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

An HTA Perspective

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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 of those of NICE

Health Technology Assessment (HTA)

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" … 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/

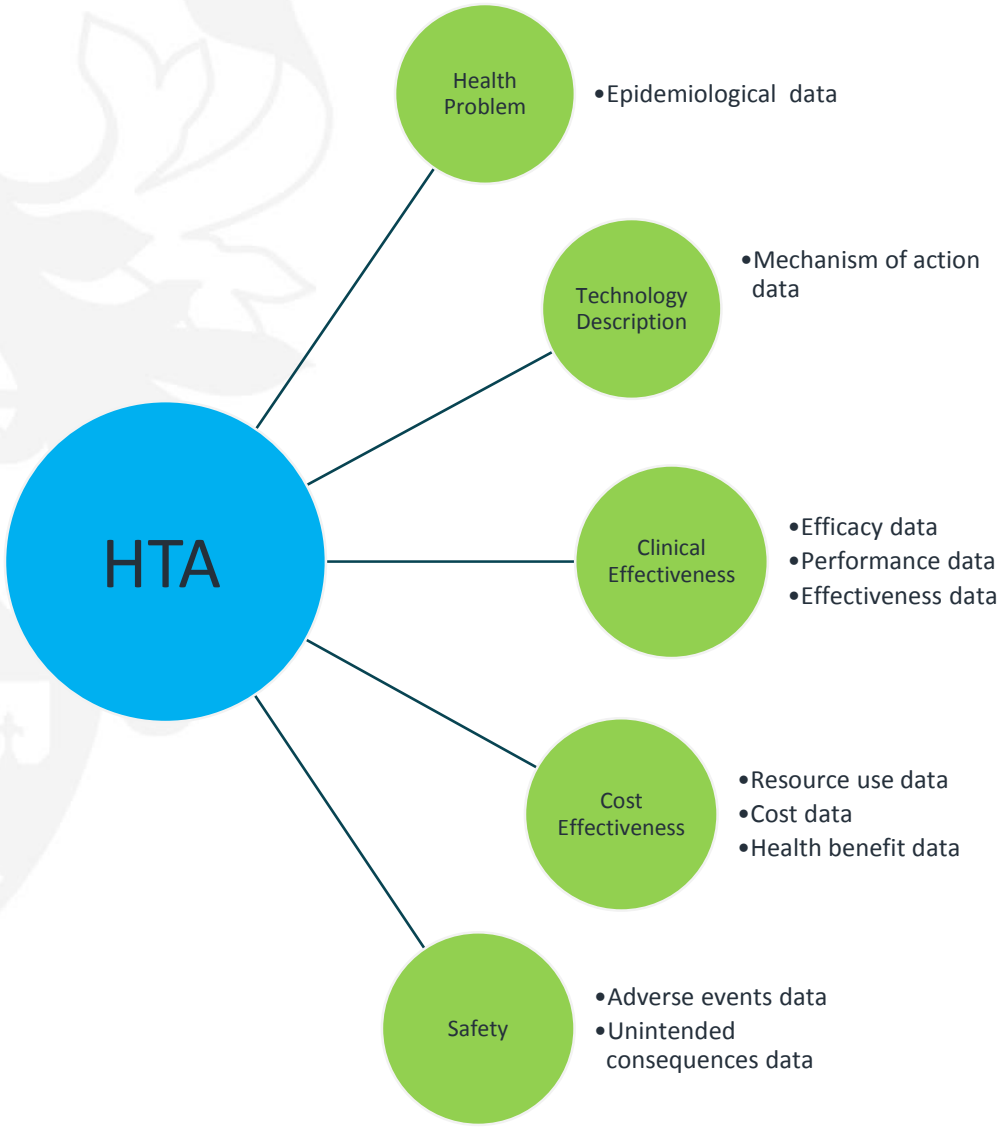
" … multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a **systematic**, **transparent**, **unbiased**, **robust** manner … It informs policy- and decision-making in specific political, economic and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

Source: Kristensen FB (2006). EUnetHTA and health policy-making in Europe. Eurohealth, 12(1):36–38.

" …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."

