From idea to Innovative Product :

Regulatory for Medical Devices

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CMO
Anaconda Biomed
Barcelona, Spain

Overview

From idea to Innovative Product :

Regulatory aspects for Medical Devices

Introduction: Patient safety and Need for regulation

Medical Device regulations

Regulation for clinical studies

Clinical Trial design and implementation

Reporting of Clinical data, a case study

Who am I ?

Electrical Engineer, Biomedical Engineer, PhD. (University Ghent, Belgium)

Experience in small and large Medical Devices companies

- InControl, Guidant, Boston Scientific, Endosense, St Jude Medical,
- Co-founder of ONWARD Medical
- Current: CMO, Anaconda Biomed, Barcelona, Spain

Involved in Clinical and Regulatory for pre-market and post-market studies

- High Tech and innovative
- Implantable and Class III products

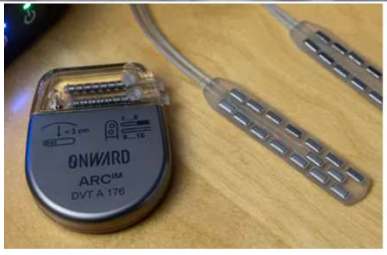
Invasive cardiac, vascular and neuromodulation therapies

In Europe, US (and beyond)

Close interaction with physicians and patients

- Field Clinical Engineer
- Manager of Training Institute for physicians
- VP Clinical and Regulatory / CMO

Parkinson's disease: a neuroprosthetic to correct walking disorders



HLN

Anaconda Biomed – Mechanical Thrombectomy after stroke

Barcelona based Medical Device start-up

Mission: to provide the best thrombectomy system to health care professionals
https://anaconda.bio/

Concept of Mechanical Thrombectomy

Medical Device Definition - MDR

MDR – Medical Device Regulation (EU) 2017/745

Medical Device

means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,
- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,
- providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations,

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

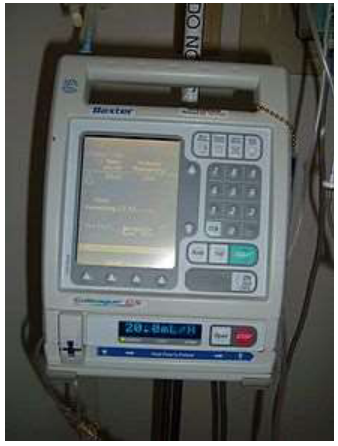
The following products shall also be deemed to be medical devices:

- devices for the control or support of conception;
- products specifically intended for the cleaning, disinfection or sterilisation of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point.

Englobes a wide variety of products

A **medical device** is any device intended to be used for medical purposes. Thus what differentiates a medical device from an everyday device is its **intended use**.

Class I



Class II

Class III

Classes of increasing safety requirements

What comes first in your mind…

When you think of rules and regulations at EPFL ?

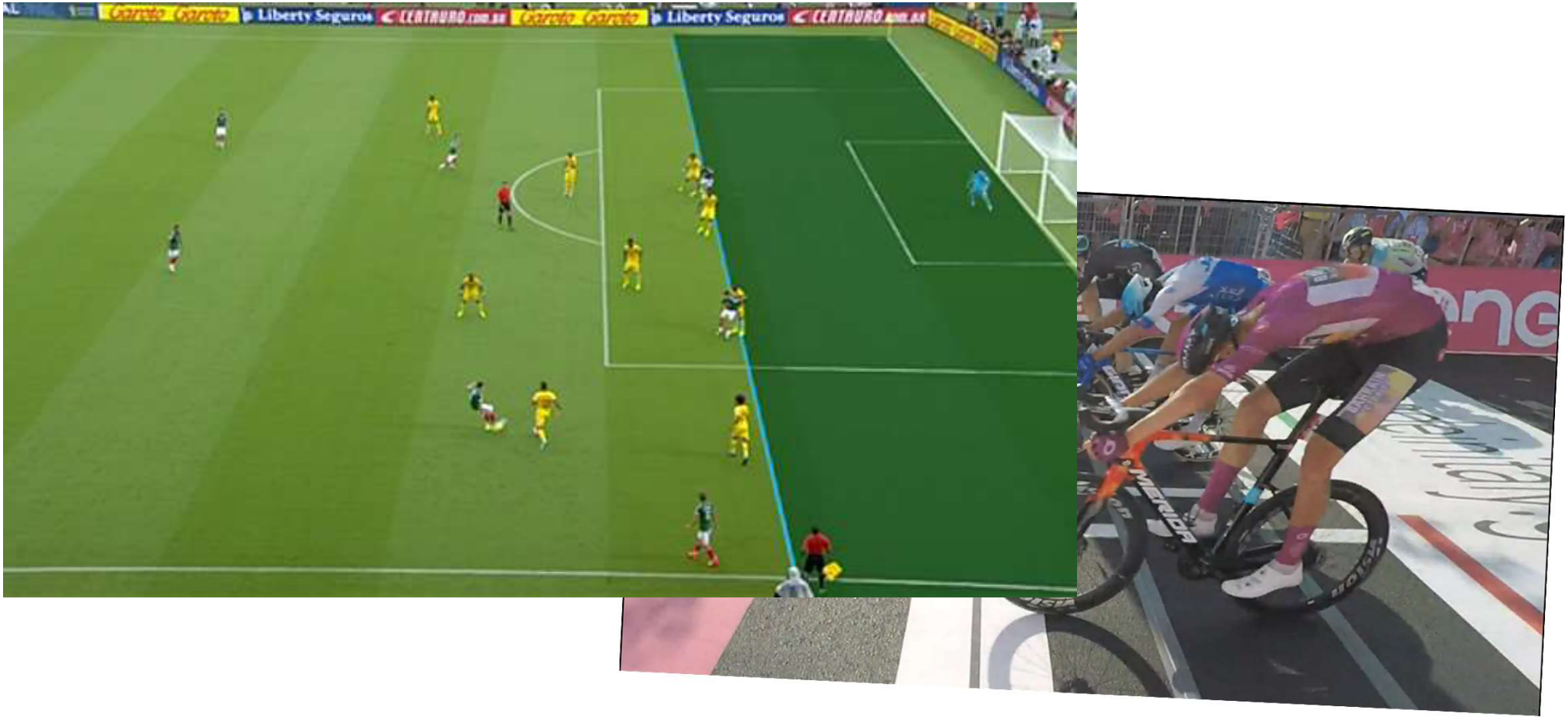
Fun, essential, creative.
First thing to think of in the morning.

It needs to be done.
If I get through it, I'll get my Master.

Burden, cost, waste of time and money.
It limits the creativity of the students

Rules are food for endless discussions…

Rules are food for endless discussions…



Imagine a world without regulations…

Regulation in Health Care products…
The power of certification

My product is safe and performs well !!

With no Regulations:

- Explain it to every customer again
- Subjective interpretation
- No confidentiality

With (international) Regulations:

- Explain it **only once** (to Notified Body)
- Based on objective rules
- To experts who are knowledgeable
- Who keeps confidentiality in case of mistakes
- Creates Trust

Let’s understand the rules of the regulatory game!

Medical Device Regulation

Introduction: Patient safety and Need for regulation

Medical Device regulations

- Patient Safety
- Product life cycle
- Hierarchy from Law to Technical Standards
- Approval Framework
- Specific EU regulations

Medical Device regulations

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Patient Safety

A patient is more vulnerable than a healthy person:

Patient status
- can be critical: increased sensitivity
- reacts passively, or not (unconscious, anesthetized, immobilized, …)

Energy supply
- functional: correct place and correct dose (electricity, heath, radiation, water, oxygen, …; calibration)
- through erroneous current, leakage current, …

Limitation of perceptibility
- Ionizing and electro-magnetic radiation

Sensitive for infections

Skin punctures (catheter, needle for infusion, electrode, …) eliminate the natural barrier
- Increased risk to electrocution
- Increased risk to infection

(inter-)connection of multiple medical equipment
- Internal organs are connected with conductors

Dependent of equipment fulfilling vital functions
- Respiration equipment, heart – lung machine, …

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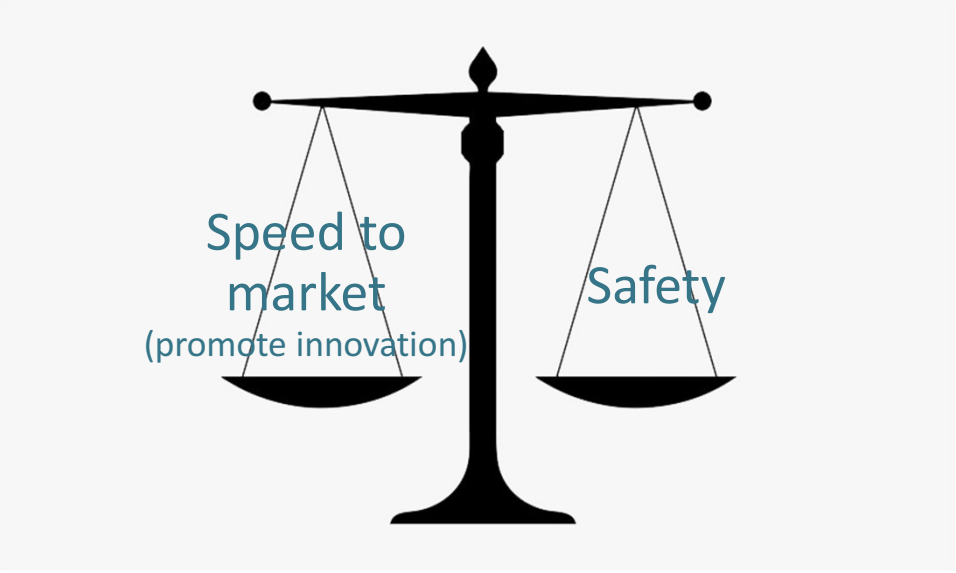
Strong need for regulation to ensure patient safety !

