HAS THE TIME COME TO REPLACE RCTS WITH RWD?
THE CASE OF MDs
An HTA Perspective

Cynthia P Iglesias Urrutia MSc PhD
Associate Professor, Department of Health Sciences, University of York
Visiting Scientist, Department of Population Health, Luxemburg Institute of Health
Professor , Department of Business and Management , Aalborg University
E-mail: cynthia.iglesias@york.ac.uk
Disclaimer

I am employed by the University of York (UK) and sit on the Medical Technologies Advisory Committee (MTAC) of the Medical Technologies Evaluation Programme (MTEP) of the National Institute for Health and Care Excellence (NICE) for England and Wales,

however

The **views** expressed in this presentation **are my own** and do not necessarily reflect the position of my employer or those of NICE
Health Technology Assessment (HTA)

“... multidisciplinary field of policy analysis. It studies the medical, social, ethical and economic implications of development, diffusion, and use of health technology”

Source: International Network of Agencies for Health Technology Assessment (INAHTA) http://www.inahta.org/

“... multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner ... It informs policy- and decision-making in specific political, economic and institutional contexts ... to be useful HTA has to be designed with processes and outputs that fit the relevant context.”


“... a method of evidence synthesis that considers evidence regarding clinical effectiveness, safety, cost-effectiveness and, when broadly applied, includes social, ethical, and legal aspects of the use of health technologies... A major use of HTA is in informing reimbursement and coverage decisions, in which case HTAs should include benefit-harm assessment and economic evaluation.”

MDs HTA Data Requirements

- **Health Problem**
  - Epidemiological data

- **Technology Description**
  - Mechanism of action data

- **Clinical Effectiveness**
  - Efficacy data
  - Performance data
  - Effectiveness data

- **Cost Effectiveness**
  - Resource use data
  - Cost data
  - Health benefit data

- **Safety**
  - Adverse events data
  - Unintended consequences data
MDs HTA Data Scarcity

- Premarket explanatory RCTs available for MDs associated with greater level of risk
  - RCTs of MDs is challenging
  - Explanatory RCTs provide evidence of efficacy
- Pragmatic RCTs are the gold standard source for clinical effectiveness
- Scarcity of evidence for HTA of MDs
  - Delaying decisions is costly - benefits forgone by those who could have timely accessed innovative health technologies
- HTA Agencies require a pragmatic approach to the available evidence to achieve reasonable and defendable decisions
“For too long a false conflict has been created between those who advocate randomised trials in all situations and those who believe observational data provide sufficient evidence. Neither position is helpful. There is no such thing as perfect method; each method has its strengths and weaknesses. The two approaches should be seen as complementary.... When trials can not be conducted, well designed observational methods offer an alternative to doing nothing.”

Source: Black, N. Why we need observational studies to evaluate the effectiveness of healthcare. BMJ.1996. 312;7040:1215-18.
### MDs Evidence Generation: Challenges and Solutions

<table>
<thead>
<tr>
<th>RCT rigid to evaluate MDs</th>
<th>Blinding difficult to ensure</th>
<th>Rapid incremental development</th>
<th>Outcome measurement time span</th>
<th>Practitioner and patients’ preferences impact on treatment effect</th>
<th>Variations in technical proficiency impact on treatment effect (learning curve)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pragmatic RCTs: seek to inform clinical decision making by evaluating an intervention in a realistic clinical setting)</td>
<td>Use nonstandard creative strategies</td>
<td>Tracker trials: continue follow up of trial participants beyond trial follow up as a prospective cohort</td>
<td>Comprehensive cohort design</td>
<td>i) Base treatment allocation on patient’s preferences ii) Comprehensive cohort design iii) Statistically explore relationship between preferences and outcomes</td>
<td>i) Single healthcare provider ii) Statistically explore learning curve effect in main trial outcome</td>
</tr>
</tbody>
</table>
## HTA Agencies’ Perspective