Source: Luce BR, Drummond M, Jönsson B, Neumann PJ, Schwartz JS, Siebert U, Sullivan SD. EBM, HTA, and CER: clearing the confusion. Milbank Q. 2010 Jun;88(2):256-76

MDs HTA Data Requirements



MDs HTA Data Scarcity

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- 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

Perspective – RCT and RWD

"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

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

HTA Agencies' Perspective

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

	Drug ($N=18$)		Device ($N=27$)		Drug versus device	
	n (%)	Median (range)	n (%)	Median (range)	P-value for %[b]	P-value for median[a]
Type of clinical study						
RCTs	17 (94)	5 (1; 35)	18 (67)	5 (1; 82)	0.03	0.92
Non-RCTs	4 (22)	5.5 (1; 18)	12 (44)	6 (2; 29)	0.13	0.43
Observational studies	3 (17)	46 (13; 92)	13 (48)	25 (4; 53)	0.03	0.24
Evidence synthesis[c]	6 (33)	5.5 (5; 30)	8 (30)	5 (1; 15)	0.79	0.30
Other[d]	1 (6)	89 (NA)	2 (7)	1.5 (1; 2)	0.81	0.22
Number of patients						
RCTs	13 (72)	4203 (34; 66 477)	12 (44)	1482 (291; 35 597)	—	0.23
Non-RCTs	3 (17)	4917 (926; 184 372)	5 (19)	836 (79; 12 217)	—	0.18
Observational studies	1 (6)	7636 (NA)	7 (26)	646 (76; 13 890)	—	0.51
Evidence synthesis[c]	1 (6)	102 594 (NA)	1 (4)	102 594 (NA)	—	0.32
Type of economic evaluation						
Cost analysis	1 (6)	5 (NA)	4 (15)	1.5 (1;2)	0.33	0.14
Cost minimisation analysis	0 (0)	—	0 (0)	—	—	—
Cost-effectiveness analysis	8 (44)	4 (1; 20)	9 (33)	2 (1; 8)	0.45	0.53
Cost–utility analysis	8 (44)	3.5 (1; 8)	9 (33)	1 (1; 4)	0.45	0.11
Cost–benefit analysis	0 (0)	—	1 (4)	1	0.41	—
Cost–consequence analysis	0 (0)x	—	0 (0)	—	—	—

RCTs, randomised controlled trial; HTA, health technology assessment.
[a]Mann–Whitney test.
[b]Fisher's exact test.
[c]Systematic reviews, meta-analyses and HTA reports.
[d]Rapid reviews and sources of evidence that do not fall into the aforementioned hierarchy of evidence categories.

Source: Ciani O et al. Linking the regulatory and reimbursement processes for MDs: the need for integrated assessments. Health Econ. 26(Suppl 1):13-29 (2017).

RWD Contribution to MDs HTA Requirements

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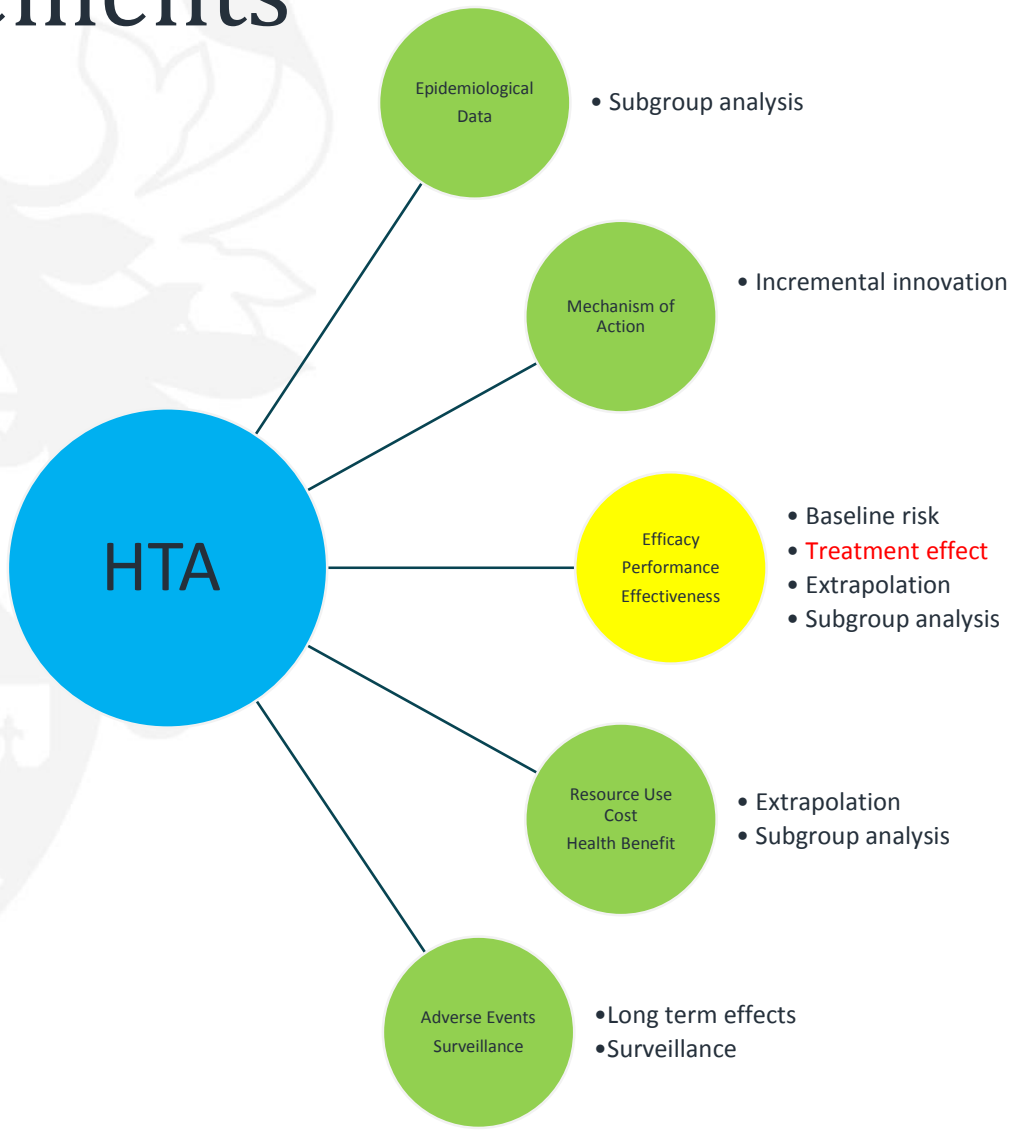

