HTAi Conference, Cologne, June 2019
HTA Beyond 2020: Ready for the New Decade?

Sponsored Symposium Report
Adaptive HTA for innovative implantable medical devices?

Key points

- An adaptive approach to HTA is needed to ensure innovation (in terms of technical advances, clinical expertise and patients' perspectives) is evaluated and adopted in a timely manner.
- The concepts of Adaptive Pathways developed for medicines, including early engagement, iterative development and Coverage with Evidence Development could be used by HTA, with innovative implantable medical devices as the first pilots.
- Adaptive HTA for innovative implantable medical devices should include
    - horizon scanning to support good financial planning by health systems including early consideration of reimbursement models
    - multi-stakeholder early dialogues to agree outcomes in all HTA domains – clinical, economic, organizational and patient issues
    - pragmatic HTA methodological approaches that integrate RCTs and real-world evidence
    - clinical guidelines to support optimal care and disinvestment.
- The HTA pathway could be adapted, as has been the case in Germany, where there is a two-step process with early assessment of potential benefit followed by later full assessment. However, HTA methods should not be adapted as there will always be a need for high-quality data.
- Innovative implantable medical devices are part of a pathway of care and so clinical involvement in any adaptive approaches will be key and the EU strategy for "Innovation Procurement" could act as a facilitator for Adaptive HTA.

- Given the challenges of the learning curve and the iterative evaluation of different patient populations and device evolutions, analysis of real-world data plays a key role for medical devices. HTA bodies consider that such real-world data should be seen as complementary to data from randomized controlled trials to answer questions about long-term safety, volume-outcome relationships and local economic value. Industry sees the potential for use of big data and artificial intelligence to determine effectiveness, in particular extension of indications. This would allow progressive aggregation of data to capture the iterative nature of implantable medical devices.

- Although HTA bodies may be limited by lack of mandate or restricted capacity, developing effective and efficient multi-stakeholder Early Dialogue processes is the first essential element of Adaptive HTAs for innovative implantable medical devices.

- There is potential for Adaptive HTA for innovative implantable medical devices, but more work needs to done by all stakeholders to continue to discuss the potential of real-world data over the life-cycle of a technology and develop and harmonise processes and pilots. This symposium was a first step in that discussion, but further work is needed. The HTAi community is well placed to take these discussions forward.

Contents

About HTAi

Health Technology Assessment international (HTAi) is the global scientific and professional society for all those who produce, use, or encounter HTA. HTAi has members from over 65 countries and embraces all stakeholders, including researchers, agencies, policy makers, industry, academia, health service providers, and patients/consumers. HTAi is the neutral forum for collaboration and the sharing of leading information and expertise.

Status of this report

This report is a summary of the presentations and discussion in the HTAi 2019 Sponsored Symposium. It has been prepared by the moderator, Karen Facey. All presenters approved the written summary of their own contributions, the contents do not necessarily reflect the views of all contributors. The report is to become a public record of the HTAi 2019 Sponsored Symposium.

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Glossary

CED	Coverage with Evidence Development
COMED	Cost and Outcome analysis of Medical technologies
CtE	Commissioning through Evaluation
DRG	Diagnosis Related Groups
EMA	European Medicines Agency
EUnetHTA	European network for HTA
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HTA	Health Technology Assessment
InEK	Institut für das Entgeltsystem im Krankenhaus (Institute for the Hospital Remuneration System)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAPP	Medicines Adaptive Pathways to Patients
NUB	Neue Untersuchungs- und Behandlungsmethoden (New Diagnostic and Treatment Methods)
RCT	Randomised Controlled Trial
TAVI	Transcatheter Aortic Valve Implantation

Adaptive HTA for innovative implantable medical devices?

1. Introduction

Dr Karen Facey, Evidence Based Health Policy Consultant, Scotland

Dr Facey welcomed participants to the opening symposium of the HTAi 2019 conference to consider whether a new form of "Adaptive HTA" is needed for innovative implantable medical devices.

A one-size-fits all approach to HTA, and in particular using processes for appraisal of medicines, does not work well for medical devices. Medical devices differ from medicines in many ways (including regulatory requirements, effectiveness dependent on user's expertise and localised reimbursement). A bespoke process is needed, as recognised in HTAi by the launch of the new multi-stakeholder Interest Group for Medical Device HTA[1] at this conference.

However, a one-size fits all approach to medical device HTA may also not be appropriate. As identified by the ADVANCE HTA[2] project, medical devices include technologies for diagnostic or therapeutic purposes and range from assistive technologies to artificial body parts and implanted devices (bandages and thermometers to implantable cardiac defibrillators). Perhaps a special form of "Adaptive HTA" is needed for the most complex devices such as the innovative implantable medical devices[3] that draws on the learnings of Adaptive Pathways in medicines regulation.

This needs to be considered within a clear understanding of what HTA is, or should be. The recent international consultation on the definition of HTA shown in the box below helps us to think about HTA beyond the traditional confines of the evaluation of clinical effectiveness, safety and economic implications. It calls for consideration of the broader elements of value including the patient and organisational issues, which might be crucial for innovative implantable medical devices. It also points to the need to assess value at different points in the technology life cycle – pointing to an adaptive HTA approach.

> HTA is a multidisciplinary process that uses explicit and scientifically robust methods to assess the **value* of using a health technology at different points in its lifecycle**. The process is comparative, systematic, transparent and involves multiple stakeholders. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.
>
> *The dimensions of value for a health technology may be assessed by examining its clinical effectiveness and safety, costs and economic implications, wider implications for the patient and caregivers, and any ethical, social, cultural, or legal issues**, as well as organisational and environmental aspects**. The overall value may vary depending on the perspective taken, and the decision context**.**
>
> Definition under international consultation – spring/summer 2019.

