Outlook on the upcoming medical device and in vitro diagnostics regulations in the EU

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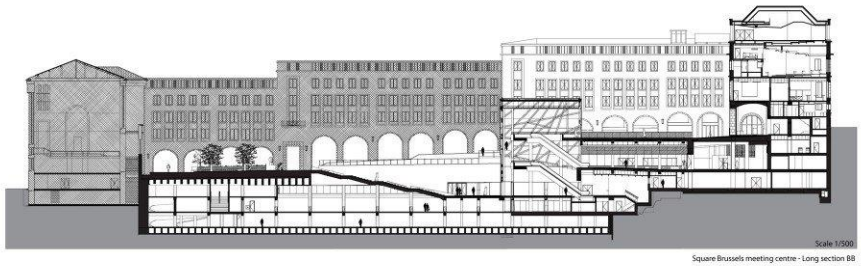
3rd Joint Conference
of
European Human Pharmacological Societies
(AGAH, Club Phase I, BAPU, AHPPI)

European Competitiveness in Early Clinical Drug Development: Threats and Opportunities

SQUARE
BRUSSELS MEETING CENTRE

21 – 22 May 2015
Brussels, Belgium

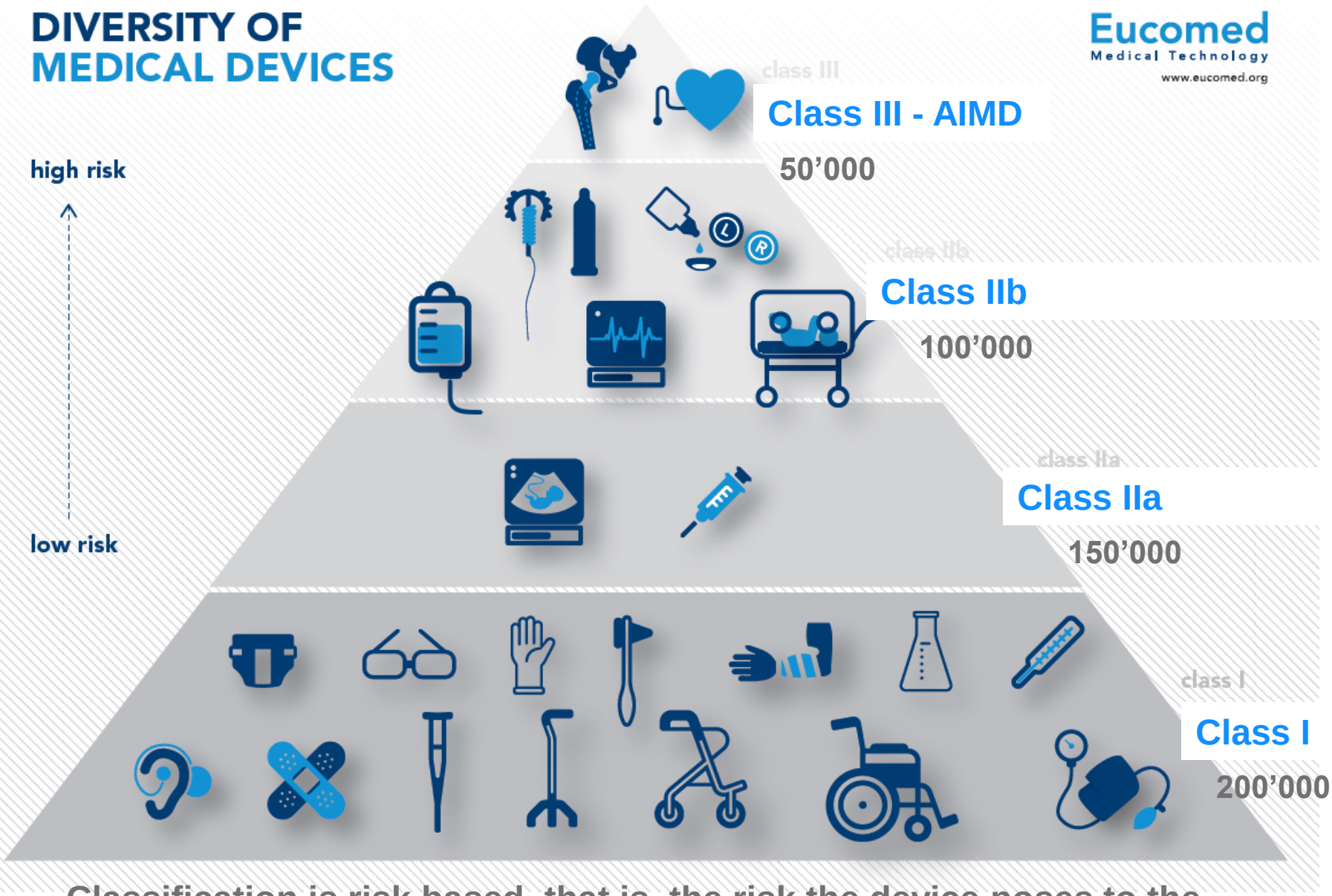


EU Medical Devices – Facts and Figures

- Apr 500,000 medical technologies currently available to healthcare professionals
- 22,500 medical technology companies in Europe
  - 80% of these are SME
- The EU medical device industry employs apr. 500,000 persons
- On average, 8% of sales is spend on R&D

