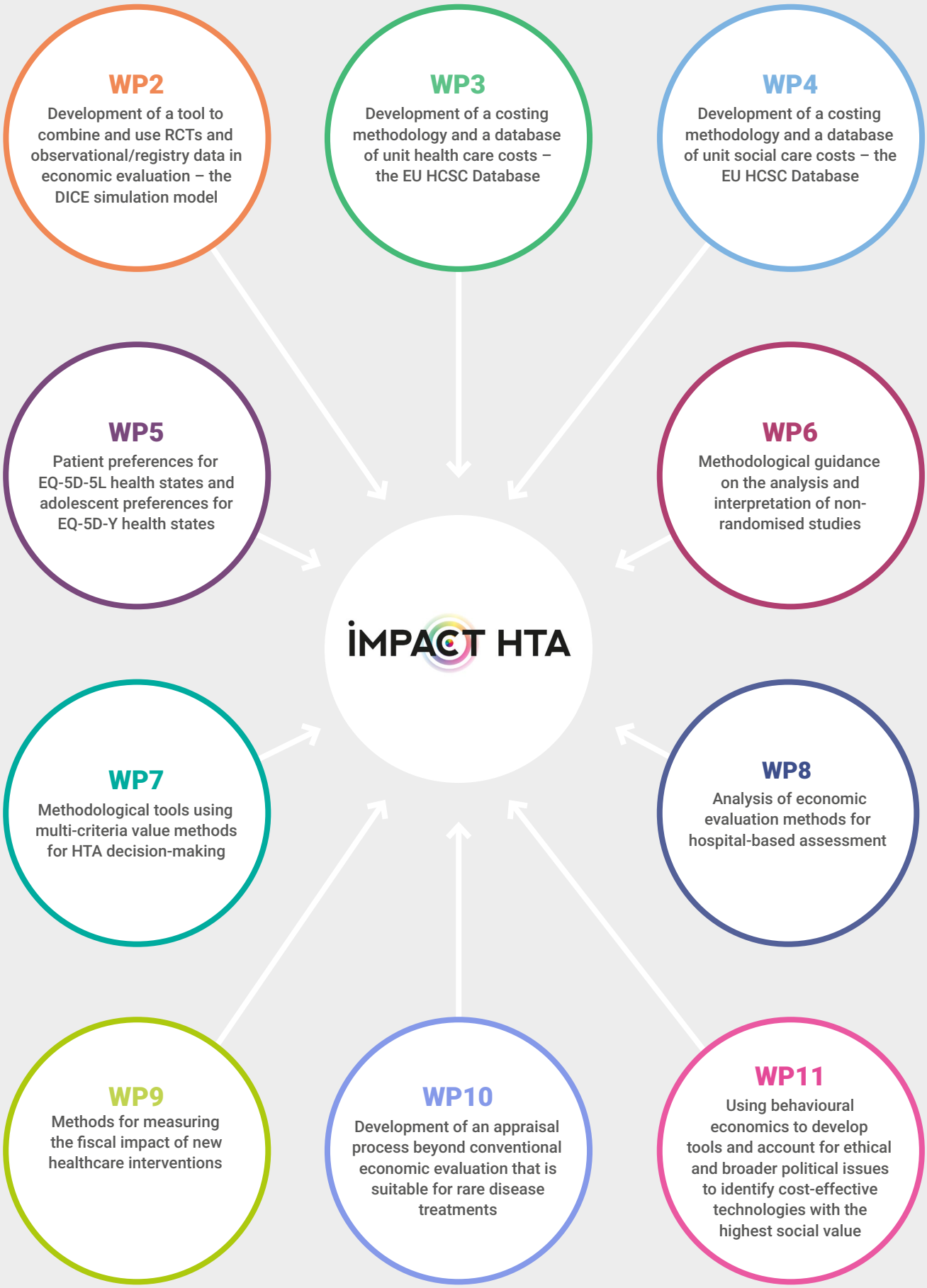
Although health and social care policy remains the responsibility of EU Member States, there is an increasing perception that there is an opportunity for improving the effectiveness and efficiency of health technology procurement by implementing cross-country collaboration in a range of activities, including Health Technology Assessment (HTA). Recent years have also seen significant changes such that data on costs and health outcomes are now available from an increasing range of sources underscoring the need for better data integration and evidence synthesis, as well as the strengthening of data generation processes for economic evaluations and the improvement in methodological quality. Based on these challenges, the overall objectives of IMPACT HTA are:

- To contribute to the understanding of variations in costs and health outcomes within and across countries, the rationale and criteria for decision-making across different settings as well as the factors and preferences that shape HTA recommendations;
- To develop and disseminate innovative methodologies, toolkits, frameworks, processes and software aiming to aid decision-making and improve efficiency in resource allocation in a number of areas including: extrapolation from RCT data; the development of a common and comparable dataset on health and social care costs across EU countries; quality of life measurement with emphasis on patient preference elicitation; a value assessment of medical technologies framework, including multi-criteria decision analysis; and guidance on how non-randomised studies can inform health economic evaluations; and
- To develop and disseminate tools facilitating EU-wide collaboration across Member State governments, HTA agencies, health care professionals, patients and the broader stakeholder community.

These objectives translate into the ten research work packages (WPs) of IMPACT HTA (Figure 1, see p7).

These as well as their achievements and expected impact are outlined in the sections that follow.

Figure 1. The IMPACT HTA Work Packages*



*WP1 is an administrative work package dealing with data management ethics.
WP12 is the synthesis and dissemination work package.

WP2 Development and application of a tool to combine and use Randomised Clinical Trials (RCT) and observational/registry data in economic evaluation

Objectives and Methodology

The main objective of this WP is to develop a new, generic and publicly accessible platform to enable direct modelling of cost-effectiveness analysis (CEA) by HTA agencies.

HTAs normally have access to data on the efficacy of health care interventions. If undertaking CEA to assess value for money, HTAs have to convert this efficacy data into life-time health benefits through extrapolation, as well as extrapolate lifetime treatment costs for the population at risk, to undertake such assessments. The first task of the WP was to provide reviews of methods to match available HTA data with secondary observational data to allow such extrapolation. These reviews highlight the available methods that could be used to facilitate and support the development of the Discretely Integrated Condition-Event (DICE) simulation model which forms the primary objective within this WP, as any modelling approach can be improved if it is supported with better data. Such up-to-date reviews are important as newer techniques are continually being developed that allow matching across sample population distributions, therefore giving a better match to the whole of the sample population rather than a single parameter extracted from the distribution.

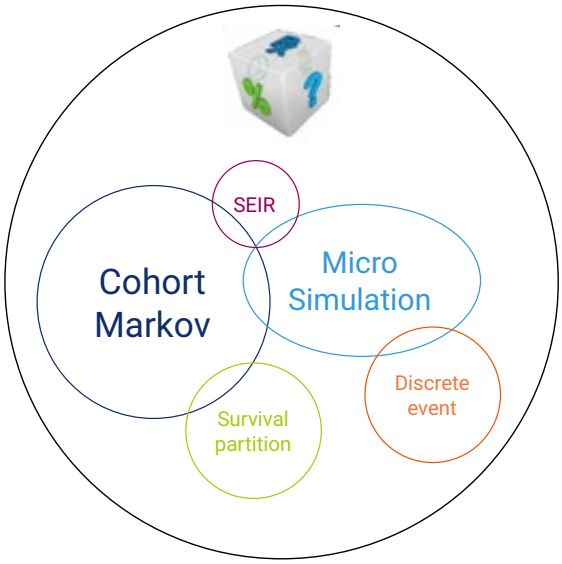
HTAs are commonly constrained by the level of resource they are able to devote to the assessment of any given intervention. This WP addresses this fundamental concern by providing guidance on the methods to be adopted to extrapolate both treatment costs and effects using data sets complimentary to RCT data, as well as providing an open-source Excel based platform that is simple, accessible and generic in its approach: the DICE simulation model.

Outputs

The DICE platform is a simple, yet sophisticated, tool that allows HTA staff to undertake quick, robust cost-effectiveness evaluations using local data with minimal training (Figure 2, see p9). The DICE model allows specification of a full choice of the type of structural CEA model to be used (either an operational Markov cohort model or a discrete event model), operates transparently through 3 Excel spreadsheets, is easily populated with local data and gives fully presentational results in the form of calculated incremental cost-effectiveness ratios. Several DICE trainings were held with HTA agencies and with academic teams involved in HTA. A website has been created as a repository of all the open-source materials, including the DICE engine, various templates, build guides, user guide, technical documentation etc. This site is freely available as an open-source site and all contents are available for download.

“The DICE platform is a simple, yet sophisticated, tool that allows HTA staff to undertake quick, robust cost-effectiveness evaluations using local data with minimal training.”