RWD contribution to MDs HTA

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

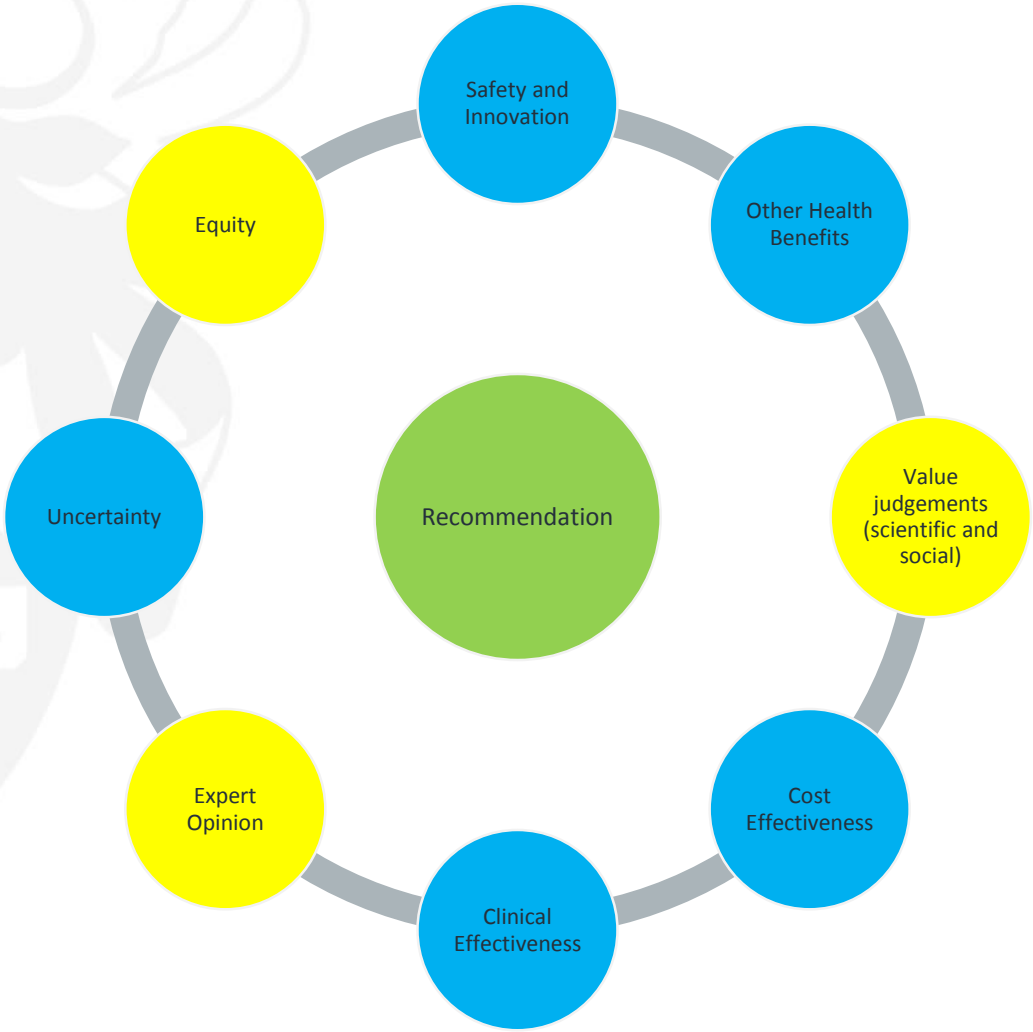
	RWD accepted/requested			RWD appraisal		
HTA agency	RWD accepted	RWD to inform treatment effects	RWD to inform other parameters	Hierarchy of evidence adopted	Conclusions on treatment effects on the basis of RWD regarded as circumspect	Conclusions on treatment effects on the basis of RWD possible in exceptional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