Table II. Nature of evidence considered by health technology assessment reports

<table>
<thead>
<tr>
<th>Type of clinical study</th>
<th>Drug (N = 18)</th>
<th>Device (N = 27)</th>
<th>Drug versus device</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Median (range)</td>
<td>n (%)</td>
</tr>
<tr>
<td>RCTs</td>
<td>17 (94)</td>
<td>5 (1; 35)</td>
<td>18 (67)</td>
</tr>
<tr>
<td>Non-RCTs</td>
<td>4 (22)</td>
<td>5.5 (1; 18)</td>
<td>12 (44)</td>
</tr>
<tr>
<td>Observational studies</td>
<td>3 (17)</td>
<td>46 (13; 92)</td>
<td>13 (48)</td>
</tr>
<tr>
<td>Evidence synthesisc</td>
<td>6 (33)</td>
<td>5.5 (5; 30)</td>
<td>8 (30)</td>
</tr>
<tr>
<td>Otherd</td>
<td>1 (6)</td>
<td>89 (NA)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Number of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCTs</td>
<td>13 (72)</td>
<td>4203 (34; 66 477)</td>
<td>12 (44)</td>
</tr>
<tr>
<td>Non-RCTs</td>
<td>3 (17)</td>
<td>4917 (926; 184 372)</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Observational studies</td>
<td>1 (6)</td>
<td>7636 (NA)</td>
<td>7 (26)</td>
</tr>
<tr>
<td>Evidence synthesisc</td>
<td>1 (6)</td>
<td>102 594 (NA)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Type of economic evaluation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost analysis</td>
<td>1 (6)</td>
<td>5 (NA)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Cost minimisation analysis</td>
<td>0 (0)</td>
<td>—</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cost-effectiveness analysis</td>
<td>8 (44)</td>
<td>4 (1; 20)</td>
<td>9 (33)</td>
</tr>
<tr>
<td>Cost-utility analysis</td>
<td>8 (44)</td>
<td>3.5 (1; 8)</td>
<td>9 (33)</td>
</tr>
<tr>
<td>Cost–benefit analysis</td>
<td>0 (0)</td>
<td>—</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Cost–consequence analysis</td>
<td>0 (0)</td>
<td>—</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

RCTs, randomised controlled trial; HTA, health technology assessment.

aMann–Whitney test.
bFisher’s exact test.
cSystematic reviews, meta-analyses and HTA reports.
dRapid reviews and sources of evidence that do not fall into the aforementioned hierarchy of evidence categories.

RWD Contribution to MDs HTA Requirements

- Epidemiological Data
  - Subgroup analysis
- Mechanism of Action
  - Incremental innovation
- Efficacy
  - Baseline risk
  - Treatment effect
  - Extrapolation
  - Subgroup analysis
- Resource Use
  - Cost
  - Subgroup analysis
- Health Benefit
- Adverse Events
  - Surveillance
  - Long term effects
  - Surveillance
### RWD contribution to MDs HTA

**Table 3 – Summary of policies on RWD accepted or requested and the appraisal of RWD in the context of IRD per agency.**

<table>
<thead>
<tr>
<th>HTA agency</th>
<th>RWD accepted</th>
<th>RWD to inform treatment effects</th>
<th>RWD to inform other parameters</th>
<th>Hierarchy of evidence adopted</th>
<th>Conclusions on treatment effects on the basis of RWD regarded as circumpect</th>
<th>Conclusions on treatment effects on the basis of RWD possible in exceptional circumstances (e.g., orphan diseases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLV</td>
<td>Yes</td>
<td>Under specific circumstances</td>
<td>Not mentioned</td>
<td>Yes; with regard to evidence for treatment effects</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>NICE</td>
<td>Yes</td>
<td>Under specific circumstances</td>
<td>Epidemiological data (e.g., incidence and prevalence), resource use data, and cost data</td>
<td>Yes; with regard to evidence for treatment effects</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>IQWiG</td>
<td>Yes</td>
<td>Under specific circumstances</td>
<td>Epidemiological data (e.g., incidence and prevalence) and resource use data</td>
<td>Yes; with regard to evidence for treatment effects</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>HAS</td>
<td>Yes</td>
<td>Under specific circumstances</td>
<td>Not mentioned</td>
<td>Yes; with regard to evidence for treatment effects</td>
<td>Yes</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>AIFA</td>
<td>Yes</td>
<td>Under specific circumstances</td>
<td>Not mentioned</td>
<td>Yes; with regard to evidence for treatment effects</td>
<td>Yes</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>ZIN</td>
<td>Yes</td>
<td>Under specific circumstances</td>
<td>Epidemiological data (e.g., incidence and prevalence), resource use data, and cost data</td>
<td>Yes; with regard to evidence for treatment effects</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

AIFA, Italian Medicines Agency; HAS, High Authority for Health; HTA, health technology assessment; IQWiG, Institute for Quality and Efficiency in Healthcare; IRD, initial reimbursement discussion; NICE, National Institute for Health and Care Excellence; RCT, randomized controlled trial; RWD, real-world data; TLV, Dental and Pharmaceutical Benefits Agency; ZIN, National Healthcare Institute.