The dilemma of the Regulator….

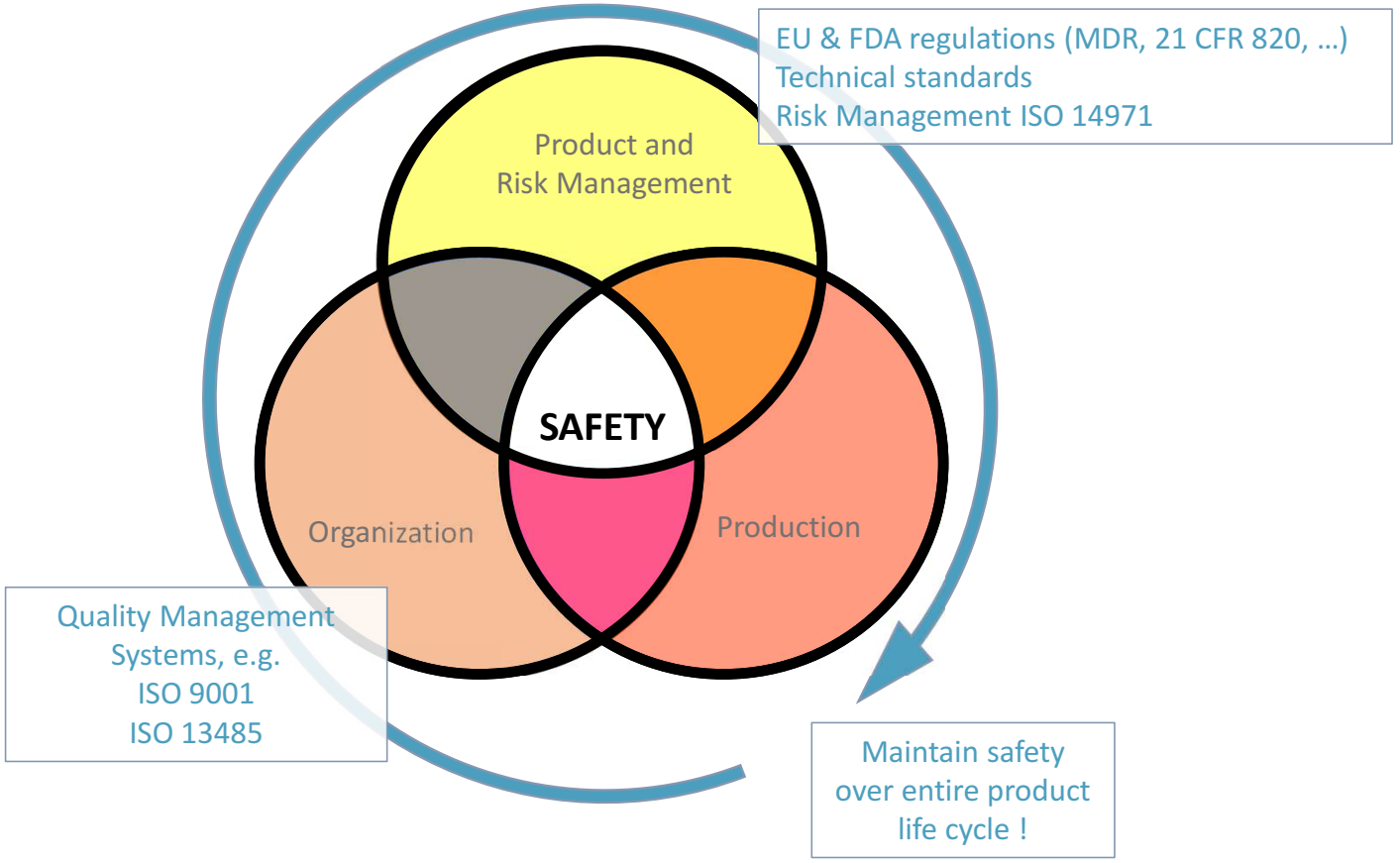


MDD → MDR (2017 – 2021)

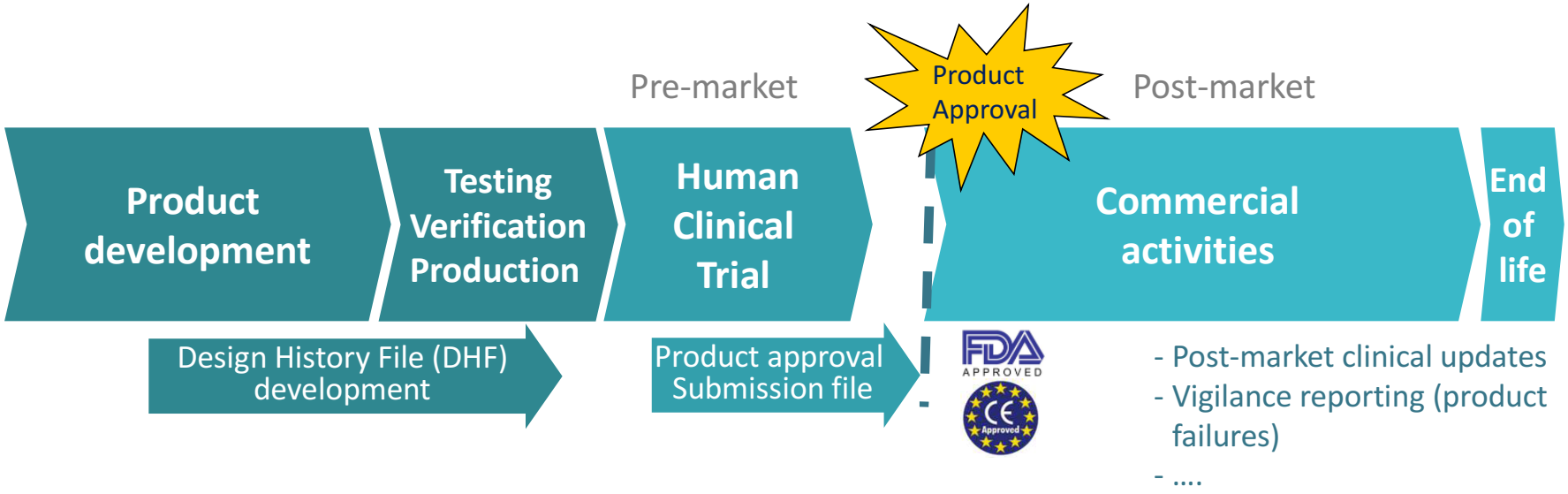
Accelerated pathway for Breakthrough Devices

PMD Act, 2014

Development and supply of safe devices



Product life cycle - regulated by law



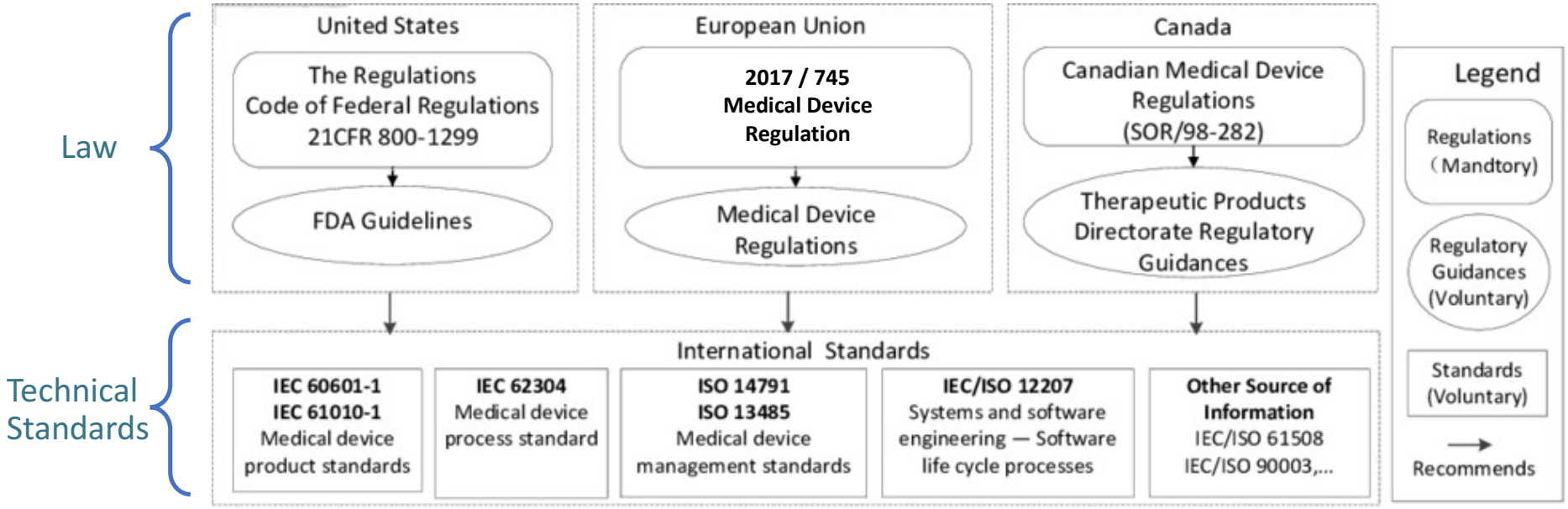
Product certification (entire life cycle) regulated by law:

- EU: Medical Device Regulation 2017/745 * → *General Safety and Performance Requirements*
- US: Code of Federal Regulations (CFR) Title 21, subchapter H: Medical Devices ** → *Safe and Effective devices*

* 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

** Code of Federal Regulations , Title 21 – Food and Drugs, Chapter 1, Food and Drug Administration (FDA), Department of Health and Human Services, Subcapter H: Medical Devices. Part 812 (clinical investigation), Part 820 (Quality System Regulation), Part 11 (electronic records)

The hierarchy from Regulation to Standards



Technical Standards:

- Electrical safety
- Mechanical
- Electro-magnetic compatibility
- Chemical
- Software
- Clinical Evaluation
- Usability / HFE
- Biocompatibility
- Sterilization
- In-vivo animal studies
- …

HFE: Human Factor Engineering
IEC: International Electric Committee
ISO: International Standardardization Organization

Regulation Vs Standards

Regulation (Law)

- details on how laws are to be enforced or carried out
- has very general (vague) language.
- Sets requirements
- Tells what you have to do but not how to do it

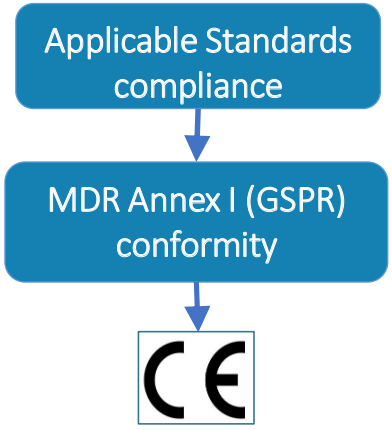
Standards

- describe how to meet regulatory requirements
- are very precise and has technical language.
- Provides specifications and test methods
- Tells how to do what you have to do

MDR, Annex I - General Safety and Performance Requirements (GSPR) describes how a device shall be safe and effective. Conformity to GSPR is mandatory to obtain market approval (CE Mark)

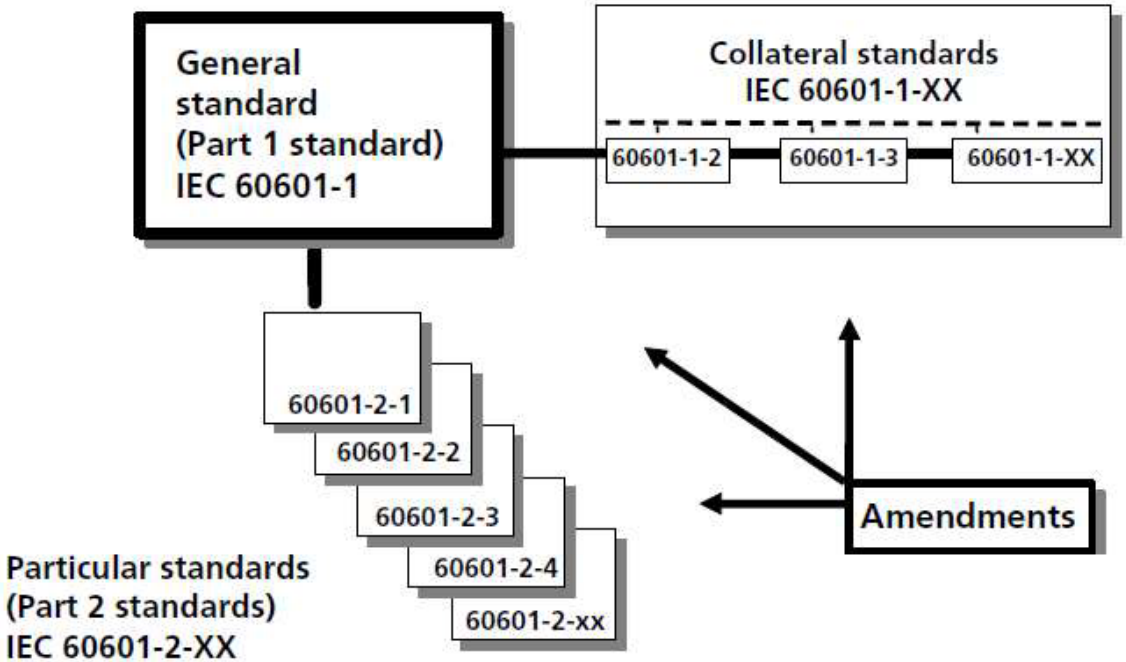
Compliance to Harmonized Standard gives the presumption of conformity to GSPR

Compliance to standards, leads to conformity to GSPR, hence market approval (CE-mark)



Types of Standard

1. Product Standard or Vertical Standard indicating necessary safety and performance aspects of specific products and/or processes, e.g. IEC 60601, Medical Electrical Equipment
   - IEC 60601 – 1 Basic Safety and Essential Performance
2. Basic Standards or Horizontal Standards safety and performance aspects
   - ISO 13485 – Quality Management System
   - ISO 14971 – Risk Management
3. Group Standards or Semi-Horizontal Standards indicating aspects applicable to families of similar products and/or processes
   - ISO 11135 – Sterilization of health-care products – Ethylene oxide
   - ISO 11137 – Sterilization of health-care product – Radiation



Regulatory framework in Europe is changing

Medical Device Directive
(MDD 93/42/EEC)
Active Implantable Device Directive
(AIMDD 90/385/EEC)

→ MDR
Medical Device Regulation
EU 2017/745

In Vitro Diagnostic Directive
(IVDD 98/79/EC)

→ IVD R

MDR and IVD R published in European Journal in May 2017

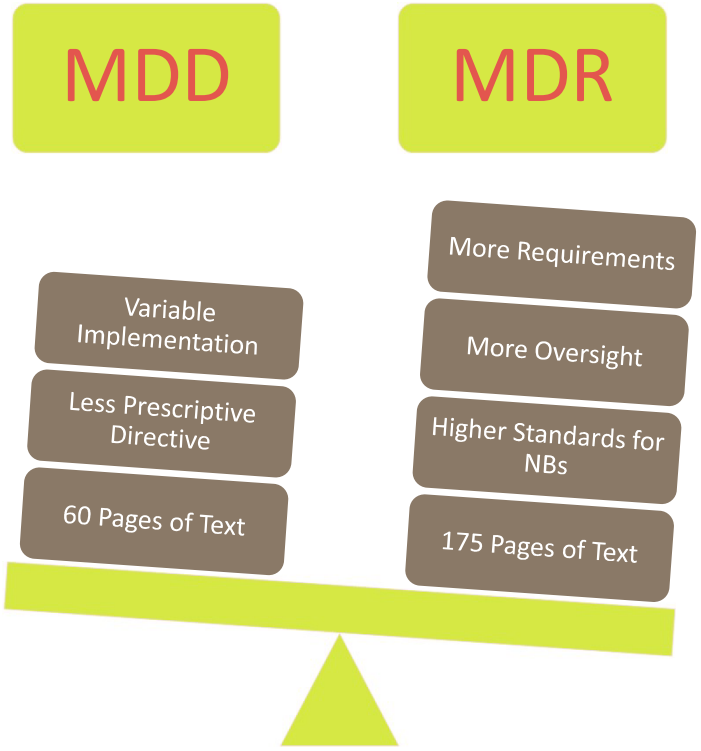
Transition period:

- MDR: 4 years (May 2021)
- IVD R: 5 years (May 2022)

Focus on 1) Clinical data, 2) full product Life Cycle

MDD/AIMD/MDR Differences

AIMD	17 Articles 9 Annexes 20 Pages
MDD	23 Articles 12 Annexes 60 Pages
MDR	123 Articles 17 Annexes 175 Pages



- Most **Significant** Regulatory change in **Europe** in over **20 years**!
- Increased and specific requirements for the Quality Management System (QMS)
- Additional **classification** rules and changes in existing classifications for higher risk devices
- The Essential Requirements have been replaced with **General Safety and Performance Requirements** (GSPR)
- Greater emphasis on **clinical data, clinical evidence, clinical evaluation** and **Post Market Clinical Follow-up**
- NB will now consult with **expert groups** prior to high risk devices being put on the market
- More scrutiny of technical documentation
- Notified Body to be re-designated
- Addition of **UDI** requirements and **Eudamed** Database implementation
- New specific **post-market surveillance** document requirements and improved trending requirements

CE-marking

CE-marking = “Conformité Européene”

It declares the conformity with the

- Regulation (MDR), and its General Safety and Performance Requirements (Annex I)

  Previously: Directives (MDD) and its Essential Requirements for safety, health and environment (Annex I)

CE granted by an external expert or “Notified Body”, e.g.