Figure 2. The DICE platform in a snapshot



1 Specification of a DICE model is done in a text *Blueprint* that enumerates:

- Dynamic conditions
- Outputs
- Events
  - Time of occurrence
  - Consequences
- Static conditions
  - Profiles
  - Interventions
  - Settings and constants
  - Other inputs

2 Implementation of a DICE model:

- Lists all elements in simple MS excel tables
- This makes it very transparent, flexible and easy to modify

3 Execution of a DICE simulation is done by:

- A simple VBA macro that reads the lists and carries out the instructions
- The VBA "engine" is free to download
- No special software ius required but can use other software (e.g., C#, Python, R).

Impact

The ease with which DICE models are modified allows for easy local adaptation of a general structure. This flexibility enables sharing models across agencies and even from one appraisal to the next in a therapeutic area. It is recommended that agencies in adopting the DICE methodology provide support mechanisms for this model sharing.

Future direction

The IMPACT HTA project successfully demonstrated that DICE simulation can be used to create complex models that provide the same results as more traditional implementation but in a simpler, more transparent, more flexible structure. By providing a much faster engine as an open-source EXCEL platform, it is hoped that the advantages of the DICE simulation can be widely leveraged and used extensively.

A further iteration of the DICE engine will include an interface for users to further adapt the model. It is hoped that an even faster engine and interface will be produced at a later stage, using an open-source language like Python. For further information on the DICE model, please visit dice.impact-hta.eu.

WP3 Developing a costing methodology and a database of unit costs

Objectives and Methodology

The main ambition of this WP is to develop an easily accessible and usable minimum common dataset of international costs in nine European countries (England, France, Germany, Italy, Poland, Portugal, Slovenia, Spain and Sweden), which can feed into health-economic evaluations carried out by transferring economic evaluation analyses and models across countries. The dataset may also be used to compare costs and to explain the factors that account for differences in health care costs across settings.

This was achieved through four specific objectives:

1. **Produce a core dataset that incorporates direct health care costs across jurisdictions;**
2. **Propose a methodological framework for computing homogenous cost data across countries in a sustainable basis over time;**
3. **Enable cost comparability across settings, including the explanation of factors that account for differences in health care costs across settings; and**
4. **Produce a core dataset including both direct and indirect costs across nine European countries.**

The methodology applied had several components. The first component consisted of designing the EU Healthcare and Social Cost Database (HCSCD) structure, based on a literature review of different costing methodologies, taking as references the manuals for economic evaluation, costing guidelines and accounting manuals of the Centre for Health Economics of the University of York. It encompassed the decision on the number and type of costing items to be included in the database, the category and subcategory each item belongs to and a number of attributes for each item. The second methodology component consisted of searching on each country's Health Ministries' and health organisations' websites to identify cost databases of costing items selected in the previous step, along with any publicly available documents describing the cost-accounting methodology used to construct them. Consortium partners verified these searches and identified any additional official databases with relevant data. Furthermore, a semi-structured questionnaire was designed to obtain information from partners. All responses were validated in an online workshop.

Outputs

The European Healthcare and Social Cost Database (EU HCSCD) includes 27 costing items organised in three main categories, namely primary resources, composite goods and services, and complex services and interventions. In turn, each category is further divided into sub-categories such as medicines, medical devices, health products/consumables and personnel (primary resources), outpatient visits, hospitalisations, image diagnosis, laboratory tests, ambulance services, diagnostic procedures and therapeutic procedures (composite goods and services), inpatient medical and surgical processes and day case procedures/outpatient services (complex services and interventions).

For primary resources, it was challenging to obtain recent costs of items in some countries. Furthermore, comparing costs of medicines, medical devices and health products was hampered by the variety of existing brands and/or models.

Items included in composite goods and services resulted in numerous cross-country differences. For instance:

- In England, these costs are all based on DRGs, whereas in France, Germany, and Poland only some are, while in Italy, Portugal, Spain and Sweden none of them are
- The cost of an outpatient visit depends on whether it is performed by a general practitioner, a nurse or a specialist, and whether it is performed at a health centre, the patient's home, by telephone, or it is web-based;
- The type of specialist influences the cost of a visit. Usually, the cost is set per visit, but in Slovenia, the cost of an Accident and Emergency visit is costed by team/year as well;
- The cost of a hospitalisation day is not estimated in France, Germany, Italy and Slovenia;
- The cost of image diagnosis in England depends on duration, contrast (yes/no), patient age, the number of target areas and whether the patient had accessed the service directly or the access was obtained through his/her primary doctor (England). In France, Germany, Italy and Portugal, this only depends on the part of the body scanned. In Poland, it depends on the part of the body scanned, the contrast (yes/no) and the number of target areas. In Spain and Sweden, it depends on the part of the body scanned, and the contrast (yes/no);
- For laboratory tests, the cost of an individual test is available in all countries except England. In Spain, the total cost excludes the cost of extraction and of processing the request;
- The cost of ambulance services differs across countries because of differences in the unit of measurement used (journey, intervention, distance (in kilometres), patient/year, mobile unit/year, hour), and the type of service (e.g. urban, inter-urban, transport for dialysis).
- The cost of diagnostic and therapeutic procedures varies depending on the item subtype (e.g., acute or chronic haemodialysis, oxygen therapy using liquid oxygen or portable concentrator, etc.).

The major reason for differences in costs is the type of resources included in the costing item. However, these differences are not always verifiable, either because of lack of transparency and/or the lack of publicly available costing documents. Complex services and interventions are organised in DRGs, which may have attributed costs and/or tariffs. Most direct costs and variable overheads are included in costing items of all countries. Fixed overheads, such as teaching costs, research costs, infrastructure depreciation and financial costs, present an issue as they are included in DRGs in some countries, but not in others. Teaching and research costs are included in Slovenia and are partially included in Portugal. Infrastructure depreciation is included in all countries except Germany, Slovenia and Spain. Financial costs are included in England, France, Poland, Portugal and Sweden.

> The EU HCSCD is the first European database of healthcare unit costs. It saves researchers' time and effort in searching costs and allows cross-country comparisons and understanding of the variation in costs within and across countries.

Impact

The EU HCSCD is the first European database of healthcare unit costs. It saves researchers' time and effort in searching costs, and allows cross-country comparisons and understanding of the variation in costs within and across countries. Additionally, all costs are automatically converted into Euros and are updated to 2020 using both the Gross Domestic Product deflator and the Consumer Price Index (CPI). The database is publicly available and is accompanied by a User's Manual, making it very user-friendly.

Recommendations and Future Direction

In order to further leverage the comparative nature of the costing database, it is recommended that a consortium be set up in charge of improving, updating and ensuring the continuity of the EU HCSCD for economic evaluation analyses, beyond the lifetime of IMPACT HTA. Although the database updates costs directly according to the most recent GDP deflator and CPI, each time the cost of an item is updated in the database of any country, it should be manually introduced into the EU HCSCD in order to maintain the database as up-to-date as possible. The consortium would progressively increase the list of cost items and the number of participating countries in the database.

Furthermore, it is recommended that an EU Task Force be set up to periodically revise, improve, harmonise, and standardise the costing methodologies in healthcare at EU level and apply them to generate unit cost data for the EU database. Finally, it is recommended that a procedure be developed to regularly issue lists of standard country unit costs to be used as the preferred option (or base case) in economic evaluations for pricing and reimbursement decisions.

WP4 Social costs and their role in economic evaluation for health care decision-making

Objectives and Methodology

The overall objectives of this WP are as follows:

1 Determine which wider effects, with specific emphasis on "the societal perspective", need to be measured in the context of economic evaluation. For this purpose, the methodological aspects applied to the identification, measurement and valuation of social costs in economic evaluations were revised. A narrative and analytic report was developed revising the most relevant methodological studies on economic evaluation carried out on the topic of valuation of social costs in the last decades.

2 Identify how the wider effects are valued and whether they can be incorporated into decisions within the health sector in a formal way. A series of selected case studies was developed to quantify different ways of incorporating the societal perspective into an economic analysis to inform European decisions. Several systematic reviews were carried out to analyse whether the inclusion/exclusion of social costs (mainly, informal care and labour productivity losses) could modify the results and conclusions of the economic evaluations performed in different diseases. The search strategies were launched from 2000 until November 2018, using two different databases: Medline and CEA TUFTS registry. The diseases analysed were Alzheimer's disease (AD), depression, diabetes mellitus, multiple sclerosis and rare diseases.

3 Produce a core dataset that helps to incorporate the societal perspective across jurisdictions and a methodology that will ensure sustainable data collection/reporting over time. Therefore, this component of "The EU HCSCD" (as per the previous WP) was created including unit costs of lost work time and the value of informal and formal care time. For this purpose, unit costs of societal resources were identified and collected based on the previous systematic literature reviews. Sources included in the case studies were used to obtain up to date unit costs and methodologies. For the unit cost of labour productivity losses, wages by age and sex, employment rates and the number of worked paid hours were obtained from Eurostat.