DIVERSITY OF MEDICAL DEVICES

Eucomed
Medical Technology
www.eucomed.org

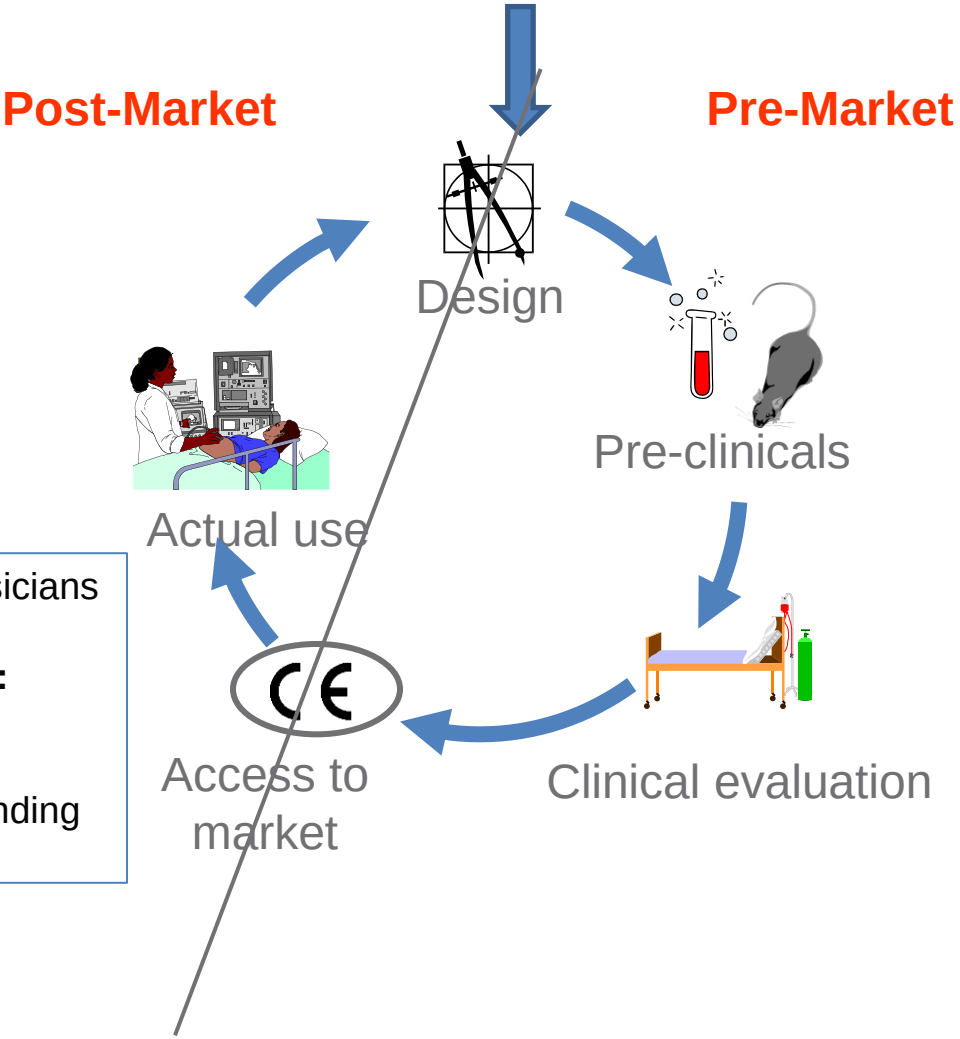


Classification is risk based, that is, the risk the device poses to the patient and/or the user is a major factor in determining the class to which it is assigned

Device Lifecycle

Conception and development of innovative / new device
Not previously used; e.g. new material, new indication, new therapeutic approach

