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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?"
ISPOR Tokyo Sept 8th-13th 2018

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
 - diagnostic

Health Expectations (ISSN: 1369-6513) is available online at www.sciencedirect.com.
Journal homepage: www.elsevier.com/locate/he

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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 performed to assess the predisposition to venous thromboembolism (VTE) of women who request oral contraceptives. Given the high prevalence of factor V Leiden mutation (already at risk i.e. familial history or previous event of VTE), the study aimed to assess whether cancer screening practices in Italy are cost-effective. **Methods:** Two theoretical models accrued costs and quality-adjusted life years (QALYs) annually from the perspective of the National Health Service. The two models were developed under different assumptions about screening practices and contraceptive management (pill/oral and emergency contraceptives). **Results:** Health care costs were compiled 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 market; otherwise, the data were taken from the International literature. **Conclusion:**

Genetic testing for factor V Leiden and factor II are not cost-effective. Reproductive cost utility analysis, genetic testing, Italy, venous thromboembolism.

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Challenges in assessing medical devices 2/5

BMJ (ISSN: 0959-8139) is a weekly medical journal published online first.

EDITOR'S CHOICE

The scandal of medical device regulation
From Sunday editor, BMJ

The scandal of medical device regulation
An increasing number of patients are being harmed by medical devices. So why does the EU continue to allow them on the market? Deborah Cohen and Matthew Billingsley compare the regulatory systems.

MEDICAL DEVICES

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.

MEDICAL DEVICE REGULATION

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

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The breast implant scandal and European Medical Device Regulation

by Maria Dicenso and Roger Grie

The recent silicone breast implant scandal in Europe has left 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.

What were the events that led to the discovery of substantial numbers being used to manufacture the breast implants?

During the last quarter of 2009, the French Company Aesthetix, for medical devices, the defense company de Boissey vendée des produits de santé (DBPS) issued increasing numbers of adverse-event reports of silicone-filled breast implants manufactured by the French company Poly Implant Prothese (PIP).

Following several unsuccessful exchanges with PIP in March 2010, Aesthetix conducted an inspection of the company, which

How are medical devices, specifically breast implants regulated in Europe?

Breast implants are regulated by the Medical Devices Directive (93/42/EEC; MDD), covering the vast majority of medical devices, which became mandatory in June 1998. Directives must be transposed into European national laws in order for them to requirements to be met. Medical devices that comply with any national interpretation of the Directive can be affixed with the CE mark and sold throughout Europe.

The European regulatory system for medical devices is risk-based. 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 sort of tree found in Annex II 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 III (higher intermediate risk), and class IV (highest risk).

The committee assessment procedures, which are

MEDICAL DEVICE REGULATION

Faulty hip implant shows up failings of EU regulation

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

Deborah Cohen investigations editor

BMJ London WC1P 9EE, UK

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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

Learning curve, i.e. what

inexperience with the

tion:

f medical devices

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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*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, Prevotnik Rupej 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

The image shows two screenshots of journal websites:

- International Journal of CARDIOLOGY**: A screenshot of the journal's website showing the cover of an issue from April 10, 2018, Volume 238, Pages 102-103. The abstract for the article "Real-world cost effectiveness of MitraClip combined with Medical Therapy Versus Medical therapy alone in patients with moderate or severe mitral regurgitation" by Pedro Alvarez, Pablo Elizalde, Rosario Tornatore, David Caceres, and Mario F. Hernandez, Carrasco is visible.
- Value in Health**: A screenshot of the journal's website showing the cover of an issue from March 2017, Volume 20, Issue 3, Pages 296-304. The abstract for the article "Real-World Data for the Evaluation of Transarterial Radioembolization versus Sorafenib in Hepatocellular Carcinoma: A Cost-Effectiveness Analysis" by Carla Pignatti, Paolo D'Onghia, PhD, Silvia Scattolon, PhD, Alessandro Izzo, PhD, and Giacomo Piscitelli, PhD is visible.

