



ASSESSMENT OF MEDICAL DEVICES: KEY FEATURES AND MAJOR CHALLENGES

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Workshop "How can HTA methods be adapted to meet the special characteristics of medical devices?"
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Premise

- Health Technology Assessment (HTA) is undoubtedly the most widespread approach to set priorities and help supporting the allocation of scarce resources in the health care sector
- If it originally responded to an ever increasing squeezed healthcare systems' budgets, HTA has now found a better place in the new value-based healthcare paradigm
- Health Technology Assessment has diffused having pharmaceuticals in mind
- Assessment of medical devices are more challenging than drugs in several respects*

*Drummond M, Griffin A, Tarricone R. Economic evaluation for devices and drugs: same or different? Value in Health 2009;12(4):402-406

Challenges in assessing medical devices 1/5

- They are
 - multiple
 - diagno:

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ORIGINAL RESEARCH
 Economic Evaluation

Genetic Screening for the Predisposition to Venous Thromboembolism: A Cost-Utility Analysis of Clinical Practice in the Italian Health Care System

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ABSTRACT

Objectives: In the Italian health care system, genetic tests for factor V Leiden and factor II are routinely prescribed to assess the predisposition to venous thromboembolism (VTE) of women who require oral contraceptives. With a specific reference to two subpopulations of women already at risk (i.e., familial history or previous event of VTE), the study aimed to assess whether current screening practices in Italy are cost-effective. **Methods:** Two decisional models assessed costs and quality-adjusted life years (QALY) annually from the perspective of the National Health Service. The two models were derived from a decision analysis exercise concerning testing practices and consequent prescribing behavior for oral contraceptives conducted with 150 Italian generalists. Health care costs were computed on the basis of 20-year hospital discharge records and the activities of a thrombosis center. Whenever possible, input data were based on the Italian context; otherwise, the data were taken from the International literature. **Results:** Current testing practices on women with a familial history of VTE generate an incremental cost-effectiveness ratio of 473,433/QALY, which is well above the accepted threshold of cost-effectiveness of 48,000 to 49,000/QALY. In the case of women with a previous event of VTE, the most frequently used testing strategy is cost-effective and leads to an overall loss of QALY. **Conclusions:** This study represents the first attempt to conduct a cost-utility analysis of genetic screening practice for the predisposition to VTE in the Italian setting. The results indicate that there is an urgent need to better monitor the indications for which tests for factor V Leiden and factor II are prescribed. **Keywords:** cost-utility analysis, genetic testing, Italy, venous thromboembolism.

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Challenges in assessing medical devices 2/5

BMJ

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EDITOR'S CHOICE

The scandal of medical device regulation

From: Deborah Cohen, BMJ

The scandal of medical device regulation is a complex issue that involves multiple stakeholders, including manufacturers, regulators, and patients. It is a challenge that requires a multi-faceted approach to address the various aspects of the problem.

The breast implant scandal and European Medical Device Regulation

By Maria Correia and Roger Cox

The recent silicone breast implant scandal in Europe has led to questions about whether or not European medical device regulations are sufficient to protect patients not only from unsafe breast implants, but unsafe medical devices in general.

How are medical devices, specifically breast implants regulated in Europe?
 Breast implants are regulated by the Medical Devices Directive (MDD), covering the vast majority of medical devices, which became mandatory in June 1994. Directives must be transposed into European national laws in order for their requirements to be mandatory. Medical devices that comply with any national transposition of the Directive can be affixed with the CE mark and sold throughout Europe.

The European regulatory system for medical devices is robust. As the risks related to the use of a device increase, so does the level of regulatory control. The MDD requires that manufacturers determine the classification of their devices based on a set of rules found in Annex B of the Directive. The four classes of devices under the MDD correspond to increasing levels of risk and therefore control class I (lowest risk), class II (lower intermediate risk), class IIb (higher intermediate risk), and class III (highest risk).

The continuous assessment procedures, which are

Europeans are left to their own devices

When it comes to medical devices, Europeans seem to get a worse deal than US patients. Deborah Cohen and Matthew Billingsley compare the regulatory systems.