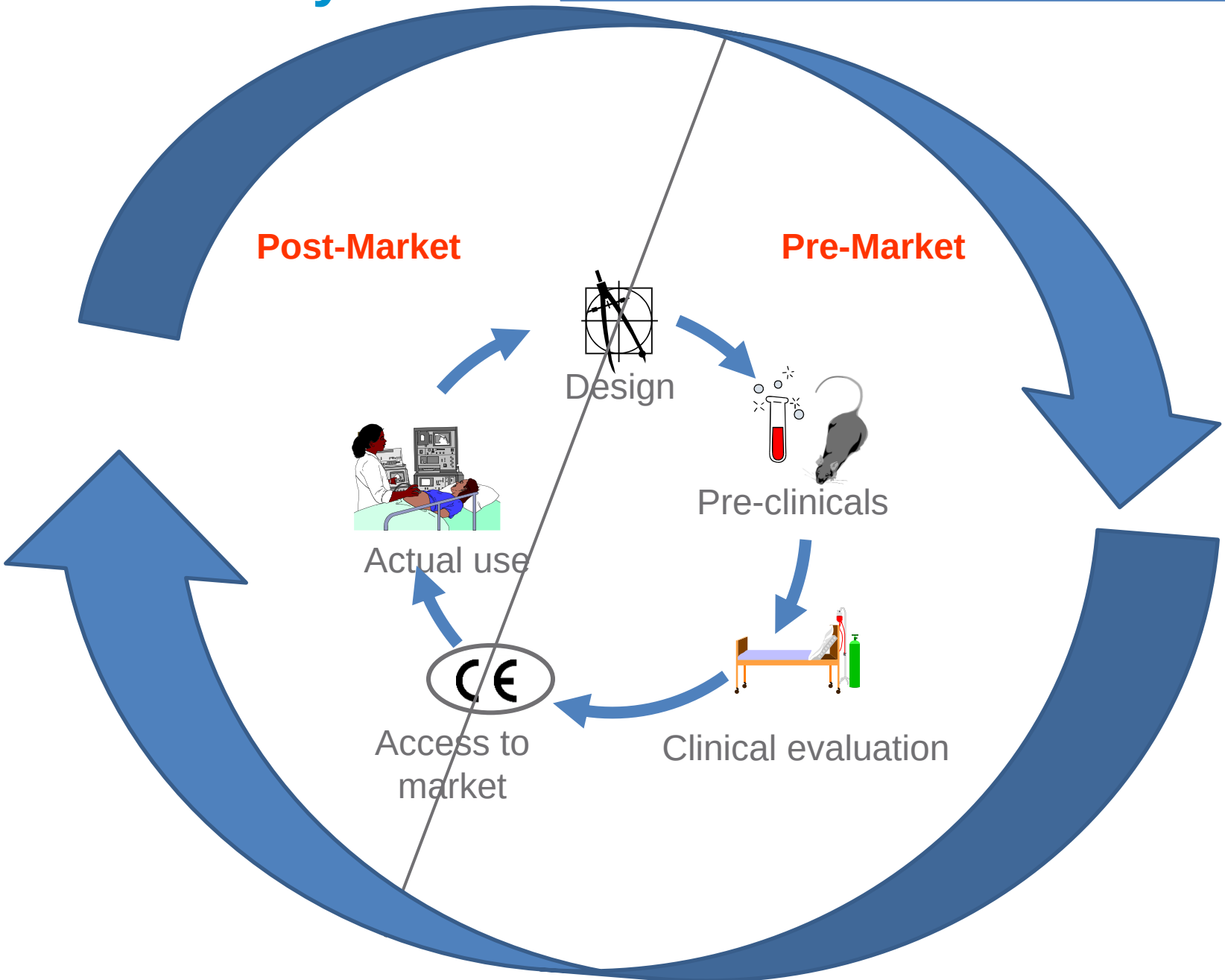
- Engineering and technology developments
- Manufacturing improvements
- Bench testing



- feedback from physicians or users
- Product complaints: returned product analyses
- Adverse events trending

