Health Economics

Key Recommendations from the MedtecHTA Project

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ABSTRACT

There are particular characteristics of Medical Devices, such as the device-user interaction, the incremental nature of innovation and the broader organizational impact that lead to additional challenges for health technology assessment (HTA). The project explored key aspects of the conduct and methods of HTA for MDs. Systematic reviews and original research studies were conducted to determine improvements in processes and methods that could enhance the potential for HTA and optimize the diffusion of MDs.

Regulatory processes for MDs should be more closely aligned, the HTA evaluative framework should be harmonized and processes for conditional coverage and evidence development should be used. The methods for HTA should consider MDs as complex interventions, require the establishment of high quality registries, consider an iterative approach to the evaluation over time, recognize and allow for the particular characteristics of devices and use appropriate approaches for confounder adjustment in comparative effectiveness studies. To optimize the diffusion a common classification should be developed across countries in order to facilitate international comparisons, factors driving diffusion should be explored in HTA reports and physicians' personal goals and motivation should be better understood.

The key recommendations of the MedtecHTA project should improve the conduct and use of HTA for MDs.

1. Introduction

In this paper we present the key recommendations from the MedtecHTA project, organized under three themes (i) improving the process for HTA of medical devices (ii) developing methods for HTA of medical devices and (iii) optimizing the diffusion of medical devices. In each case we outline the issues that the recommendations seek to address, followed by the recommendations themselves. The research underpinning them is described in the papers emanating from the respective work packages, including the other papers in this supplement.

2. Improving the process for HTA of medical devices

The major issues identified regarding the process for the HTA of medical devices were that (i) the procedures for granting market access to new devices did not always encourage the generation of the clinical data, prior to product launch, necessary to undertake reliable HTAs, and (ii) that the specific characteristics of medical devices (eg the learning curve) were not explicitly considered in the methods guidelines of those organizations conducting HTAs. Furthermore, since the clinical evidence base is often not mature when devices are granted market access, an approach that encourages the generation of more data after product launch is required.

In their paper in this supplement, Ciani et al (2016) argue that (i) more stringent requirements supported by appropriate methodological choices are needed to provide clinical trial data for high-risk devices (ii) post-marketing surveillance based on device and user real world data should be encouraged

(iii) international harmonisation of practices will benefit the manufacturers and (iv) progressive alignment of regulatory and HTA evaluation for parallel submissions will improve efficiency in the health systems and promote timely access to affordable effective technologies.

Additionally, in their paper Rothery et al (2016) point 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. They show the circumstances under which requiring additional research after product launch, accompanied by conditional approval for reimbursement, may be an appropriate policy choice. They also show 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.

Against this background, we make the following recommendations.

Recommendations A: Improving the process for HTA of medical devices

A1. Align regulatory and HTA processes for devices with respect to data requirements, through:

- *joint scientific advice by regulatory and reimbursement bodies for data collection for the device industry*
- *designing studies that allow collection of data on effectiveness that jointly fulfill the requirements of regulators and payers*

A2. Harmonize the HTA evaluative framework (collection & synthesis of clinical evidence and economic evaluation) for devices across international

HTA agencies, through:

- *developing a standardized international risk classification for MDs*
- *determining appropriate levels of evidential requirements by risk category*

A3. Recognize that assessment of expected cost-effectiveness is not sufficient: conditional coverage and evidence development decisions should be assessed

- *the value of the device and future value of research needs to be quantified and used to identify the optimal timing of reimbursement decisions in the device's life cycle*
- *implementation may commit resources that cannot be recovered*

A4. Consider the implications of the learning curve (LC) on policy decisions (and vice versa)

- *the LC does not only change the estimate of effectiveness but also affects the uncertainty in the decision*
- *identify the mechanisms of learning likely to cause change over time and assess the profile of investment risk according to user experience affected by the rate of uptake of the device in practice*

A5. Consider the likely prospects of research and who should pay for it

- is it priority for public funding or for manufacturers to undertake?

3. Developing methods for HTA of medical devices

The methods for assessing the clinical and cost-effectiveness of medical devices need to adhere to the general standards for all health technologies, but also take account of the specific characteristics of medical devices. These include the existence of the learning curve, incremental innovation, dynamic pricing and organizational impact. The reviews of the literature conducted for the MedtecHTA project found that, although the general standards were good, more attention needs to be paid to these specific characteristics. In terms of the assessment of comparative effectiveness, it is best to consider procedures involving the use of medical devices to be 'complex interventions'. In terms of economic evaluation, the changes due to the learning curve, incremental innovation, dynamic pricing and organizational impact need to be modeled adequately.

