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Challenges in the Assessment of Medical Devices: the MedtecHTA project

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ABSTRACT

Assessing medical devices (MDs) raises challenges which require us to reflect on whether current methods are adequate. Major features of devices are: (i) device-operator interaction can generate learning curve effects; (ii) incremental nature of innovation needs to be addressed by careful identification of the alternatives for comparative and incremental cost-effectiveness analysis) (iii) broader organizational impact in terms of training and infrastructure, coupled with dynamic pricing, requires a more flexible approach to costing.

The objective of the MedtecHTA project was to investigate improvements in HTA methods to allow for more comprehensive evaluation of MDs. It consisted of several work packages concerning i) the available evidence on the currently adopted approaches for regulation and HTA of medical devices; ii) the geographical variation in access to MDs; iii) the development of methodological frameworks for conducting comparative effectiveness research and economic evaluation of MDs; iv) the organizational impact of MDs.

This introductory paper summarises the main results of the project and draws out the main overarching themes. This supplement represents a comprehensive report of all the main findings of the MedtecHTA project and it is intended to be the main source for researchers and policy makers wanting information on the project.

1. Background to the MedtecHTA project

Health technology assessment (HTA) has become increasingly important in health care decision-making in Europe. Although in principle HTA can be applied to all health technologies, its major use in a decision-making context has been in the pricing and reimbursement of pharmaceuticals. However, there are over 200,000 medical devices on the European market (Fraser et al, 2011). These represent a very heterogeneous family of technologies that needs to be better classified for the purpose of HTA. "Medical device", according to the EU Directive (2007) 2007/47/EC amending Council Directive 93/42/EEC~~2007/47/EC~~, is defined as "any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination.… to be used for human beings for the purpose of diagnosis, prevention, treatment, monitoring or alleviation of disease".

While some devices require very simplified assessment, others need to be assessed through a full evaluation of safety, efficacy, effectiveness and economic impact. A thorough HTA would require consideration of final outcomes in terms of life expectancy and health-related quality of life, going far beyond the assessment that devices currently undergo to obtain a CE (European Conformity) mark, to enable them to be marketed in the European Union. This is particularly true for implantable devices used in cardiology (Boriani et al., 2009; Boriani, Maniadakis, Auricchio, & Vardas, 2010; R. Tarricone & Drummond, 2011), which represent the main focus of the MedtecHTA project.

The current EU legal framework already requires for all devices, especially for class III devices, to have safety and performance testing for decision on CE mark.~~The current EU legal framework already requires all high risk devices (class III) to have safety and performance testing for decisions on market authorization~~. Essentially,

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manufacturers must accomplish a conformity assessment and undergo an inspection and certification procedure by one of the Notified Bodies within the EU. In addition, there is stringent post-marketing surveillance, requiring manufacturers of devices to implement a post market clinical follow up plan and a medical device vigilance system ~~"medical device vigilance system"~~ to monitor their products once they are on the market (Cohen & Billingsley, 2011). Conversely, in the United States, a much greater importance is given to pre-market approval (PMA), requiring clinical testing to inform the market about safety and effectiveness. Nevertheless a much lighter ex-post conformity assessment is in place. It must be noted however that the EU Directives for the regulation of medical devices have been the object of relevant amendments in recent years and, although the final document is not available yet, the orientation is for more stringent clinical evidential requirements in the pre-market phase (European Commission, DG Growth, 2016).

Nevertheless, medical devices have traditionally been less regulated than pharmaceuticals and the amount of evidence collected for licensing medical devices is generally lower (Fattore, Maniadakis, Mantovani, & Boriani, 2011; Schreyögg, Bäumler, & Busse, 2009; Taylor & Iglesias, 2009). The EU directive in 2007 made some significant changes in this respect by recognizing that it is necessary to enhance the provisions on clinical evaluation, including clarification that clinical data are generally required for all devices (2007/47/EC). Consequently, medical devices placed on the EU market or put into service after March 21st 2010 must be in conformity with these new requirements. However, in contrast to the requirements for pharmaceuticals, due to peculiarity of medical devices, the studies can be small clinical trials or even non randomized clinical investigation, and long term efficacy data are not generally required in the premarketing phase, although a post market

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A full HTA, such as that applied to pharmaceuticals in many EU member states, would require a thorough examination of the clinical and cost-effectiveness of devices. However, medical devices differ from other health technologies in a number of respects: i) they often change rapidly; ii) clinical outcomes often depend on the training, competence and experience of the end-user (Ramsay et al., 2001); iii) pricing is typically more dynamic than that of pharmaceuticals; iv) costs often comprise both procurement costs (including the associated infrastructure) and running costs (including maintenance and consumables).