Key Findings

With respect to the valuation of patient´s paid time, the debate about whether the human capital approach or the friction cost method should be used is still far from over. In the case of informal caregiving time valuation, the debate about the different available methods has been less intense. However, there seems to be agreement on the ease of applying the opportunity cost method as it is the most commonly used approach to value informal care costs in cost of illness studies and the economic evaluations reviewed. The debate around which is the most appropriate perspective (the health care financier perspective, the societal perspective, or both) and the methods that should be applied when the inclusion of social cost is considered relevant is present in international guidelines and in the empirical literature.

The inclusion of social costs, mainly productivity losses and informal care costs, is limited in the current literature. The inclusion of social costs led to a relevant change in results of economic evaluations, ranging from 18 per cent to 30 per cent, depending on the case study considered. However, it should be noted that the consideration of the societal perspective leads to changes in the conclusions of some of the economic evaluations reviewed, although differences between diseases were found.

> The inclusion of social costs led to a relevant change in results of economic evaluations, ranging from 18 per cent to 30 per cent, depending on the case study considered.

Impact

The EU HCSCD is the first European database of healthcare **and** social care unit costs. Researchers could access the online dataset freely and search for unit costs needed in economic studies that apply a societal perspective. Future projects that need to use unit costs could find in this tool a useful repository where wages or formal and informal care unit cost data can be easily located. Additionally, all costs are automatically converted into Euros and updated to 2020 using both the Gross Domestic Product deflator and the Consumer Price Index (CPI). The database is publicly available and is accompanied by a User's Manual, making it very user-friendly.

Recommendations and Future Direction

The valuation of social costs has experienced significant methodological developments in recent years, particularly regarding the accuracy of time identification and valuation tools, for both patients and informal caregivers. Nonetheless, more research in this field is needed to improve the bulk of existing scientific evidence.

To increase the consideration of the societal perspective in economic evaluations, it would be necessary to:

1. have a greater methodological homogeneity in the evaluations performed in this field;
2. promote the inclusion of spill-over effects on the health of family members when informal care is a relevant resource of the intervention evaluated;
3. develop a general strategy to improve the access to data sources in the previous phases of identification and measurement of social resources; and
4. promote the application of their recommendations through appropriate incentives for researchers for those countries that recommend the consideration of the societal perspective in their guidelines.

WP5 Exploring health preferences on different sub-population groups using EQ-5D

Objectives

This WP focuses on patient reported outcomes used in economic evaluation of treatments and health care approaches. In this context, generic preference-based health-related quality of life (HRQoL) instruments, which have value sets available, are necessary to enable the calculation of quality-adjusted life years (QALYs). Value sets are based on health state preferences, an example of which are the EQ-5D instruments that are recommended in many national health economic guidelines. Even if it is the standard in most countries, those value sets of HRQoL instruments are based on adult general population preferences. There is an ongoing discussion on whether this is the most appropriate reference population to obtain health state valuations.

Within this scope, this WP first examines differences in health state preferences of two patient groups compared to those of the general population in two countries, Germany and Spain. Second, it aims to develop value sets for the youth-specific EQ-5D instrument, the EQ-5D-Y (Youth), and to compare health state preferences obtained from the adult general population and from adolescents of the general population in three countries, i.e. Germany, Slovenia and Spain.

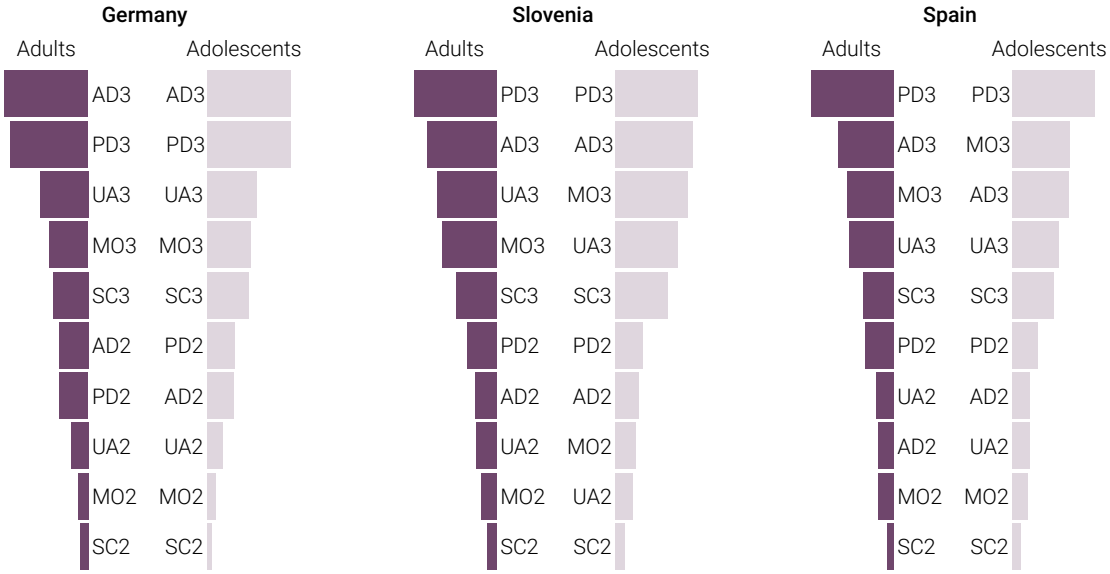
Methodology and Outputs

1 **Comparison of patient and general population preferences for EQ-5D-5L health states**
EQ-5D-5L health state preferences were obtained by online discrete choice experiments (DCEs) with rheumatic and diabetic patients in Germany and Spain. Preferences of 1,700 patients were compared to EQ-5D-5L general population preferences of national value sets. German and Spanish patients gave more importance to the dimensions of mobility, self-care, or usual activities and less importance to pain/discomfort and anxiety/depression than the general population. An approach combining patient preferences from DCE and the utility scale from national values sets was developed.

2 **Comparison of adult general population and adolescent preferences for EQ-5D-Y health states**
Health state preferences were obtained by online DCEs from two samples in each of Germany, Slovenia and Spain. Adults of the general population valued EQ-5D-Y health states on behalf of a 10-year-old child, while adolescents valued EQ-5D-Y health states for themselves. Health state valuations of 3,109 adults and 2,129 adolescents differed significantly between the two samples in all countries (Figure 3, see p16). The overall relative importance of health dimensions was similar between adolescents and adults. The rank-order of dimension levels between adults and adolescents differed slightly in Germany, Slovenia and Spain.

3 **Value sets for EQ-5D-Y in Germany, Slovenia and Spain**
Preference data for EQ-5D-Y health states obtained by DCE from adults in the general population in Germany, Slovenia and Spain were complemented with data from 200 composite time-trade off (cTTO) interviews in each country (additional funding: EuroQol Research Foundation). This was necessary to rescale DCE model coefficients to a 1 (full health) to 0 (dead) scale by anchoring on the mean value of the worst possible health state of EQ-5D-Y (33333) obtained through cTTO. Due to the data structure, slightly different modelling approaches were used to produce a value set for EQ-5D-Y in each country.

Figure 3. Relative importance of health dimensions and levels



Impact

This WP results are relevant for the outcome measurement in economic evaluation in the HTA and health care decision making context. For QALY calculation and cost-utility analysis, availability of appropriate and widely accepted preference-based HRQoL instruments is crucial. The evidence revealed by this work first led directly to the development of new value sets. Second, it impacts on the discussion on whose preferences should be used in health state valuation.

The results show that patient preferences differ from those of the general population and, further, adult preferences differ from adolescent preferences. Therefore, we provide additional evidence that the reference group in valuation studies has an impact on the utility decrements and, thus, on economic evaluation in which value sets are applied. Decisions for using one value set might lead to different decisions in the context of HTA and HTA agencies need to be aware of this. The differences in preferences between disease areas suggest that several patient-based value sets for different disease groups would be required. However, this will limit comparisons across diseases commonly made in the context of HTA and health care decision making. The question on which value sets to use will always involve to some extent a normative decision and, ultimately, depends on the application context (clinical vs. resource allocation), the health care system and the position taken by decision-makers.

Further, the preferences of diabetic and rheumatic patients in Germany and Spain show which dimensions of HRQoL are important for those patient groups. This information can be used for treatment decisions in clinical settings and in organising health care processes for those patients. The recruited patients represent population-based samples of both disease groups. Thus, the data can be applied as a benchmark for comparison with future studies or sub-populations.

For youth-specific instruments, there is a lack of preference-based HRQoL measures. The work of WP5 contributed to the methodologically challenging topic of valuing youth health states. Our results confirmed earlier evidence that adolescents' preferences for EQ-5D-Y health states differ from those of adults valuing health states of a child. However, differences are only small and vary by country. These results contribute to and inform the current discussion on the best approach to value youth health states. Besides, the information on the relative importance of HRQoL dimensions for adolescents might be relevant in the context of clinical decisions as well.

As one of the first studies, we used the recently developed EQ-5D-Y valuation protocol. The methods suggested were shown to be feasible and experiences made were reflected back to the EuroQol Group to advise future EQ-5D-Y valuation studies. The three developed EQ-5D-Y value sets are among the first value sets for this youth-specific instrument. They enable the use of EQ-5D-Y in economic evaluations of paediatric health care and treatment approaches from now on.