Device Lifecycle

Continuous Improvement



Pacemakers (IPGs) Through the Years

5800

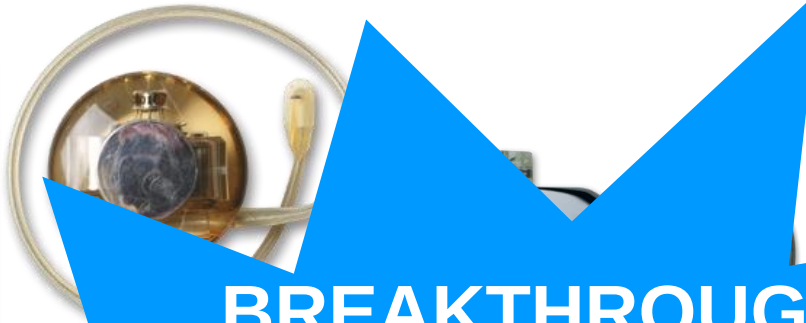
First Exte

1958

1960

First Implantable P

Chardack-Greatbat



a®

EnPulse®

Full

2004

1998

Revo MRI™

First
MR-Conditional
pacing system

2011

2006

MVP, Full

Adapta™

BREAKTHROUGH TECHNOLOGY followed by ITERATIVE DEVELOPMENT & CONTINUOUS IMPROVEMENT

OVERSIGHT AND GOVERNANCE

Manufacturer

- Medical Device Directives
  - Essential Requirements
- Standards

Post-Market

Pre-Market

Competent Authority

Authorization Clinical Studies
AE reports

Market Surveillance / Inspections /Vigilance Reporting

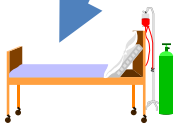
Recall / Field Action

Surveillance of NBs

Actual use

Design

Pre-clinicals



Clinical evaluation

CE

Access to market

Notified Body

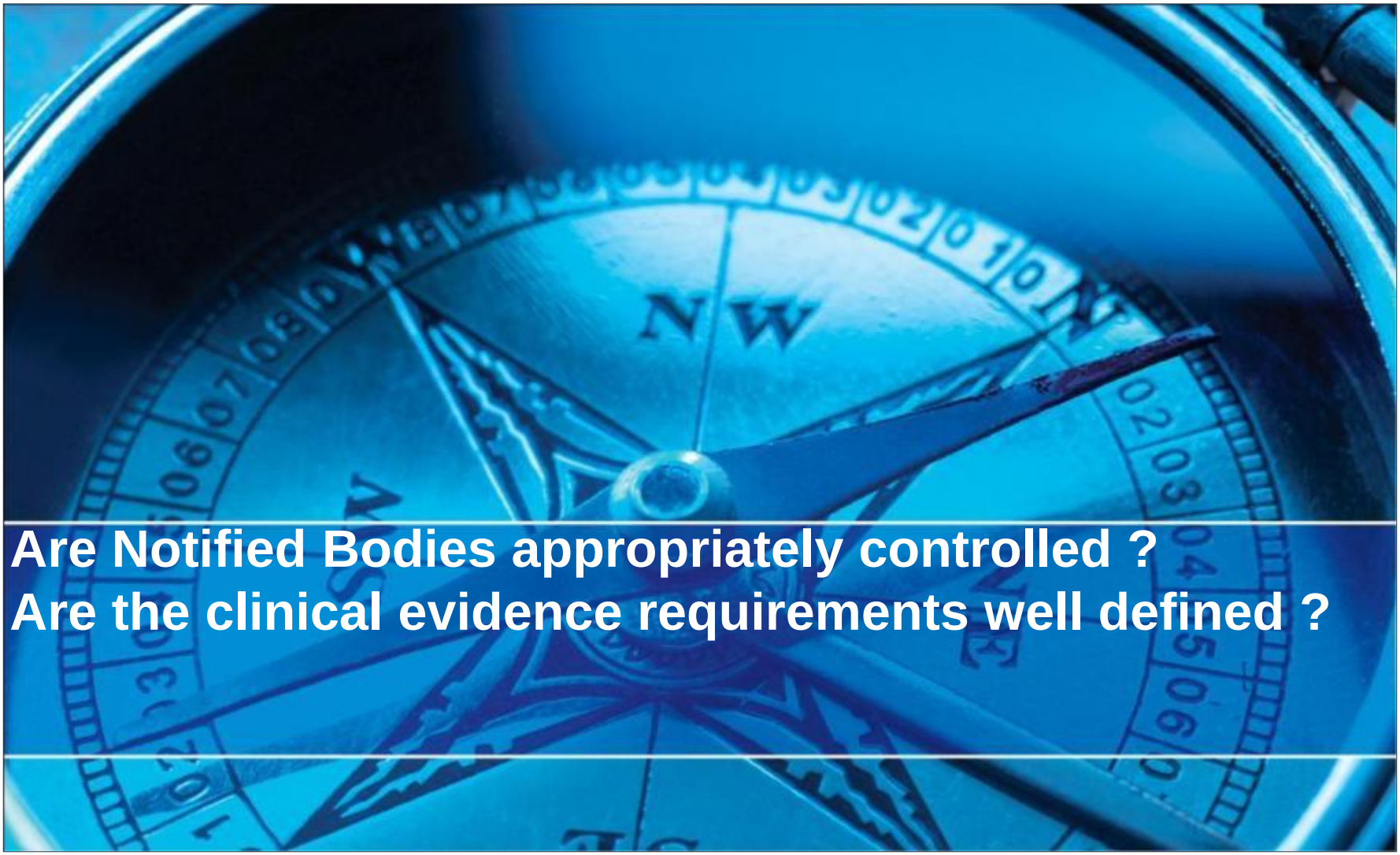
Conformity assessment

Quality audits

THE EU MEDICAL DEVICE DIRECTIVE – in principle, an effective legal framework

THE EU MEDICAL DEVICE DIRECTIVE – in support of European Competitiveness

Are there any opportunities for improvement of the Regulatory System ?



Are Notified Bodies appropriately controlled ?
Are the clinical evidence requirements well defined ?

CURRENT Clinical Data requirements before CE marking

- **Clinical Evaluation is conducted by the manufacturer before CE-marking as part of the Conformity Assessment**
  - Required for all classes of devices.

- Clinical data may come in the form of
  - Clinical trial(s) of the device concerned
  - Clinical investigation(s) reported in the scientific literature of a similar device for which **equivalence** to the device in question can be demonstrated