It has been claimed that these special characteristics of devices raise additional challenges which require the HTA community to reflect on whether the current methods are adequate (Drummond, Griffin, & Tarricone, 2009). Three major features of devices deserve special attention: (i) the device-operator interaction can generate learning curve effects and thus risk biases in estimating the size of the benefits; (ii) the incremental nature of innovation (e.g., longer battery life, improvement of the software systems, miniaturisation) needs to be addressed by careful identification of the alternatives for comparative and incremental cost-effectiveness analysis (Fattore et al., 2011; Sorenson, Tarricone, Siebert, & Drummond, 2011; R. Tarricone & Drummond, 2011; Taylor & Iglesias, 2009) (iii) the broader organizational impact in terms of training and infrastructure, coupled with dynamic pricing, requires a more flexible approach to costing. Whether these differences between medical devices and pharmaceuticals require a different framework for HTA needs to be investigated.

1. The MedtecHTA project

The objective of MedtecHTA project was to investigate improvements in HTA methods to allow for more comprehensive economic evaluation of medical devices. The project consisted of seven work packages (WPs), organized in three parts. (see Table 1.)

- TABLE 1 HERE ABOUT -

2.1 Cross country analysis of regulation and HTA of medical devices

Part 1 of the project was essentially preparatory and included the necessary groundwork for the subsequent research activities. WP 1 considered the available evidence on the currently adopted approaches for the HTA of medical devices and on international regulatory guidance on the licensing of medical devices. Tarricone et al (2014) reviewed regulatory practices in the EU, US and 5 other countries and concluded that a number of actions are required to make the clinical evidence gathered through the regulatory process more relevant to HTA. These include the development of international standards on the types of clinical evidence required for the market approval of medical devices and agreement on the balance of clinical data collection pre- and post-launch. The latter is important because of the possibility that, owing to the learning curve and the organizational impact of devices, data from pre-launch clinical trials may not be ideal for assessing effectiveness and cost-effectiveness.

Ciani et al (2015) reported the results of a cross-country analysis of HTA guidelines and available HTA reports on medical devices in assigned countries using a standardized template for comparison. In order to analyse the state of the art in the

application of guidelines reviewed, a sample of HTA reports was selected from the University of York Centre for Reviews of Dissemination HTA database and systematically reviewed at three levels (i) assessment of the nature of evidence included in the reports (ii) HTA methods applied by reports considering medical devices, and (iii) assessment of approaches and methods used to address uncertainty. They found that although 75% of the agencies surveyed had adopted HTA-specific approaches for medical devices, these were largely organizational or procedural in nature. Only one agency had adopted methodological guidelines specific to medical devices.

In the second paper in this supplement, Ciani et al (2016) focus on the second phase of their research, in which they analysed a sample of HTA reports in the field of cardiovascular disease in order to assess whether there are any key differences in how methods are applied. They found that here were several differences, in the types of clinical studies forming the basis for the HTAs, how the health problem and use of the technology was considered, the description and technical characteristics of the technology and the consideration of the organizational aspects of the use of the technology. Most of these differences arose due to the relative 'complexities' in the use of devices, in terms of the number of interacting components. These include the number and difficulty of the actions required by those delivering or receiving the intervention, the number of groups and organizational levels targeted by the intervention, the number and variability of the outcomes and the degree of flexibility or tailoring of the intervention.

2.2 Geographical variation in the use of medical devices in the EU

Work Package 2 considered the geographical variation in the use of medical devices in EU countries by estimating the rate of adoption of selected medical technologies in the field of electrophysiology. This subspecialty of cardiology widely uses implantable medical devices whose efficacy has been demonstrated by a number of randomized clinical trials. In one respect these devices resemble pharmaceuticals as they have a curative and/or a secondary prevention function and ~~can~~ might be tested in clinical trials similar to those conducted on drugs. On the other hand, they differ from pharmaceuticals because they are subjected to incremental changes (e.g. dimensions and software), learning curve effects due to device-operator interactions and price dynamics which make trial designs similar to pharmaceuticals not always suitable for medical devices. These overall characteristics make the area of electrophysiology an interesting case to study.