Recommendations and Future Direction

Based on this WP results, the following policy recommendations should be considered in the context of HTA in terms of health state valuation and application of value sets for HRQoL instruments:

1. Patient preferences differ from general population preferences. For many countries, the established standard is the use of general population preferences in the HTA context, since it offers comparability of health gains across different disease groups. For national contexts where patient preferences are preferred, our results suggest a feasible approach to combine patient preferences and national general population-based values sets (reference to Ludwig et al. 2021).
2. The generic youth-specific EQ-5D-Y has now value sets available in Germany, Slovenia and Spain. Therefore, EQ-5D-Y can be used in economic evaluations, mainly cost utility analyses of paediatric treatments in these countries. EQ-5D-Y offers comparability to the corresponding adult version EQ-5D-3L which is an established instrument for economic evaluations in many countries.
3. Overall, the discussion on whose preferences values sets of HRQoL instruments to use should not solely take place in the community of researchers. Especially for countries that base reimbursement decisions on economic evaluations, it would be important to initiate a future discussion on this topic including different stakeholders e.g., decision makers, representatives of the clinical perspective and HTA agencies.

Our suggested approach on how to incorporate patient preferences in value sets needs further exploration. Further research is needed to understand the reasons why patient preferences differ from general population preferences and why adolescent preferences differ from adult preferences. In addition, with the youth-specific HRQoL instrument being available, further research is needed to explore how these youth-specific value sets should be handled in economic evaluations of treatments that affect the whole life span.

> The question on which value sets to use will always involve to some extent a normative decision and, ultimately, depends on the application context (clinical vs. resource allocation), the health care system and the position taken by decision-makers.

WP6 Methodological guidance on the analysis and interpretation of non-randomised studies to inform health economic evaluations

Objectives

An essential basis for regulatory and HTA decisions about the availability of new health technologies is an unbiased estimate of the treatment effect – an estimate of how well a drug or other technology works that is not systematically different from the true effect. Due to their methodological rigour, randomised controlled trials (RCTs) have traditionally been the mainstay of evidence generation for new heath technologies. However, non-randomised studies are playing an increasingly important role in regulatory and HTA decisions. Against this background, this WP has two key objectives:

1. **To empirically assess whether non-randomised studies are likely to produce valid and unbiased estimates of relative effectiveness.**
2. **To generate recommendations that help HTA agencies assess when and how non-randomised studies can inform coverage and reimbursement decisions.**

Methodology and Outputs

The *first objective* was addressed through the largest empirical analysis of effect estimates in randomised and non-randomised studies to date.

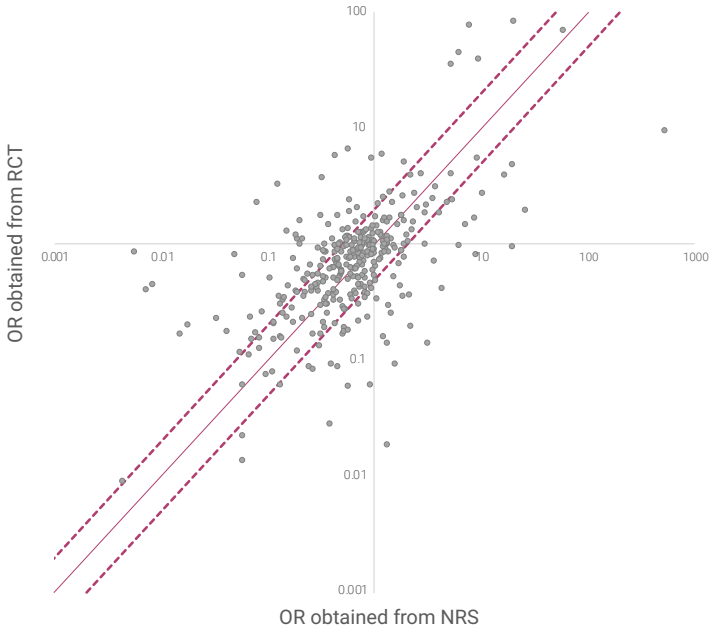
Empirically, we were interested in the question of whether we can trust that non-randomised studies produce unbiased estimates of treatment effects. We approached this question through a meta-epidemiological analysis that compared effect estimates obtained from randomised and non-randomised studies.

We identified 346 clinical questions about the effectiveness of drugs that had at least one randomised and one non-randomised study conducted for the same population (totalling over 2,700 unique studies). For each of these topics, we compared the effect estimates obtained from the two types of studies. We assessed how often randomised and non-randomised studies agreed about the conclusions drawn about a new drug (is it effective or not?) and about effect sizes (how effective is the new drug?). We then produced a summary measure of discrepancies in treatment effects across all clinical topics (the ratio of odds ratios, ROR).

The meta-epidemiological study found that:

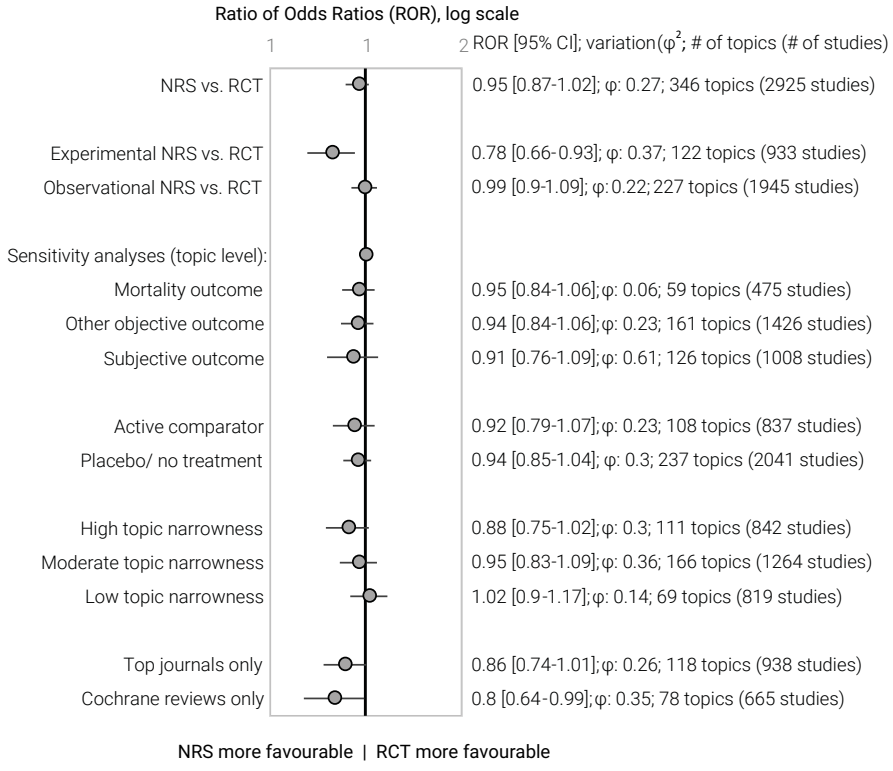
- For more than one in three of the 346 clinical questions, non-randomised and randomised studies led to different conclusions about whether a drug has therapeutic benefit (Figure 4, p19).
- Non-randomised studies can severely over- or underestimate the effect obtained by randomised studies: for 38 per cent of clinical questions, the effect estimate obtained from one study type was twice as large as that obtained from the other.
- On average, there was no significant difference in magnitude of effect between randomised and non-randomised studies (pooled ROR across all 346 clinical topics was 0.95, 95 per cent CI: 0.87-1.02). However, this masked substantial variation in how effect estimates from the two study types compared to each other (Figure 5, p19).
- Experimental non-randomised studies produced on average 22 per cent larger treatment effects compared to matched RCTs.

Figure 4. Agreement of pooled effect estimates (odds ratios, OR) obtained from randomised (RCT) and non-randomised (NRS) studies for 346 clinical topics.



> The meta-epidemiological study conducted as part of this WP showed – alongside previous studies – that decision-makers need to be aware of substantial scope for uncertainty about the effectiveness of new health technologies, including potentially exaggerated treatment effects, when relying on non-randomised studies.

Figure 5. Pooled estimates of discrepancies between treatment effects obtained from randomised and non-randomised studies for the full set of 346 clinical topics, and for a set of subgroups.



The *second objective* was addressed through a critical review of the literature and stakeholder consultations, resulting in a set of recommendations about the use of non-randomised evidence to estimate treatment effects in HTA.

We conducted pragmatic reviews of existing guidelines and recommendations by HTA and other health organisations, as well as the empirical literature on the internal validity of non-randomised studies. We also held workshops with regulators and HTA bodies from eight European countries to gather their views on key issues and to validate draft recommendations.