How a fake hip showed up failings in European device regulation

Deborah Cohen investigates how EU authorities would be prepared to allow a fake hip prosthesis with dangerous design flaws onto the market.

Deborah Cohen, investigations editor

Faulty hip implant shows up failings of EU regulation

Deborah Cohen describes an investigation showing how a fake hip prosthesis with dangerous design flaws should be approved for the EU market.

Deborah Cohen, investigations editor

Challenges in assessing medical devices 3/5

- Clinical evidence is often poor in quantity and quality:
 - Current regulatory systems aim at assessing safety, performance and – sometimes – efficacy of medical devices
- What clinical evidence?
 - Large Randomized Controlled Studies (RCTs) represent the standard to look for causal relationships between outcomes and interventions, however...
 - MDs' features often make RCTs unethical, inapplicable or very difficult and too costly (e.g. proven effectiveness, learning curve, incremental innovation)

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Challenges in assessing medical devices 4/5

Research Article

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Learning effect and diffusion of innovative medical devices: the case of transcatheter aortic valve implantation in Italy

Journal of Comparative Effectiveness Research

Aim: We investigated the diffusion of transcatheter aortic valve implantation (TAVI) since its introduction into the Italian market aimed at identifying the potential drivers of uptake and diffusion at hospital and regional levels. **Materials & methods:** We estimated the determinants of TAVI diffusion in Italy from 2007 to 2015 with a regression analysis based on registry data. **Results:** Since 2007, TAVI has shown significant diffusion rates in Italy. The diffusion is positively correlated with implanting centers' experience and with the presence of key opinion leaders. Regional recommendations on the use of TAVI negatively influence the diffusion. Reimbursement policies do not exert a relevant impact. **Conclusion:** Learning effect seems to be the major driver of TAVI diffusion in Italy.

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learning curve, i.e. what

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*Spinner et al. "Do different clinical evidence bases lead to discordant health-technology assessment decisions? An in-depth case series across three jurisdictions" *ClinicoEconomics and Outcomes Research* 2013;5:69-85

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Challenges in assessing medical devices 5/5

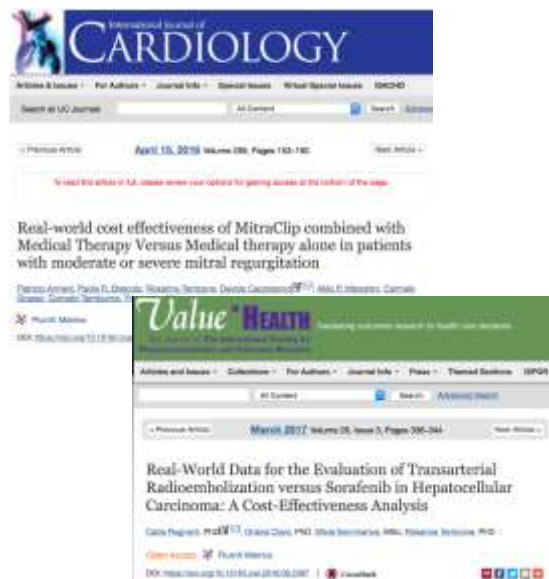
- **Timing** of assessment (i.e. Buxton Law's "It is always too early until, unfortunately, it's suddenly too late"):
 - Shall we wait until the use of the innovative MD becomes as experienced as the standard of care or shall we assess the innovative device at an early stage so to allow patients to access better care if cost-effective?
 - challenge to assess long-term benefits and/or spillovers vs. upfront costs
- Medical devices have **wider economic implications** (e.g. organisational impact): rarely assessed*:
 - It's important to widen the perspective (i.e. NO silos-mentality and silos-budgeting)
- **Pricing** strategies also depend upon country-based procurement policies: instability of ICERs across jurisdictions and over time

*Tarricone R, Callea G, Ogorevc M, Prevolin Rupel V. Improving the methods for the economic evaluation of medical devices. Health Economics 2017;26(Suppl S1):70-92.