*However, agency explicitly recognizes limitations associated with strictly adopting evidence hierarchies in guidelines and states that such hierarchies should not preclude the exclusion of valuable non-RCT evidence from decision making.*

MDs HTA Decision Making

- Safety and Innovation
- Other Health Benefits
- Value judgements (scientific and social)
- Cost Effectiveness
- Clinical Effectiveness
- Expert Opinion
- Uncertainty
- Equity

Recommendation
MDs Evidence Analysis: Issues and Potential Solutions

• Bias assessment and adjustment
  – Complementary use of RCT and observational data
    – Bayesian generalised evidence synthesis
    – Bayesian expert elicitation

• Uncertainty characterisation
  – Characterisation of anecdotal evidence
    – Bayesian expert elicitation
  – Estimate cost of decision uncertainty
    – Comprehensive EE
    – Bayesian decision analysis
    – Bayesian value of information analysis

• Unifying research and reimbursement decisions
Examples

Does assessing the value for money of therapeutic medical devices require a flexible approach?


Cynthia P Iglesias
Department of Health Sciences, The University of York, YO10 5DD, UK
and York Medical School, The University of York, YO10 5DD, UK

Regulation criteria for licensing pharmaceuticals and medical devices are asymmetric. This has affected the type, quantity and quality of the evidence provided in support of MDs. This paper has three objectives: to examine the reasons behind the current licensing criteria for MDs; to identify key methodological challenges associated with pre- and post-market evaluation of MDs; and to assess the extent to which existing methods for the economic evaluation of pharmaceuticals can be applied to the evaluation of MDs. The belief that MDs cannot be properly evaluated stems from a combination of historical events and complexities in implementing rigorous RCTs in this field. Existing challenges to conduct sound economic evaluation of MDs have begun to be addressed in medical research using mixed research methods. While more challenging to implement, robust evaluations of therapeutic MDs can and need to carried out to safeguard individual's well-being.

Pharmacoeconomics (2016) 34:1161–1172
DOI 10.1007/s11136-016-0623-9

ORIGINAL RESEARCH ARTICLE

Reporting Guidelines for the Use of Expert Judgement in Model-Based Economic Evaluations

Cynthia P Iglesias,Alexander Thompson, Wolf H Rogowski and Katherine Payne

Published online: 30 June 2016 © Springer International Publishing Switzerland 2016

Abstract
Introduction Expert judgement has a role in model-based economic evaluations (EBEs) of healthcare interventions. This study aimed: (1) to develop reporting criteria for two types of study design to use expert judgement in model-based EBE: (i) an expert elicitation study (EES) and (ii) a Delphi study to collate qualitative expert opinion. Methods A two-round Delphi study was conducted. Consensus was achieved for four core definitions (expert, expert parameter values, expert elicitation study and expert opinion). These were used as the basis for developing a Delphi study to collate expert opinion. The initial set of reporting criteria comprised 17 items. For the expert elicitation study a further 15 items were added. An expert elicitation study was added to the Expertise criteria: (i) an expert elicitation study (EES) and (ii) a Delphi study to collate expert opinion (1 criteria).

Conclusions
This study has produced guidelines for reporting expert judgement in model-based economic evaluations. It is the first time guidelines have been developed for the expert elicitation study. The guidelines are in addition to definitions and recommended reporting criteria for EEs and Delphi studies to collate expert opinion. The guidelines are intended to improve the reporting of expert judgement in model-based economic evaluations.

Methods to Assess Cost-Effectiveness and Value of Further Research When Data Are Sparse: Negative-Pressure Wound Therapy for Severe Pressure Ulcers

Maria O. Souris, MSc, Jo C. Danville, PhD, Rebecca L. Ashby, PhD, Cynthia P. Iglesias, PhD, Laura Bokar, PhD, Una Alderley, MSc, Elizabeth McGinnis, PhD, Nikki Stubbis, MSc, David J. Torgerson, PhD, Karl Claxton, PhD, Nicky Gulliford, PhD

Health care resources are scarce, and decisions have to be made about how to allocate funds. Often, these decisions are based on sparse or imperfect evidence. One such example is negative-pressure wound therapy (NPWT), which is a widely used treatment for severe, chronic wounds. However, there is currently no robust evidence that it is effective or cost-effective. This work conducted a decision to adopt a negative pressure wound therapy (NPWT) model. The model was constructed using a decision analytic modeling approach. Literature searches were conducted to identify existing evidence on model parameters. Given the limited evidence base, a second source of evidence, beliefs elicited from experts, was used. Judgments from experts on relevant (unknown) quantities were obtained through a Delphi study. The results of the trial were also used to inform the model. The 3 sources of evidence were collated, and the impact of each on cost-effectiveness was evaluated. An analysis of the value of further information indicated that a randomized controlled trial may be worthwhile in reducing decision uncertainty, where a set of alternatives designs. A learning trial with longer follow-up was estimated to be the most efficient. The analyses presented demonstrate how allocation decisions about medical tech- nologies which are beneficially for patients are made and how this kind of analyses can be used to gauge future research prioritization, and only indicating whether further research is worthwhile but what type of research is needed and how it should be designed. Key words: Markov model; elicited evidence; pilot trial; negative pressure wound therapy; evidence synthesis; expected value of information; research design; cost-effectiveness analysis. (Med Decis Making 2015;05:415–430)