[1] https://htai.org/interest-groups/medical-devices/
[2] https://cordis.europa.eu/docs/results/305/305983/final1-advance-hta-final-report-final.pdf page 97.
[3] transcatheter heart valves, patient specific implants (3D printed materials), retinal Implants, neuromodulation implants, bioreabsorbable stents

The HTA definition recognises that a multidisciplinary process is essential. Hence this panel was established with speakers from different stakeholder groups across Europe who were asked to consider whether innovative implantable medical devices need a new adaptive form of HTA, which might draw on the adaptive approach that has been proposed for some medicines.

2. Adaptive HTA for innovative implantable medical devices – a clinician's view

Prof Dr Thorsten Wahlers, Director of Cardiothoracic Surgery, Cologne University Hospital, Germany

Professor Dr Wahlers outlined his extensive experience with all forms of cardiac surgery and his particular interests in minimally invasive procedures and transcatheter aortic valve implantation (TAVI).

For consideration of whether an adaptive approach to HTA is needed for innovative implantable medical devices, it is helpful to consider a case study in detail. TAVI involves placing a catheter-based valve into the correct aortic position in a minimally invasive procedure that takes about one hour. It was developed in 2005 and introduced into clinical practice in Germany in 2008.

When considering whether a technology is innovative, it is important to consider three dimensions:

- technical innovation
- clinical expertise and insights
- patients' preferences and perceptions.

Considering the three dimensions of innovation for TAVI:

1. The technical innovation of the catheter-based valve is demonstrated when it is compared to the mechanical valve it has replaced, which is implanted via open heart surgery in a procedure that has been undertaken for about 60 years (Figure 1).

Figure 1. Technical innovation of heart valves

Starr-Edwards Mechanical Valve 1960

Edwards Sapien 3 Tissue Valve 2016

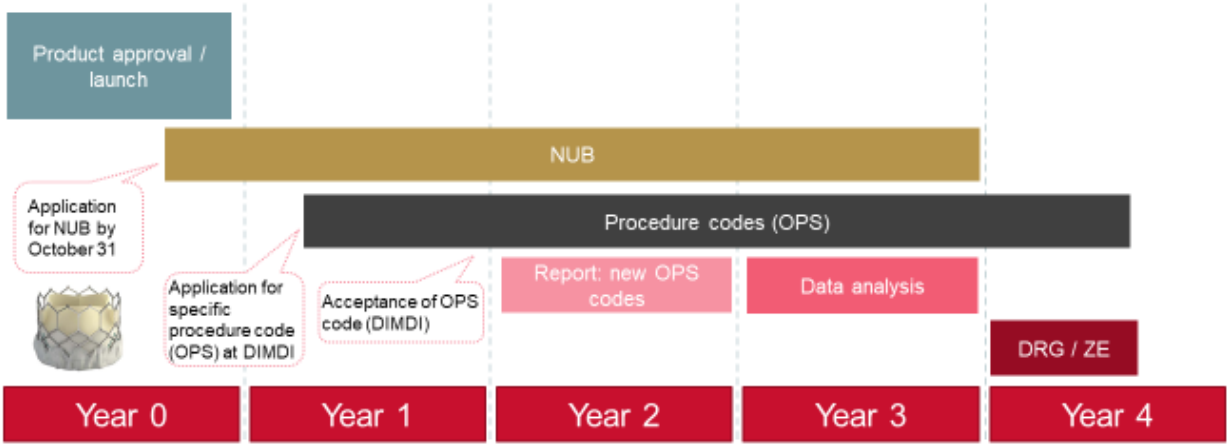
2. The benefits of TAVI are seen by surgeons in terms of better haemodynamics and lower paravalvular leak.
3. There is a direct impact on patients in terms of faster recovery, reduced length of hospital stay and lower need for rehabilitation.

At an overarching level, since the first catheter-based valves came to the market in 2007, a range of companies have developed different forms of the device and improved them in an iterative manner. In the Cologne University Hospital, over the 12 years since the launch of the first device, 30-day mortality has reduced from 4-15% with the first implantations to 1-2% with the latest Sapien 3 valve. This compares to a published 30-day mortality rate of about 2-5% with the mechanical valve in open heart surgery.

This clinical perspective needs to be compared with the process for evaluation of new technologies to bring them into routine use in the health service, which incorporates HTA. In Germany, the process is complex. The NUB procedure (New Diagnostic and Treatment Methods) is a payment scheme for cost-intensive, innovative services and technologies that are used in addition to procedures reimbursed by the standard DRG system. Once per year, hospitals can file submissions to InEK, which determines if the NUB innovation status holds. If the NUB decision is favourable, the hospital can enter into negotiations with the local healthcare payer (statutory health insurance, sickness fund) about an acceptable price for the extra budgetary spend on the new treatment, which is outside the DRG. Each hospital needs to apply separately to their payers and approved applications are monitored by InEK. In 2014, only 15% of the medical device NUB submissions received a favourable evaluation. However, in 2016, the process changed to include an early benefit assessment for completely new, high-risk medical devices (§137h).

While NUB status is decided within a few months, it may take several years until standard DRG reimbursement is available for a new in-hospital procedure (Figure 2). Obtaining NUB status or DRG reimbursement does not necessarily require proof of clinical benefit, except for procedures that are based on completely new, high-risk devices (such as TAVI).

Figure 2. German reimbursement system for new medical devices used for in-hospital procedures



From a clinical perspective, it takes a long time to assess new technologies and incorporate them into the health system for routine use. Given increasing pressures on payers, assessments may take longer in future and there will be continued pressure on prices. Alongside this, the longer-term benefits of technologies do not seem to be determined or assessed. As the process in Germany takes so long compared with other countries, there is a concern that its leading role in the introduction and adoption of innovative medical devices could be affected. Hence, perhaps an adaptive process to HTA for innovative medical devices is needed.