- CEBEC (Identification number 0649)
- TÜV-SÜD (Identification number 0123)

Product certification granted by Notified Bodies

A notified body is an (independent) organization designated by an EU country to assess the conformity of certain products before being placed on the market

These bodies carry out tasks related to conformity assessment procedures set out in the applicable legislation

Applicable to all EU Directives and regulations (e.g. electronics, EMC, toys, Medical Devices, ….)

Approved products carry the CE-mark

CE

Declaration of Conformity to MDR

XENIOS | A FRESENIUS MEDICAL CARE COMPANY

EU Declaration of Conformity

according to the Regulation (EU) 2017/745 on Medical Devices (MDR), Annex IV

We, the manufacturer

Xenios AG
Im Zukunftspark 1
74076 Heilbronn
Deutschland
SRN: DE-MF-000006233

declare herewith under our sole responsibility

that the in the category: Holder (ACCH)
Basis UDI DI: 4057224-0000-0000-ACCH-Y2

following medical devices include: **Xenios compact holder** **Ref. Nr. 30000145**

of risk class: I (according to rule 1 set out in annex VIII of Regulation (EU) 2017/745)

CE-marked with: CE

to which this declaration relates,
meet(s) all the provisions of Regulation (EU) 2017/745 of the European Parliament and of the Council on Medical Devices which apply to it and be carried out according to the Quality Management System EN ISO 13485.

This declaration of conformity is valid latest until June 11th 2026.

Heilbronn, June 11th, 2021

Thomas-Helge Junesch
Person Responsible for regulatory compliance
Xenios AG

Dr. Peter Schenck
Head of Regulatory Affairs
Xenios AG

Declaration-of-Conformity_ACC-H_CH_EN_V001
Form: F 09-01001P_V001EN
Valid from: 20.FEB.2020
supersedes: n/a first edition

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Certified Notified Bodies for MDR

Body type	Name	Country
NB 2265	3EC International a.s.	Slovakia
NB 0086	BSI Assurance UK Ltd	United Kingdom
NB 2797	BSI Group The Netherlands B.V.	Netherlands
NB 2409	CE Certiso Orvos- és Kórháztechnikai Ellenőrző és Tanúsító Kft.	Hungary
NB 1912	DARE!! Services B.V.	Netherlands
NB 0344	DEKRA Certification B.V.	Netherlands
NB 0124	DEKRA Certification GmbH	Germany
NB 2460	DNV GL Presafe AS	Norway
NB 0297	DQS Medizinprodukte GmbH	Germany
NB 0459	GMED	France
NB 0051	IMQ ISTITUTO ITALIANO DEL MARCHIO DI QUALITÀ S.P.A.	Italy
NB 2862	Intertek Medical Notified Body AB	Sweden
NB 0483	MDC MEDICAL DEVICE CERTIFICATION GMBH	Germany
NB 0482	MEDCERT ZERTIFIZIERUNGS- UND PRÜFUNGSGESELLSCHAFT FÜR DIE MEDIZIN GMBH	Germany
NB 0050	National Standards Authority of Ireland (NSAI)	Ireland
NB 0197	TÜV Rheinland LGA Products GmbH	Germany
NB 0123	TÜV SÜD Product Service GmbH Zertifizierstellen	Germany

43 Notified Bodies are certified for Product certification under MDR

(96 under MDD)

Medical Devices Regulation

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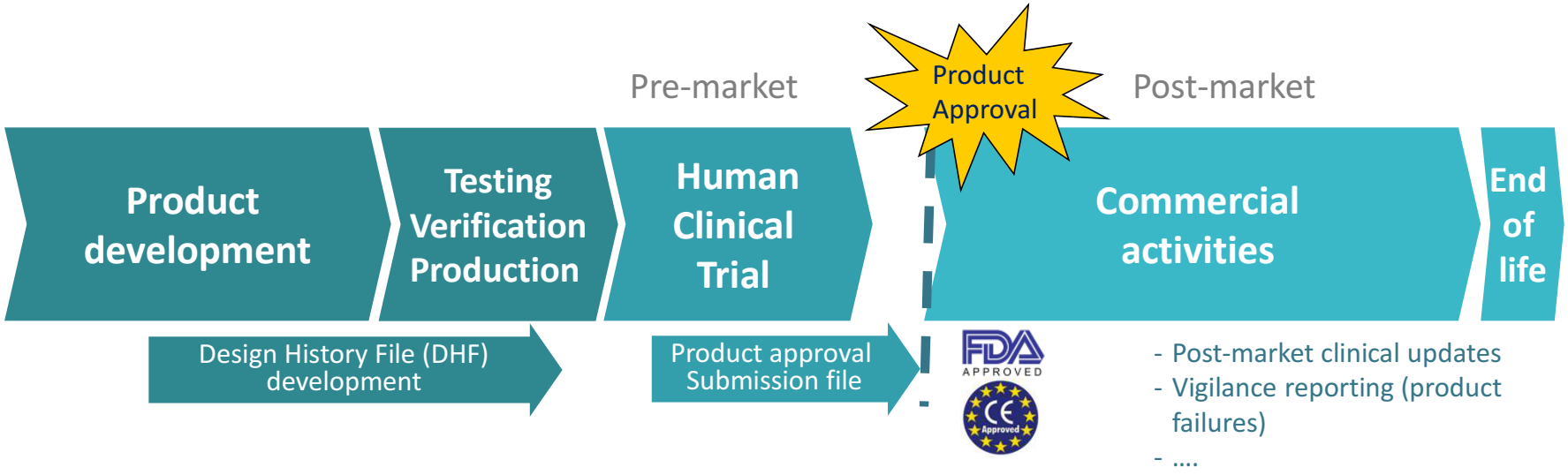
Clinical Trial design and implementation

Reporting of Clinical data, a case study

Clinical Data critical prior to market approval



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** Code of Federal Regulations , Title 21 – Food and Drugs, Chapter 1, Food and Drug Administration (FDA), Department of Health and Human Services, Subcapter H: Medical Devices. Part 812 (clinical investigation), Part 820 (Quality System Regulation), Part 11 (electronic records)

What is Clinical Data ?

Clinical Evaluation (any clinical data)

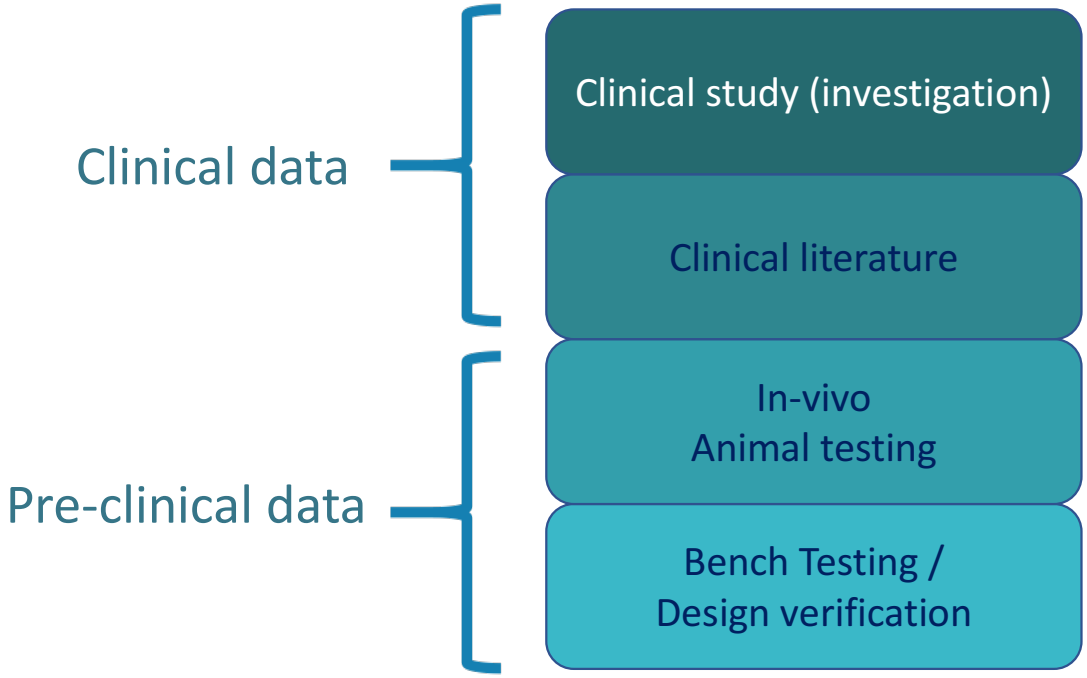
- Animal in-vivo data
- Public clinical data
  - Scientific publications
  - Public databases
- Non-public clinical data (e.g. company sponsored studies)
- Clinical Investigation (=Trial)

Clinical Investigation (= Clinical Trial = Clinical Study):

- Investigation in Human beings
- Can be pre- or post-market
- Study to be conducted following GCP standard ISO 14 155
- Change of indication according to labelling is considered ‘pre-market’.