We developed the following 13 evidence-based recommendations across six key topics:

1 Planning and design

1.1 Justify the need for a non-randomised study and demonstrate that the research question is amenable to being answered using non-randomised data

1.2 Prospectively plan studies and engage with early scientific advice procedures

2 Analysis

2.1 Understand potential risks of bias and address using appropriate analytical strategies

2.2 Perform extensive sensitivity analyses

3 Reporting

3.1 Register protocols before study conduct

3.2 Report data, methods, and results transparently

3.3 Describe potential biases and report the overall risk of bias

3.4 Convey and ideally quantify the uncertainty

4 Strengthening HTA systems

4.1 Strengthen and standardise scientific advice procedures

4.2 Strengthen conditional reimbursement processes to ensure generation of further informative evidence after initial reimbursement decisions

4.3 Invest in and develop staff skills in the design, analysis, and interpretation of non-randomised studies

5 Issuing and enforcing best practice guidance

6 Supporting future research and initiatives

Detailed results of the meta-epidemiological study and explanations of the 13 recommendations is available in two research papers.

Impact and Recommendations

Decision-makers assessing whether a new technology should be made available to the population, typically paid for by public funds, need to have robust evidence on whether the technology works. Our findings and recommendations provide much needed empirical evidence and guidance for regulatory and HTA agencies on the use of non-randomised studies for these decisions.

The meta-epidemiological study conducted as part of this WP showed – alongside previous studies – that decision-makers need to be aware of substantial scope for uncertainty about the effectiveness of new health technologies, including potentially exaggerated treatment effects, when relying on non-randomised studies. Accordingly, we developed a set of evidence-based recommendations for the use of non-randomised studies to estimate treatment effects in HTA that emphasises the need to justify the need for a non-randomised study, to prospectively plan such studies and carry them out with a clear idea about possible biases and how to address them, and to transparently report the methods used.

The increasing use of non-randomised studies to estimate treatment effects also calls for a strengthening of HTA systems to better be able to use and appraise such evidence.

WP7 Methodological tools using multi-criteria value methods for HTA decision-making

Objectives

WP7's starting point is that the value of a health care technology spans across a multi-dimensional domain going beyond their clinical benefits and costs, traditionally captured in economic evaluation approaches; as such, HTA decisions could be informed following a value assessment and appraisal process that includes all relevant value domains and stakeholders.

This WP first, develops an actionable model on the determinants of HTA recommendations, which is tested empirically, providing decision-makers with insights on the relative importance of different criteria beyond costs and effects at therapeutic class and country level; second, it uses participatory processes, such as Delphi panels, decision conferences and workshops, to propose a value framework that captures the value concerns of different stakeholders that are involved in the decision-making process; third, it applies and tests this value framework to demonstrate its adaptability for different decision contexts focusing on a number of alternative therapies across settings; and, fourth, it contributes to the discussion on resource allocation by adopting a Multi Criteria Decision Analysis (MCDA) approach for the value assessment of medicines to inform decision-making by HTA agencies and health insurers.

Methodology

WP7 has involved different methodological instruments to meet its objectives, including statistical and econometric analysis, and quantitative decision analysis in the form of MCDA. First, a model of determinants of HTA recommendations is proposed that captures salient features of individual medicines, country characteristics, regulatory variables, therapy-related clinical and economic performance, evidence uncertainties, and social value judgements, and is tested empirically using historical evidence from eight country settings and based on a panel of 219 unique medicine-indication pairs. Second, it structures a generic MCDA model of value concerns within a common framework to evaluate new medicines within the context of HTA, reflecting what is relevant for HTA agency decision-makers and the broader stakeholder community; in doing so, it brings together alternative participatory processes and questioning protocols to elicit value preferences. By engaging with a number of different stakeholders as part of a collaborative value modelling approach, comprised of a web-Delphi and decision conference process, it proposes the IMPACT HTA Value Framework capturing the value concerns of the different stakeholder groups. Third, it implements the IMPACT HTA Value Framework through a collaborative value modelling approach in the form of case studies, for the context of different therapeutic and disease areas across countries to demonstrate its flexibility and adaptability to the requirements of individual therapies and the value concerns of decision makers across settings.

Methodological contributions relating to the development of IMPACT HTA Value Framework and model(s) have been tested in real policy-making contexts for the evaluation of medicines, in collaboration with national HTA agencies and national insurance organisations in different European settings.

> The IMPACT HTA Value Framework contributes to the discussion on value assessment of medicines and informs resource allocation decisions.

Outputs

The statistical and econometric model

Funding recommendations are the outcome of a robust assessment by HTA agencies and are shaped by a multiplicity of criteria, most of which are linked to a new medicine's perceived value; among them, are the type of medicine under consideration and how it fits into therapeutic pathways, the clinical and economic evidence and their robustness based on scientific criteria and appropriate benchmarks, respectively, the restrictions in the new medicine's use, evidence uncertainty, considerations capturing value dimensions beyond costs and effects, and time. Consequently, the funding recommendation, F, in country i and product j, can be positive (either unrestricted or with restrictions) or negative and can be expressed as a function of a number of parameters as shown in equation (1):

$$F_{ij} = Y_0 + \delta_1 C_{ij} + \delta_2 D_{ij} + \delta_3 U_{ij} + \delta_4 W_{ij} + \delta_5 S_{ij} + \delta_6 Z_{ij} + v_i \quad (1)$$

Where F_{ij}, is the "HTA funding recommendation" for product *i* in country *j*; C_{ij} is a group of parameters relating to the drug type, D_{ij} is a vector of parameters relating to the quality of evidence supporting HTA submissions, U_{ij} relates to the impact of clinical uncertainties, W_{ij} refers to the impact of economic uncertainties, while S_{ij} captures the range of social value judgments (SVJs) that may be relevant to the product or the therapeutic indication in question; Z_{ij} is a vector of country- and time-specific variables, while v_i is the error term.

Empirical analysis has found positive and statistically significant associations between funding decisions and clinical performance, economic variables and social value judgements; and negative associations between funding decisions and clinical and economic uncertainties. Whereas an overwhelming majority of drugs (87.3 per cent) have been recommended for funding, empirical evidence suggests that most coverage recommendations are associated with significant clinical restrictions in new drug use or/and financial agreements in order to mitigate uncertainty and optimise on cost.

The IMPACT HTA Value Framework

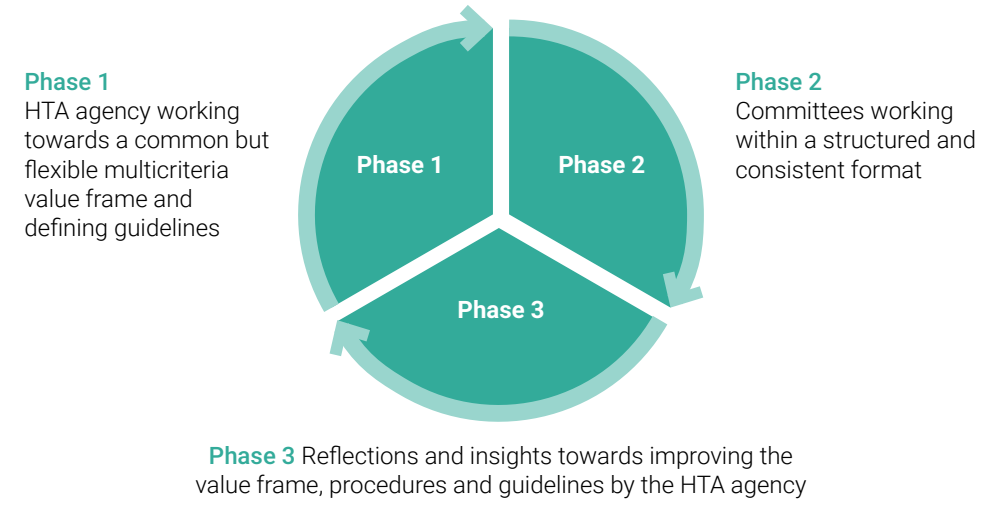
The empirical investigation informed the development of the IMPACT HTA Value Framework, which was dynamic, involving three distinct phases (Figure 6, p23).

In Phase 1, the HTA agency would involve its stakeholders and experts in setting a common but flexible multicriteria value frame in which a comprehensive set of value aspects would be identified as relevant for evaluations; these would then be assigned a relevance level for different therapeutic contexts; the value aspects and their relevance, together with the respective evidence, data, and the MCDA procedure guidelines, would then set for work by HTA committees.

In Phase 2, committees work under the value frame set for the respective therapeutic indications and follow MCDA-specific procedures and guidelines provided by the HTA agency for the purpose of preference elicitation (e.g. using the MACBETH approach and the respective questioning protocols).

In Phase 3 the HTA agency would analyse and reflect upon the evaluation results from HTA committees and upon feedback from committee members, to continuously improve the value frame and tools for its use and implementation in the future.

