ISPOR Report

21st Annual
European Congress
Barcelona, Spain
November 2018

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costello medical

Foreword

Sophie Costello, Director and CEO

Costello Medical celebrated our 10th anniversary on 11th November 2018, which fittingly coincided with the 21st European International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Congress.

Members of our team have been attending ISPOR at its various worldwide locations since the company was founded. We have seen ISPOR grow both in terms of attendance and in the breadth and depth of the topics covered, reflecting the changing nature of healthcare over the last 10 years. We have learnt so much from these meetings and have all benefitted from the opportunity to be involved in a community committed to ensuring that healthcare decisions are informed by the very best scientific research. We have also been delighted to contribute to ISPOR through our own issue panels, oral presentations and posters.

Beyond educating us on novel methodologies and approaches, our experiences at the congress have also opened our eyes to other healthcare markets. In fact, it was our participation in the ISPOR Asia-Pacific meeting in 2012 that drove us to expand into this region, with our Singapore office established in 2014 and an office in Shanghai planned for 2019.

We look forward to presenting more of our own research at ISPOR 2019 in New Orleans, the same year that we will establish Costello Medical's first US base. For more information about our global expansion, please contact **Craig Brooks-Rooney** (**craig.brooks-rooney@costellomedical.com**).

The Congress

21st Annual European ISPOR Congress, Barcelona Spain, 10th–14th November 2018

New Perspectives for Improving 21st Century Health Systems

>5,000 healthcare stakeholders

2,500 presentations

Our report summarises key learnings and insights from the Costello Medical team that attended the meeting, covering the following themes and challenges facing 21st century health systems.

Understanding Value in New Contexts

Valuing Curative Therapies

Increasing numbers of therapies offer potentially curative treatment in a wide range of indications, such as gene therapies for monogenic diseases (e.g. haemophilia or sickle cell disease), chimeric antigen receptor T (CAR-T) cell therapies in oncology, and direct-acting antivirals for hepatitis C. In contrast to chronic treatments that result in substantial long-term costs, these curative treatments tend to be associated with high upfront costs and thus substantial budget impact, whilst their available evidence is associated with significant uncertainty. In light of these considerations, the IP16 panel discussed whether standard health technology assessment (HTA) methods are sufficient to ensure value for money and efficient budget allocation for health systems, whilst maximising patient access, in the face of uncertainty that is likely to persist over many years.[1]

Mark Sculpher, Professor of Health Economics (University of York), argued that the challenges facing the evaluation of curative therapies are not necessarily unique or new, and that methods are available to address them (e.g. value of information [VoI] analysis), but not widely used. Thus, instead of radical changes to the current framework, existing methods need to be promoted and developed further.[1] In principle, this seems plausible. However, until these methods become fit-for-purpose and integrated with decision-making, risks remain: for instance, reimbursing a treatment for which the long-term benefit was overestimated, or preventing patient access to a treatment due to uncertainty and later finding that the treatment did offer significant long-term benefit.

> Time seems an important factor here. We aren't seeing particularly strong signals from NICE (which typically might be expected to lead the way in such things) that new methods such as VoI analysis will be formally adopted to inform decision-making any time soon; if these methods aren't going to be used, then their existence in the academic sphere offers little reassurance for imminent decisions on curative therapies. Managed access/risk-sharing agreements are important tools to avoid potentially harmful restriction of access in the current context, and we have seen the value of this option with the approval of CAR-T therapies for acute lymphoblastic leukaemia and diffuse large B-cell lymphoma via the Cancer Drugs Fund in England. However, this fund is unique to oncology, and therefore as long as payer acceptance of managed access and risk-sharing agreements remains as lukewarm as it has been, curative non-oncologic therapies remain particularly exposed under the status quo. Therapies of curative potential are here now, so simply carrying on with the current framework **AND** current methods is not an option – one of the two has to give.
>
> *– Matt Griffiths, Head of HTA and Health Economics*

Additionally, as long as achieving reimbursement of curative therapies is difficult or unpredictable following standard HTA methods, the current framework may not be providing incentives for manufacturers to invest in the research and development of curative therapies, instead favouring chronic alternatives that may have a more reliable return on investment.