Results obtained in this field also have a higher degree of transferability to other class III medical devices. Through the analysis of national/local guidelines and data from registries and administrative databases, rates of utilization were mapped to provide evidence of different degrees of access within member states, and whether this adoption is in line with the existing evidence on clinical and cost effectiveness. Valzania et al (2015) reported a systematic review of the literature on implant rates for cardiac implantable electrical devices (CIEDs) in Europe. They found that there had been a recent rise in implant rates, with large geographic differences. For example, the ratio between the regions with the highest and lowest implant rates within the same country ranged from 1.3 and 3.4 for cardiac pacemakers, whereas the ratio between the countries with the highest and lowest implant rates ranged from 2.3 and 87.5. The determinants of these differences (namely epidemiological, cultural,

and socio-economic factors) were only partly explored and differences in study methodology could be one reason for the reported differences.

Therefore, in a subsequent phase of the research, reported in the third paper in this supplement, Torbica et al (2016a) undertook a new study of implant rates, the first to use the national hospital discharge datasets available in 5 EU countries. They provide evidence on differences in use of medical devices within and between member states, investigate the determinants of differences in access to CIEDs, and assess the potential and limitations of administrative databases for the analysis of utilization rates of medical devices in electrophysiology.

It is the first international paper to explore simultaneously differences both between countries and within the regions of those countries. Results show ~~,~~ that higher levels of tertiary education among the labor force and % of aged population are positively associated with implant rates of CIED. Regional per capita GDP and number of implanting centers appear to have no significant effect. Institutional factors, captured by fixed country effect, are shown to be important for the diffusion of CIED.

~~Regional per capita GDP appeared to have a small, but significant, effect on use of CIEDs. In addition, the % of residents having tertiary education, the age of the population and life expectancy were associated with higher implant rates. Increased competition (expressed in terms of the implant rates in each region), fostered the use of technologies.~~ However, even after controlling for clinical, epidemiological and (crude) economic indicators, significant variation in implant rates still exist. They argue that there should be closer examination of the role of organizational factors and

clinical preferences in the adoption of devices. These issues are explored further in WP6 of the MedtecHTA project (discussed below).

2.3 Methods for assessing the comparative effectiveness of medical devices

The core part of the project (Part II) sought to develop an improved methodological framework for conducting HTA of medical devices by acknowledging the complexities which arise from their integration into clinical practice. The research conducted in WP3, began by considering the approaches and methodologies used for comparative effectiveness research by conducting a systematic review of the methodological literature. It was found that, although most of the good research practices in the evaluation of all health technologies apply to medical devices, the interventions involving the use of medical devices should be considered as complex interventions, owing to the importance of user and context independence. Therefore, specific randomized controlled trial designs need to be considered, dealing with surgeons' and patients' preferences, incremental product development and user dependence. In addition, high quality disease- or device-based registries are needed to assess safety and long-term effectiveness (Schnell-Inderst et al, 2016a).

This preliminary research activity provided the basis for the development of improved methods for evaluating comparative effectiveness of medical devices including recommendations for analytic methods and data collection. The research was an important input to the development of guidelines for the evaluation of Therapeutic Medical Devices under the auspices of the EUnetHTA Joint Action 2 (EUnetHTA, 2015).

The framework and new methodological approaches were then tested on medical devices at different stages of development and diffusion within the health care system. First, the use of a method of evidence synthesis that allows for the meta-analysis of RCT and observational data, using bias adjustment based on a formal elicitation exercise involving experts, was explored in the case of total hip replacement. This is reported in the fourth paper in this supplement (Schnell-Inderst et al, 2016b).