Other key challenges relate to the relative lack of randomized controlled trials, as compared with pharmaceuticals, and the inherent uncertainty about clinical and cost-effectiveness at the time of product launch. Therefore, efforts may be necessary to collect data on safety and effectiveness post-launch. In addition, because of the likely reliance on observational studies, such as registries, appropriate methods of bias-adjustment need to be applied. Finally, the decision to approve, or not approve, a new device for reimbursement is closely linked to the decision on whether to collect more data and the nature of the data collected.

In their paper in this supplement, Schnell-Inderst et al (2016) consider medical devices to be complex interventions and argue that evaluation of their clinical

effectiveness differs in some aspects from the evaluation of pharmaceuticals. One of the main challenges they identify is the lack of robust evidence and a need for combining experimental and observational studies (OS) in quantitative evidence synthesis accounting for internal and external biases. They address this challenge by performing an elicitation exercise to determine the strength of belief of methodological and clinical experts regarding the size of internal and external bias affecting estimates of treatment effect estimates. These bias-adjusted treatment effects were then fed into a generalized evidence synthesis. In the evidence synthesis, they applied frequentist and Bayesian statistical models using relative risks with 95% confidence/credibility intervals as effect estimates.

Although such bias-adjusted estimates of treatment effects can be useful for economic evaluations in situations where there is a relative lack of controlled clinical studies, economic studies also need to consider the effects, on costs and benefits, of the particular characteristics of medical devices, such as the learning curve, incremental innovation and organizational impact. In their paper in this supplement, Tarricone et al (2016) point to the inadequacies in existing economic evaluations and make recommendations for improvements in future studies.

A major challenge is to obtain an accurate estimate of the impact of the learning curve. In their paper in this supplement, Varabyova et al (2016) demonstrate how this can be done by using administrative data on over 40,000 patients admitted with unruptured abdominal aortic aneurysm to 553 different hospitals over the years 2006 to 2013. They examine two patient

outcomes, namely, in-hospital mortality and length of stay (LOS) using hierarchical regressions with random effects at the hospital level. The estimated models control for patient and hospital characteristics and take learning interdependencies between endovascular aneurysm repair (EVAR) and fenestrated EVAR (fEVAR) into account. They argue that to foster the consideration of learning in economic evaluations of medical devices a general framework for estimating learning effects needs to be devised.

Finally, in their paper, Rothery et al (2016) develop a general framework for considering the uncertainties in the economic evaluation of devices and linking the gathering of additional information with policies on approval for reimbursement.

Against this background, we make the following recommendations.

Recommendations B: Developing methods for HTA of medical devices

B1. Refine existing methods (for collection and synthesis of clinical and economic data) for handling the common 'complexities' of devices, including:

- *synthesis of observational and trial evidence*
- *incorporating learning curves into decision analytic models*
- *recognizing the potential for incremental innovation*

B2. Consider the MD-related intervention as a complex intervention; in particular, include the intervention's components and the relation between intervention, modifying factors and outcome in the formulation of the research question

B3. Consider specific study designs and analysis methods, in addition to general recommendations for RCTs, in order to assess the comparative effectiveness of MDs

- *these approaches should address challenges often associated with devices, including rapid incremental development, the device/user interface and effect modification by contextual factors*

B4. Establish disease-based or device-based registries of high quality for the long-term study of the effectiveness and safety of MDs.

B5. Design such registries to allow comparative analyses:

- *routinely collecting information on possible confounding factors*
- *collecting information on treatment patterns to facilitate HTA*

B6. Use appropriate methods for confounder adjustment in comparative effectiveness or safety analyses and try to address residual confounding

B7. If data from large registries are available for inclusion in the evidence synthesis in HTA, consider bias-adjustment based on expert elicitation as one scenario in the sensitivity analysis.

B8. Document research using suitable existing reporting guidelines.

B9. Consider MD-specific application of guidance on the methods for evidence synthesis from the framework on complex interventions.

B10. Assess the applicability of findings considering the challenges arising from patient eligibility, user dependence, study design, and rapid evolution of the technology

B11. In economic evaluations and HTAs of MDs, pay particular attention to the particular characteristics of MDs and explore their quantitative impact on cost-effectiveness as part of the study.

B12. Consider an iterative process to the evaluation of devices as additional evidence and learning emerges over time

B13. Consider the likelihood of future price changes

- *price influences the benefits of early approval and the benefits of additional research*
- *it may be useful to identify effective price thresholds for which guidance changes*

B14. Determine whether manufacturers should be expected to conduct the research, based on an assessment of:

- *the commercial value to manufacturers of early evidence*
- *the potential for Approval with Research and for improving research timelines*

4. Optimizing the diffusion of medical devices

Optimizing the use of medical devices would involve ensuring that they are used only in situations where they are clinically and cost-effective. The review of the literature conducted in the MedtecHTA project showed that there are wide geographical variations in the use of implantable cardiac devices, but very little understanding of why these variations exist. In order to obtain a better understanding of the use of devices, it is important to have standardized methods of data collection, so that differences between regions and countries can be reliably studied.