MEDDEV 2.7.1 – guideline provides **CURRENT** criteria for **Equivalence**

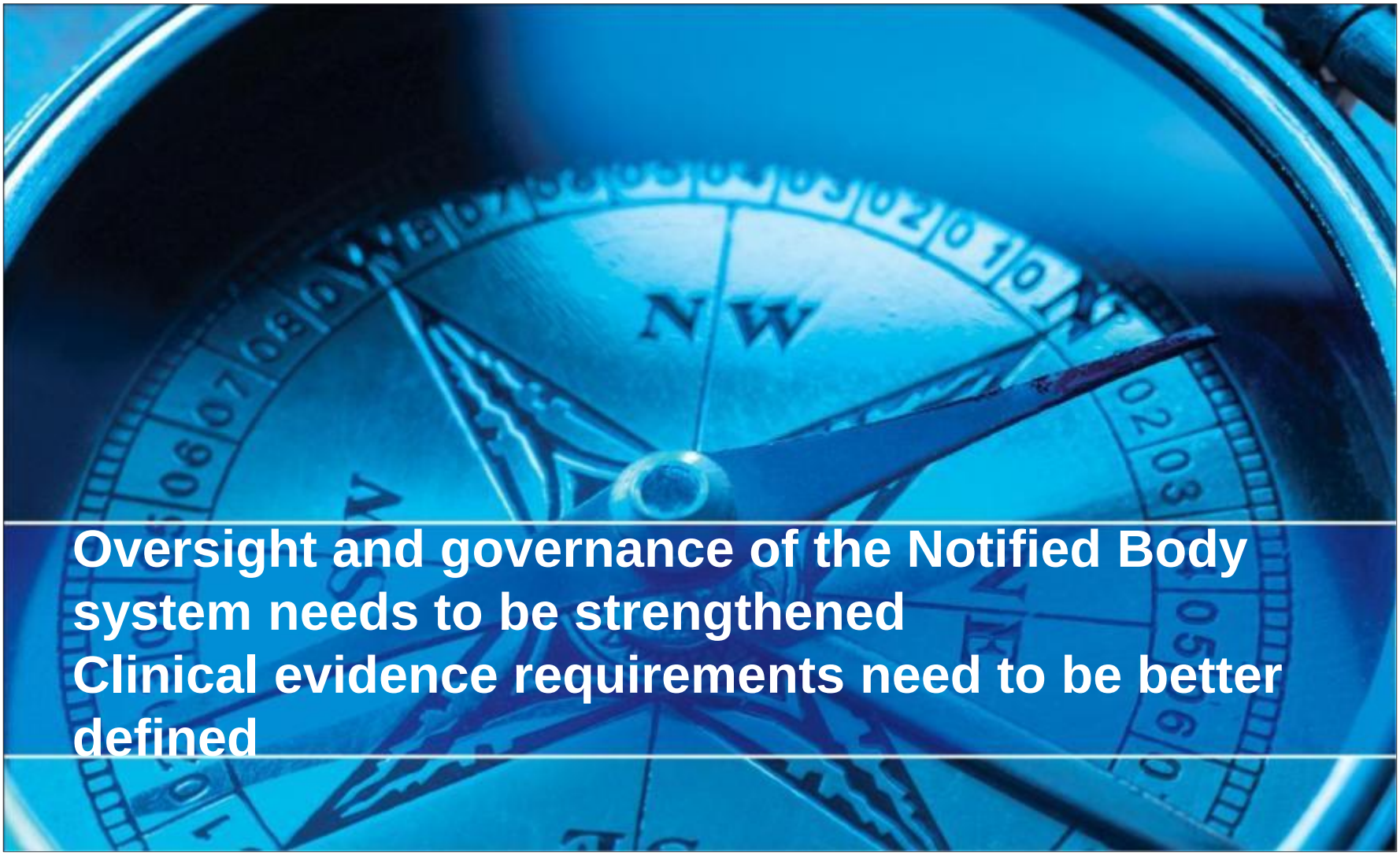
CURRENT Clinical Data requirements after CE marking

- **Post-market Clinical Follow Up (PMCF) is mandatory for all medical devices**
  - PMCF is a clinical study in human subjects of a CE-marked device

CURRENT Clinical Data requirements Issues identified

- **Pre-market CT is not done**
- **PMCF study is not done**
- **PMS (post-market surveillance = product complaint handling) is done**
  - **Product is placed on the market on the basis of technical performance testing only and with reference to predicate device on the basis of equivalence**

Opportunities for improvement of the Regulatory System



Oversight and governance of the Notified Body system needs to be strengthened

Clinical evidence requirements need to be better defined

New Regulations for Medical Devices

26 September 2012

EU Commission submitted 2 proposals to the Council and European Parliament

1.proposal for a Regulation on medical devices, aiming at replacing Council Directives 90/385/EEC on active implantable medical devices, and 93/42/EEC on medical devices; and

2.proposal for a Regulation on *in vitro* diagnostic medical devices, aiming at replacing Council Directive 98/79/EC of the European Parliament and the Council on *in vitro* diagnostic medical devices,

QUESTION 1

Will the Medical Device Regulation change the pre-market development of medical devices ?

NEW MEDICAL DEVICE REGULATION


100
60
5
10
15
20
25
30
35
40
45
50
55

Can certain Drug Regulations and Practices apply to Devices?

YES

- Post-market vigilance systems and procedures
  - PSUR
  - RMP
- Registries

Pharmacovigilance REGULATION (EU) No 1235/2010 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 15 December 2010

Can certain Drug Regulations and Practices apply to Devices?