A BIAS-ADJUSTED EVIDENCE SYNTHESIS OF RCT AND OBSERVATIONAL DATA: THE CASE OF TOTAL HIP REPLACEMENT

PETHA SCHNELL-INDERERT, CYNTHIA P IGLESIAS, MARIAN ARVANDI, ORIANA CIANI, RAFFAELLA MATTEUCI GOTH, JAIME PETERS, ASHLEY W BLOOM, ROD S TAYLOR and UWE SIEBERT

1 Institute of Public Health, Medical Decision Making and Health Technology Assessment, Department of Public Health, Health Services Research and Health Technology Assessment, UMEF—University for Health Sciences, Medical Informatics and Technology, Eberswalde
2 Department of Health Sciences, University of York, Heslington, UK
3 Hull and York Medical School, University of York, UK
4 Hoffmann-La Roche, Inc, Basel, Switzerland
5 Institute of Health Services Research, University of Essen Medical School, Essen, UK
6 Center for Research on Health and Social Care Management, Bocconi University, Milan, Italy
7 Center for Health Decision Science, Department of Health Policy and Management, Harvard T.H. Chan School of Public Health, Boston, MA, USA
8 Institute for Technology Assessment and Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Abstract
Evaluation of clinical effectiveness of medical devices differs in some aspects from the evaluation of pharmaceuticals. One of the main challenges identified is lack of robust evidence and a will to make use of experimental and observational studies (OSAs) in quantitative evidence synthesis accounting for internal and external biases. Using a case study of total hip replacement to compare the risk of revision of cemented and uncemented implant fixation modalities, we provide treatment effect estimates from OSAs and RCTs, and simplified existing methods for bias-adjusted evidence synthesis to enhance practical application. We performed an elicitation exercise using methodological and clinical experts to determine the strength of beliefs about the magnitude of internal and external bias affecting estimates of treatment effect. We incorporated the bias-adjusted treatment effect estimates into existing network meta-analysis models. The results were compared to those obtained from the unadjusted treatment effect estimates. The summary estimates obtained using the bias-adjusted treatment effect estimates from OSA and RCTs were compared using a generalised mixed linear model. The methodological variability was estimated relative risks as summary effect estimates with 95% confidence/credibility intervals to capture uncertainty. We used network meta-analysis for synthesizing evidence and demonstrated that the pooled effect size strongly depended on the inclusion of observational data as well as on the use bias-adjusted estimates. We demonstrated the feasibility of using observational studies in meta-analyses to complement RCTs and incorporate evidence from a wide spectrum of clinically relevant studies and healthcare settings. To ensure internal validity, OS data require sufficient correction for confounding and selection bias, either through study design and primary analysis, or by applying post-hoc bias adjustment to the results. © 2017 The Authors. Health Economics published by John Wiley & Sons, Ltd.

CHARACTERISING UNCERTAINTY IN THE ASSESSMENT OF MEDICAL DEVICES AND DETERMINING FUTURE RESEARCH NEEDS

CLAIRE ROTHERY, KARL CLAXTON, STEPHEN PALMER, DAVID EPSSTEIN, ROSANNA TARRICONE and MARK SCULPHER

1 Centre for Health Economics, University of York, York, UK
2 Department of Economics and Related Studies, University of York, York, UK
3 Centre for Applied Epidemiology, University of Granada, Granada, Spain
4 Centre for Research on Health and Social Care Management, Bocconi University, Milan, Italy
5 Department of Policy Analysis and Public Management, Bocconi University, Milan, Italy

Abstract
Decisions about the adoption of medical interventions are informed by evidence on their costs and effects. For a range of reasons, evidence relating to medical devices may be limited. The decision to adopt a device early in its life cycle when the evidence base is least mature may impact on the prospects of acquiring further evidence to reduce uncertainty. Equally, rejecting a device will result in no uptake in practice and hence no chance to learn about performance. Decision options such as "only in research" or "approval with research" can overcome these issues by allowing patients early access to promising new technologies while limiting the risks associated with making incorrect decisions until more evidence or learning is established. In this paper, we set out the issues relating to uncertainty and the value of research specific to devices: learning curve effects, incremental device development, innovation and irrecoverable costs, and dynamic pricing. We show the circumstances under which an only in research or approval with research scheme may be an appropriate policy choice. We also consider how the value of additional research might be shared between the manufacturer and health sector to help inform who might reasonably be expected to conduct the research needed. © 2017 The Authors. Health Economics published by John Wiley & Sons, Ltd.