In their paper in this supplement, Torbica et al (2016) report the first investigation of the determinants of temporal and geographical variations in pacemaker (PM) and implantable cardioverter defibrillator (ICD) implants and replacements at regional level across 5 EU countries. They found that (i) regional per capita GDP appears to have no effect on implant rates of cardiac implantable electrical devices (CIEDs) (ii) regions with greater proportion of residents with higher level of tertiary education, an aged population, and greater life expectancy have higher implant rates of CIEDs and (ii) higher numbers of implanting centres foster access to technologies.

This last finding suggests that it is important to gain a better understanding of the clinical, professional and organizational factors that encourage or discourage the use of the clinical procedures involving the use of devices. Therefore, more study is required of the motivational factors facing patients, physicians and the institutions in which they work. In addition, attention needs to be paid to the relevant demographic factors and the impact of health care financing and organization.

Therefore, in their paper in this supplement, Hatz et al (2016) conducted a comprehensive analysis to investigate which environmental, organizational, individual and technological factors impact the adoption and utilization of cardiovascular devices. The data were collected from a large-scale online survey that was sent to members of the European Society of Cardiology. Seven random intercept hurdle models were estimated using the data obtained from the survey. They found that better manufacturer support increased the adoption probability of "new" devices (i.e., in terms of CE mark approval dates), that budget pressure increased the adoption probability of "old" devices and that larger hospitals and urban locations were associated with higher adoption probabilities across devices. Other variables, such as financial aspects, motivation or organizational effects of adoption, were not statistically significant across models, suggesting that these factors are less important than other factors for the adoption of devices.

Against this background, we make the following recommendations.

Recommendations C: Optimizing the diffusion of medical devices

C1. Leverage routinely collected data (administrative data) to investigate the adoption and diffusion of MDs, provided that coding system allows for valid and reliable identification of the technology

C2. Endorse the use of a common classification for medical devices (unique identification code) across countries to facilitate international comparisons

C3. Include factors driving adoption of medical devices systematically in HTA reports to estimate the impact of the interplay of:

- *physician characteristics,*
- *organizational, regional, environmental factors and manufacturers' actions*

C4. Consider divergent effects by stratifying by medical devices type (e.g. "old" and "new" medical devices)

C5. Concentrate on the identification of key opinion leaders in hospital to better understand the adoption and the diffusion process

C6. Focus on developing the understanding of physicians' personal goals and motivation and their role in the adoption of medical devices

C7. Monitor manufacturers' actions, as they seem to be very relevant for the adoption of "new" medical devices

C8. Consider regional (e.g. rural vs urban hospital location) and environmental factors (e.g. GDP and out-of-pocket payment) to understand where the diffusion process is likely to take place

- *in large hospitals, with relatively large specialist departments*
- *in high income countries with lower shares of out-of-pocket payments*

5. Future research

Although the recommendations made by the MedtecHTA project will go a long way towards improving the conduct and use of HTA for medical devices, the project also identified several possible future research initiatives.

5.1 Developing innovative approaches for the assessment of devices

One of the recommendations made to improve the process for HTA of MDs concerned the collection of data on effectiveness that jointly fulfill the requirements of regulators and payers. One way of achieving this would be to encourage regulators and payers to work more closer together. A number of European collaborations already exist in the area of safety monitoring, such as the European Databank on Medical Devices (https://cemarking.net/european-databank-for-medical-devices-to-boost-control/). The research in MedtecHTA identified some innovative approaches for integrating the regulatory and health technology assessment, such as the EXCITE programme in Ontario, Canada (https://www.marsdd.com/systems-change/mars-excite/mars-excite/). In this programme, the data needs of future HTA are anticipated early in the regulatory process.

In addition, whilst the MedtecHTA project established that the special characteristics of MDs suggested some differences in the approach to HTA as compared with pharmaceutical, further research is required to determine which of these needs can be met by changes in organization and process, or whether they require a completely different methodological approach.

5.2 Estimating learning curves for medical devices

The case study conducted as part of the project demonstrated that it is possible to model the learning curve for devices. Since ideally it would be desirable to predict the likely impact of the learning curve for a new device, further research should be conducted to explore whether it is possible to categorize devices in terms of their likely learning curve (eg according to types of technologies (diagnostic or therapeutic), medical specialties, device risk classes or a combination of different criteria). Then, if a new device were developed in a given category, one might be able to predict its learning curve in advance. Apart from helping determine the most appropriate approach to determining the need for further research, this has organizational implications, such as determining whether more complex devices should be concentrated in a small number of centres, where users can be adequately trained. In fact, the learning effect does not attain to the use and experience with the new device only but often also refers to a more complex system of attributes such as the quality and quantity of clinical teams (eg level of training, incentives to innovation), the level of capital equipment present in healthcare centres, the types of centres and how they are organized and managed (e.g. district hospitals vs independent trusts, models of care based upon levels of intensity vs medical specialties). To investigate the learning effect of medical devices as exclusively depending upon number of procedures delivered by clinicians can therefore be a narrow approach. The learning curve may reach its steady state with a relatively low number of procedures but with a high attention to patients' selection or with a good level of interactions between clinical teams in the hospitals (eg interventional cardiologists and surgeons for cardiac procedures implying new cardiac devices). Further research aimed at

investigating and measuring the impact of learning curve onto costs and outcomes of the introduction of medical devices need therefore to identify all potential explicative variables as independent variables to be included in the model.