2.4 Methods for the economic evaluation of medical devices

Work Package 4 focused on exploring different methods for economic evaluation of medical devices currently adopted in EU countries in order to make suggestions about the development of new methods and offer guidance on future directions in the use of economic evaluation for medical devices. The first part of the research considered how differences in culture and values in EU countries lead to differences in the methodology and use of economic evaluation for policy decisions such as coverage and reimbursement without distinguishing between health technologies (e.g. pharmaceuticals and medical devices). For example, in northern Europe, economic evaluation is widely used in decisions about the reimbursement of new health technologies and cost-utility analysis (with the quality-adjusted life-year as the primary measure of benefit) is the predominant approach. In UK, the National institute for Health and Clinical Excellence (2011) has differentiated between health technologies and has developed the Medical Technologies Evaluation Programme to specifically assess medical devices and diagnostics. In contrast, in central and southern Europe, there is more resistance to the use of economic evaluation in decision making and, where it is used, benefits are more often assessed in terms of clinical added value. In these countries however no distinction is made between health

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technologies and policy decisions on coverage and reimbursement of medical devices are generally not subject to any type of economic analysis. This part of the research provided useful insights into the potential for increasing the use of economic evaluation in various EU member states (Torbica et al, 2016b).

The second part of the research, reported in the fifth paper of this supplement (Tarricone et al, 2016a) used two case studies of implantable cardiac devices in order to demonstrate current, and possible future approaches to the use of economic evaluation. The case studies, implantable ~~converter~~ cardioverter defibrillators (ICDs) and transcatheter aortic valve implantation (TAVI) were chosen in order to explore a wide range of device characteristics, including the significance of irreversible decisions and the complexity associated with evolving technologies. Most of the published economic evaluations and HTA reports located in the literature review did not take account of the special features of medical devices (i.e. learning curves, incremental innovation, dynamic pricing and organizational aspects) in the base case analysis, but were sometimes considered in sensitivity analyses. Overall, the conclusion was that the existing economic evaluations did not pay enough attention to the specific characteristics of devices explored in the MedtecHTA project.

Finally, building on the findings of both WP3 and WP4, the impact of the learning curve on effectiveness and cost was estimated for endovascular aneurysm repair (EVAR) and fenestrated EVAR (fEVAR). This research is reported in the sixth paper in this supplement (Varabyova et al, 2016). It was found that, in the case of EVAR there was a moderate, but significant effect of learning on both in-hospital mortality and hospital length of stay. The same impact was not found for fEVAR, one reason for which could be its similarity to EVAR, meaning that much of the learning in EVAR was transferable to the new procedure

2.5 Uncertainty in the economic evaluation of medical devices

Work Package 5 focused on characterizing uncertainty in the economic evaluation of medical devices and determining future research needs. This research, reported in the seventh paper in this supplement (Rothery et al, 2016), sets out a number of conceptual issues when dealing with uncertainty and the value of research in the context of some of the specific characteristics of devices such as learning curve effects, incremental device innovation and dynamic pricing. It uses value of information analysis to explore the optimal timing of reimbursement decisions and the suitability of conditional coverage decisions, such as 'only in research' and 'approval with research'.

Such conditional reimbursement policies are now becoming popular in a number of countries, given the growing recognition that, for medical devices, there will always be considerable evidence gaps, particularly in evidence on effectiveness. As in the other WPs, a case study is chosen to illustrate the use of methods at different stages of device development and diffusion. The example chosen is enhanced external counterpulsation (EECP), a device used to provide symptomatic relief from chronic refractory angina, where the existence of substantial irrecoverable costs and price changes have a substantial impact on coverage decisions.

2.6 Organizational impact of medical devices

The final methodological issue investigated in the MedtecHTA project was the organizational impact of medical devices. In this part of the project the aim was to propose a methodology that will allow for incorporating organizational issues in a broader HTA framework. A systematic review of the literature was conducted, which

was used to develop a large, (54 item) survey of cardiologists, conducted in collaboration with the European Society of Cardiology. The objective was to explore the role of physicians' motivation and organizational factors in the adoption and diffusion of medical devices. The survey focused on 7 different catheter-based or implantable cardiovascular devices. Multivariate hierarchical modeling was used to determine the associations between the various motivational and organizational factors and device diffusion and use. This research is reported in the eighth paper in this supplement (Hatz et al, 2016).

2. Dissemination of project findings

In the final phase of the project (Part III), the findings and results from the previous phases were collated into a final report (WP7), which provides recommendations for decision-makers, in formulating health policy, within the medical devices industry, as well as in the management of health care organizations. In addition, recommendations on developments in methodology were made for the scientific community. These recommendations are summarized in the final paper in this supplement (Tarricone et al, 2016b). These are divided into; recommendations for policy, recommendations for methods and recommendations for further research.