GCP: Good Clinical Practices

Validation data for your Design History File



Particular features for MedTech Solutions

Wide range of products:

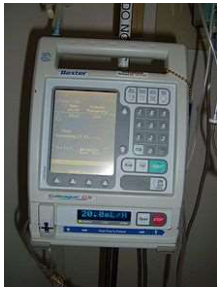
- SW, HW, combination of products,
- Drug device combinations.

Classification of devices, dependent on Risk level

- Class I (low)
- Class IIa, IIb (medium)
- Class III (high)

Clinical study definitions

- Not: Phase I, Phase II, III, IV (for drug studies)
- Pre-clinical: bench testing, animal testing
- Human studies: Feasibility → Pilot → Pivotal → Post-market



Market approval based on

- Safety + device performance + Benefit versus Risks(EU)
- Safety + effectiveness (US)

Authorities involved in Protocol approval

Europe

Ethics Committee (per hospital / region)

- Safety and Study ethical aspects in protocol
- Mainly organized per hospital
- Any study

Competent Authority (CA, per country, e.g. Swissmedic)

- Protection of public health
- Safety from investigational products
- Part of National government (Ministry of Health)
- All Serious Adverse Events should be reported to CA
- Protocol approval for Pre-Market studies

Notified Body (EU level)

- Responsible for product safety and for product approval (CE-Mark) in EU
- 'independent' organization, supervised by local Competent Authority
- Evaluates if primary endpoint provides correct Clinical data for product approval
- Only for 'Pre-market' studies

Other

- E.g. BfS for radioprotection in Germany

Can become very complex in Multicenter, Multinational study !

BfS: Bundesamt für Strahlenschutz (German Federal Office for Radiation Protection)

Authorities involved in Protocol approval

USA

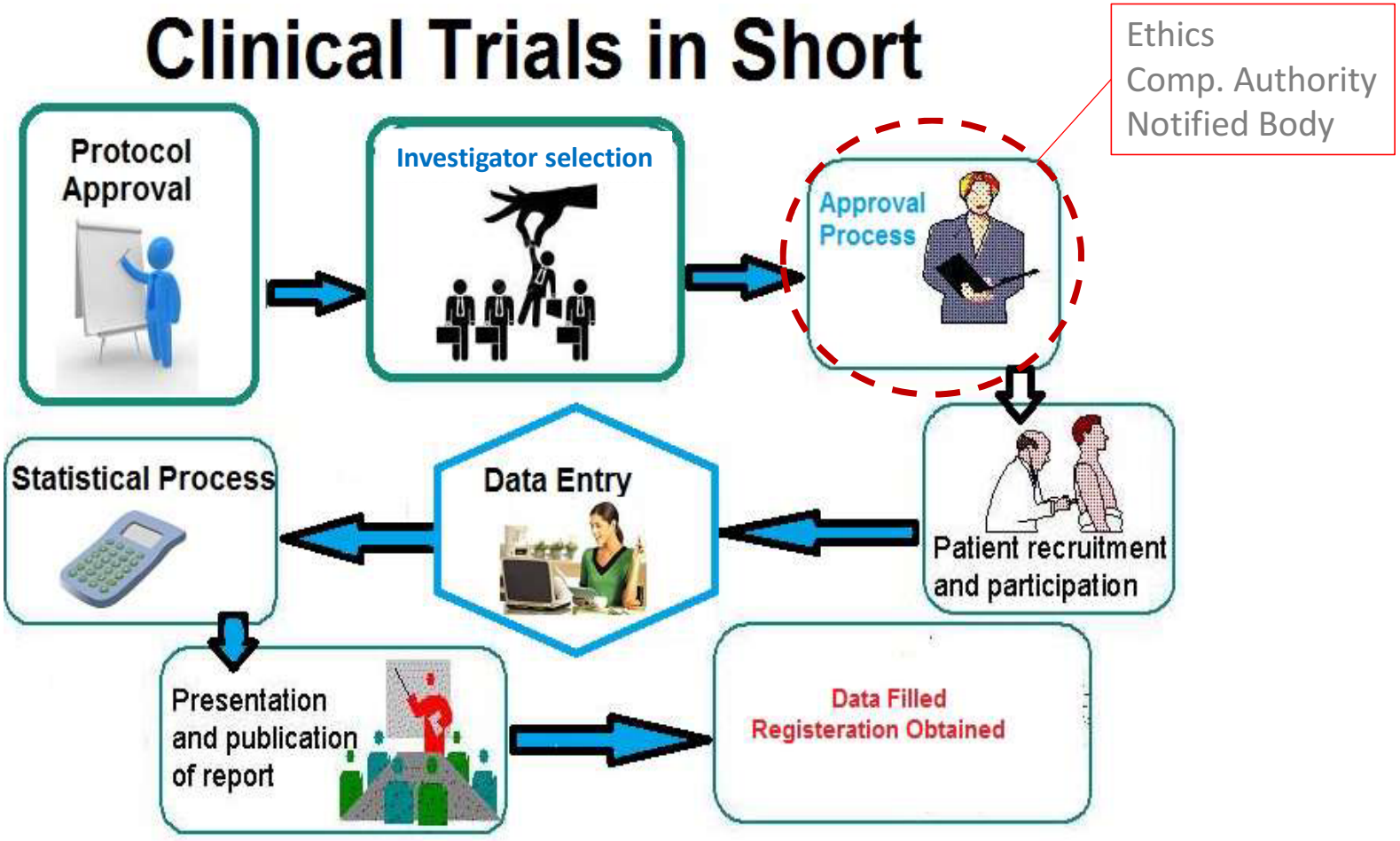
Investigational Review Board (IRB, per hospital)

- Identical to Ethics Committee in Europe
- Safety and Study ethical aspects in protocol
- Mainly organized per hospital
- Any study

FDA (Food and Drug Adminstration)

- Combines the function as Competent Authority and Notified Body:
- Part of US Federal government (Ministry of Health)
- Protection of public health
- Safety of investigational products
- Responsible for product safety and for product approval in US

Clinical Trials in Short



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Design and implementation of (prospective) Clinical study

CIP: detailed description on which data to collect, when, how

Only data points that are identified in CIP can be collected during study execution (unless protocol revision / approval)

CRF: Case Report Form

Design and implementation of (prospective) Clinical study

Primary Endpoints

- EU: Safety, device performance, clinical benefit
- US: Safety and efficacy
- Prospective confirmation of hypothesis
- Determines sample size
- Follows prospective statistical analysis plan (SAP)

Secondary endpoints:

- Allows data collection for other scientific purposes
- Retrospective analysis and future prospective hypothesis formulation
- Description statistics possible (mean, standard deviation, t-test, ….)

Study protocol and organization needs to be reviewed and approved by regulatory authorities prior to it start

- Ethic committee per hospital (or region)
- Competent authority per country (for studies using non-approved medical devices) – E.g. Swissmedic, FDA, …

canton de vaud
LIBERTÉ ET PATRIE

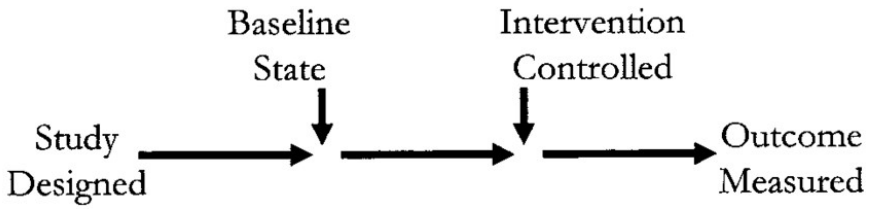
CER-VD
Commission cantonale d'éthique de la recherche sur l'être humain

swissmedic

CRF: Case Report Form

Prospective versus Retrospective study

Prospective Study

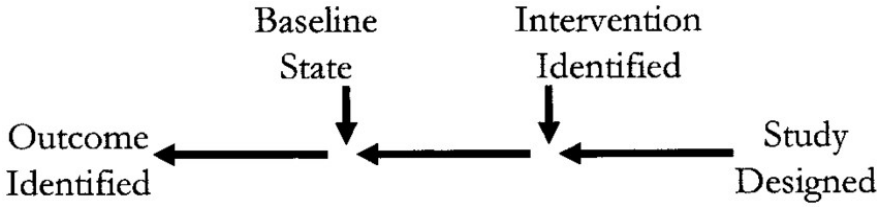


Formulate hypothesis (e.g. Device is safe, Treatment is 20% more effective)

