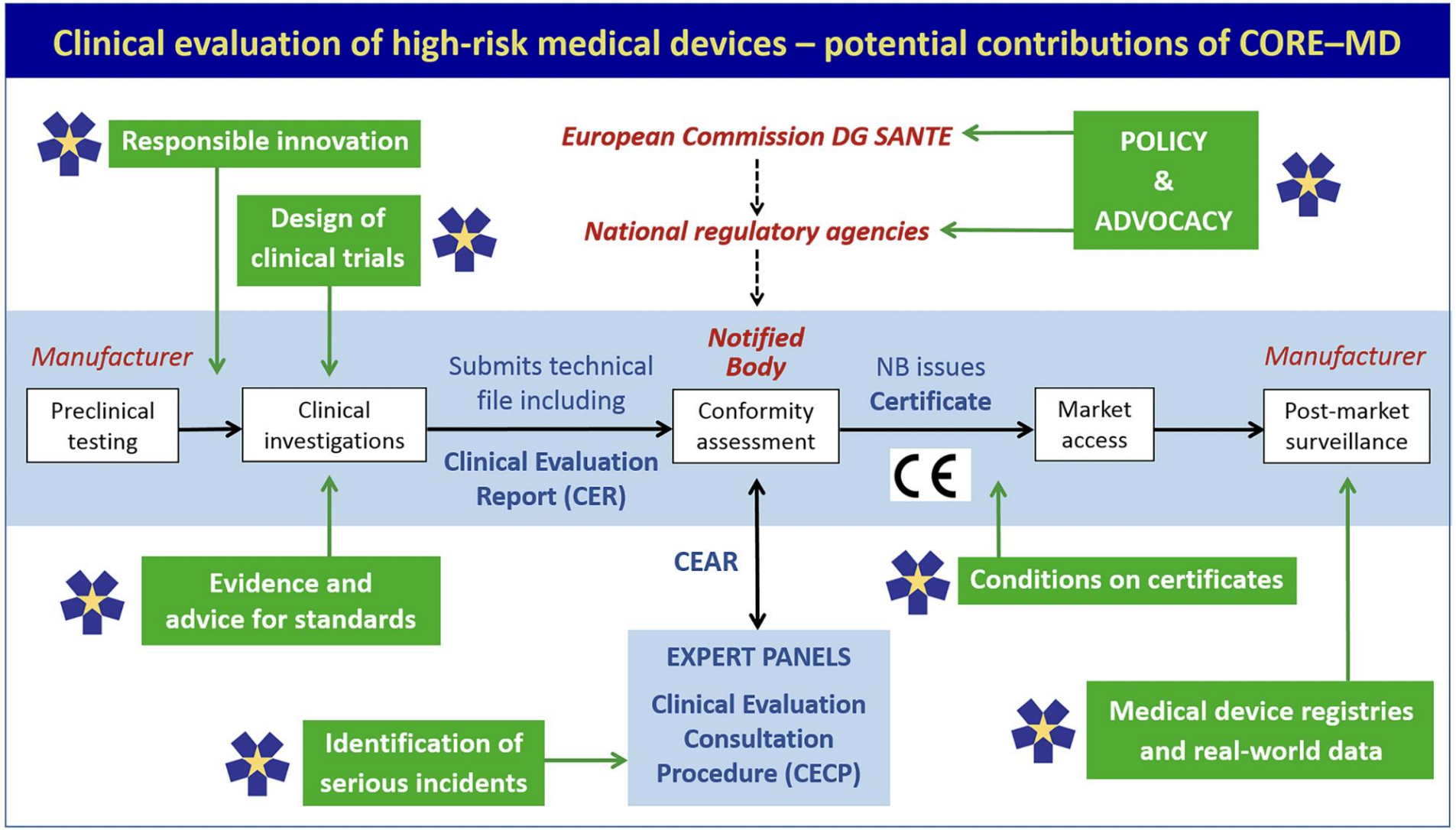
CORE–MD

Coordinating Research and Evidence for Medical Devices

Recommendations from the CORE–MD consortium

CORE-MD Final Conference, Brussels, 15 March 2024