Various potential solutions were discussed by the panel, including annuity payments, performance-based risk-sharing agreements and managed access agreements, which can provide the opportunity for coverage whilst uncertainty is resolved. Panellists also suggested that existing funding models for preventative medicines (e.g. vaccines) could potentially provide inspiration, given that these therapies face some similar issues. However, the implications of such approaches must be carefully considered – disinvestment would be appropriate should further evidence development fail to prove a therapy is cost-effective, but the consequences should be clear from the outset, including the potential impact on patients already receiving treatment.

Until we see a change in the framework or further adoption and development of new methods, the best manufacturers can do to maximise their chances of reimbursement is to be robust in their use and justification of approaches for modelling curative therapies, making the best use of all data available, including evidence other than short-term trial data such as RWE and expert elicitation.

Methodologies for such approaches were the subject of many other sessions at the congress and are discussed further in *Evidence Collection and Modelling: an Update on the Latest Technical Discussions* on p. 12 of this report.

Valuing Combination Therapies

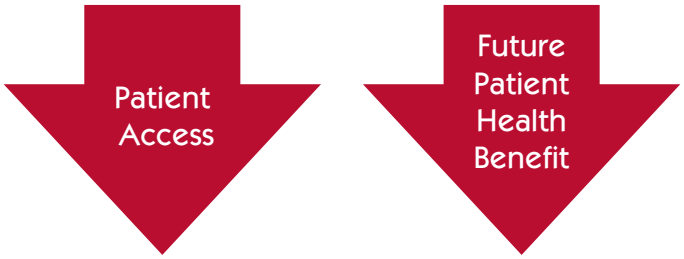
Matt Griffiths, Head of HTA and Health Economics

Combination therapies pose a significant problem for value assessment frameworks, and IP17 made it clear that there are no easy solutions.[2] The key challenge is that the combined price of each constituent of a combination therapy is often not commensurate with the value-based price of the combination therapy. This challenge is heightened when the constituents of a combination therapy are manufactured by different companies (referred to hereafter as 'multi-manufacturer combinations'), which can significantly complicate the pricing equation and limit pricing flexibility.

For multi-manufacturer combinations there are three potential scenarios, with distinct implications for immediate patient access and long-term incentivisation of future research into combination therapies.

Scenario 1

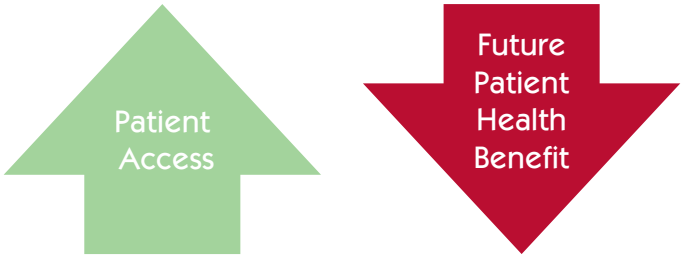
A value-based price cannot be agreed



Research into combination therapies disincentivised = reduced innovation and foregone future patient health benefit

Scenario 2

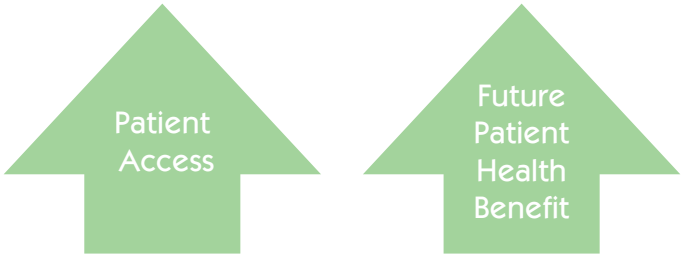
A value-based price is achieved through price "concessions" from **one** manufacturer* of a constituent of the combination therapy



Research into combination therapies disincentivised = reduced innovation and foregone future patient health benefit

Scenario 3

A value-based price is achieved through price "concessions" from **each** manufacturer of a constituent of the combination therapy



Future investment into R&D for combination therapies incentivised

*In practice this would be the manufacturer bringing the combination therapy to the table (i.e. the manufacturer adding their therapy to existing therapy(ies) to present a novel combination).
Indicated outcomes are a simplification for illustration and predicated on the assumption that combination therapies do offer patient health benefit and represent an innovation that is worth R&D investment from the perspective of future patient health.
Abbreviations: R&D: research and development.

