‘What is dead may never die’ — Cost-minimization analysis in the context of medical devices in Europe

A.J.N. Raymakers *
Health Economics and Policy Analysis Centre, National University of Ireland Galway, Galway, Ireland
CURAM Centre for Research in Medical Devices, National University of Ireland Galway, Galway, Ireland
S. O’Neill
Health Economics and Policy Analysis Centre, National University of Ireland Galway, Galway, Ireland
N. O’Leary
Health Research Board (HRB), Clinical Research Facility, National University of Ireland Galway, Galway, Ireland
P. Gillespie
Health Economics and Policy Analysis Centre, National University of Ireland Galway, Galway, Ireland
CURAM Centre for Research in Medical Devices, National University of Ireland Galway, Galway, Ireland

Introduction

The application of health economic evaluation methods to inform reimbursement decisions for medical devices has been markedly different from pharmaceutical products. Methods such as cost-utility analysis (CUA) and cost-effectiveness analysis (CEA) have been widely applied to inform decision-making for the latter, but generally not for the former. The relative lack of application of the methods of economic evaluation for medical devices is related to several factors, including the nature of the development and usage of medical devices themselves, which often inhibits the generation of evidence for the evaluative process, and the regulatory environment, which dictates the level of evidence that is provided to inform approval and reimbursement decisions [1]. This issue has been discussed in detail in several previous publications [1–3]. However, recent changes to the regulatory environment will likely lead to increased requirements for economic evidence on medical devices, particularly, but not limited to high-risk or ‘Class III’ devices [4]. The nature of the regulatory changes, along with the complexity of applying economic evaluation methods to medical devices, will have important implications for practitioners and users of these methods going forward. In this article, we consider one such implication: the potential re-emergence of cost minimisation analysis (CMA) as a method of economic evaluation for medical devices resulting from new evidentiary requirements. In 2001, Briggs and O’Brien published an article in the journal *Health Economics* entitled the ‘The death of cost-minimization analysis?’ [5]. In their article, the authors argued that unless a study has been specifically designed to show the clinical equivalence of treatments in terms of effects, it is inappropriate to conduct CMA. Indeed, their article informed current ‘best practices’ in economic evaluation whereby the majority of analyses currently take the form of CEA or CUA, rather than CMA. Given the regulatory changes outlined below, it is timely to consider whether the updated guidelines might lead to the re-emergence of CMA as a

method to inform reimbursement decisions for medical devices and the inappropriate use of this method in this context if clinical equivalence is not considered.

The regulatory environment for medical devices and the implications for health economic evaluation

The regulatory framework for the approval of medical devices in the European Union (EU) has recently been revised and is currently in a transition phase prior to new regulations being fully implemented by 2020 [4]. As a component of the changes, all devices currently in use may face a need to be re-approved, without current devices necessarily being given any special status. While the details of this aspect of the change in policy are yet to be confirmed, what is clear is that the requirements for device approval will become more stringent. Two significant implications for medical device reimbursement decisions may result; first, currently used medical devices may need to be re-approved and, as such, may require evidence for re-approval, presumably incorporating some form of economic evaluation. Second, the incoming process for device approval will likely require greater standards of clinical evidence than the previous process where approval of a device could be based entirely on technical and biological equivalence to predicate devices. The consequence of this change in policy will be an increased requirement on manufacturers to conduct clinical investigations for device approval, while at the same time reimbursement agencies are increasingly requiring economic evidence to inform decisions [6].

The generation of clinical and economic evidence for the approval of health technologies involves the comparison of the new technology to the existing standard of care. Typically, to generate clinical evidence for the superiority of a new health intervention, a randomized controlled trial (RCT) is conducted to determine the efficacy of the intervention in comparison to another intervention or placebo; this data is often a primary data source for an economic evaluation. Economic evaluation typically involves conducting an incremental analysis, calculating point estimates for the incremental costs and effects of the alternatives, and quantifying the uncertainty around those point estimates [7]. If the new health intervention is more costly and more effective than the alternative, then an incremental cost-effectiveness ratio (ICER) is calculated and compared to a country- (or region-) specific cost-effectiveness threshold value [7]. Most reimbursement agencies prefer that economic evaluations take the form of a CUA, whereby health benefit is quantified using the quality-adjusted life-year (QALY), an outcome measure that simultaneously incorporates both quality and quantity of

life, and is comparable across disease areas. For certain interventions, CEA may also be used, but this typically requires explicit justification, as benefits are measured in terms of natural units and are often limited to a specific disease. The central feature of both CUA and CEA is to estimate the joint distribution of costs and effects, and the uncertainty around those estimates, of an intervention relative to the standard of care. It is this feature that clearly distinguishes CEA and CUA from CMA as a means of economic evaluation.

A key issue that arises in the case of medical devices, in contrast to pharmaceuticals, is that medical device development is often iterative in nature, with small changes to the structure and materials of a device leading to incremental changes in its safety profile, ease of use, and performance. In this context, the superiority RCT might not be the principal method used to generate evidence for new devices or new iterations of existing devices [8]. This evidence, instead, may come from trials that only aim to show non-inferiority or the clinical equivalence of a device relative to the standard of care [9]. It is in this specific context that the case may re-emerge for CMA. In CMA, the effectiveness of the alternative strategies is deemed to be 'equivalent', often without consideration of the uncertainty surrounding this equivalence, and the cost-effectiveness of an intervention is determined solely if the new alternative is cost-saving. A key point raised by Briggs and O'Brien [5] , and further developed by Dakin and Wordsworth [10] , becomes relevant here; that is, unless a study is specifically designed to have a pre-specified acceptable equivalence or non-inferiority margin [11] and sufficient sample size to ensure adequate power to determine non-inferiority, then CMA is an inappropriate approach and may bias reimbursement decisions. We direct the interested reader to these publications for further details on the limitations of CMA, and how its use might lead to poor health services decisions [5,10].