Fraser AG et al; Eur Heart J Qual Care Clin Outcomes. 2022; 8: 249–258

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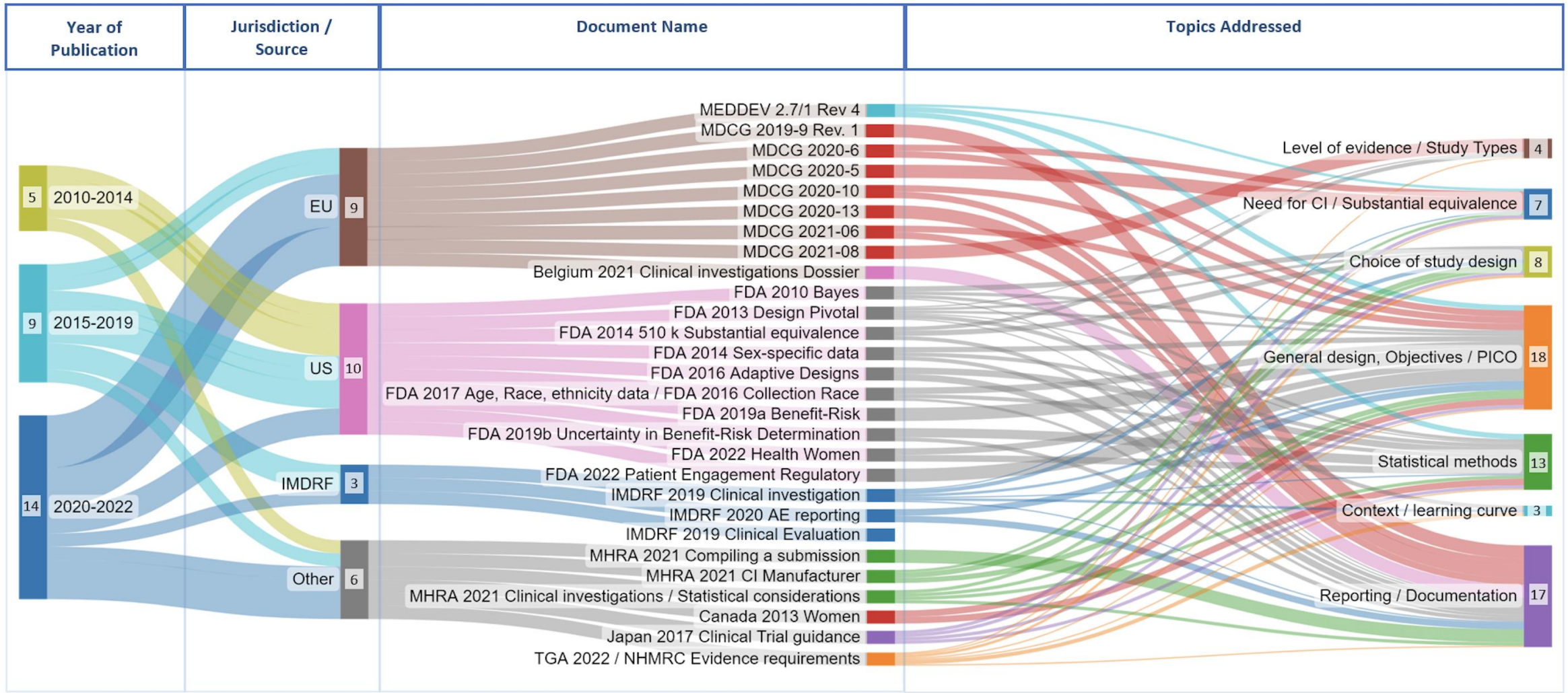
Recommendations on methodologies for clinical evaluation of high-risk medical devices