Combination-specific (and/or indication-specific) pricing may provide part of the solution by permitting greater price flexibility and therefore raising the likelihood of agreeing a value-based price. However, this *alone* doesn't seem sufficient to achieve the twin goals of patient access and incentivising future research. The final combination price would still be a product of strategic negotiations potentially involving multiple manufacturers and the payer. There would be many complex factors at play in such negotiations, not all necessarily aligned to a goal of affordable patient access to the novel combination (e.g. confidentiality of prices; protecting existing monotherapy market share; denying market entry to a competitor).

IP17 discussed the concept of attribution, whereby each constituent of the combination therapy is priced according to its contribution towards the overall value of the combination.[2] Theoretically, this seems fair (assuming acceptance of the premise of a value-based assessment framework), but practically the methodological issues with determining attribution are clear. Complex clinical trial designs can help robustly estimate the benefit of the combination and each monotherapy constituent, but synergistic effects of combining treatments mean that the relative benefits of each constituent as monotherapy may not be proportional to their relative contribution to the value of the combination therapy.

However methods of attribution might develop, the scope and incentive for divergent interpretations and disagreements amongst manufacturers seems large. Could this indicate a role for evaluation of combination therapies by independent assessment groups? NICE's multiple technology appraisal process provides a part-blueprint for this kind of approach. In theory, an independent assessment group could define attributable value-based prices, or at least how any final price should be relatively apportioned between constituents. However, this may be a move to "price-taking" for manufacturers (so quite a change from the current approach, for the UK at least). Of course, manufacturers could decline engaging with such a value-assessment, or decline to meet the determined price, but there could be flexibility for negotiation and this process would at least provide a starting point for discussion that seems more "neutral" amongst the constituent manufacturers of multi-manufacturer combinations compared to the current paradigm. It's just an idea – this is a challenging area with no simple solutions, but it's clear that flexible thinking is likely to be required to avoid foregoing patient health benefits by failing to achieve access to effective combination therapies and failing to incentivise research into these novel therapies.

Valuing Digital Health

William Marsh, Head of MedTech

Digital technologies represent an evolving, heterogenous market with a clear unmet need for understanding value, and loosely structured access and reimbursement pathways. Digital health is prized as a solution for many challenges facing modern healthcare systems, by enabling the population to track, manage and improve their own health. There were a number of discussions around the value that digital technologies could bring to healthcare research, with IP4 focussing on this topic. Above the direct impact of digital technologies on health outcomes, the panel focussed on the power of digital to capture health outcomes for data scientists.

Integrated with medical records, these data could drive further research to help prevent or manage disease, for example, using machine learning to predict health events based on data from wearable technology. Leaders from industry also discussed how digital technologies could drive value for other medical technologies when used to collect data for patients undergoing new treatments as part of value-based reimbursement agreements.[3]

However, the future of digital technologies in healthcare is not without its challenges...