3. Adaptive HTA for innovative implantable medical devices – an HTA analyst view

Prof Rod Taylor, Professor of Population Health Research, University of Glasgow, UK

Professor Taylor recalled the seminal paper by Eichler et al. published in 2012, which proposed adaptive licensing as an evolution in the route to approval for some medicines[4]. The goal is to allow patients timely access to new medicines in areas of high medical need, where it is difficult to collect data via traditional routes and where large clinical trials would unnecessarily expose patients who are unlikely to benefit from the medicine[5]. Adaptive licensing requires stepwise learning for acknowledged uncertainties, with iterative phases of data gathering and regulatory evaluation.

The concept of adaptive licensing was adopted by the European Medicines Agency (EMA), evolved into Medicines Adaptive Pathways to Patients (MAPPs) and is now known as Adaptive Pathways.

Adaptive Pathways are based on three principles:

- iterative development, which means either:
  - approval in stages, beginning with a restricted patient population then expanding to wider patient populations;
  - confirming the benefit-risk balance of a product, following a conditional approval based on early data considered predictive of important clinical outcomes;
- gathering real-world evidence to supplement clinical trial data;
- early involvement of patients and HTA bodies in discussions on a medicine's development.

Adaptive Pathways build on existing regulatory processes for medicines of

- scientific advice
- compassionate use and conditional approval for medicines addressing life-threatening conditions
- patient registries and other pharmacovigilance tools.

Adaptive pathways do not change the standards for the evaluation of benefits and risks or the requirement to demonstrate a positive benefit-risk balance to obtain marketing authorisation. They are intended to provide a multi-stakeholder, iterative approach including HTA bodies and patients and as a result the imi project, AdaptSmart[6] was undertaken to provide a multi-stakeholder enabling platform.

An Adaptive Pathways pilot project was reported on by EMA in 2016[7]. EMA received 62 applications from a wide range of therapeutic areas, with oncology accounting for a third of the total initial submissions. Seven of the applications progressed to formal scientific advice (six were parallel advice with HTA bodies).

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[4] Eichler HG, Oye K, Baird L et al. Adaptive licensing: taking the next step in the evolution of drug approval. Clin Pharmacol Ther. 2012 Mar;91(3):426-37. doi: 10.1038/clpt.2011.345. Epub 2012 Feb 15.
[5] https://www.ema.europa.eu/en/human-regulatory/research-development/adaptive-pathways
[6] http://adaptsmart.eu/home/
[7] https://www.ema.europa.eu/en/documents/report/final-report-adaptive-pathways-pilot_en.pdf

The pilot concluded that Adaptive Pathways:

- are not a new route of approval for medicines, but make use of existing regulatory tools
- are not meant to be applicable to all medicines, but only to medicines that are likely to offer help for a patient population with an unmet medical need
- enable additional data collection to reduce uncertainty after an initial (conditional) marketing authorisation based on surrogate endpoints, early time points/interim analyses, or a smaller population
- require all involved stakeholders to agree a plan for post-licensing knowledge generation for a medicine, before the medicine is authorised, and the marketing authorisation holder commits to carrying out this plan. Once a marketing authorisation has been granted, the post-authorisation plan becomes a legally binding regulatory obligation.
- further refine determination of the benefit/risk profile, therapeutic value and price of a medicine.

These conclusions could be applicable to medical devices and HTA, but it would be important to define what is meant by certain concepts, especially 'unmet need', which could relate to a medical device that has a large therapeutic effect or one that creates a cost saving in the health system.

For medicines, three areas of 'adaptive activity' have been identified that could apply equally well to medical devices:

1. prospective planning – early engagement with payers
2. clinical development – iterative development based on conditional licensing such as coverage with evidence development (CED)/Managed Entry Agreements
3. post authorisation – gathering evidence from real-life use to supplement clinical trial data.

It would be imperative for HTA bodies and payers to be involved in the early engagement to contribute to the planning. In fact, a model for this part of the process already exists in the form of EUnetHTA Early Dialogues, which are not just for medicines, but also for medical devices. Furthermore, Early Dialogues and early assessment approaches for medical devices are also being evaluated in Work Package 6 of the COMED Project[8], which is pushing the boundaries of cost and outcomes analyses of medical technologies. This is the second EU funded project focusing on HTA methods for medical devices and it will report at the end of 2020.

Work Package 7 of COMED is studying CED schemes and recent COMED interviews show that only a few HTA bodies across Europe appear to be undertaking CED for medical devices. Of the four regions in the UK, only one had a major programme for CED at the time of interview, namely England[9]. The Commissioning through Evaluation (CtE) programme was established in 2013 by NHS England, with technical support from NICE and a budget of £25,000,000. Its purpose is to generate real world evidence on 'promising' technologies where current clinical and economic evidence are insufficient to allow full commissioning.

[8] http://www.comedh2020.eu/wps/wcm/connect/Site/COMED/Home

[9] The Irish Government may be establishing a process but no details were available at time of interview with HiQA.

Table 1. Commissioning through Evaluation studies in NHS England[10]

	Design	Timing	Outcomes	Policy decision
Selective dorsal rhizotomy: spasticity in cerebral palsy children	Single arm registry 140 participants 5 centres	April 2014-March 2016 (extended to 2018)	function/HRQoL/cost-effectiveness analysis 2-year follow up	Routinely commission service [July 2018]
Selective internal radiation therapy: selected liver/colorectal cancer	Single arm registry 339 participants 10 centres	Dec 2013-March 2017	HRQoL/mortality/ cost utility analysis 2-year follow up	Routinely commission service [Dec 2018]
Percutaneous mitral valve leaflet repair (MitraClip): mitral regurgitation	Single arm registry 199 participants 3 centres	Oct 2014-Nov 2017	mitral valve regurgitation/HRQOL/ mortality 2-year follow up	Commissioning decision pending
Patent foramen ovale: adults at risk of stroke	Single arm registry 900 participants 20 centres	Oct 2014-Aug 2017	neurological events/mortality/cost utility analysis 2-year follow up	Commissioning policy under review
Left atrial appendage occlusion: atrial fibrillation	Single arm registry 525 participants 10 centres	Oct 2014-Aug 2017	neurological & ischemic events/ mortality/cost-consequence cost analysis 2-year follow up	Routinely commission service [Dec 2018]

Table 1 shows the five medical devices/clinical procedures that have been conditionally commissioned with specific data collection and data capture programmes. Once these data have been analysed, a policy decision about full commissioning has been made by NHS England (the payer). The CED studies are all single arm registry trials with no comparator evaluating the real-world effect in the NHS in England and the economic value. The determination of economic value has varied across the studies (not just cost/QALY). Four of the six projects have been completed and have resulted in full-service commissioning.