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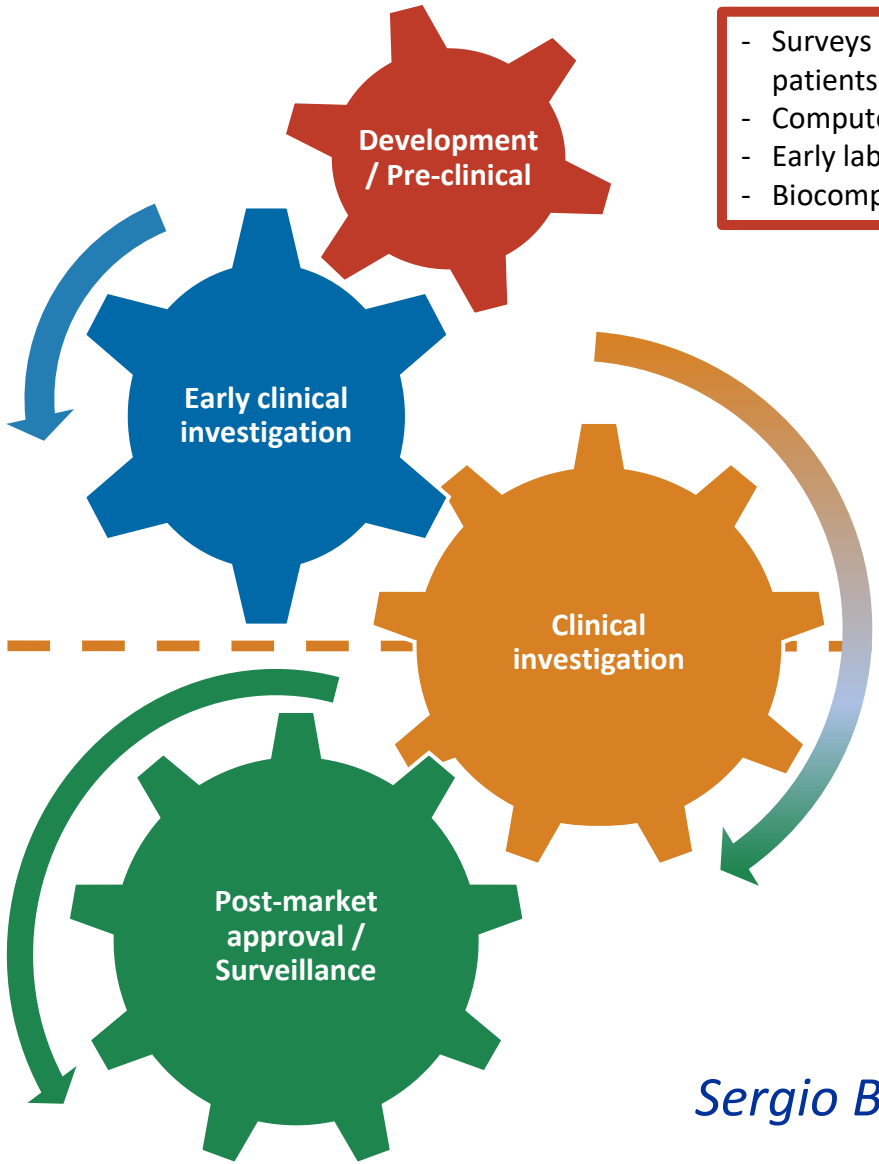
Petra-Schnell Inderst et al, UMIT Tirol

❖ From the perspective of the European regulatory system under the MDR, there is too little substantive guidance on evidence standards for the design of confirmatory clinical studies for high-risk medical devices.

Implications of these systematic reviews

- ❖ The evidence that is publicly available from clinical investigations of high-risk medical devices before their regulatory approval and CE-marking is insufficient to enable physicians to make informed recommendations to patients of which device to use.
- ❖ Clinical trial evidence should be published when new devices are approved.
- ❖ More systematic and efficient methods are needed to evaluate the long-term safety and performance of high-risk medical devices.

Methods for evaluation and clinical investigation of devices throughout their life-cycle



- Surveys of unmet needs/expectations among patients and physicians
- Computer projects/simulation
- Early laboratory/animal testing
- Biocompatibility analyses

- Individual case reports (perhaps based on compassionate use)
- Small case series (e.g. 20 – 30 patients) assessing early feasibility/adverse events
- Analysis of learning curves

- Single-arm reports in larger cohorts of consecutive patients (>100 patients)
- Preliminary assessments of efficacy (objective performance criteria, matched case-control analyses, etc.)
- Small RCTs assessing surrogate endpoints

European conformity assessment and CE mark

Rigorous assessment of comparative efficacy and safety for clinical outcomes:

- RCTs in selected cohorts of patients
- **Large simple RCTs enrolling larger proportions of eligible patients by applying minimal exclusion criteria**

- Prospective registries of specific devices
- IT systems for collecting and disseminating safety reports (EUDAMED)
- National/international registries collecting device-oriented information

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Sergio Buccheri, Stefan James, et al

Example 1: Recommendations for clinical investigations of an innovative or orphan medical device

	Initial clinical studies	Early clinical studies	Rigorous clinical evaluation	Longterm clinical evaluation
Preferred designs	• Case report(s) of first implants. • Planned case series with prospective documentation.	• Prospective observational study (e.g. single-arm with consecutive patients).	• RCT versus current 'state of the art', with blinded determination of clinical end-points.	• Mandatory registry.