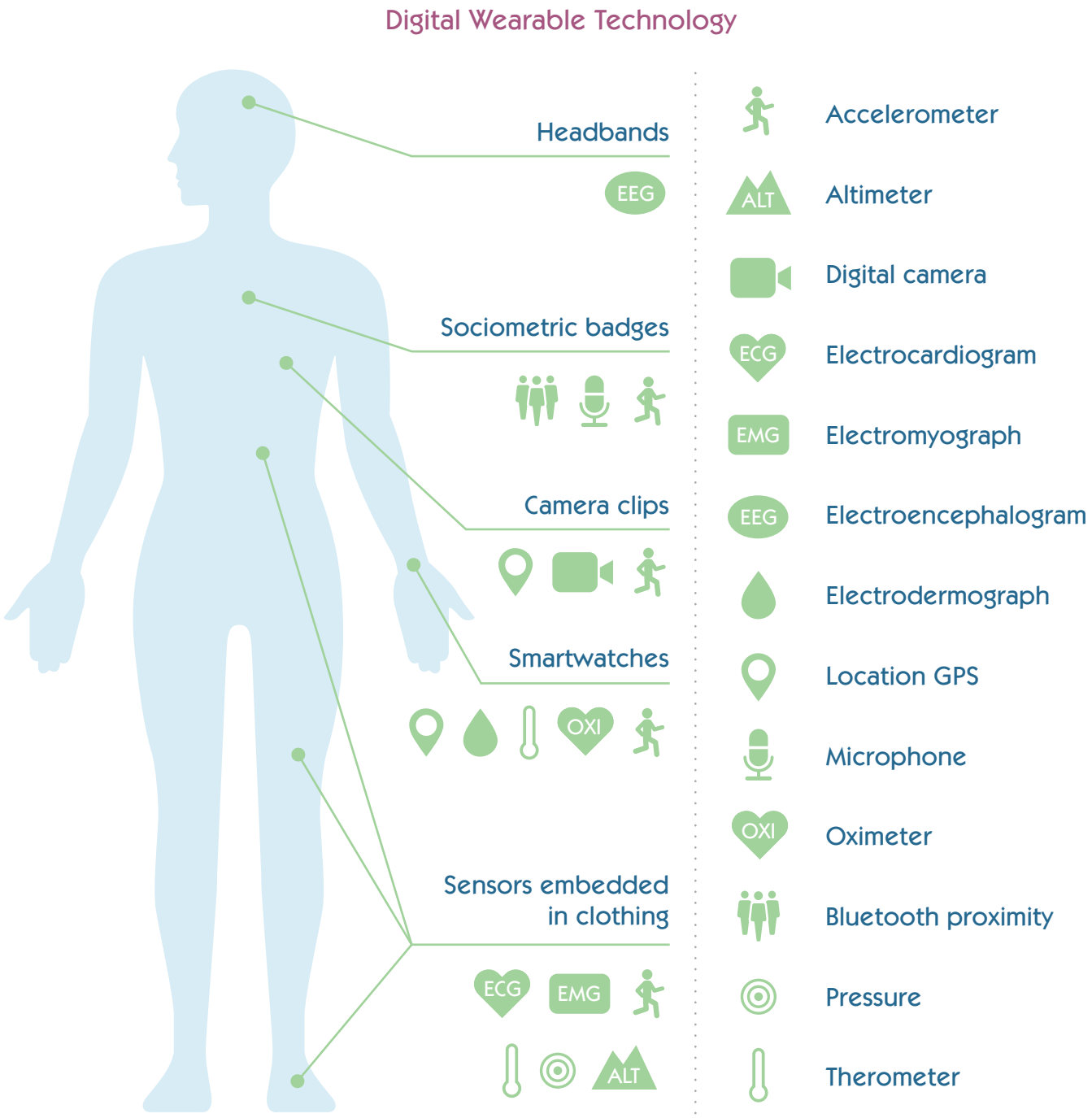
Data Access

For digital health to deliver these benefits, patients are required to grant access to their health data. IP13 discussed the ramifications of General Data Protection Regulation (GDPR), which protects such data for patients in the European Union (EU).[4] Whilst GDPR provides clear benefits for patient privacy, thus instilling trust when consenting to share data with manufacturers, the regulation introduces additional hurdles for app developers and data scientists, who need to track how data from digital technologies has been used in order to allow erasure of such data. Likewise, the hefty penalties for violating GDPR may be sufficient to dissuade developers from entering the market or collecting health data in the first place, which in turn may delay potential health benefits from being realised.

Appraisal of Digital Health Technologies

Costello Medical presented research highlighting the infancy of appraising digital health technologies across Europe, with few national HTA agencies providing guidance on how such technologies should be appraised and even fewer conducting any formal assessment.[5] NICE also touched on this topic by discussing their trial advice products for assessing digital technologies (Medtech Innovation Briefings [MIBs] and Improving access to psychological therapies Assessment Briefings [IABs]). From these trials, NICE concluded that their role in the future may be to layout an assessment framework to guide local decision-making, instead of developing national advice or recommendations; such a framework could set an early precedent for other markets to follow.[6]

Clearly, the evolution of digital technologies is outpacing the development of frameworks by which these technologies can be valued and appraised. Given how heterogenous these technologies are (from educational, to monitoring, to diagnostic, to service-based) and the influence these technologies can have on patient safety, it is no wonder there is such uncertainty in how to approach their assessment. Indeed, the discussions at ISPOR this year bring into question whether standardised guidelines are even appropriate for digital technologies, or whether such technologies should instead fall under existing frameworks for determining value for wider MedTech despite the limitations of this approach.