Taken together, the papers in this supplement represent a comprehensive report of all the main findings of the MedtecHTA project and give references to other published outputs for the project. It is intended to be the main source for researchers and policy makers requiring information on the project.

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Table 1 Overview of project work plan

Parts of the overall project	Work packages included
I: Cross-country analysis of HTA practices and utilization of medical devices	**WP 1** Cross-country Analysis of HTA
	WP 2 Geographic variation in access to medical devices
II: Methodological issues in HTA of medical devices	**WP 3** Comparative effectiveness of medical devices
	WP 4 Economic evaluation of medical devices: overview of different approaches
	WP 5 Uncertainty and Value of Information for medical devices
	WP 6 Organizational impact of medical devices
III: Conclusions, synthesis and recommendations	**WP 7** Recommendations on HTA methods for medical devices

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2.1 Cross country analysis of regulation and HTA of medical devices

Part 1 of the project was essentially preparatory and included the necessary groundwork for the subsequent research activities. WP 1 considered the available evidence on the currently adopted approaches for the HTA of medical devices and on international regulatory guidance on the licensing of medical devices. Tarricone et al (2014) reviewed regulatory practices in the EU, US and 5 other countries and concluded that a number of actions are required to make the clinical evidence gathered through the regulatory process more relevant to HTA. These include the development of international standards on the types of clinical evidence required for the market approval of medical devices and agreement on the balance of clinical data collection pre- and post-launch. The latter is important because of the possibility that, owing to the learning curve and the organizational impact of devices, data from pre-launch clinical trials may not be ideal for assessing effectiveness and cost-effectiveness.

Ciani et al (2015) reported the results of a cross-country analysis of HTA guidelines and available HTA reports on medical devices in assigned countries using a standardized template for comparison. In order to analyse the state of the art in the application of guidelines reviewed, a sample of HTA reports was selected from the University of York Centre for Reviews of Dissemination HTA database and systematically reviewed at three levels (i) assessment of the nature of evidence included in the reports (ii) HTA methods applied by reports considering medical

devices, and (iii) assessment of approaches and methods used to address uncertainty. They found that although 75% of the agencies surveyed had adopted HTA-specific approaches for medical devices, these were largely organizational or procedural in nature. Only one agency had adopted methodological guidelines specific to medical devices.

In the second paper in this supplement, Ciani et al (2016) focus on the second phase of their research, in which they analysed a sample of HTA reports in the field of cardiovascular disease in order to assess whether there are any key differences in how methods are applied. They found that here were several differences, in the types of clinical studies forming the basis for the HTAs, how the health problem and use of the technology was considered, the description and technical characteristics of the technology and the consideration of the organizational aspects of the use of the technology. Most of these differences arose due to the relative 'complexities' in the use of devices, in terms of the number of interacting components. These include the number and difficulty of the actions required by those delivering or receiving the intervention, the number of groups and organizational levels targeted by the intervention, the number and variability of the outcomes and the degree of flexibility or tailoring of the intervention.

2.2 Geographical variation in the use of medical devices in the EU

Work Package 2 considered the geographical variation in the use of medical devices in EU countries by estimating the rate of adoption of selected medical technologies in the field of electrophysiology. This subspecialty of cardiology widely uses implantable medical devices whose efficacy has been demonstrated by a number of randomized clinical trials. In one respect these devices resemble pharmaceuticals as

they have a curative and/or a secondary prevention function and might be tested in clinical trials similar to those conducted on drugs. On the other hand, they differ from pharmaceuticals because they are subjected to incremental changes (e.g. dimensions and software), learning curve effects due to device-operator interactions and price dynamics which make trial designs similar to pharmaceuticals not always suitable for medical devices. These overall characteristics make the area of electrophysiology an interesting case to study.