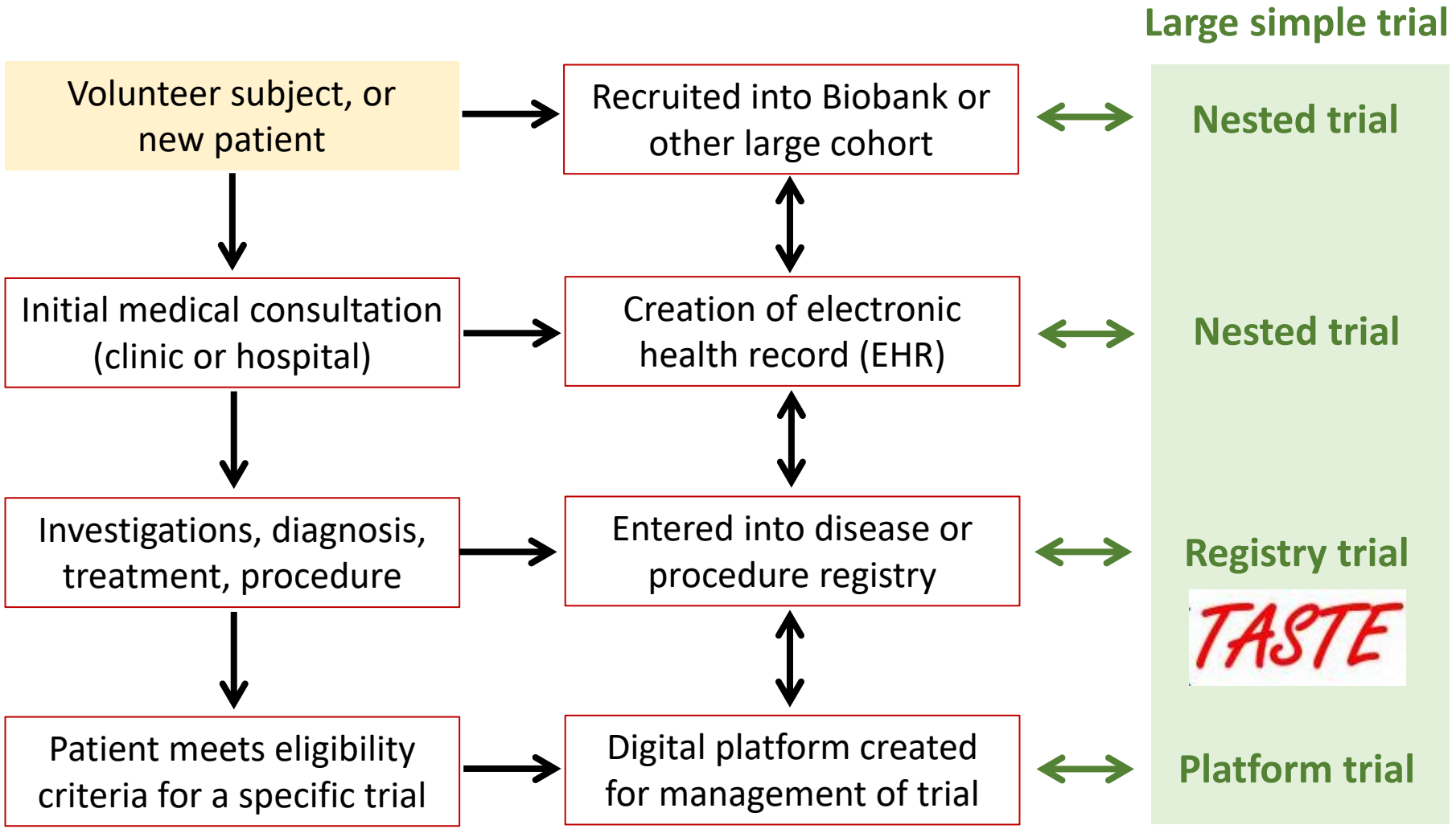
Example 2: Recommendations for clinical investigations of a new medical device in an established class

	Initial clinical studies	Early clinical studies	Rigorous clinical evaluation	Longterm clinical evaluation
Preferred designs	• Case report(s) of first implants. • Prospective case series.	• RCT with surrogate end-point. • Observational study with objective performance criteria.	• RCT against active comparator. • RCT powered for non-inferiority.	• Prospective registry with complete recruitment, recording primary end-points and adverse events.