In conclusion, there has been limited application of one part of the process that could be termed as adaptive HTA for medical devices in the UK, namely CED.

At the European level, there are important policy discussions on implementation of the new medical devices regulation and on HTA collaboration. Given the distinct regulatory processes for devices and medicines, is there an opportunity for the HTA community to lead on developing adaptive pathway processes for medical devices and perhaps innovative, implantable medical devices could be the first pilots?

[10] https://www.england.nhs.uk/commissioning/spec-services/npc-crg/comm-eval/. Accessed 17 September 2019.

4. Adaptive HTA for innovative implantable medical devices – an industry view of a shared value platform

Andrea Rappagliosi LLM, VP Market Access and Public Affairs, Edwards Lifesciences

Mr Rappagliosi reflected on the potential for adaptive approaches in HTA for innovative, implantable medical devices to determine their real value, recognising that a one-size fits all approach does not work for all forms of health technologies.

Innovative implantable medical devices are at the crossroads of biology and engineering and so their effectiveness is dependent on how they are implanted and how an individual's disease is managed. The learning curve is important, as the clinical team adapts its approach to implantation through experience. The effectiveness of the 500th implantation could be better than the first and the device itself is likely to evolve over time. Furthermore, given innovative implantable medical devices would initially only be given to patients with few alternative options, it is imperative to integrate robust evidence about patients' experiences and preferences into the value determination.

An initial reaction to a call for adaptive approaches, can be that this is simply a call to lower evidentiary standards. Actually, it is exactly the opposite. It is elevating the standards of value assessment using customised methodologies to develop the best evidence for particular health technologies where there is high unmet medical need and delivery via specialist services. It is important to discuss what we all mean by unmet medical need. The 1960s mechanical valve could be considered as having met unmet medical need, but this would ignore patient experience. Consider a patient who has to have thoracic surgery, stopping the heart, with extracorporeal circulation of blood and months of rehabilitation vs a minimally invasive approach with local anaesthesia and return to physical activities within a few days. Is this addressing unmet medical need? Methodologies should be used to capture this and it would be unethical not to do so.

There needs to be a shared understanding of innovative implantable medical device development as an evolution of knowledge from first in man testing to use as the standard of care. Adaptive HTA could support this and it would not be about simply replacing randomised controlled trials (RCTs). It could provide a framework for evidence generation able to integrate different forms of evidence over time to ensure that the true value of the medical device is understood.

Prospective systems of evaluation and reimbursement need to be developed and validated, which can evaluate the evidence that accumulates over the life cycle of an innovative implantable device to optimize its performance and maximize its value. Furthermore, as HTA is relatively new and only performed on a small proportion of medical devices, it is important that innovation is not stifled by use of older or unassessed technologies.

For innovative implantable medical devices, there needs to be a bespoke process for HTA, which is a patient-centred, societally meaningful Adaptive HTA. This needs to include:

- horizon scanning to support good financial planning in health systems
- multi-stakeholder early dialogues to agree outcomes to be studied in all the HTA domains – clinical, economic, organizational and patient issues
- pragmatic HTA methodological approaches that integrate RCTs and real-world evidence
- clinical guidelines to support optimal care and disinvestment to encourage health system improvements.

5. Adaptive HTA for innovative implantable medical devices – an HTA view

Prof Dr Stefan Sauerland, Head of Department Non-Drug Interventions, IQWiG, Germany

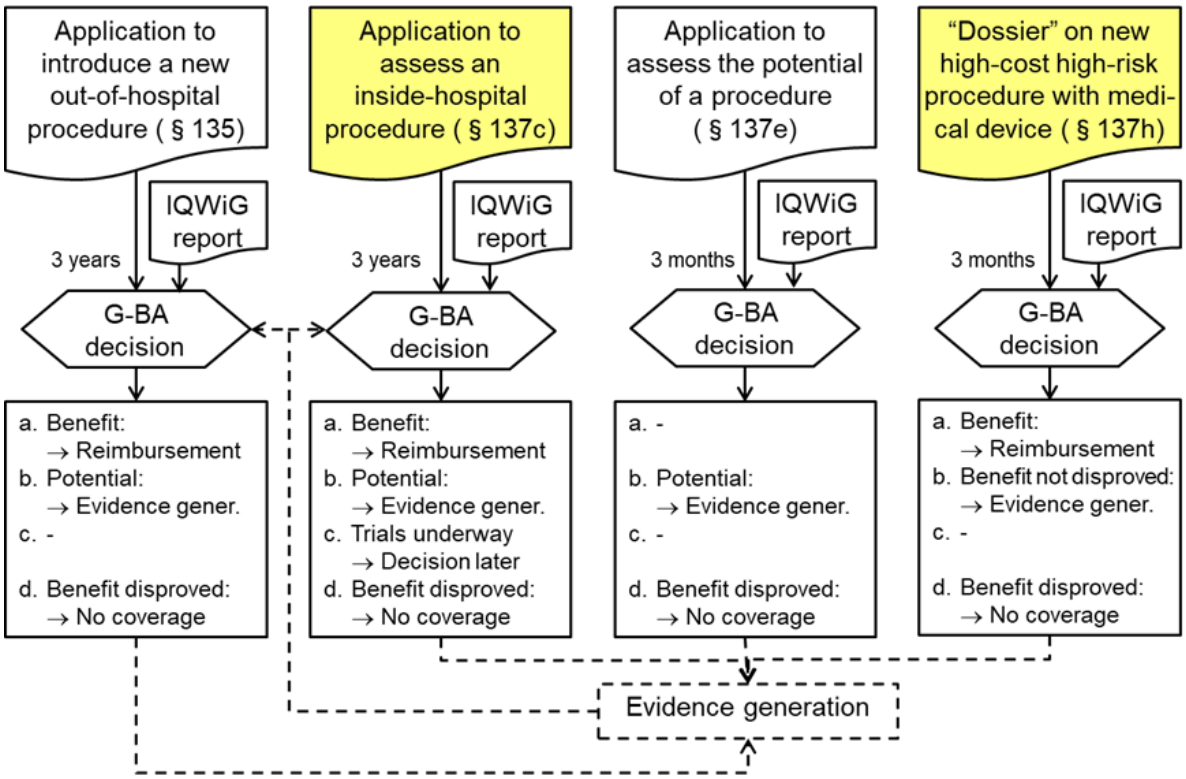
Professor Dr Sauerland used his experience in surgical research and as leader of the non-medicines department in IQWiG to reflect on the need for adaptive HTA for innovative implantable medical devices.