Define statistical method

Confirm hypothesis

Retrospective Study



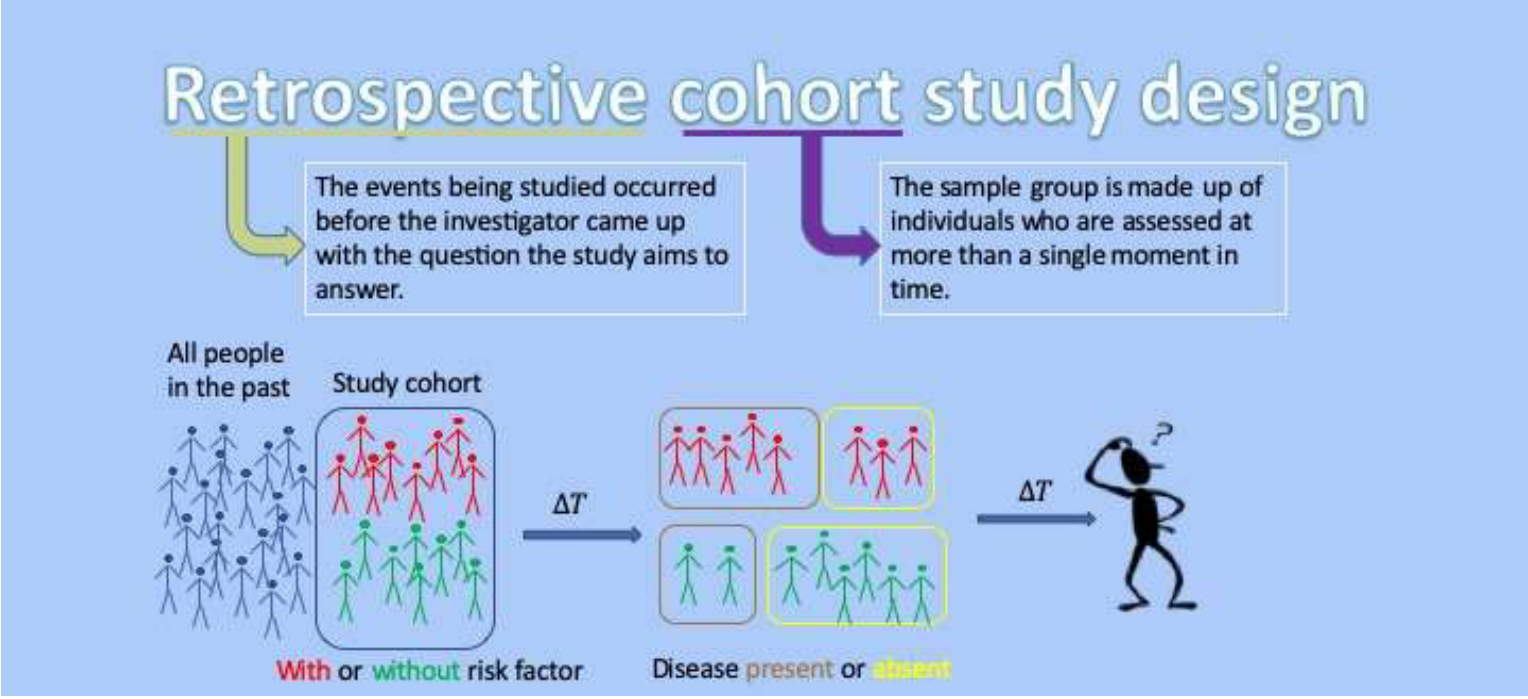
Confirm Sub-group
Identify new virus
…

Formulate observation, e.g.
- Subgroup is more reactive to treatment)
- Disease pattern from new virus
- ….

Clinical Trials for Product approval **must be Prospective**,
to confirm hypothesis of Device Safety and Efficacy

Most academic studies are mainly retrospective

Retrospective analysis, Good or Bad ?



Good

- Inexpensive and quick to do
- Identify new trends and observations in existing study cohorts
- The only way to identify new phenomena (e.g. Covid first diagnosis, trends of toxic polution, …

Caution

- Making subgroup analysis → reduced sample size and statistical power
- Too many analysis on the same data set → Increase likelihood of false positives (Type I error). For p=0.05 → 5% likelihood to make wrong conclusion)
- No control over the quality of data (incomplete, inaccurate, inadequate for this study question)

Benefit vs pain of a clinical trial

The clinical trial should serve

YOU

Make your choices during the Clinical Protocol development !!
You are in control !

Clinical study should bring you all data you need for:

- Market approval (Regulatory)
- Data for Sales and Marketing claims
  - Clinical benefit
  - Cost effectiveness
  - ….

Special considerations for Blinded RCT

Double blind studies are very common in drug studies → They ensure highest level of objectivity to avoid investigator bias

Medical devices dependent often on the handling skills of the investigator

Double blinding becomes nearly impossible

Single blinding often through ‘Sham’ technique in control arm (e.g. fake electrical stimulation)

RCT: randomized clinical trial

Example:
STIMO FEASIBILITY STUDY

STIMO
STIMULATION
MOVEMENT
OVERGROUND

EPFL

G. Courtine
Scientist

CHUV

J. Bloch
Neurosurgeon

uniklinik balgrist

A. Curt
Paraplegiologist

ONWARD
EMPOWERING MOVEMENT

Medtronic

First time, demonstration of functional restoration of movement after paralysis (neuroplasticity)

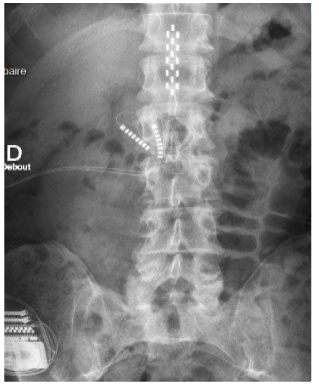
Combination of EPFL proprietary SW with existing devices off-label (Medtronic)

5 months rehabilitation training, 3-6 years follow-up (optional).

Enrolment completed: 10 patients with chronic injuries (up to 13 years after lesion),

- 7 patients with severity ranging AIS C-D – MDT lead
- 3 patient AIS A – ONWARD lead

Results on 3 cervical patients published in Nature (Wagner et.al., 1 Nov 2018)



Example
STIMO FEASIBILITY STUDY

STIMO
STIMULATION
MOVEMENT
OVERGROUND

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Scientist

CHUV

J. Bloch
Neurosurgeon

uniklinik balgrist

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ONWARD
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5 months reha… in progress

Currently … up to 13 years …

- 7 … ranging AIS C-D – MDT lead
- 3 patient AIS A – GTX Go-2 Lead

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Review and approval of

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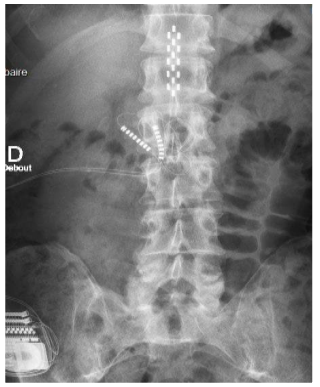
CER-VD
Commission cantonale d'éthique de la recherche sur l'être humain

swissmedic



Structure for submission and regulatory approval

Clinical Documentation
- Clinical protocol
- Informed consent
- Case report Forms (CRF)
- Monitoring Plan
- …

Technical documentation
- Device + Therapy description
- Test Plans
- Test Reports
- Risk Management
- User Manuals
- …