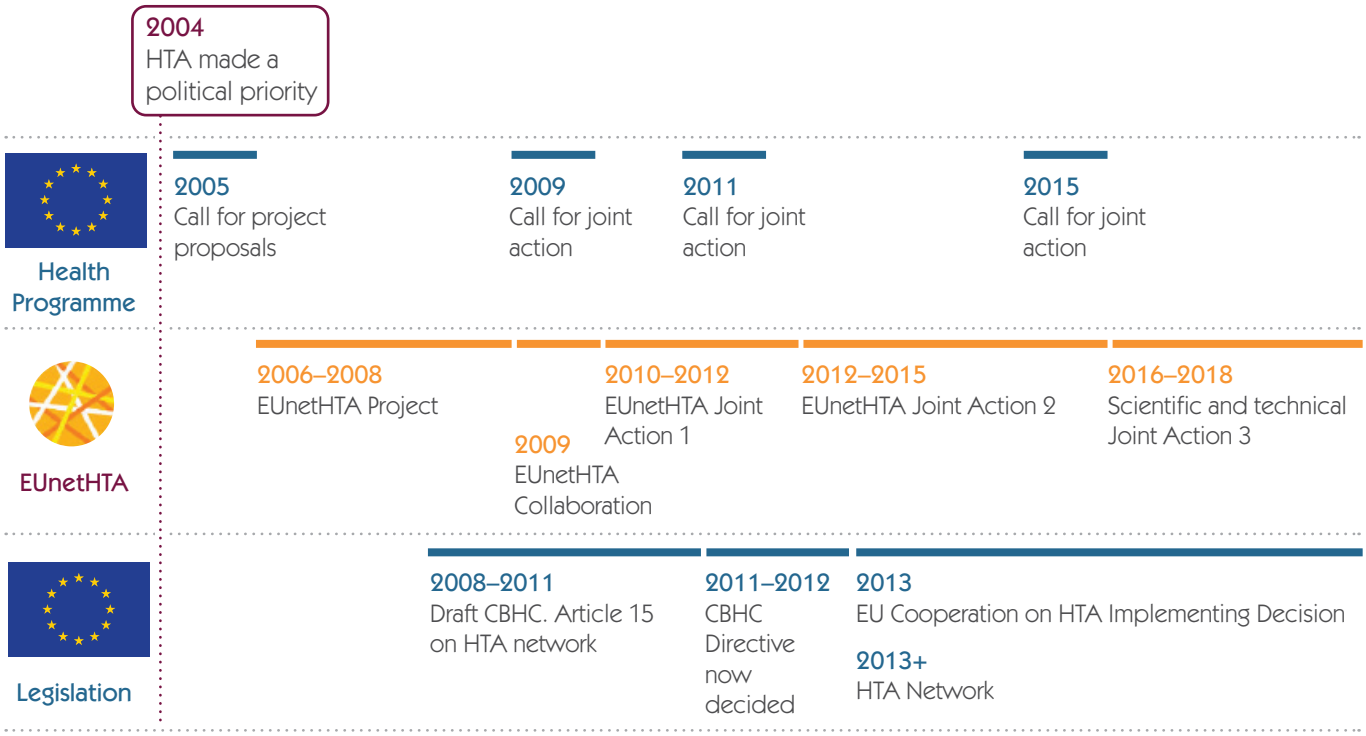


Abbreviations: GPS: Global Positioning System. Adapted from: IP13, ISPOR Europe 2018.[4]

European Cooperation Via Joint Assessment

Annabel Griffiths, Head of Rare Diseases

Aligning assessment of health technologies across Europe continues to be a focus at European ISPOR meetings. Indeed, a meeting wouldn't be complete without discussion of the European Network for Health Technology Assessment (EUnetHTA); however, this year it was evident that the tide may be turning. Following on from HTAi in June,[7] this year's opening plenary acknowledged scepticism amongst the community with the title "Joint assessment of relative effectiveness: trick or treat for decision makers in EU member states".[8] Speakers representing academia, EUnetHTA, patient groups, industry, the European Commission and payers showcased the substantial progress that has been made since HTA was made a "political priority" across Europe in 2004 (see figure).[9] Despite the seemingly circular discussions in the field of health economics and outcomes research (HEOR) about how joint assessment should be performed, the following highlight that headway has been made: the generation of common tools (e.g. submission templates), legislative progress (e.g. directive on patients' rights to cross-border care) and the increasing number of case studies of jointly produced HTA.[10]



Abbreviations: CBHC: Cross Border Healthcare Directive; EUnetHTA: European Network for Health Technology Assessment; HTA: health technology assessment. Adapted from: First Plenary Session, ISPOR Europe 2018.[8, 10]