Divergent outcomes in non-randomised and randomised cardiovascular studies

Type of device	Observational study	Smaller RCT	Larger RCT
First-generation DES *vs.* bare metal stents ↓ / = / =	**PMID** 17296822 / 2007	12050336 / 2002	14724301 / 2004
	• Propensity-score adjusted analysis (n=19,771) • **Increased mortality** with DES vs. BMS	• 1:1 randomization (n=238) • No in-stent restenosis with DES • No stent thrombosis • **No difference in mortality**	• 1:1 randomization (n=1,314) • Less restenosis and repeat revascularization with DES • **No difference in mortality**
Absorb bioresorbable vascular scaffold *vs.* everolimus-eluting metallic stent = / ↓ / ↓	26875648 / 2016	27806897 / 2016	26457558, 30266412, 31553222, 37207924 / 2015–2023
	• Propensity-score matching (n=905 pairs) • **No difference** in clinical outcomes	• **ABSORB II** • 2:1 randomization (n=501) • No difference in vasoreactivity • **Higher late luminal loss** with Absorb • **Higher TV-MI** with Absorb	• **ABSORB III** • 2:1 randomization (n=2,008) • Noninferiority of BVS for TLF at 1 yr • **More TLF, TV-MI, thrombosis** to 5 yrs • **ABSORB IV** • 1:1 randomization (n=2,604) • Noninferiority of BVS for TLF, 30 d & 1 y • **More TLF** through 5 yrs
Manual thrombus aspiration *vs.* standard PCI ↓ / ↑ / =,↓	20550973 / 2010	18256391, 18539223 / 2008	23991656, 25176395 / 25853743, 26474811 / 2013–2016
	• Multivariable adjustment (n=22,632) • **More deaths** with thrombus aspiration (RR 1.16, 95% CI 1.05–1.28)	• **TAPAS, TAPAS-FU** • 1:1 randomization (n=1,071) • Better reperfusion and clinical outcomes with thrombus aspiration • **Reduced risk of cardiac death** with thrombus aspiration	• **TASTE, TASTE-FU** • 1:1 randomization (n=7,244) • **No difference in mortality** at 30 d & 1 y • **TOTAL, TOTAL-FU** • 1:1 randomization (n=10,732) • **Composite CV outcomes ns** 30 d & 1 y • **Increased risk of stroke**

Large simple trials



RECOVERY
Randomised Evaluation of COVID-19 Therapy

Sergio Buccheri, Stefan James, et al.
Marion Mafham, Martin Landray, et al.

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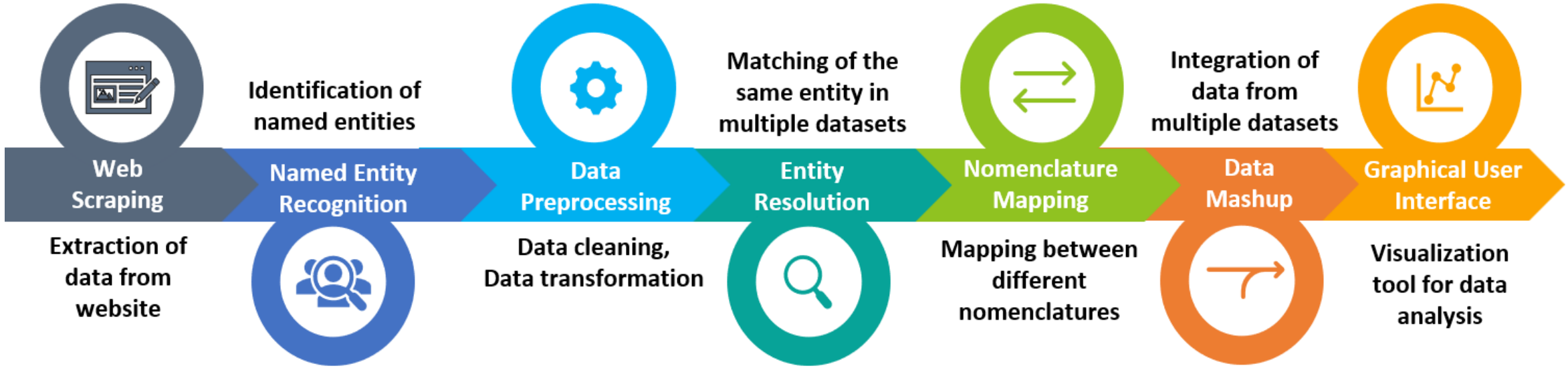
Automated surveillance of post-market device reports (safety notices)