Investigator Brochure

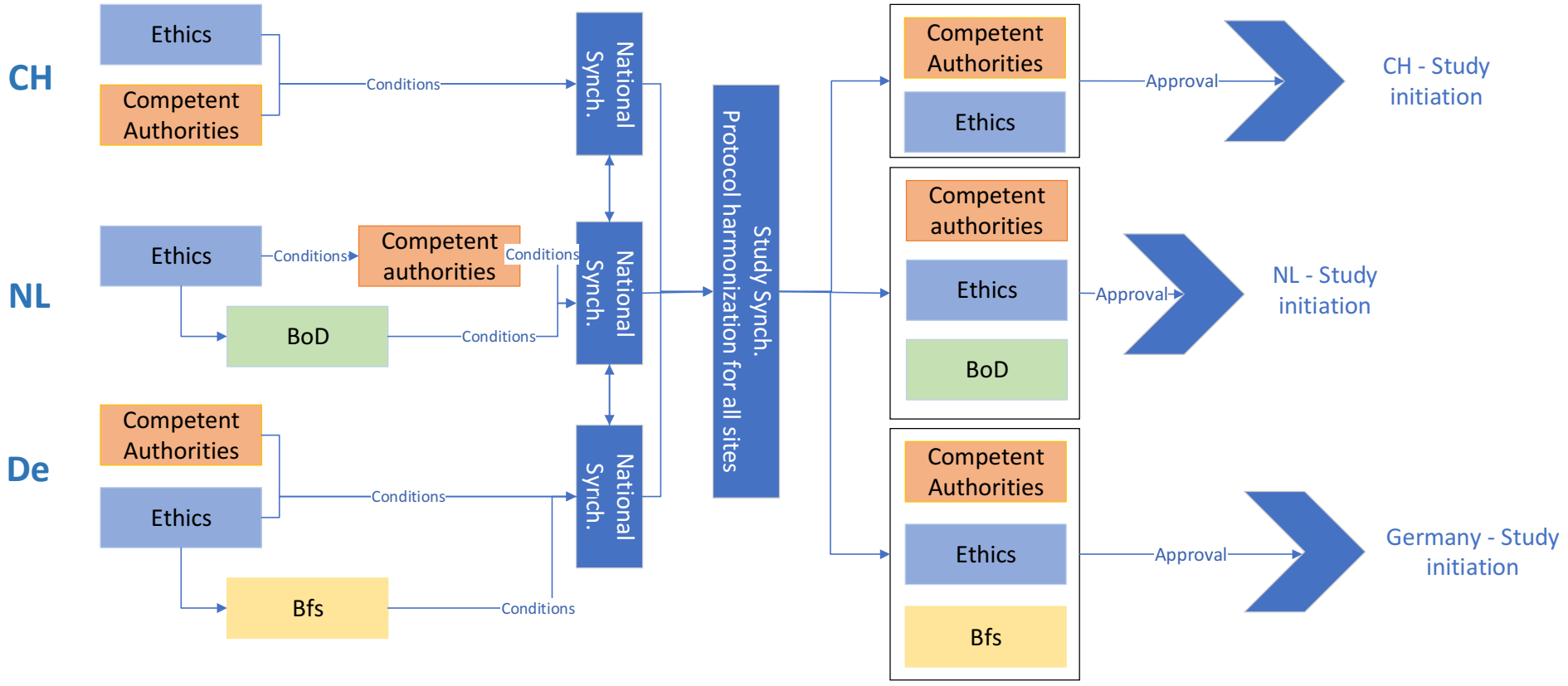
Organizational documents
- Financing
- Contracts
- Suppliers
- Investigator CV + declarations
- …

canton de vaud

CER-VD
Commission cantonale d'éthique de la recherche sur l'être humain

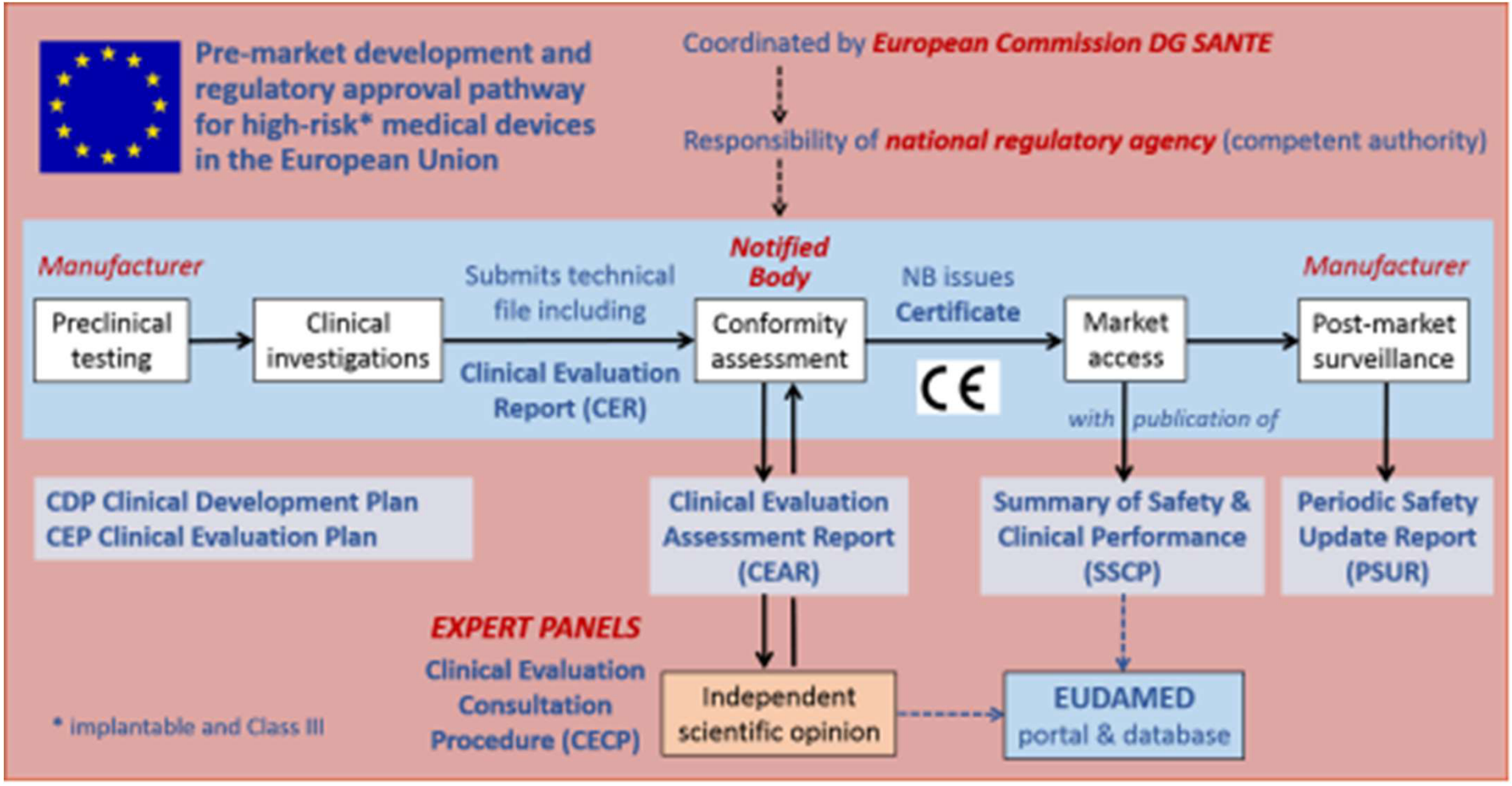
swissmedic

Approval process in multicenter study



BoD: Hospital Board of Directors
BfS: Bundesamt für Strahlenschutz (German Federal Office for Radiation Protection)

European Regulatory Framework



PMCF Reporting obligations of manufacturers

Report	Class I	Class IIa	Class IIb	Class III/Implants
Clinical Evaluation Report 61-12/Annex XIV part A-4/Meddev 2.7.1 rev4	When needed	2-5 years	2-5 years	Annually
PMCF Evaluation report - part of CER 61-11 Annex XIV Part B-7	When needed	When needed or at least 2-5 years	When needed or at least 2-5 years	At least annually
Summary of safety and clinical performance 32,83-3(d)	N/A	Every 2 years	Every 2 years	Annually
Risk Management Report Annex I. Chapter 1-3	Regular systematic update	Regular systematic update	Regular systematic update	Regular systematic update
PSUR 86-2, 86-3, 92-1(d)	N/A	At least every 2years	At least annually	At least annually
PMS report Art 85	When necessary	N/A	N/A	N/A

Source graphical setup: Courtesy of Philippe Auclair / Abbott – RAPS Convergence 2017
CER: Clinical Evaluation Report
PSUR: Periodic Safety update report
PMS: Post market Surveillance

Residual risks and root cause for safety events evolve during product life-cycle

# patients:	0 – 100	100 – 1000	> 1000
Design	+++	+	
Operator / training / usability	+	+++	++
Production		+	+++

- Patient #1000 is the your most important patient ！
  - includes design, usability, production, real world feedback.
  - Keep him in mind from the very start of product development
- PMCF is essential to capture early on new failure modes


Questions?