Following the decision to "localise the decision" but "globalise the evidence" (i.e. limit EUnetHTA to joint clinical assessments, leaving economic evaluations and decision-making at the local level), the rationale for opposing joint assessment is on shakier ground. There remain, however, practical challenges when implementing such an approach, the most notable being the question of timeliness. Working on the principle that the objectives of joint clinical assessments are to improve efficiency and reduce costs associated with European HTA by minimising duplication, it still seems hard to imagine how joint clinical assessments will be produced early enough to avoid the need for separate local assessments of the clinical evidence base, especially where national HTA agencies seek early decision-making. Furthermore, points raised during discussions at the World Orphan Drug Congress in Barcelona the previous week included the potential for substantial delays to access by relying on this pan-European approach and, on the other hand, the potential data release issues if the report were to be published prior to marketing authorisation. These challenges are further confounded by other pan-country initiatives such as BeNeLuxA and FINOSE, which seem to run further risk of increasing, rather than reducing, duplicated efforts.

This being said, a compelling case was made for potentially expedited decision-making and cost savings if joint clinical assessments are used effectively and quality standards are maintained or, ideally, improved. Furthermore, joint approaches could allow capacity issues to be solved by combining expertise across countries. The need for such pooled efforts, particularly for more innovative medicines such as those increasingly being seen within the rare diseases space, is clear; however, the overarching issue, which cannot be avoided, is the political commitment from member states. With uptake of jointly produced assessments largely limited to countries with less established HTA programmes than the global leaders in HTA, the commitment of these global leaders to joint HTA will be of paramount importance if this initiative is to realise its potential across Europe.

Evidence Collection and Modelling: An Update on the Latest Technical Discussions

Incorporation of RWE in Health Economic Models

Amy Buchanan-Hughes, Evidence Development Consultant

As highlighted in this report's discussion of *Valuing Curative Therapies* (p. 6), an important step to better quantify the value of these therapies – and indeed, any treatment or health technology – is better use of all available data. As such, a number of workshops and presentations focused on the use of RWE in economic modelling.[11, 12] Most models already incorporate a range of RWE, from epidemiology to resource use or long-term survival data. Over the past few years, the dialogue in this area has shifted: from whether we should use RWE to how we should use it and how we should adjust for its inherent limitations (e.g. **Issue 1**).[13]

Across the various talks on diverse methods, one common theme was that sensitivity analysis is essential for testing the assumptions underlying any analysis incorporating RWE; factors to be considered could include the study design, length of follow-up, populations, interventions, outcome definitions, quality of the study, quality of the source of the evidence, parametric models for survival curves or approaches to handling missing data.[12] At the moment, it is unclear which sensitivity analyses are essential, but until further methods and guidance are developed the most important thing is for modellers to make sure sensitivity analyses are both performed and reported.

Issue 1

Standard parametric survival models may not reflect real-world survival in older populations; for example, a log-logistic model of survival in metastatic melanoma may predict that a 75 year-old will live another 30 years.[13]

Tool

Using a mixed model to combine real-world data on general population mortality with disease-specific hazards derived from randomised controlled trials (RCTs) can give a better reflection of reality: the disease-specific hazard decreases over time, but the total hazard still increases.

As with RCTs, a big problem with RWE is missing data, leading to loss of statistical power and increased risk of bias. In particular, RWE used for effectiveness evidence is generally only based on "on-treatment" data, so it is not possible to generate the equivalent of an intention-to-treat population without making assumptions about treatment persistence; it is important to take this into account when combining evidence from RCTs and RWE. ISPOR's special interest group for statistical methods in HEOR is currently working on the development of methods to account for missing data **(Issue 2)**.

A major limitation of any attempts to provide standardised guidance for the use of RWE in HEOR is the inherent heterogeneity of the data sources and the questions being asked from these data. Therefore, a more useful approach would be to focus on providing toolkits that let statisticians select methods appropriate to a specific situation. This also highlights the importance of having a strong interdisciplinary team involved in modelling: an apparently technologically superior statistical technique that does not take into account the real-world clinical situation is of little value.

Issue 2

HEOR data, such as costs obtained from RWE studies, may have unusual distributions; for example, many individuals in an observational study could have zero costs. Common techniques for modelling missing data, which rely on normal distributions, may give clinically implausible results in such cases.[14]

Tool

Using a Bayesian approach to model the relationships between observed and unobserved variables allows us to incorporate prior knowledge about the distributions or limits of variables.