Under the updated EU regulations for medical devices, an important theme is the need for new devices to show, at minimum, 'equivalence' to the existing standard of care [4]. The regulations state, "*A clinical evaluation may be based on clinical data relating to a device for which equivalence to the device in question can be demonstrated* " and that under this claim of equivalence the technical, biological, and clinical characteristics of the device shall "*be similar to the extent that there would be no clinically significant difference in the safety and clinical performance of the device"*. The guidelines further state that, "*Considerations of equivalence shall be*
based on proper scientific justification."

If the standard for efficacy data for medical devices becomes that of clinical equivalence, then CMA could conceivably re-emerge as a method of economic evaluation. Certainly, given the nuances that exist for evidence generation in the context of medical devices [1] , it seems logical that the requirement for clinical evidence for approval and reimbursement might shift away from the superiority RCT design, and toward 'non-inferiority' or 'equivalence' RCTs. Should this happen, it will pose important challenges for reimbursement agencies charged with generating and interpreting economic evidence for decisions regarding medical devices. If the nature of the data provided for a medical device is of insufficient quality to demonstrate clinical equivalence, but is viewed as 'equivalent' in terms of some other technical, biological, or clinical characteristics, then the application of CMA will be inappropriate and can lead to suboptimal reimbursement decisions.

This leaves reimbursement agencies with two practical problems. First, the guidelines for economic evaluation in most jurisdictions recommend the use of CUA (or CEA), which is often reliant on data from superiority RCTs. In the case of medical devices, however, this approach to economic evaluation might not be directly applicable, and may need to be adapted. Second, if CMA does re-emerge, agencies should be critical of this approach and ensure that the evidence underpinning such analyses adequately addresses the question of clinical equivalence, in terms of acceptable, pre-specified non-inferiority or equivalence margins and sufficient sample sizes to power the study. What is clear is that reimbursement agencies should consider carefully the consequences stemming from the new regulations in terms of the re-emergence of CMA and its usage leading to potentially incorrect decision-making.

Concluding comment

We suspect that an unintended consequence of the new regulatory environment for medical devices in Europe may be the re-emergence of CMA to provide economic evidence for reimbursement decisions. While this may appear to be an attractive option for medical devices manufacturers given new evidentiary requirements, we assert that decision-makers should carefully consider the limitations of this method. However, we simultaneously acknowledge the pragmatic reality of evidence generation in the case of medical device technologies and the pressures this reality places on manufacturers and reimbursement agencies. We therefore argue that a discussion needs to begin involving EU regulatory and reimbursement agencies,

medical device manufacturers, patient groups, and analysts conducting economic evaluations on the nature of economic evidence generation in the context of medical devices. Indeed, with this article, we hope to provide an impetus for such a discussion to ensure agencies charged with making reimbursement decisions have the best possible evidence, and not simply the most convenient, with which to make those decisions.

Funding

Support for this work was provided by Science Foundation Ireland and the European Regional Development Fund (grant number 13/RC/2073). The funders played no part in the conceptualization, manuscript preparation, nor publication decisions.

References

[1] Tarricone R , Torbica A , Drummond M . Challenges in the assessment of medical devices: the MedtecHTA project. Health Econ 2017;26(February):5–12 .

[2] Drummond M, Tarricone R, Torbica A. Economic evaluation of medical devices. Oxford Research Encyclopedia of Economics and Finance; 2018. Internet[cited 2018 June 7]; Available from: http://economics.oxfordre.com/view/ 10.1093/acrefore/9780190625979.0 01.0 0 01/acrefore-9780190625979- e- 105 .

[3] Kirisits A , Redekop WK . The economic evaluation of medical devices: chal- lenges ahead. Appl Health Econ Health Policy 2013;11(February (1)):15–26 .

[4] European Parliament, Council of the European. Regulation (EU) 2017/745 of the European parliament and of the council [Internet]. [cited 2018 February 3]. Available from: http://eur-lex.europa.eu/eli/reg/2017/745/oj .

[5] Briggs AH , O'Brien BJ . The death of cost-minimization analysis? Health Econ. 2001;10(March (2)):179–84 .

[6] Council Directive 93/42/EEC [Internet]. http://eur-lex.europa.eu/legal-content/ EN/TXT/HTML/?uri=CELEX:31993L0042&from=EN . [cited 2018 Apr 9]. Avail- able from: http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX: 31993L0042&from=EN

[7] Drummond MF , Sculpher MJ , Claxton K , Stoddart GL , Torrance GW . Methods for the economic evaluation of health care programmes. Oxford University Press; 2015 . 461 p.

[8] Neugebauer EAM, Rath A, Antoine S-L, Eikermann M, Seidel D, Koenen C. Specific barriers to the conduct of randomised clinical trials on medical devices. Trials [Internet]

2017(September):18. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5597993/ .

[9] Snapinn SM . Noninferiority trials. Curr Control Trials Cardiovasc Med 20 0 0;1(1):19–21 .

[10] Dakin H , Wordsworth S . Cost-minimisation analysis versus cost-effectiveness analysis, revisited. Health Econ 2013;22(January (1)):22–34 .

[11] Span MM , TenVergert EM , van der Hilst CS , Stolk RP . Noninferiority testing in cost-minimization studies: practical issues concerning power analysis. Int J Technol Assess Health Care 2006;22(2):261–6 .