5.3 Use of observational data in assessing the comparative effectiveness of devices

The case study on the use of bias-adjustment should be repeated for other devices in order to confirm its promise. In addition, while the case study considered bias-adjustment in a situation where there was evidence from both RCTs and observational data, in many situations there may only be observational data. Therefore, future research could explore the use of these methods in those situations, particularly if an RCT were planned or ongoing in order to compare with the results of the bias-assessment based only on the observational data.

In addition, although registries are commonly used to assess the safety and longevity of devices, further research is required to determine how the design of such registries would need to be adapted to facilitate economic evaluation. A critical feature would be for registries to be able help us assess the relative effectiveness of treatments. In order to do so there needs to be treatment variation, for example patients with similar characteristics receiving different treatments within the registry. In addition, the risk categories of patients should be classified in order to enable assessments of cost-effectiveness by sub-groups, details of resource use are also required and, if important for the

treatment choice(s) being examined, the quality of life of patients should be measured.

5.4 Studying the diffusion of devices

The research in the project has added to our understanding of the factors influencing the diffusion of devices, but there is still a large amount of unexplained variation. Further research could be undertaken to explore the extent to which the observed rates of device utilization were consistent with research-based clinical guidelines where these exist. Further studies should also investigate the impact on diffusion of the motivational factors facing patients, surgeons and the institutions in which they work. Previous studies on diffusion of medical technologies had pointed to the key roles of social networks and peer communications rather than clinical guidelines and published evidence (Rogers, 1995). However in recent times the role of evidence has gained more attention and has become crucial for regulatory and HTA bodies and for the scientific ommunity at large. Today, variables other than peer communication can influence clinicians' beliefs and attitude towards the introduction of new medical technologies and need to be investigated in order to achieve a better understanding of how the diffusion process is evolving across time and across different jurisdictions.

5.5 Coverage with evidence development for medical devices

The research in the project set out a conceptual framework for the assessment of policies for coverage with evidence development. Further research could explore the actual implementation of such policies and explore

practical issues such as determining who should fund the research and issues of study design. This is important in order to ensure the appropriate diffusion of devices that have the potential to be clinical and cost-effective.

6. Conclusions The use of Health Technology Assessment has grown dramatically worldwide over the last 20 years in order to determine the appropriate level of reimbursement and coverage of medical technologies. Nevertheless HTA has diffused having pharmaceuticals in mind. Recent changes in the regulation of medical devices together with the fast pace of innovation that characterize the industry of medical devices have turned the attention to this class of medical technologies and raised the issue of whether methods to assess pharmaceuticals effectively fit this other type of technologies. While there is agreement on the consideration that medical devices are different from drugs, it is not entirely clear whether these difference really matter.

The project MedtecHTA has revealed that medical devices' key features make their assessment more challenging than drugs and need to be considered in order to correctly inform final policy recommendations.

Based on multiple methods, MedtecHTA has developed a three-year research agenda aimed at improving current methods to assess MDs by issuing several recommendations. Regulatory processes for MDs should be more closely aligned, the HTA evaluative framework should be harmonized and processes for conditional coverage and evidence development should be used. The methods for HTA should consider MDs as complex interventions, require the establishment of high quality registries, consider an iterative

approach to the evaluation over time, recognize and allow for the particular characteristics of devices and use appropriate approaches for confounder adjustment in comparative effectiveness studies. To optimize the diffusion a common classification should be developed across countries in order to facilitate international comparisons (GHTF, 2012), factors driving diffusion should be explored in HTA reports and physicians' personal goals and motivation should be better understood.

Taken together, the key recommendations of the MedtecHTA project should improve the conduct and use of HTA for MDs. Several actors have been identifies as relevant to improving the assessment of MDs. Regulatory bodies, clinicians, patients, policy-makers, healthcare managers and analysts are all called to play their part and to converge towards these key principles.

If any of the recommendations are implemented it will be important to assess their impact. For example, will the various initiatives to encourage the generation of more timely and higher quality medical evidence on MDs lead to their more appropriate adoption and diffusion? Such evidence will be important if the HTA of medical devices is to continue to develop.

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