- Full application of Unique Device Identification, using common nomenclature
- Including standard data fields for clinically important details
- Complementary to data from medical device registries with comprehensive coverage

Ren Y et al, Ther Innov Reg Science. 2023; 57: 589–602

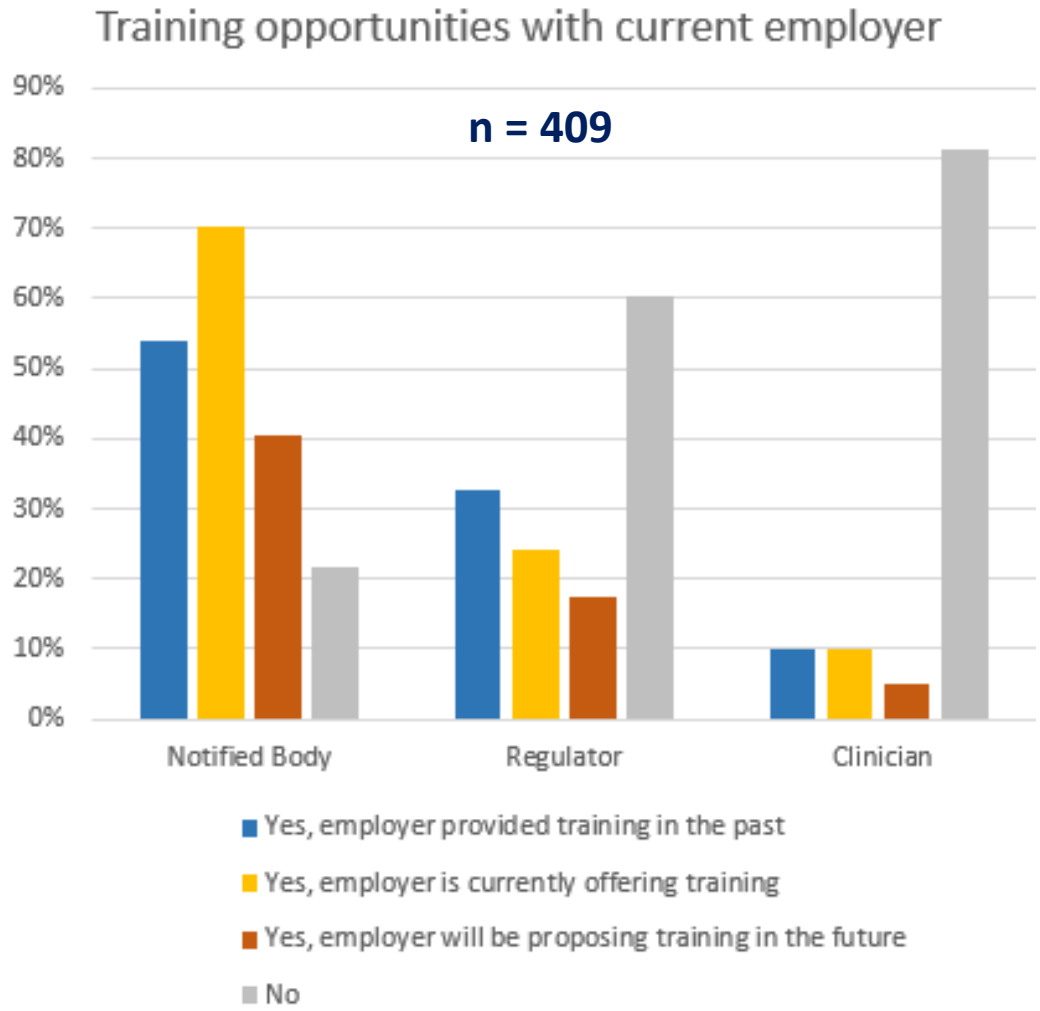
Training, education, and capacity building – Roadmap with educational objectives