YES

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  - PSUR
  - RMP
- Registries

But don’t forget….

Device specificities need to be taken into consideration

QUESTION 2

What is the difference in early clinical development between drugs and devices ?

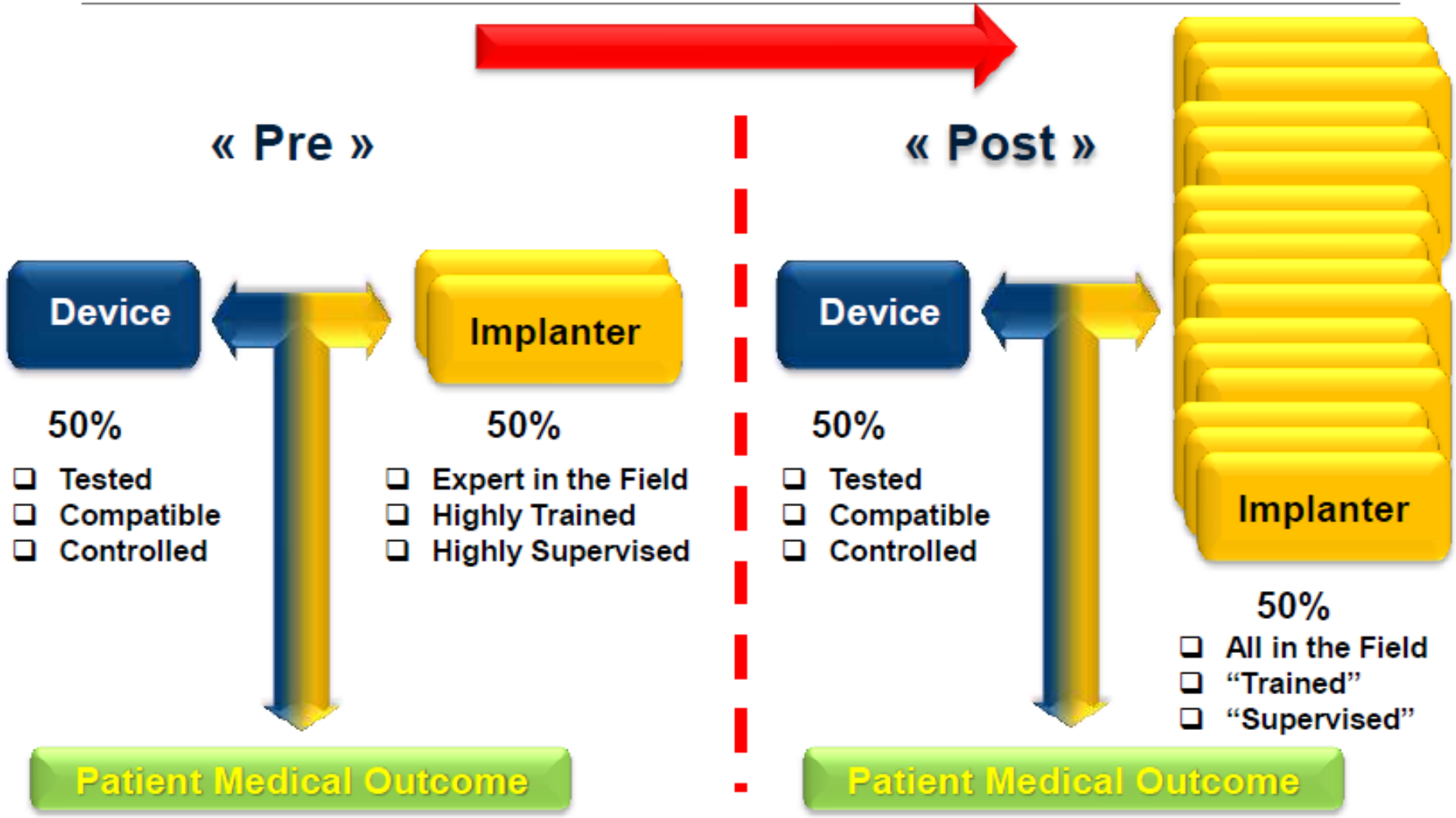
DRUGS VERSUS DEVICES

Specificities of clinical trials for devices

- Phase 1 CT does not exist
  - it would be unethical to subject healthy volunteers to implant surgery, hence medical device trials are all done in patients

- Clinical outcome is a function of,
  1. the physician's / user's skill
  2. the device-patient interaction

Assessing 'Implanter Dependancy'



QUESTION 3

Should the Randomized Controlled Trial (RCT) be the gold standard for Medical Device trials ?