Figure 6. Underlying development and testing cycle of the IMPACT HTA framework by HTA agencies

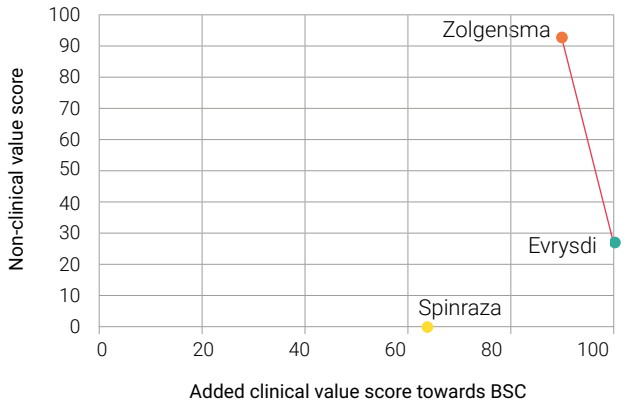


Following the application of a collaborative value modelling approach with the Belgian health insurance fund, INAMI-RIZIV, earlier findings of the project on relevant value aspects for HTA stakeholders at international level were validated and supplemented with INAMI stakeholders to generate HTA agency-specific lists of generic value aspects for the evaluation of new medicines in Belgium, for two specific decision contexts: first, indication expansion relating to metastatic prostate cancer, and, second, a life threatening orphan disease (spinal muscular atrophy) (Table 1, see p24).

As part of a two-step interactive process, a case study on Spinal Muscular Atrophy (SMA) initially involved a web-questionnaire to collect individual value judgments from eight participants on the performance of three treatments relative to Best Supportive Care (BSC), on four clinical value aspects. Group majority judgements were then derived from them, based on which a prototype multicriteria clinical value model was built. Following the first web-questionnaire step, a virtual decision conference took place with INAMI participants to develop a shared multicriteria model on clinical and non-clinical value aspects, therefore enhancing the preliminary model prototype.

A comparison of treatments' added clinical value scores (versus BSC) compared to treatments' non-clinical value scores, is illustrated in the X-Y plot (Figure 7).

Figure 7. X-Y plot of SMA treatments' added clinical value scores (versus BSC) compared to treatments' non-clinical value scores for INAMI in the Belgian context



Impact and the future

The impact of WP7 lies in the following domains:

- First, it has developed and validated a new methodological approach concerning the collection and analysis of evidence needed for the evaluation of new medicines in HTA, including the analysis of data and informing the design of information systems.
- Second, it has developed an actionable Value Framework on the determinants of HTA recommendations based on primary analysis of secondary micro-level data and primary data collection, which can provide valuable insights to HTA decision-makers and other stakeholders on the relative importance of different criteria beyond costs and effects at therapeutic class and country level.

- Third, it has proposed an innovative value-based assessment approach, the IMPACT HTA Value Framework to assist with the evaluation of health technologies across multiple dimensions in a structured way. It has adopted a sociotechnical participatory process – leveraging a collaborative value modeling approach comprised of web-Delphi and decision conferences – enabling the collection of views from a large number of stakeholders located in different settings in a virtual format (while promoting consensus).
- Fourth, it has applied and tested the IMPACT HTA Value Framework, via case studies on specific evaluation topics, combining objective (quantitative and qualitative) data with subjective judgments from committee members in a structured way, resulting in explicit evaluation ranking of therapies considering their performance on multiple value aspects and their trade-offs, not necessarily limited to clinical elements.

Further validation of the IMPACT HTA Value Framework will take place with a view to facilitating an informative and continuous assessment of health interventions that have the potential to improve resource allocation at health system level.

Table 1. The IMPACT HTA Value Framework value aspects identified as part of a collaborative process with Belgian health insurance stakeholders (INAMI) in two separate decision contexts

IMPACT HTA Value Framework criteria	Indication expansion w/in existing indication, for severe disease area with a number of treatments available, e.g. monoclonal antibodies expansion from post-chemo to pre-chemo in the case of metastatic prostate cancer	Life threatening orphan disease with limited number of symptomatic treatments available and new entry of very expensive advanced therapy with uncertain long-term benefits, e.g. gene therapy for spinal muscular atrophy
A Severity of the disease		
B Unmet need of the disease		
C Medicine's impact on mortality		
D Medicine's impact on morbidity		
E Medicine's impact on health-related quality of life		
F Medicine's adverse events profile		
G Medicine's tolerability to patients		
H Medicine's ease and convenience for patients		
I Medicine's impact on wider public health in terms of disease risk reduction in the community		
J Medicine's economic impact		
K Medicine's affordability		
L Medicine's efficiency		
M Risk of bias due to flaws in the design, conduct, analyses and reporting of the medicine's clinical trials		
N Impact of the medicine's adoption on the health care system's organisation and delivery of care		
O Impact of the medicine's adoption on equity and ethical issues		
P Medicine's value as a bridge therapy		
Q Medicines' impact on patient functionality		
R Medicine's time for treatment effect		
S Medicine's duration of treatment effect(s)		
T Medicine's duration of adverse/unwanted treatment effect(s)		
U Disease frequency (e.g. rarity)		
V Medicine's spill-over effects		
W Medicine's mechanism of action		

Colours indicate perceptions of criteria as "essential", "influential", or "complementary".
None of the criteria were deemed as "irrelevant" in the two disease contexts depicted.

WP8 Analysis of economic evaluation methods for hospital-based assessment

Objectives

A significant challenge for Health Technology Assessment (HTA) is the operational implementation of recommended technologies in clinical settings. Even in the most effective and efficient health care organisations, production and diffusion of HTA recommendations for the appropriate use of technologies do not automatically produce a positive change in clinical practice, thus improving final performance.

This WP identifies the extent organisational/contextual factors influence the effectiveness of use of medical technologies, which, in turn, might cause clinical variation in their implementation, affecting hospital performance.

Methodology and Outputs

It is recognised that hospital performance is a multi-faceted concept and must be measured accordingly. Multiple hospital contextual factors can change the ways in which health technologies may influence such performance. Additionally, the use of technologies that were previously to be inefficient can still be optimised when the organisation supports a more efficient use of health resources (i.e. professionals, duration of surgical operations, usage of other medical equipment).

Through a mixed methods approach, including quantitative and qualitative approaches as well as case studies, two toolkits were created. The first toolkit (Toolkit to assess hospital performance) assesses the overall hospital performance and is intended as a multi-faceted concept. The second toolkit (Toolkit to assess the transferability of evidence produced in other jurisdictions and decision-making levels) provides a methodological framework to assess the contribution of contextual factors in the full implementation of a new technology (Table 2, see p26). The tootlkits can be found on the IMPACT HTA website.

In addition, a decision model, focused on cost minimisation analysis and efficiency assessment using benchmark frontiers, was developed. The model identifies the technologies with the same efficacy and safety that are more subject to clinical variation and assesses different intervention actions to improve the performance of healthcare delivery. It also allows for the prediction of possible savings due to efficiency gains arising from decreases in clinical variation costs and using a probabilistic model.

Impact

HTA activities should be carried out while considering hospitals' unique features. These are a key element in driving the contribution of health technologies. The toolkits and model created represent a methodology aimed at supporting, advising, informing and recommending strategic decisions in the field of medical devices by increasing the set of information available about the way in which they are used during the overall clinical pathway, which also involves the utilisation of organisational assets and resources.

Table 2. Main contextual domains and sub-topics within the toolkit to assess the transferability of evidence produced in other jurisdictions and decision-making levels

Hospital infrastructure and architecture

- University/non-university hospital
- Architectural type of hospital
- Organisational chart of hospital (e.g., Vertical vs Horizontal)
- Patient pooling approach(es) to group patients within ward units
- Number of staffed beds in the hospital
- Current number of hospital employees
- Annual number of hospital discharges
- Annual number of ambulatory consultations at the hospital
- Roles of the hospital in the uptake territory
- Clinical pathways and itineraries for patients' categories (e.g., emergency pathway or mother and child pathway)
- ICT tools regularly used within the hospital
- Level at which electronic health records are fully integrated and coordinated
- Health Technology Assessment activities or initiatives within the hospital
- Presence of a dedicated hospital-based HTA unit at location

Availability of financial resources at hospital level

- Which responsibility centres hold annual budgets (e.g. Departments, clinical wards, horizontal clinical pathways)
- The assignment process of a budget to the various clinical settings (e.g. defined by top management, negotiation with clinical settings)
- How the annual budget of the clinical setting is broken down
- Use of a Balanced Scorecard or similar methods to evaluate key performance areas and indicators

Leadership styles

- Top-down vs. bottom-up approach
- Rigid vs. shared decision-making processes

Human resource management tools

- Job evaluation activities
- People evaluation activities
- Performance evaluation activities
- Activities aimed at evaluating human resources' potential

WP9

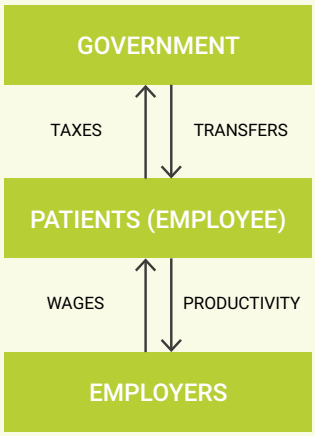
Expanding economic analysis for HTA: methods for measuring the fiscal impact of new healthcare interventions

Objectives

The scientific literature provides a standardised set of methods to estimate social costs due to productivity losses resulting from a particular health condition. One of the most commonly used methods is the human capital approach. The basic hypothesis of this approach is that workers "produce" in fair proportion to the income received and that the salary reflects the actual contribution of the worker to the productive activity. Additionally, the human capital approach can be used to extend the societal perspective beyond the effect of productivity losses on individuals, social insurance or employers.