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.

Source: Makadi A et al. Policies for use of RWD in HTA: A comparative study of six HTA agencies. Value in Health. 20(S2017):520-532.

MDs HTA Decision Making



MDs Evidence Analysis:
Issues and Potential Solutions

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- 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

EXPERT REVIEWS

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

Expert Rev. Pharmacoecon. Outcomes Res. 15(1), 21–32 (2015)

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Regulation criteria for licensing pharmaceuticals and medical devices (MDs) are asymmetric. This has affected the type, quantity and quality of the evidence produced 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 be carried out to safeguard individual's wellbeing.

PharmacoEconomics (2016) 34:1161–1172
DOI 10.1007/s40273-016-0425-9

ORIGINAL RESEARCH ARTICLE

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

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Published online: 30 June 2016

Abstract
Introduction Expert judgement has a role in model-based economic evaluations (EEs) of healthcare interventions. This study aimed to produce reporting criteria for two types of study design to use expert judgement in model-based EE: (i) an expert elicitation (quantitative) study; and (ii) a Delphi study to collate (qualitative) expert opinion.
Methods A two-round online Delphi process identified the degree of consensus for four core definitions (expert; expert parameter values; expert elicitation study; expert opinion) and two sets of reporting criteria in a purposive sample of experts. The initial set of reporting criteria comprised 17 statements for reporting a study to elicit parameter values and/or distributions and 11 statements for reporting a (using a pre-defined 75 % 'consensus' threshold) on the definitions and suggested reporting criteria. Free-text comments were analysed using thematic analysis.
Results The final panel comprised 12 experts. Consensus was achieved for the definitions of expert (88 %); expert parameter values (83 %); and expert elicitation study (83 %). The panel recommended criteria to use when reporting an expert elicitation study (16 criteria) and a Delphi study to collate expert opinion (11 criteria).
Conclusion This study has produced guidelines for reporting two types of study design to use expert judgement in model-based EE: (i) an expert elicitation study requiring 16 reporting criteria; and (ii) a Delphi study to collate expert opinion requiring 11 reporting criteria.

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

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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 pressure ulcers; however, there is currently no robust evidence that it is effective or cost-effective. This work considers the decision to adopt NPWT given a range of alternative treatments, 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 (uncertain) quantities were obtained through a formal elicitation exercise. Additionally, data derived from a pilot 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 from a set of alternative designs, a 3-arm trial with longer follow-up was estimated to be the most efficient. The analyses presented demonstrate how allocation decisions about medical technologies can be explicitly informed when data are sparse and how this kind of analyses can be used to guide future research prioritization, not 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; sparse; evidence synthesis; expected value of information; research design; cost-effectiveness analysis.* ***(Med Decis Making 2013;33:415–436)***

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Sciences

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

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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 (OSs) 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 pooled treatment effect estimates from OS 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 effects into a generalized evidence synthesis, calculating both frequentist and Bayesian statistical models. We estimated relative risks as summary effect estimates with 95% confidence/credibility intervals to capture uncertainty.

When we compared alternative approaches to synthesizing evidence, we found 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 wider 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 adjustments to the results. © 2017 The Authors. Health Economics published by John Wiley & Sons, Ltd.

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

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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 uncertainties. 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 innovation, investment 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.