The key question is – what part of HTA do you want to adapt? Is it the HTA pathway or the methods? The HTA pathway could be adapted, but not the methods, as there is a need for clear, high quality data, before unconditional, general reimbursement can be granted.

Germany has already adapted its HTA processes with different routes for non-medicine technologies and medicines. Furthermore, as shown in Figure 4, non-medicine technologies have four potential routes for coverage that relate to clinical setting (ambulatory vs inpatient) and stage of technology develop (early assessment of potential vs full HTA dossier for high-cost, high-risk procedures with medical devices).

The two yellow boxes in Figure 4 show the processes that are relevant for an innovative implantable medical device. At the outset, (potential) benefits are evaluated under §137h. This assessment is mandatory for all devices that are completely new, high-cost and high-risk. (If TAVI had been launched in 2019, it would have to enter into this HTA process.) If the benefit of the new procedure can be demonstrated already, the §139h pathway leads to reimbursement (as for any other lower-risk device). If RCTs and other convincing data are lacking, reimbursement is still granted, but the manufacturer has to fill the evidence gaps by conducting or at least funding an RCT.

Figure 4. Adaptation of HTA pathways for non-medicines interventions in Germany



The vast majority of medical devices intended for in-hospital use are reimbursed without any HTA. However, if high-quality data subsequently raise doubts regarding their effectiveness, the payers or other stakeholders may initiate a §137c process (second column in Figure 4). This process could lead to rescinding the procedure's reimbursement. To date, the §137c process has only seldom been used. As RCT data on TAVI are positive, it is very unlikely that TAVI will be challenged by this pathway.

The requirement for a dossier on new high-cost, high-risk procedures with Class IIb/III medical devices (§137h) is new and will include innovative implantable devices, like TAVI. Experience with this process is limited, as only few devices fulfil the assessment criteria. In the §137h process, hospitals (after consultation with the manufacturer) need to submit data for a short assessment. It is understood that at this early stage of development, RCT data may not be available, but this will lead to a CED requirement. Based on recommendations by IQWiG, the policy-maker (G-BA in Germany) defines the key elements of the RCT, such as comparator, outcomes, or length of follow-up. A reassessment is then required when the RCT is complete and a decision can be made by the policy maker (G-BA in Germany).

So, an adaptive HTA process is already available in Germany, which shows that Germany is open to innovation, not stifling it. This was demonstrated when Germany was identified as the world's leading country for use of TAVI.[11] On the other hand, early adoption of a new procedure also entails risks, which was also shown for TAVI in Germany.[12]

Germany has a system that allows nearly every new health technology to enter the hospital (without an HTA). For new high-risk devices, there is a two-step evaluation process. This is the best form of HTA – combining the reimbursement of a technology with the generation of evidence. Given the early access routes for new interventions in Germany, there doesn't seem to be a need to further adapt HTA pathways, but perhaps the pathways need to include more technologies, such as more Class IIb devices and some new surgical procedures that do not use a device. There are other countries, where a technology cannot be introduced in a hospital without an HTA recommendation. In such systems, there may be a need for more adaptations to the HTA process.

When considering the potential for adaptive processes, it is important to consider whether there would be any unintended consequences. For example, they might hinder recruitment to clinical trials. In which case, further adaptation to HTA processes might be needed to expand recommendations. At the moment "only with research" means there must be research, but not all patients need to be in the trial, whereas "only in research" means that all patients treated with the devices must in the trial[13]. These two different forms may be too extreme and it could be helpful to generate alternatives, for example, every second patient should enter the trial.

There have been discussions about CED across several countries in Europe. This is obviously more complex, but has the potential to develop good data to inform decisions. This needs to be done recognizing that RCTs produce the best data to demonstrate clinical effectiveness. For TAVI these data were initially available for high-risk patients, then for medium-risk patients. Hopefully other innovative, implantable medical devices will be evaluated in the same rigorous manner.