*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. 113

BACKGROUND: The SOURCE 3 Registry (SAPEN-Aortic Stenosis: European Outcomes) is a European multicenter, observational registry of the latest generation of transcatheter heart valve, the SAPEN-3 T3 Edwards Lifesciences, Inc., 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 committed to support their comparative experience with the SAPRIEN 3 transsthoracic 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 86 centers in 10 countries were enrolled between July 2014 and October 2015. Of those, 1947 patients underwent transcutaneous aortic valve implantation (TAVI) with the SAPIEN transcatheter aortic valve system (TAVS). Mean patient age was 81.6 ± 6.5 years; 58.1% female. Mean comorbidities included: coronary artery disease (55.5%), renal insufficiency (27.4%), diabetes mellitus (29.0%), chronic obstructive pulmonary disease (15.5%), and a mean logistic EuroSCORE of 18.3 ± 3.3. Transcatheter access was used in 87.1% (n=1696), nontransfemoral in 12.2% patients. Concomitant procedures were used in 59.9% of nontransfemoral operations, and in 50.5% of femoral

1996 was performed without aortic balloon counterpulsation. Implantation success (1 valve in the intended location) was 98.3%. Conversion to conventional surgery (0.6%) and use of cardiopulmonary bypass (0.7%) were rare. Adverse events were low, with unreported 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 pacemaker implantation of 12%. Moderate or greater paravalvular regurgitation was observed in 3.1% of reporting patients.

CONCLUSIONS: Results from the SOLARCT-3 Registry demonstrate contemporary European trends in clinical outcomes of IBD in daily practice when the thioguanine class drugs are used.

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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

Key element	ICCs	SW studies
Learning venue	Not provided Topics can be listed if the outcome indicates this consideration of the research	Can be re-examined if the unit(s) experience of the outcomes is known. However, it is difficult to draw substantiated conclusions from the data
Selection bias	Not applicable by design However, some specific studies allow selection bias to be assessed. In that case, if it is possible to provide relevant data this should be included; in other cases, selection bias is treated as a potential confounder.	The study should assess: - appropriate inclusion and exclusion criteria pre-specified - whether inclusion and exclusion criteria were followed - whether inclusion and exclusion criteria were pre-specified
Affordance to the real clinical practice	No if the RCT is a protocol analysis & it does not reflect a usual intervention because the treatment and control interventions are different and/or it is often stated that usual practice would be a mixture of patients' responses criteria and treatment processes	Yes
Generalizability	Some trials will not recruit representative patient populations or will not report generalizability. This has increased the use of pre-specified criteria for generalizability and reporting this often lead to multiple recommendations (SI).	Where relevant, pre-specified, and clearly defined, generalizability of the trial
Order	Sequence logic: A sequence of randomizations are needed But it is not clear	Look if the study is a crossover Compare it with an RCT if the study is a crossover
Blinding process	Should be reported by item 10 as it contributes to bias in other interventions	Clinical processes as not defined and reflect actual medical management processes
Assessment of function	Function is not always measured during the study period but after intervention with previous disease	Possible to provide for assessment of function The strategy should be described and explained as part of the study, the study effect on function should take time into account
Sample	Measures required by the response magnitude of the effect	Large Depends on the statistical requirements A RCT sample size must rarely characterize a treatment effect. The sample size may be too large to be justified by the effect size, especially if the person effect is greater than the intervention difference (4-40%)
Time to results	3-4 years on the protocol	Depends on the primary hypothesis However, the study may be terminated earlier or the study may be stopped
Internal validity	High	Strong evidence for S2D's However, systematic study has found additional evidence that was independently developed RRI study has been independently developed RRI study has been independently developed
External validity	Low	High The conclusion of the RCT does not reflect those others

*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, Boscolo P.R, 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

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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

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

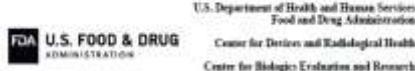
Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

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 301-796-5997 or CDERClinicalEvidence.fda.gov.
For questions about this document regarding CBER-regulated devices, contact the Office of Communications, Outreach, and Development (OCOD) at 1-800-435-4308 or 240-462-8018.



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



Brussels, 31.1.2018
COM(2018) 51 final
2018/0018 (COD)

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
on health technology assessment and amending Directive 2011/24/EU

(Text with EEA relevance)
[SWD(2018) 41 final] - [SWD(2018) 42 final]

- 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