RCT- THE GOLD STANDARD

Specificities of clinical trials for devices

- Inability to blind the user/patient
  - This limits trial design
  - Double-blind Randomized Controlled Trials are a challenge with medical devices
- Limitation in comparative trial design for implanted devices

QUESTION 4

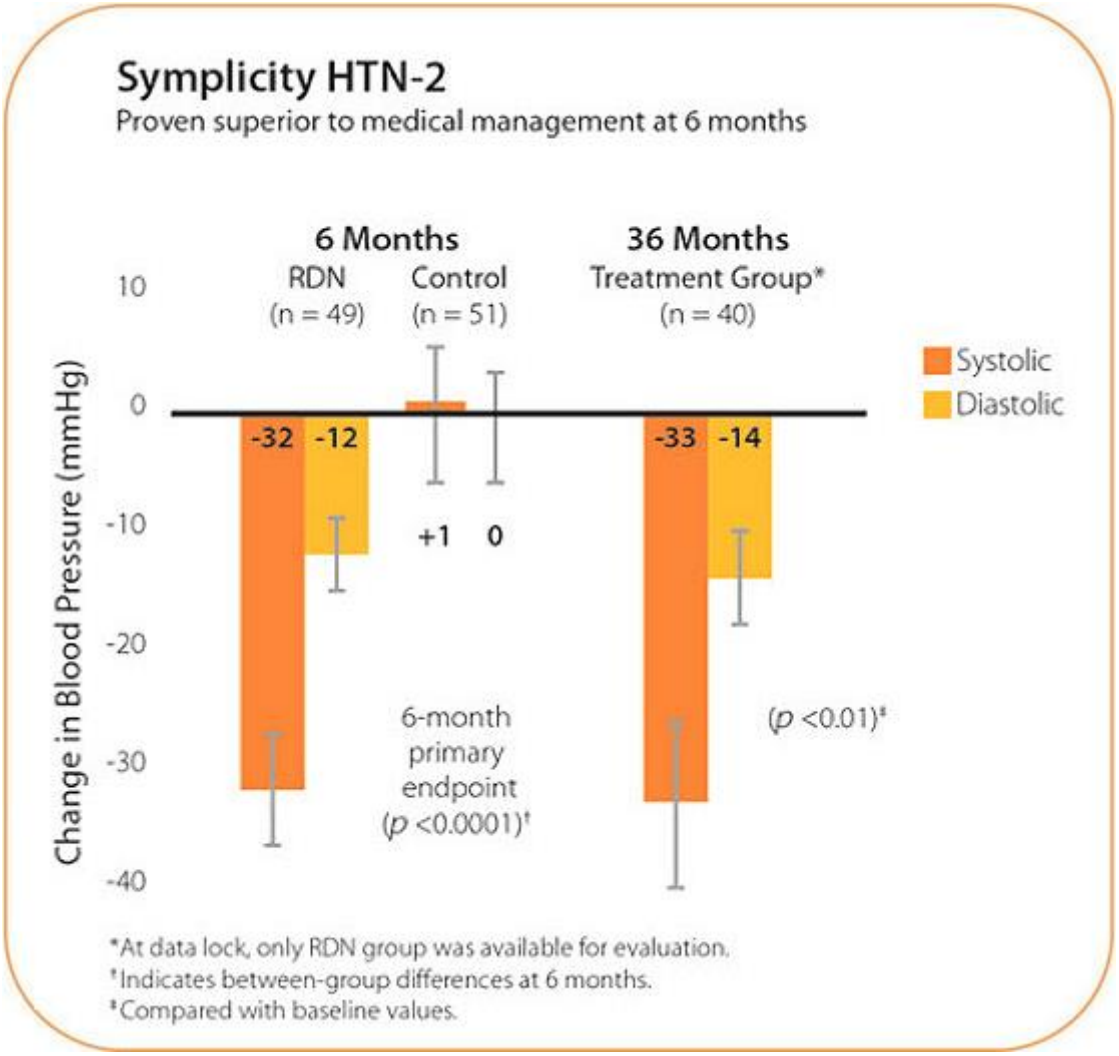
Is it ethical to subject patients to a sham trial (Medical Device placebo) if the device is an active implantable medical device ?

SHAM AND ETHICS

Specificities of clinical trials for devices

- It is ethical if the sham patients will be offered the treatment afterwards, or,
- if the trial is set up as a switch or cross-over trial where half of the patients start with the active device and the other half with the sham device and midway the trial these two populations are switched
- Such a trial can’t be a double blind controlled trial but only single blind

Symplicity HTN-2 was a **randomised, controlled clinical trial** of 106 patients. **Patients randomised to RDN therapy plus antihypertensive medications achieved a significant reduction in mean blood pressure (-32/-12 mmHg) at 6 months**, whereas patients in the control group randomised to receive antihypertensive medications alone had blood pressures that did not vary from baseline (+1/0 mmHg).