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[11] Mylotte et al.; Adoption of transcatheter aortic valve implantation in Western Europe. Interv Cardiol 2014; 9: 37-40. https://www.ncbi.nlm.nih.gov/pubmed/29588776

[12] Krasopoulos et al., European real-world trans-catheter aortic valve implantation: systematic review and meta-analysis of European national registries. J Cardiothorac Surg 2016;11: 159. https://www.ncbi.nlm.nih.gov/pubmed/27899128

[13] Walker et al.; Coverage with evidence development, only in research, risk sharing, or patient access scheme? A framework for coverage decisions. Value Health 2012; 15: 570-9. https://www.ncbi.nlm.nih.gov/pubmed/22583469

6. Adaptive HTA for innovative implantable medical devices – a payer/provider view

Dr. a Laura Sampietro-Colom, Head of Evaluation of Innovation and New Technologies, Hospital Clinic Barcelona, Catalonia (Spain)

Dr Sampietro-Colom explained that the Hospital Clinic Barcelona is a high-tech hospital for specialised care across Spain, but it is also acting as a community hospital for an area of Barcelona city. She reflected on the potential for Adaptive HTA from her experience as a physician and leading a hospital based HTA unit, working closely with practicing clinicians, including the cardiovascular leader of the hospital.

EMA indicates that Adaptive Pathways could be used with conditional licensing of a medicine where there is a high unmet public health need and evidence is lacking or it is not possible to do RCTs. This could be applied to situations where reimbursement processes do not fit the needs of new technologies and services, such as in the case of innovative implantable medical devices.

An essential element of Adaptive HTA for medical devices would be to prospectively develop a plan with clinicians and hospital managers for iterative evidence generation, including clear decision points where the reimbursement decision might be reversed.

An important consideration for innovative, implantable medical devices is that there could be greater risks using Adaptive HTA. If a safety issue is identified with a medicine, it can be discontinued easily. However, extracting a medical device requires a surgical procedure that is associated with risks and costs. Who will pay for that – the hospital or the manufacturer?

Implantable medical devices are not used in a vacuum, they are part of a pathway of care. When innovative solutions are introduced into a hospital, it is essential to consider the organisation of care and issues such as the learning curve of the surgeon. Thinking about this broader setting, the EU has launched a new strategy for “Innovation Procurement” that could be an inspiration to support development of Adaptive Pathways for medical devices.

Innovation Procurement is a forward-looking innovation procurement strategy that drives innovation from the demand side[14]. It refers to any procurement that has one or both of the following aspects:

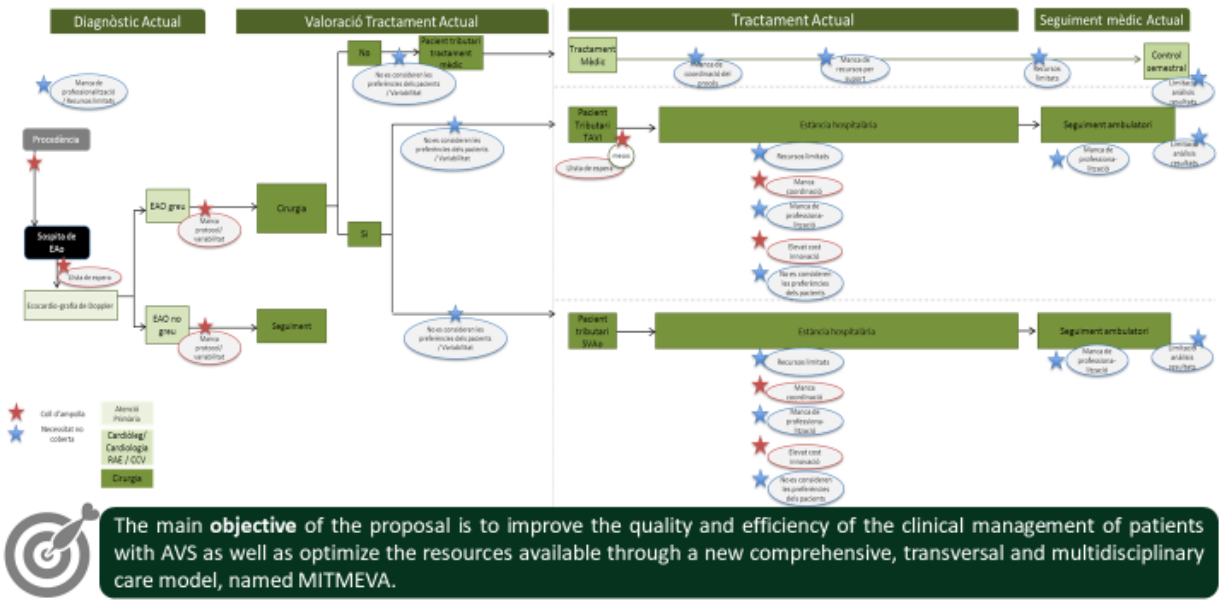
1. buying the process of innovation – buying the research and development services of products, services or processes, which do not exist yet. The public buyer describes its need, prompting businesses and researchers to develop innovative products, services or processes to meet the need.
2. buying the outcomes of innovation created by others - instead of buying off-the-shelf, the public buyer acts as an early adopter and buys a product, service or process that is new to the market and contains substantially novel characteristics. [15]

Innovation Procurement utilises the concepts of Pre-Commercial Procurement (PCP) and Public Procurement of Innovative solutions (PPI) in a complementary way. PCP can be used when there are no near-to-the-market solutions available and new research and development is needed. PCP can then compare the pros and cons of alternative competing solutions approaches. PPI is used when innovative solutions to challenges are nearly ready or already in small quantity in the market and do not need new research and development.[10]

[14] https://ec.europa.eu/digital-single-market/en/innovation-procurement
[15] European Commission. Commission Notice. Guidance on Innovation Procurement. 2018 Ares (2018)2515047 - 15/05/2018