Incorporation of Expert Elicitation in Modelling

Natalie Hearmon, Consultant Health Economist

Potential approaches to expert elicitation for economic modelling, and the validity of the procedure as a tool for obtaining relevant information, was a key topic for discussion at this year's congress.[15, 16] The need for consultation with clinical experts is commonplace when designing and building economic models – whether that be to validate a model structure, give insight into appropriate input parameter values where published data are lacking, or to interpret key model results and ensure these are representative of clinical practice. Although some formats for obtaining consensus expert opinion are well established, such as Delphi panels, no clear and generally applicable guidelines or protocols exist for engaging key opinion leaders (KOLs) to inform, for example, economic modelling for HTA submissions.

The use of expert opinion as a proxy data source has drawn criticism for a potential lack of objectivity and as a source of bias due to reliance on an individual's experience and potential for conflicts of interest. However, it can be argued that relying purely on alternatives (such as statistical extrapolation or fitting techniques) runs the risk of producing results which, although unbiased and objective, are not clinically plausible. Furthermore, certain approaches appear to have become widely accepted without any clear justification or evidence base, such as the practice of introducing default parameter variations for sensitivity analyses in the absence of reported confidence intervals or standard errors. A pragmatic approach, therefore, would seem to be taking all potential methods into account as far as possible to maximise advantages and balance out drawbacks across the board.

Several of these points were part of discussions at ISPOR,[15, 16] and from both these discussions and our experience it is clear that more robust, transparent and thorough methods are required when considering undertaking expert elicitation. It's therefore crucial that sufficient thought and time is dedicated to such engagement exercises when developing an economic model; to aid this process, we have put together a number of considerations and insights in a structured 'Practical Toolbox' ready for next time you need to consider validation of an economic model.

Practical Toolbox for Engagement with Experts

When?

- Before, during or after model development?
  - Early engagement has the advantage of ensuring key model development decisions are made in an informed manner, reducing the need for subsequent 'filtering' out of clinically implausible scenarios
  - Validation after model build ensures implementation of initial feedback has led to realistic representation of clinical outcomes

Who?

- Sample size – sufficient vs practical
  - To avoid consulting too many experts, choose e.g. KOLs involved more widely than just local practice, and with different perspectives to avoid potential bias
- Recognise that some questions may not have any 'experts' e.g. if the technology under consideration may fundamentally change the existing treatment pathway

How?

- Face-to-face vs phone call vs remote response (survey)
  - Depending on the complexity of the topic, would it be beneficial to be able to dynamically respond to KOLs with follow-up or clarification points?
- Group vs individual (with responses collated later)
  - Is active engagement between KOLs important, or would it be more useful to obtain independent thoughts?
- Ensure full understanding of the question being asked – could this be interpreted differently by health economists vs clinicians?
  - Avoid asking leading questions wherever possible
- Can protocols from other industries be used to inform the approach in healthcare?
- Aim to obtain a range instead of point values for unknown parameters, e.g. mean, quartiles and min/max plausible, from which a probability distribution can be estimated

Interpreting Results

- Calibrate and weight results by e.g. KOL performance on a 'test' question, or range/depth of experience
- If clear subgroups of, or differences in, opinion exist, consider why these may have arisen and test impact through sensitivity and scenario analyses
- Combine with other data sources (e.g. statistical predictions) to tease out clinically plausible scenarios
- Ensure methods are robust and easily reported in a transparent manner

Further Assistance

If you would like any further information on the topics presented above, please do not hesitate to contact **Matt Griffiths** at **matt.griffiths@costellomedical.com**. Many of the presentations from the congress can be found on the ISPOR website.

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About Costello Medical

Costello Medical provides scientific support to the healthcare industry in the analysis, interpretation and communication of clinical and health economic data. Due to growing demand across an increasing range of service offerings and geographies, Costello Medical has grown organically since its foundation in 2008 to a team of over 100 based in Cambridge, London and Singapore, with new offices opening in the US and China in 2019.

Alongside our evolving technical and creative capabilities, we remain committed to our core values of high quality scientific work coupled with exceptional customer service at competitive and transparent prices. Our talented team has experience with a variety of leading pharmaceutical and device companies across an extensive range of therapy areas and geographies, including Europe, Asia-Pacific and North America. In addition to our provision of services broadly across the pharmaceutical industry, we also have dedicated teams with specific areas of expertise, for example MedTech and Rare Diseases, and can provide the full range of our services for customers specific to these areas.

For more information on our services, please visit our website at **www.costellomedical.com**.

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