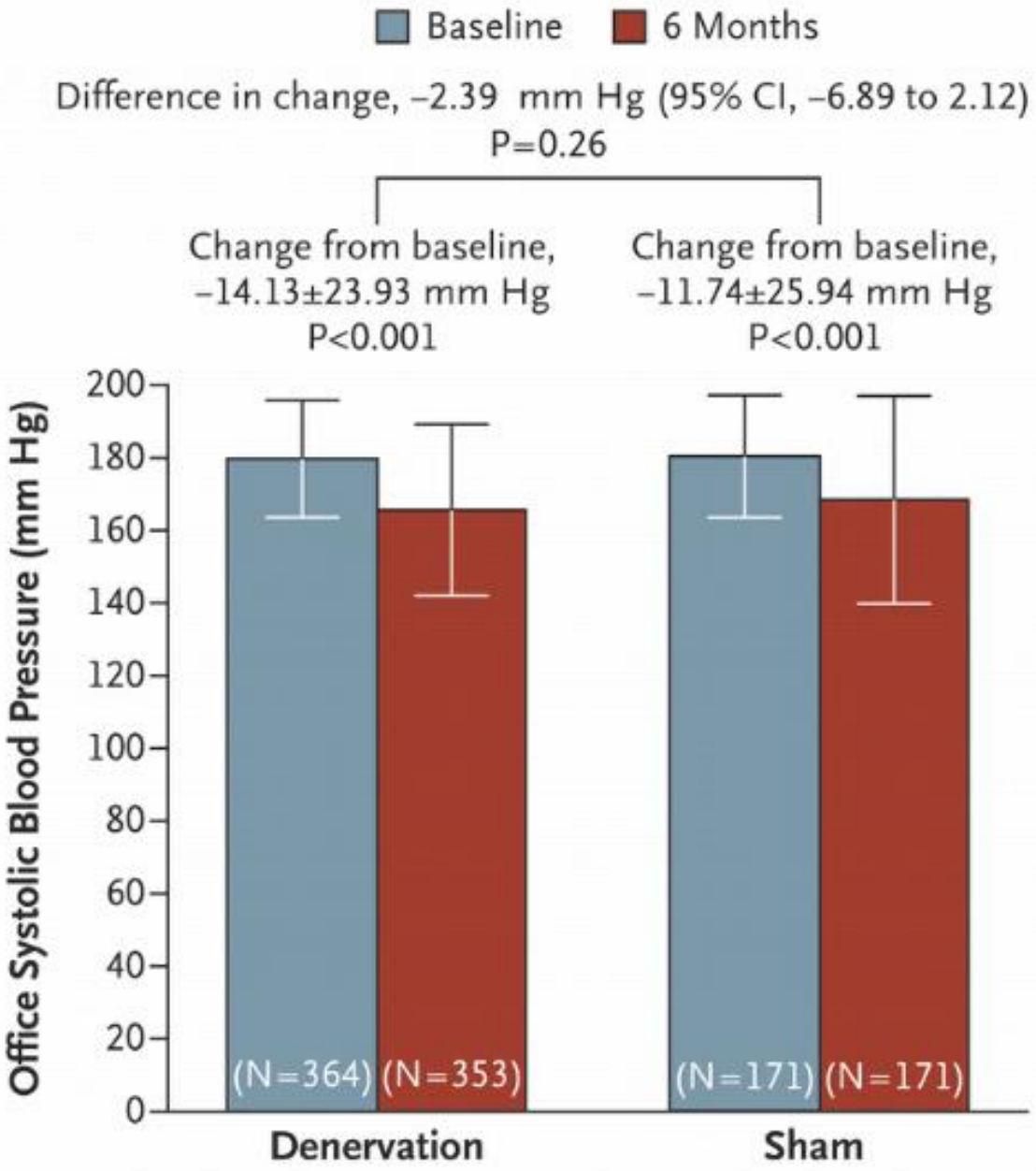


Figure 1. Primary Efficacy End Point.

A significant change from baseline to 6 months in office systolic blood pressure was observed in both study groups. The between-group difference (the primary efficacy end point) did not meet a test of superiority with a margin of 5 mm Hg. The I bars indicate standard deviations.

QUESTION 5

Should the number of patients in a medical device clinical trial to confirm the safety and performance be similar to pivotal drug trials

QUANTITY OF CLINICAL TRIAL DATA

Quantity of clinical trial data

The number of patients will depend on the clinical effectiveness of the device

- **in case of a pacemaker, each patient will demonstrate improved pacing, hence only a small number of patients is needed to demonstrate performance / effectiveness**
- **To demonstrate safety, the number of patients needs to be much larger and the follow up much longer; this can only be done during the post market phase.**

QUESTION 6

Technical performance of a medical device can be demonstrated in bench testing.

Should clinical effectiveness always be demonstrated in clinical trials before CE mark is obtained ?

PERFORMANCE AND EFFECTIVENESS

Performance and Effectiveness

Clinical effectiveness can also be demonstrated or deduced from prior knowledge in case of devices that are equivalent to earlier devices, hence it is not always necessary to demonstrate clinical effectiveness through clinical trials. The current MEDDEV 7.2.1. indicates the criteria for equivalence.

Can certain Drug Regulations and Practices apply to Devices?

YES

- Post-market vigilance systems and procedures
  - PSUR
  - RMP
- Registries

But don't forget….

Device specificities need to be taken into consideration

- **Clinical trials may need a specific approach based on device specificities and therapeutic application**
- Number of patients significantly less (in most cases)
- Post-market feedback provides an important opportunity to continuously improve the benefit-Risk ratio of the device