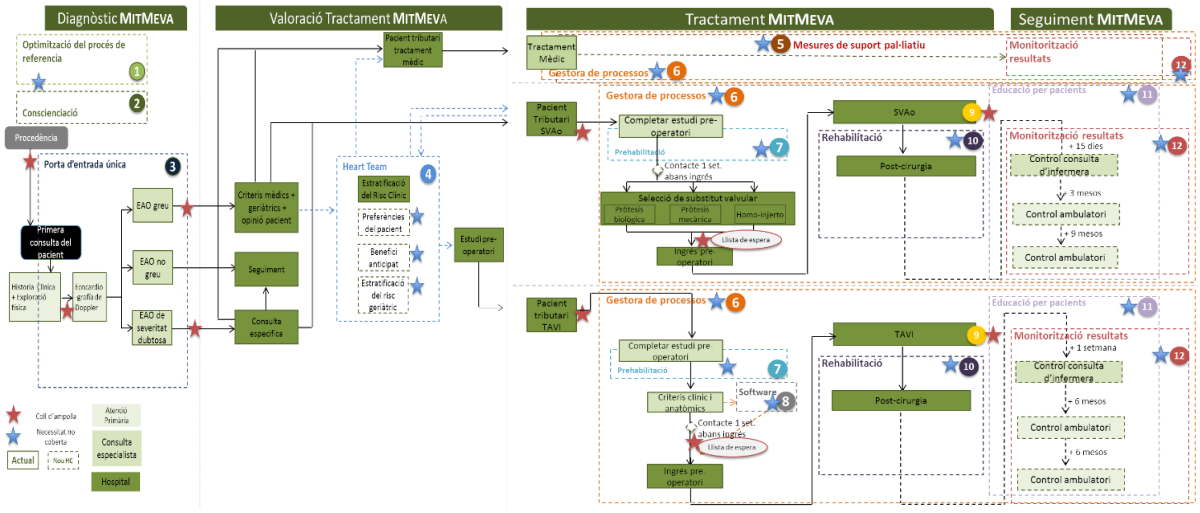
The Hospital Clinic Barcelona is undertaking Innovation Procurement. Working with its Director of the Cardiovascular Institute, a public tender is soon going to be issued to procure a new service for the entire management of aortic stenosis, including innovative and new technologies for which the hospital has identified a need. The current pathway of care for patients with aortic stenosis has been mapped from primary care through to hospital discharge. Waiting lists have been reviewed to identify bottlenecks (for example in echocardiography, hospital admission etc) and health system needs in terms of organizational aspects and technologies have been identified, as shown in Figure 5.

Figure 5. Hospital Clinical Barcelona - Current Patient Flow for Management of Aortic Stenosis with Unmet Needs and Bottlenecks (in Spanish)



After this system evaluation, a new care pathway has been designed and HTA modelling has shown that it will save money and improve quality of care. The project to deliver the new model of care is called MITMEVA (Integral, Transversal and Multidisciplinary Management of Aortic Valve Stenosis), as shown in Figure 6.

Figure 6. MITMEVA Expected New Model for Management of Aortic Stenosis with Actions (in Spanish)



In the summer of 2019, the hospital clinic issued an open market consultation about delivery of the MITMEVA model to enter into public procurement. The project will:

- include innovative health technologies
- identify patients that benefit the most
- integrate primary, secondary and social care
- achieve better outcomes and efficiency
- enable transferability - scalability to other hospitals
- use a new payment system including real-world data.

This project is trying to encourage innovation, but not in a vacuum, recognizing the needs of the health system. This could be a good example on which to build Adaptive Pathways for innovative implantable medical devices.

7. Discussion

Dr Facey thanked the panelists for their stimulating and challenging considerations of the potential for Adaptive HTA for innovative implantable medical devices. The audience were invited to ask questions.

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Francois Meyer (HAS): When considering the data on evolution of mortality over time presented by Professor Wahlers, it is important to consider all the elements that are changing over the time period, not just the device evolution, but also the kinds of patients treated. Initially TAVI was used in those contraindicated for open heart surgery, then it was used in patients at high or intermediate risk with surgery. Do the mortality figures presented combine these different populations? This is important as it highlights the challenge of interpreting real world data in this situation where eligible patient cohorts and other elements, such as the version of the device, are changing.

TW – You are correct, the current 30-day mortality rate of 1.5% is the mean for low-risk patients. At the outset TAVI was used in high risk, older patients. Over the 12 years there has been an iterative process for patient selection and further development of the devices. It is difficult to assess and it may be necessary to divide up the timeframes or present the mortality data by risk profiles. However, in general, now the risk of 30-day mortality with TAVI is about 1.5% compared to the risk of mortality with open heart surgery of about 2.5%. Therefore, in terms of risk, the new technology is considered better by clinicians and the old technique is only used when the new technology is not considered appropriate.

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Francois Meyer (HAS): Given the challenges of many things changing over the life cycle of an innovative implantable medical device, there are challenges with collecting real world data. What are the different approaches and attitudes to collecting real world data in different countries and healthcare settings?

TW – Safety data should be gathered for every device and analysed across countries.

AR – RCTs are multi-centre, multi-country with one protocol. The challenge with real-world data is that requirements for data collection vary across countries. This is why it is essential to have the relevant stakeholders agree upstream what real-world data are required. Currently there is a fragmentation of requests for, and acceptance of, observational data, such as registries. Furthermore, registries in different countries may collect different

information. This means there can be lots of local data in different regions that cannot be amalgamated. This is why I am a strong believer in RCTs but I don't think they are exhaustive. We need to develop real world evidence in a similar way to RCTs – with a clear, agreed data collection schedule.

SS – Observational data and RCT data complement each other. We need RCTs to show effectiveness but observational data, e.g. from real world studies, are also important for Germany. For example, the determination of whether cardiologists should do TAVI without backup from a cardiothoracic surgeon or the volume to outcome relationship are important to optimize implementation of a new technology but they cannot be answered in an RCT. We should move on from this old clash between randomized and non-randomized data to recognize that they are complementary.