There is no evidence on the use of the human capital approach to estimate the fiscal impact of chronic diseases. We define the fiscal impact of a disease as the decrease of income tax revenue caused by lower payments following a sickness status. Our framework (the Fiscal Impact Framework, shown in figure 8) is consistent with the theoretical background for which the accumulation of human capital and the improvement in population health are the key drivers for economic growth and the result of an endogenous process. Consequently, governments should invest in new medical technologies to increase population health and, through that, enhance productivity growth. Increases in productivity would increase income and, therefore, consumption and tax revenues that, in turn, would be used to increase investment in health.

Figure 8.
The fiscal impact framework



Methodology and Outputs

The first step of the analysis was to estimate the individual fiscal impact based on a survey applying the Italian taxation scheme to the monetary values of productivity losses due to a chronic condition. Second, a non-parametric analysis was conducted to explore the structure of our data (i.e., age, education, working days lost), following which, a parametric analysis based on a linear regression was performed. Third, the average daily wage was applied to the predicted values of working days lost and, thus, the monetary value of productivity losses and the resulting fiscal impact were derived. The approach was tested on a sample of 2,526 patients with Irritable Bowel Diseases (IBDs) with a mean age of 44, meeting the following inclusion criteria:

1. aged more than 18 years;
2. having been diagnosed with one of the IBDs;
3. having received assistance for one of the three diseases under examination: Crohn's disease, ulcerative or indeterminate colitis.

The results revealed an important regional gradient with the highest fiscal impact associated with northern regions in the Italian setting. The fiscal impact ranged from €170 to €400 for patients diagnosed with IBDs.

Impact, Recommendations and Future Direction

The fiscal impact derived from the introduction of a new medical intervention could lead to policies aimed at discriminating elderly or low-income subgroups of a population.

However, fiscal impact estimation does not represent a tool to inform rationing policies, but is rather an analysis providing additional evidence, where identified, on an additional dimension characterising the value for money of a medical intervention.

Policy makers should include the fiscal impact in their decision framework. However, they should not use it to perform cross-group comparisons among different socio-economic categories.

Further research should be performed to extend this framework to other diseases and countries.

“Fiscal impact estimation does not represent a tool to inform rationing policies, but is rather an analysis providing additional evidence, where identified, on an additional dimension characterising the value for money of a medical intervention.”

WP10 Appraisal of Orphan Medicinal Products (OMPs)

Objectives

Orphan Medicinal Products (OMPs) or Rare Disease Treatments (RDTs) are challenging to appraise given the limited clinical knowledge and evidence base and the high prices for innovative treatments. These issues lead to major uncertainties in HTA appraisal. Some HTA bodies use special processes to appraise RDTs; others add special features, or decision modifiers, to standard processes; others give no leniency to RDTs (see country vignettes). The objective of this WP is to create an appraisal process beyond conventional economic evaluation that is suitable for RDTs.

Methodology

The WP explored how different forms of evidence and inputs are curated, input, assessed and appraised to inform appraisal recommendations about the use of an RDT. It has included contact with HTA experts in countries across Europe, Canada, Australia and New Zealand, to document processes and compare case studies. Innovative ethnographic research of appraisal committees has been undertaken to explore in-depth the nuances of appraisal and its deliberative processes. It has also undertaken focused work on two particularly challenging issues for RDTs – namely use of Patient-Reported Outcomes (PROs) and implementation of Outcomes-Based Managed Entry Agreements (OBMEA). This work has involved literature reviews and several multi-stakeholder activities to explore issues, share processes and develop tools.

Outputs

The Appraisal Framework

A **fair** appraisal process for RDTs requires:

- **leniency** in critical assessment of evidence relating to RDTs to recognise the inherent limitations
- **flexibility** in the process to support determination of the value of each RDT
- **consistency** in the application of leniency and flexibility.

At the heart of the Appraisal Framework is the requirement to define a decision-making framework beyond clinical and cost effectiveness (e.g., including nature of condition, organisational issues, ethical issues), along with modifiers that can deliver levels of flexibility in appraisal. This decision-making framework and modifiers then need to drive all parts of the HTA process, so that all those involved (stakeholders and appraisal committee members) can better contribute evidence and inputs. This leads to the following eight recommendations, each of which has detailed operational guidance.

> This appraisal framework with enactment of the detailed guidance will support consistency of flexibility in appraising RDTs to ensure fairness, within a framework of accountability for reasonableness.

Evidence Submission and Critical Assessment processes address all dimensions of value and identify uncertainties	Appraisal Deliberation considers all dimensions of value
1 The entire HTA process is shaped around clearly defined decision-making domains and any decision modifiers	**5** Appraisal committees are bespoke for rare disease treatments, or general appraisal committees include several rare disease specialists
2 All relevant evidence is obtained for each domain of decision-making and all decision modifiers	**6** The deliberative appraisal discussion is driven by the domains of decision-making, and use of modifiers is clearly understood
3 Critical assessment of clinical evidence explicitly considers what evidence could have been generated in the rare condition	**7** Uncertainties are characterised in terms of form, extent and implications for decision-making
4 Critical assessment of economic models takes account of paucity of knowledge in rare diseases and judges whether the model is sufficient for decision-making	**8** Outcomes-Based Managed Entry Agreements may be used to resolve decision-relevant uncertainties, if collection of sufficient data is feasible
Clinical and patient experts are involved iteratively throughout the appraisal process to explain the context of the condition, existing care pathway and help resolve uncertainties related to determination of treatment value	
Delivering fair appraisal of Rare Disease Treatments through consistent flexibility	

Tools

To ensure the appropriate use of PROs and development of health state utility values in rare disease populations, detailed guidance is presented for the following recommendations.

1 When appraising rare disease treatments, it is essential to understand impacts of the condition and treatment on patients' quality of life (QoL)
2 When critically assessing PRO evidence, challenges related to development and administration of PROMs should be taken into account
3 During the appraisal, interpretation of PRO evidence should recognise that lack of significant effect does not necessarily imply lack of benefit on QoL
4 Other forms of evidence such as qualitative evidence and expert input should be considered to enable a fuller appreciation of the impact of a medicine on QoL
5 It is important to consider family and carer perspectives to better capture the added benefit of a medicine

To support appropriate use of OBMEA with RDTs, the following tools have been developed:

- Checklist to determine if an OBMEA is appropriate
- Template for public documentation of an OBMEA data collection agreement
- Terms of reference template for a monitoring committee responsible for overseeing implementation of an OBMEA
- Patient group submissions template for re-appraisal after an OBMEA

Impact and Recommendations

This appraisal framework with enactment of the detailed guidance will support consistency of flexibility in appraising RDTs to ensure fairness, within a framework of accountability for reasonableness (Daniels and Sabin 2008). A fair process is one that ensures inclusion of all relevant evidence and knowledge, consistently throughout the process, to allow for the best decision possible given the unique circumstances of the disease.

Hence, we make recommendations for an appraisal process that ensures every RDT is appropriately critically assessed and in which gaps in clinical evidence are complemented by other forms of evidence and inputs. The recommendations aim to ensure that leniency and flexibility are applied consistently in the appraisal of RDTs.

The Appraisal Framework can be used by individual health systems in the EU and beyond, or for collaborative HTA initiatives. It includes specific policy recommendations to support such collaboration such as an international repository for OBMEA plans and reports and has already engaged many HTA/ Payer bodies in development of these proposals.

WP11 From HTA results to guidance implementation: paving the way

Objectives

Policymaking in healthcare is most often dealing with quality- and cost- increasing interventions compared to usual care. This WP focuses on cost-saving technologies that might marginally diminish individual health outcomes; these technologies are labelled decrementally cost-effective interventions (d-CEIs). Such interventions still present an optimal cost-outcome combination as is the case for their incrementally cost-effective counterparts, i.e. "there are no other interventions that provide a better (or identical) health outcome at a lower cost" (HAS 2020). Yet d-CEIs' potential remains undervalued and they have received much less attention from HTA bodies. This WP pursues a double objective:

1 To shed light on d-CEIs implementation issues, using behavioural economics techniques: because they maximise collective gains at the expense of some individual benefits, it is essential to understand the interplay of individual and collective preferences in such situations. By designing a discrete choice experiment, WP11 contributes to a better understanding of the obstacles and levers to d-CEIs implementation;

2 To offer recommendations on how to systematically consider and possibly adopt d-CEIs in allocation decisions as well as practical guidance, bringing broader ethical and policy issues to bear on those decisions. In so doing, WP11 aims to provide decision-makers with tools to identify candidate d-CEIs with the highest social value, as well as deliberative methods improving patient and societal acceptability.