The Increasing Role of Real World Evidence

- Clinical evidence for MDs is often generated in clinical practice and often precedes (if any) RCTs:
 - E.g. 40% of high risk implantable MDs accessed the Italian market with no RCTs*
- Under certain conditions, real-world data, defined as data obtained outside the context of RCTs, can become relevant to decision makers, even in absence of RCTs
 - to be not only a complementary source of evidence but also a low-cost, rapid and valuable substitute especially for technologies whose diffusion process has already started

*Tarricone R. Use of Real-world Evidence to Shape Health Policies for Medical Devices. ISPOR Boston, 2017.



Real World Data's major advantages



Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients



Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients

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SOURCE 3 Registry

Design and 30-Day Results of the European Postapproval Registry of the Latest Generation of the SAPIEN 3 Transcatheter Heart Valve

Editorial, see p 1132

BACKGROUND: The SOURCE 3 Registry (SAPIEN Aortic Bioprosthesis European Outcome) is a European multicenter, observational registry of the latest generation of transcatheter heart valves, the SAPIEN 3 (Edwards Lifesciences, Irvine, CA). Its purpose is to document outcomes of clinical safety and performance after European approval was given.

METHODS: Here, we present the 30-day outcome of the SOURCE 3 Registry. All data are self-reported, and all participating centers have contracted to support their cooperative experience with the SAPIEN 3 transcatheter heart valve, dependent on patient consent, before the start of the study. Adverse events are defined with Valve Academic Research Consortium 2 criteria and adjudicated by an independent clinical events committee.

RESULTS: A total of 1950 patients from 90 centers in 10 countries were enrolled between July 2014 and October 2015. Of those, 1947 patients underwent transcatheter aortic valve implantation (TAVI) with the SAPIEN 3 (mean age, 81.6±6.5 years; 48.1% female). Mean comorbidities included coronary artery disease (53.0%), renal insufficiency (27.4%), diabetes mellitus (29.0%), chronic obstructive pulmonary disease (16.0%), and a mean logistic EuroSCORE of 18.3±13.2. Transfemoral access was used in 87.1% (n=1705), and transcatheter, in 12.9% patients. Coronary occlusion was noted in 59.9% of transfemoral procedures, and in 50% of patients, TAVI was performed without aortic balloon subvalvular implantation success 11 valves in the intended location) was 96.3%. Conversion to conventional surgery (6.0%) and use of cardiopulmonary bypass (5.7%) were rare. Adverse events were low, with site-reported 30-day all-cause mortality of 2.2%, cardiovascular mortality of 1.1%, stroke of 1.4%, major vascular complications of 4.1%, life-threatening bleeding of 5%, and post-TAVI paravalvular regurgitation of 1.2%. Moderate or greater paravalvular regurgitation was observed in 3.1% of reporting patients.

CONCLUSIONS: Results from the SOURCE 3 Registry demonstrate satisfactory European real-world outcomes of SAPIEN 3 TAVI practice when the third-generation TAVI device is used.

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DOI: 10.1001/jama.2016.11111

Real World Data are not problem-free (1/2)

Major concerns about RWD refer to*:

- selection bias
- Internal validity
- inaccurate recording of health events
- missing data
- opaque reporting of conduct and results
- selective publications

TABLE 1. Real-world data (RWD) and real-world evidence (RWE) studies: pros and cons