Principal educational needs / skills

Notified body reviewers (n = 37)
- assessment of benefit-risk ratio and thresholds for acceptability
- design and development of medical devices
- methods for evaluating specific high-risk medical devices

Regulators (n = 58)
- assessment of benefit-risk ratio and thresholds for acceptability
- pre-clinical testing (methodology and evaluation)
- design and development of medical devices

Clinicians (n = 278)
- study-designs and their advantages/disadvantages
- assessment of benefit-risk ratio and thresholds for acceptability
- choice of comparators (standard of care vs. sham vs. placebo)



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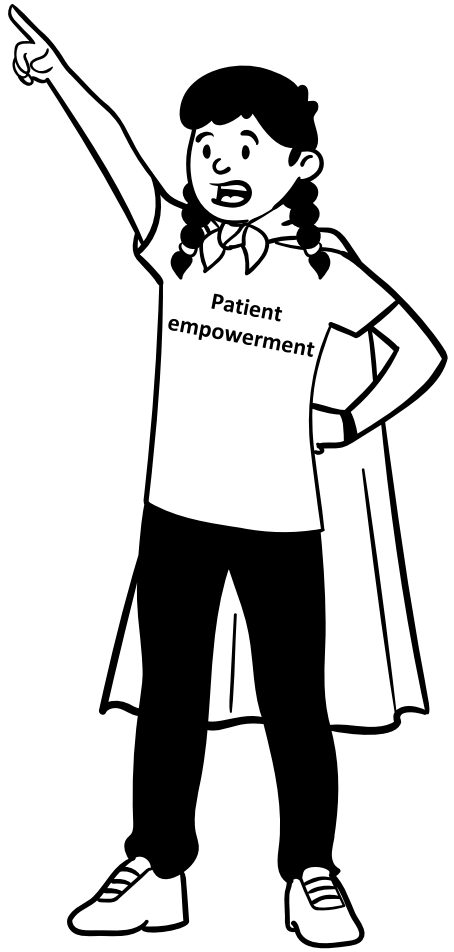
Wild C, Ettinger S. J Med Dev Reg. 2023; 20: 45–56
AIHTA, BioMed Alliance, and TEAM-NB

Recommendations for patient involvement

1. **Develop a set of core indicators for PROMs** per disease area that addresses patients' concerns and capture information that is relevant from their perspective, to inform healthcare decisions and further research needs.
2. **Develop ways to integrate PROMs** and patient experience data in the regulatory process for medical devices and assessment of the risk-benefit.
3. **Involve patients throughout the lifecycle of medical devices** including in the development of information/communication materials.



Generic outcome domains	N
Treatment satisfaction	34
Sleep quality	11
General QoL	5
Coping	4
Emotional distress	3
Cognitive function	1
Depression	1

Diabetes specific outcome domains	N
Diabetes-specific QoL	11
Diabetes-specific distress	17
Fear of hypoglycaemia	25
Hypoglycaemia awareness	12
Hyperglycaemia Fear	1

Preparation of final recommendations

- A risk score to guide requirements for the clinical evaluation of AI devices
- A hierarchy of recommended methodologies for the clinical evaluation of high-risk devices
- Priniciples of ‘large simple trials’
- A charter for ethical innovation
- A framework for using real-world evidence for post-market surveillance and clinical follow-up

‘Regulatory science’ for medical devices in the European Union

- Regulatory standards informed by high-quality scientific and clinical research
- Regulatory policies and practices that are evidence-based, and proportionate
- Need for more scientific and clinical expertise within DG SANTE
- Differences in EU governance between drugs and devices are illogical
- Full transparency of clinical evidence for devices, and decisions, is essential
- More efficient (and cost-effective) clinical trials and secondary research
- Development of special regulatory pathways (orphan devices, innovation ..)
- Engagement of the medical community with other stakeholders