Methodology and Outputs

Two complementary, documentary and experimental, methodologies were used: a systematic literature review and a discrete-choice experiment.

A systematic review was carried out to identify d-CEIs studies published since 2005 in order to inform researchers and decision-makers about the level and quality of evidence on d-CEIs. Ninety-four d-CEIs studies were identified by performing a systematic review of clinical trials registries and published literature. Among the seven health technologies selected, two with high potential financial gains were selected in order to conduct Budget Impact Analyses (BIA) from the French healthcare system perspective: triple conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD) therapy in rheumatoid arthritis (RA) and total knee replacement (TKR) due to knee osteoarthritis (OA). The savings estimated for implementing these two d-CEIs were €51m over three years.

A discrete choice experiment was designed to investigate whether decision-makers would be willing to adopt d-CEIs (or not), and under which conditions. Given a fixed budget, respondents were invited to act as a local health officer and to choose eight times among two hypothetical d-CEIs; they also answered questions, notably about their knowledge of decremental cost-effectiveness, the practice in their country, their perception of how the COVID-crisis might have affected their answers and how it might affect the acceptability of these interventions in the future. Respondents were also asked to identify additional attributes and give their preferences regarding the allocation of savings (to the same illness , to health care services or to other public expenditure such as education). The discrete-choice experiment also allowed respondents to further express their views and heuristics in open-comment boxes, providing deeper insights of the decision-making process they followed. In parallel to the standard econometric methods used to analyze the results of the discrete choice experiment, a thorough qualitative analysis of

the open comments was undertaken to provide additional material to be used for the discussion of results. The discrete choice experiment results are drawn from the 156 questionnaires that were completed by representatives from 18 countries, but with a strong representation of French respondents.

“Hence, d-CEIs offer margins of actions to scale up interventions and to maximise population health, while ensuring core values identified for European health care systems.”

The following main findings can be highlighted. Health loss and reversibility are the more important attributes, which is consistent with our hypotheses, with a clear advantage to the former (nearly two thirds of respondents); however, savings are playing a more important role in the decision-making than anticipated. Interestingly, compared to the hypothesised decision sequence which ranked the reversibility argument as second after the health loss attribute, a larger than expected number of respondents ranked the size of costs savings as the second most important attribute, with reversibility ranked third. Participants put in balance health loss and reversibility, a hardly reversible but small loss being judged acceptable, just as would be a significant health loss but reversible at any time. In addition, disease severity and uncertainty about the cost-savings were introduced as sensitivity attribute in the discrete choice experiment; a lower health loss could be balanced with a higher disease severity (from low to moderate – the discrete choice experiment intentionally excluded high severity or end-of-life care). Uncertainty about the cost-saving also tended to play a more important role in the decision-making than expected: indeed, a lower uncertainty seems to acts as a guarantee of the appropriateness of choosing a decrementally cost-effective intervention, although higher levels of cost-savings might understandably come along with a greater level of uncertainty. When asked which additional attributes would need to be addressed when considering d-CEIs’ adoption and their rank, respondents placed uncertainty about the health losses as being the most important attribute. This finding validates the approach taken in the discrete choice experiment in which uncertainty about health losses was left out as it would have dominated the other attributes.

The results of the DCE informed a “decision-tree” to guide decision-makers’ choice of adoption of decremental cost-effective interventions (Figure 9, p34). The decision-tree is a component of a toolbox comprising three tools, each covering a different stage in the decision-making process from d-CEI consideration to adoption. The toolbox is also composed of the **actual discrete choice experiment** which can be used in many different settings, such as HTA committees or for teaching purposes, in order to illustrate the individual and collective stakes associated with adopting d-CEIs, and of an **ethical/political check-list** that aims to inform the appropriateness and acceptability of considering d-CEIs as part of the healthcare basket. The toolbox was delivered together with a Political Economy Report that is analyzing the broader economic, ethical and political aspects tied to the assessment and adoption of d-CEIs.

Impact

Decrementally cost-effective interventions imply both cost-savings and potential health losses, as perceived by the patient population, compared to incrementally cost-effective alternatives. Some of these interventions have been found to be highly cost-effective but are rarely adopted. The objective of these interventions is not to save money per se but rather to maximise the cost-effectiveness of the interventions included in the healthcare basket, which offers the prospect to safeguard sustainability (by eliminating obsolete or dominated interventions), to maximise population health (by reallocating savings on interventions bringing the most health improvements), and to accommodate special needs (by prioritising costlier alternatives on target populations according to their health or social statuses). Hence, d-CEIs offer margins of actions to scale up interventions and to maximise population health, while ensuring core values identified for European health care systems.

Recommendations and Future Direction

Mainstreaming: when deciding about implementing a new intervention, decision-makers shall be encouraged to systematically consider d-CEIs as ethically licit and politically acceptable, thereby ensuring that they are systematically considered when defining the range of alternative treatments;

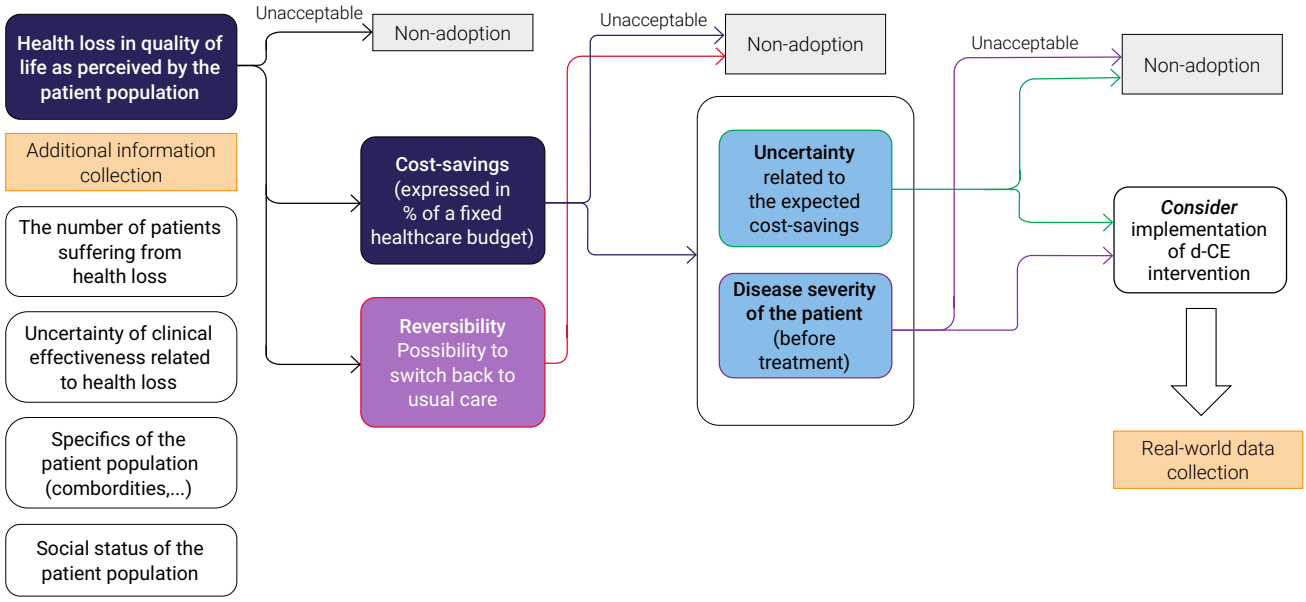
Inclusiveness and transparency in the deliberation that governs decisions are important components in securing stakeholders' understanding, participation in documenting the stakes (e.g. disease experience), and possible adherence in case of adoption;

Exhaustivity: All forms of d-CEIs should be considered, such as complementary non-pharmaceutical interventions or stepped care approaches, which implies that disease level should be monitored and treatment adjusted accordingly, stepping up when more intensive treatments are deemed necessary, stepping down where less intensive treatments become appropriate, stepping out when an alternative possibly non-pharmaceutical intervention, or when watchful waiting, is appropriate.

Social justice and ethics: Considering d-CEIs in the HTA process should provide an incentive to explicitly discuss the underlying value-judgements, ethical and social justice principles embedded in the anticipated savings reallocation.

Multi-disciplinary research in d-CEIs is only just beginning, compared to other fields of application. Workshops have shown the potential of the discrete choice experiment to illustrate the **interplay of individual and collective preferences and the potential value of d-CEIs but also their risk of being simply associated to cost-containment.** More collaborative research action is needed, jointly with HTA agencies, in order to further investigate the willingness of decision-makers in the European Union to consider the implementation of d-CEIs according to the specifics of their national healthcare systems and of the institutional differences in their legal systems. By enhancing the current European representativeness of the discrete choice experiment results, by reaching out to lay persons, in order to document population preferences, to be compared with those of decision-makers, and by expanding research to mixed approaches, such as stepped care or combined use of pharmaceutical and non-pharmaceutical interventions, useful complementary evidence could be collected on the true potential of d-CEIs.

Figure 9. The pathway from d-CEI consideration to adoption



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