Key element	RCTs	RWE studies
Learning curve	Not relevant Randomized trials select the patients before the implementation of the intervention No need for control to start data collection from the first intervention	Can be controlled if the intervention is the disease in focus Need for control to start data collection from the first intervention
Selection bias	Not applicable for design Study design, where open-label studies allow patients to drop out, if it is possible to generate selection bias Randomized trials allow patients to drop out, but selection bias is reduced and reported	The most relevant issue Appropriate data collection and statistical procedures can significantly reduce it Other studies are not randomized and report bias
Adherence to the real-world practice	Yes if the RCT is generalizable to real-world practice It is a major individual between the randomized, controlled trial and real-world practice, if it is often too complex to implement, especially in terms of patient selection criteria and treatment protocol	No
Integration	Hard to collect data on real-world practice and patients' effect over time This has increased the use of real-world evidence (RWE) studies, which analyze real-world data to support recommendations (3)	Single-center, open-label, in real-world practice, typically designed to fund
Health	Generally high If high, real-world data are more likely to be used for decision-making	Low if the study is retrospective Compared to an RCT if the study is prospective
External validity	Requires approval by ethical committees because of altered clinical practice	Clinical practice is not allowed and ethical issues usually require patients' privacy
Economic evaluation	Feasible in general Patients' real-world data can be used during the exploratory phase but often-relevant data is generated directly	Feasible in general for retrospective studies The retrospective studies, which are often used in general, however, the study effort (clinical practice) often increases (4)
Sample	Minimum required by the current regulations of the ethics	Large Depending on the individual requirements, a large sample size may be required because many observations might be lost if certain groups are excluded by RWE. Also regarding the general use for the individual intervention (4)
Data in results	It depends on the process	Depends on the process (prospective/retrospective) Data for retrospective studies are in real-world practice
Internal validity	High	High compared to RCTs However, appropriate study design and statistical methods can significantly reduce the study internal validity
External validity	Low The conditions of the RCTs and real-world practice are the primary decision-making	High The conditions of RWE studies often include patients' clinical practice

*Berger M, et al., Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. Value in Health 2017;20:1003-1008.

*Torrone R, Boccia PR, Armeni P. What type of clinical evidence is needed to assess health technologies? European Respiratory Review, 2016;25:259-265.

Real World Data are not problem-free (2/2)

Major steps have been done to address methodological and procedural concerns:

- several techniques have been applied to reduce the impact of selection bias like multivariate regression or nonparametric techniques based on the propensity score
- methodological standards have been issued by ISPOR, ISPE, the US FDA, the European Network for Health Technology Assessment - EUnetHTA and MedtechHTA**
- good procedural practices as policies about the planning, execution, and dissemination of RWD studies have been developed to assure the public of the integrity of the research process and enhance confidence in the RWE produced from RWD studies*

*Berger ML et al., Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. *Value In Health* 2017;20:1003-1008.

**Tarricone R, Torbica A, Drummond M. (for the MedtechHTA project group) Key Recommendations from the MedtechHTA Project. *Health Economics* 2017;26(Suppl S1):145-152

Is this a favorable season for Real World Evidence in regulation?

REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

(Text with EEA relevance)

Better clinical evidence for high risk and implantable medical devices based upon technologies' characteristics and previous consultation of experts leaves room for RWE

Is this a favorable season for Real World Evidence in regulation?

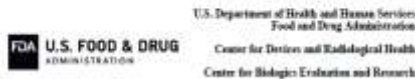
Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 31, 2017.

The draft of this document was issued on July 27, 2016.

For questions about this document regarding CDER-regulated devices, contact the Office of Surveillance and Biometrics (OSB) at 301-796-5987 or CDER.OSB@FDA.HHS.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8018.



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Is this a favorable season for Real World Evidence in policy making?



- the European Commission has proposed a regulation aimed at a better functioning of the internal market and of health protection through **Joint Clinical Assessments** (also based on RWD for medical devices)

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Concluding remarks

- HTA is an unavoidable fact of life and is now located in the value-based paradigm, i.e. HTA is here to stay
- Medical devices are technologies different from those traditionally assessed by regulators and HTA bodies, i.e. pharmaceuticals:
 - These characteristics are seldom recognised by decision-makers, i.e. this is part of the challenge
- Much work has been done to improve methods to assess MDs*
- Part of this work has started influencing policy-making:
 - Regulatory and HTA bodies consider 1) the possibility to gather real-world evidence to complement the lack of RCTs and 2) to proceed with «early dialogues» aimed at advising manufacturers on key points, e.g. type of study, comparator(s), target population
- Other work is on its way and will certainly keep improving policy-making and patients' access to modern care

*Tarricone R, Torbica A, Drummond M. (for the MedtechHTA project group) Key Recommendations from the MedtechHTA Project. Health Economics 2017;26(Suppl S1):145-152