Results obtained in this field also have a higher degree of transferability to other class III medical devices. Through the analysis of national/local guidelines and data from registries and administrative databases, rates of utilization were mapped to provide evidence of different degrees of access within member states, and whether this adoption is in line with the existing evidence on clinical and cost effectiveness. Valzania et al (2015) reported a systematic review of the literature on implant rates for cardiac implantable electrical devices (CIEDs) in Europe. They found that there had been a recent rise in implant rates, with large geographic differences. For example, the ratio between the regions with the highest and lowest implant rates within the same country ranged from 1.3 and 3.4 for cardiac pacemakers, whereas the ratio between the countries with the highest and lowest implant rates ranged from 2.3 and 87.5. The determinants of these differences (namely epidemiological, cultural, and socio-economic factors) were only partly explored and differences in study methodology could be one reason for the reported differences.

Therefore, in a subsequent phase of the research, reported in the third paper in this supplement, Torbica et al (2016a) undertook a new study of implant rates, the first to use the national hospital discharge datasets available in 5 EU countries. They provide evidence on differences in use of medical devices within and between member states,

investigate the determinants of differences in access to CIEDs, and assess the potential and limitations of administrative databases for the analysis of utilization rates of medical devices in electrophysiology.

It is the first international paper to explore simultaneously differences both between countries and within the regions of those countries. Results show that higher levels of tertiary education among the labor force and % of aged population are positively associated with implant rates of CIED. Regional per capita GDP and number of implanting centers appear to have no significant effect. Institutional factors, captured by fixed country effect, are shown to be important for the diffusion of CIED.

However, even after controlling for clinical, epidemiological and (crude) economic indicators, significant variation in implant rates still exist. They argue that there should be closer examination of the role of organizational factors and clinical preferences in the adoption of devices. These issues are explored further in WP6 of the MedtecHTA project (discussed below).

2.3 Methods for assessing the comparative effectiveness of medical devices

The core part of the project (Part II) sought to develop an improved methodological framework for conducting HTA of medical devices by acknowledging the complexities which arise from their integration into clinical practice. The research conducted in WP3, began by considering the approaches and methodologies used for comparative effectiveness research by conducting a systematic review of the methodological literature. It was found that, although most of the good research

practices in the evaluation of all health technologies apply to medical devices, the interventions involving the use of medical devices should be considered as complex interventions, owing to the importance of user and context independence. Therefore, specific randomized controlled trial designs need to be considered, dealing with surgeons' and patients' preferences, incremental product development and user dependence. In addition, high quality disease- or device-based registries are needed to assess safety and long-term effectiveness (Schnell-Inderst et al, 2016a).

This preliminary research activity provided the basis for the development of improved methods for evaluating comparative effectiveness of medical devices including recommendations for analytic methods and data collection. The research was an important input to the development of guidelines for the evaluation of Therapeutic Medical Devices under the auspices of the EUnetHTA Joint Action 2 (EUnetHTA, 2015).

The framework and new methodological approaches were then tested on medical devices at different stages of development and diffusion within the health care system. First, the use of a method of evidence synthesis that allows for the meta-analysis of RCT and observational data, using bias adjustment based on a formal elicitation exercise involving experts, was explored in the case of total hip replacement. This is reported in the fourth paper in this supplement (Schnell-Inderst et al, 2016b).

2.4 Methods for the economic evaluation of medical devices

Work Package 4 focused on exploring different methods for economic evaluation of medical devices currently adopted in EU countries in order to make suggestions about the development of new methods and offer guidance on future directions in the use of economic evaluation for medical devices. The first part of the research considered

how differences in culture and values in EU countries lead to differences in the methodology and use of economic evaluation for policy decisions such as coverage and reimbursement without distinguishing between health technologies (e.g. pharmaceuticals and medical devices). For example, in northern Europe, economic evaluation is widely used in decisions about the reimbursement of new health technologies and cost-utility analysis (with the quality-adjusted life-year as the primary measure of benefit) is the predominant approach. In UK, the National institute for Health and Clinical Excellence (2011) has differentiated between health technologies and has developed the Medical Technologies Evaluation Programme to specifically assess medical devices and diagnostics. In contrast, in central and southern Europe, there is more resistance to the use of economic evaluation in decision making and, where it is used, benefits are more often assessed in terms of clinical added value. In these countries however no distinction is made between health technologies and policy decisions on coverage and reimbursement of medical devices are generally not subject to any type of economic analysis. This part of the research provided useful insights into the potential for increasing the use of economic evaluation in various EU member states (Torbica et al, 2016b).