LSC – I agree with SS - we need to use the best methodology possible (such as RCTs) for medical devices, but real-world data can be useful to complement RCTs. However, for the extension of an indication, real world data might be useful. This was discussed at the HTAi Global Policy Forum in 2019, where it was highlighted that the FDA is approving indication extensions based on real world data from carefully conducted registry studies in the new patient population.

In the Hospital Clinic in Barcelona, we have good electronic health records but they are observational and not analysis ready, so it is difficult to generate real world evidence that would be useful for HTA. In the MITMEVA project relevant data will be collected, but it will be carefully designed to ensure that robust real-world evidence is generated.

RT – In the CtE programme in England, all the technologies had completed RCTs before additional real-world data were collected – this confirms SS's point. The uncertainty for NHS England was how do the RCTs relate to what will happen in our healthcare system – volume and outcome relationships, delivery in a specialist centre, local economic value etc. For such health system specific questions, the real-world data needs to be local and can be specified in a clear protocol. For MitraClip, NHS England was able to use an existing registry for its evaluation.

There may be some questions (such as safety issues), where a more powerful study with cross-country data is needed. Whatever process is used, the real-world evidence needs to be as reliable as an RCT. It may not be protocolized, but it should be prospective and agreed by all stakeholders.

If a health system is prepared to invest in a technology and its evaluation (only in research) for a specified time period, there needs to be a decision point where all parties come together to agree if the study objectives were achieved based on the data collected and then the commissioning decision can be made.

AR – The question is how can real world data be integrated in a smarter way with RCTs, so that the minimally sufficient dataset has smaller RCTs focused on elements that only they can answer, but some questions are substituted with real world data. For TAVI, Edwards has a family of RCTs including over 5,000 patients. The trials of other manufacturers probably include another 5,000 patients in RCTs. So, this seems to imply that someone is saying these trials are incorrect and they need to be redone. We are duplicating studies, which is not meaningful or efficient. So, we need to understand what questions can be evaluated in real life so that they can be taken out of RCTs to ensure that data generation and evaluation is optimized.

RT – We recognize that it's not always possible to do an RCT. For rare diseases with high unmet need, some medicines have received regulatory and HTA approval without RCTs. The question for me is, when there is RCT evidence, how can real world data add value to that. I understand that means additional evidence is being collected. However, in the CtE programme, the additional evidence wasn't collected by the industry, it was collected by the payer. Hence the complementarity of evidence is a good way to think.

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Colin Wight (Galbraith Wight) – Thinking about the implications of Adaptive HTA for innovative implantable medical devices. The adaptive licensing diagram helpfully depicts a life-cycle approach for HTA that includes early dialogues through clinical development to the potential for CED. But, HTA bodies are already under pressure, so what are the capacity and capability issues for HTA bodies to undertake Scientific Advice/Early Dialogue processes and CED for medical devices? Is such an Adaptive HTA approach feasible for HTA bodies?

SS – There is a need for more capacity and capability in HTA bodies for Early Dialogues. When a company is developing a new technology, there may be very limited knowledge about the comparator or the most appropriate endpoint. Hence advice about study design cannot be binding for an HTA decision some years later when RCTs have completed, as many elements in health care delivery may have changed.

IQWiG does not have a legal mandate to give formal scientific advice to industry. It does have extensive experience in assessing clinical trials, but the new German regulation has meant that we now have to propose clinical trials, but agreeing the perfect trial design is quite challenging.

LSC – It is really important to have Early Dialogues to help industry plan the best studies. However, the HTA Unit in the Hospital Clinic Barcelona is small and it is difficult to train and retain people so we do have limited capacity. We need to look innovatively at using the scarce HTA resources we have in an efficient manner.

Hospital -based HTA units are not involved in the collaborative HTA initiatives for Early Dialogues, but we work more closely with clinicians than national HTA bodies and can offer valuable advice. Hospital-Based HTA units must be involved as they understand what clinicians and hospitals need from technologies. Perhaps information and communication technologies could be used to design a more comprehensive and efficient approach to providing Early Dialogues.

RT – Agree. HTA bodies don't have sufficient resources, but all the key stakeholders need to be included in the Early Dialogues with industry, otherwise HTA does not get the data it needs. The only question is which stakeholders need to be involved? If we include hospital representatives, HTA national bodies, regulators and perhaps other layers of decision makers, an Early Dialogue meeting could include lots of people who might all give different views. So, we need to be realistic and pilot some approaches to Adaptive HTA. This is about process. It's not about changing our fundamental methodologies.

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Dr Facey asked the panelists to give a closing statement, reflecting on the other stakeholder's arguments, about whether Adaptive HTA for innovative implantable medical devices should be considered.

AR – There is potential for Adaptive HTA for innovative implantable medical devices, but there is lots of work to do, to put these ideas into practice.

TW – This panel is the first step to developing these ideas for Adaptive HTA to consider routine use of a health technology in the health system. But it is important to stress that a clinician works with individuals and would not implant a medical device he thinks is bad. He carefully assesses the best procedure for each patient.

RT – This is a unique moment in time, in terms of the EU collaboration on HTA and the new medical device regulation. There is a lot of work to do but we need to seize the opportunity and proceed together.

SS – I agree that the concept of HTA as one report undertaken at one time point in the life cycle of a health technology is over. We are moving to adaptive, may be iterative, may be continuously living HTA reports. This will be the future and we need to balance adaptation of a new intervention against the risks and the evidence generation.

LSC – There is experience from the field of medicines about what has worked in Adaptive Pathways and we all know the idiosyncrasies that make innovative implantable medical devices different. Furthermore, initiatives at the EU level encouraging innovation provide momentum and encourage us to work in an efficient manner with clinicians, academia, hospital-based HTA, industry and patients.

KF – This is the start of a conversation about iterative, efficient HTA for more complex medical devices, which are innovative and used in areas of high unmet need that we will continue to discuss in HTAi, not just at this conference but in coming years.

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