The second part of the research, reported in the fifth paper of this supplement (Tarricone et al, 2016a) used two case studies of implantable cardiac devices in order to demonstrate current, and possible future approaches to the use of economic evaluation. The case studies, implantable cardioverter defibrillators (ICDs) and transcatheter aortic valve implantation (TAVI) were chosen in order to explore a wide range of device characteristics, including the significance of irreversible decisions and the complexity associated with evolving technologies. Most of the published economic evaluations and HTA reports located in the literature review did not take

account of the special features of medical devices (i.e. learning curves, incremental innovation, dynamic pricing and organizational aspects) in the base case analysis, but were sometimes considered in sensitivity analyses. Overall, the conclusion was that the existing economic evaluations did not pay enough attention to the specific characteristics of devices explored in the MedtecHTA project.

Finally, building on the findings of both WP3 and WP4, the impact of the learning curve on effectiveness and cost was estimated for endovascular aneurysm repair (EVAR) and fenestrated EVAR (fEVAR). This research is reported in the sixth paper in this supplement (Varabyova et al, 2016). It was found that, in the case of EVAR there was a moderate, but significant effect of learning on both in-hospital mortality and hospital length of stay. The same impact was not found for fEVAR, one reason for which could be its similarity to EVAR, meaning that much of the learning in EVAR was transferable to the new procedure

2.5 Uncertainty in the economic evaluation of medical devices

Work Package 5 focused on characterizing uncertainty in the economic evaluation of medical devices and determining future research needs. This research, reported in the seventh paper in this supplement (Rothery et al, 2016), sets out a number of conceptual issues when dealing with uncertainty and the value of research in the context of some of the specific characteristics of devices such as learning curve effects, incremental device innovation and dynamic pricing. It uses value of information analysis to explore the optimal timing of reimbursement decisions and the suitability of conditional coverage decisions, such as 'only in research' and 'approval with research'.

Such conditional reimbursement policies are now becoming popular in a number of countries, given the growing recognition that, for medical devices, there will always be considerable evidence gaps, particularly in evidence on effectiveness. As in the other WPs, a case study is chosen to illustrate the use of methods at different stages of device development and diffusion. The example chosen is enhanced external counterpulsation (EECP), a device used to provide symptomatic relief from chronic refractory angina, where the existence of substantial irrecoverable costs and price changes have a substantial impact on coverage decisions.

2.6 Organizational impact of medical devices

The final methodological issue investigated in the MedtecHTA project was the organizational impact of medical devices. In this part of the project the aim was to propose a methodology that will allow for incorporating organizational issues in a broader HTA framework. A systematic review of the literature was conducted, which was used to develop a large (54 item) survey of cardiologists, conducted in collaboration with the European Society of Cardiology. The objective was to explore the role of physicians' motivation and organizational factors in the adoption and diffusion of medical devices. The survey focused on 7 different catheter-based or implantable cardiovascular devices. Multivariate hierarchical modeling was used to determine the associations between the various motivational and organizational factors and device diffusion and use. This research is reported in the eighth paper in this supplement (Hatz et al, 2016).

2. Dissemination of project findings

In the final phase of the project (Part III), the findings and results from the previous phases were collated into a final report (WP7), which provides recommendations for decision-makers, in formulating health policy, within the medical devices industry, as well as in the management of health care organizations. In addition, recommendations on developments in methodology were made for the scientific community. These recommendations are summarized in the final paper in this supplement (Tarricone et al, 2016b). These are divided into; recommendations for policy, recommendations for methods and recommendations for further research.

Taken together, the papers in this supplement represent a comprehensive report of all the main findings of the MedtecHTA project and give references to other published outputs for the project. It is intended to be the main source for researchers and policy makers requiring information on the project.

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Table 1 Overview of project work plan

Parts of the overall project	Work packages included
I: Cross-country analysis of HTA practices and utilization of medical devices	**WP 1** Cross-country Analysis of HTA
	WP 2 Geographic variation in access to medical devices
II: Methodological issues in HTA of medical devices	**WP 3** Comparative effectiveness of medical devices
	WP 4 Economic evaluation of medical devices: overview of different approaches
	WP 5 Uncertainty and Value of Information for medical devices
	WP 6 Organizational impact of medical devices
III: Conclusions, synthesis and recommendations	**WP 7** Recommendations on HTA methods for medical devices