Medical Devices Regulation

Introduction: Patient safety and Need for regulation

Medical Device regulations

Regulation for clinical studies

Clinical Trial design and implementation

Reporting of Clinical data, a case study

A cardiac ablation catheter

Clinical study for Market approval in US

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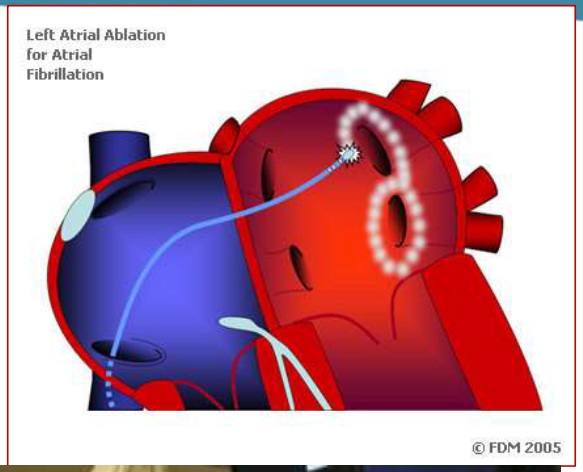
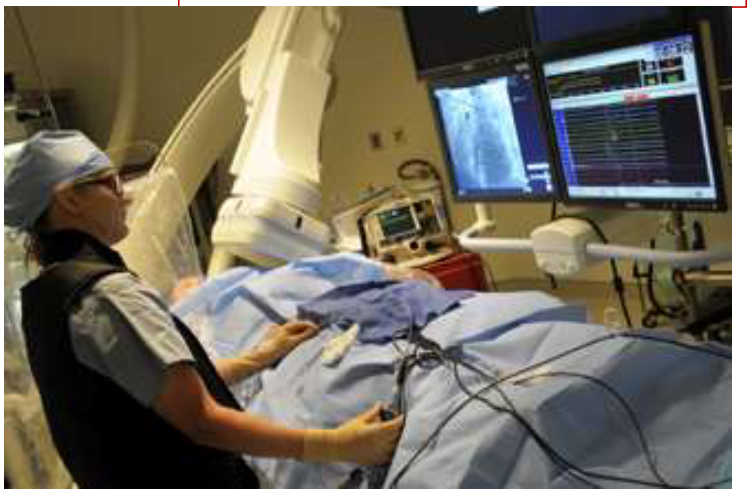
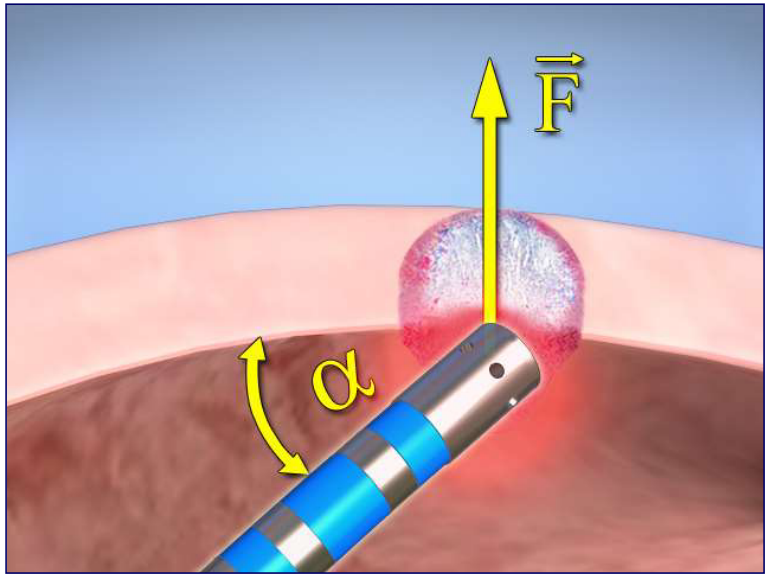
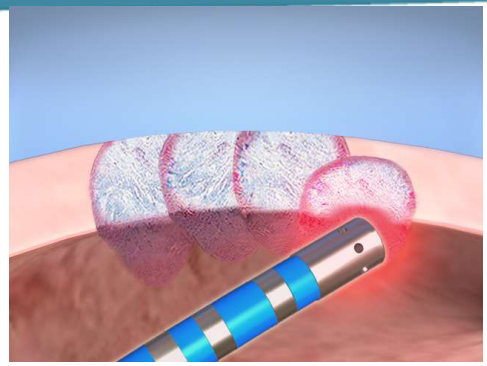
A practical example

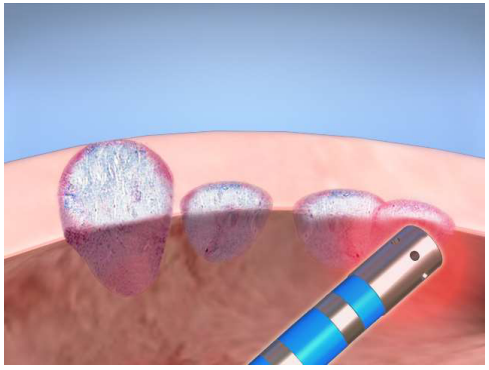
Catheter Ablation for treatment of Atrial Fibrillation (AF)











ENDOSENSE experience

TactiCath Catheter

TactiCath: Force sensing ablation catheter

- Endosense: Start-up company, 2003, Geneva, CH
- 2005: fund raising for catheter development
- 7 years development: 2005-2012 :
  - 2006 – 2010: R&D, Extensive testing + Animal studies:
  - 2008-2009: EU Clinical study
  - 2009: EU 1st CE- mark approval
  - 2012: EU 3rd CE- mark approval
  - 2010 – 2013: US clinical study
  - 2014 (Oct): US PMA approval
- Looking for Worldwide approval:
  - 2010: Australia
    - 2014: US
      - 2015- …. Canada, Japan, China, …

TOCCASTAR Clinical Study (EU + US)

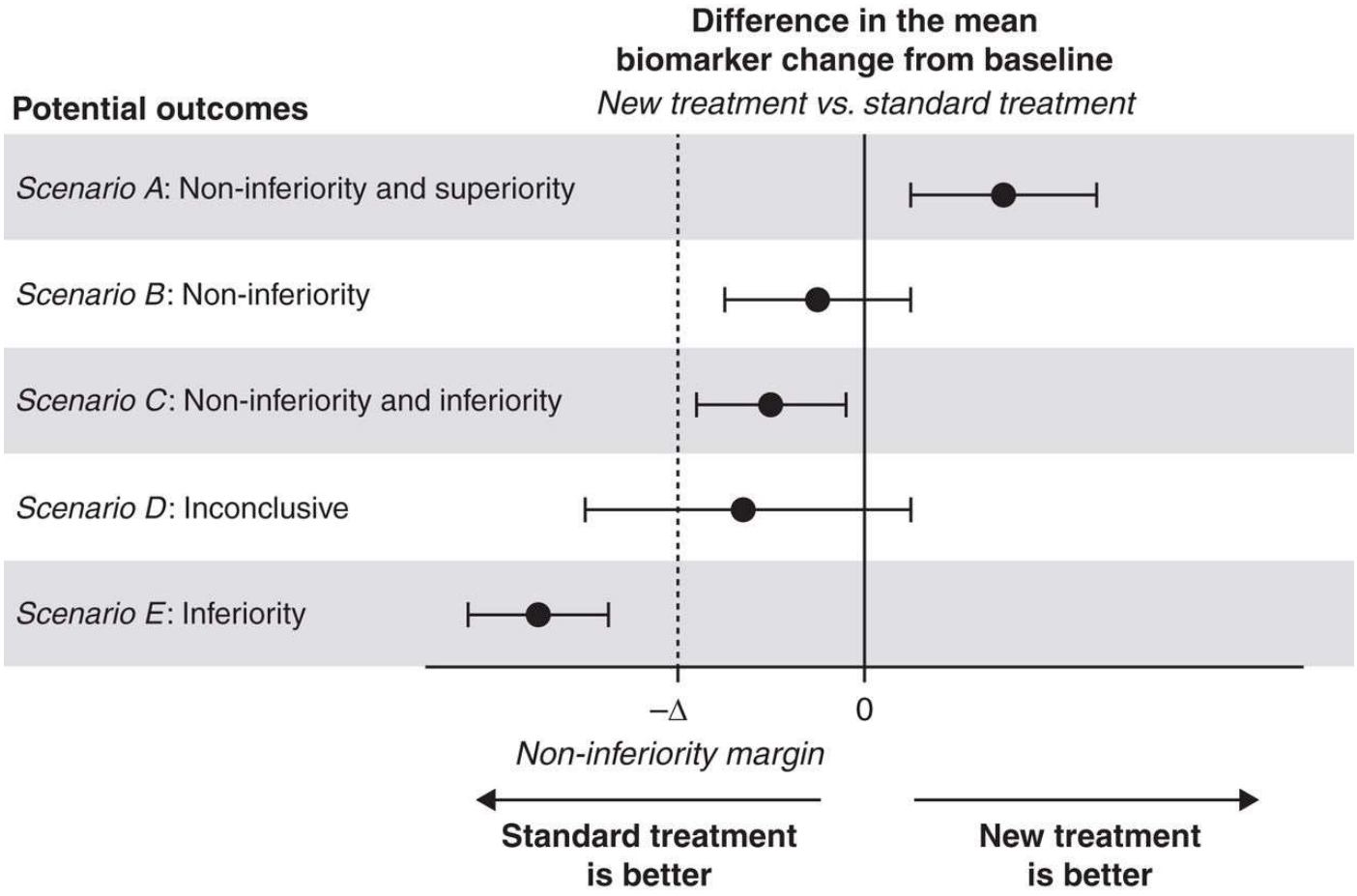
- FDA randomized pre-market (IDE) study, 300 patients, 17 centers in US and EU
  - Roll-in patients allowed (max 3 per center)
  - Compare TactiCath to standard RF ablation catheter (commercially available)

- Primary endpoints: Safety and effectiveness
  - Non-inferiority of Tacticath to control
  - 12 months follow-up period
- Secondary endpoints (statistics following hierarchical testing):
  - Contact Force data
  - Subgroup analysis

- Normal procedure with standard ablation protocol. → Supplemental data collection for Secondary and Descriptive endpoints

- Minimal Cost
  - No change to normal clinical practice
  - Field Clinical Engineer present anyhow
  - Back office: ongoing data analysis

Non-Inferiority trial

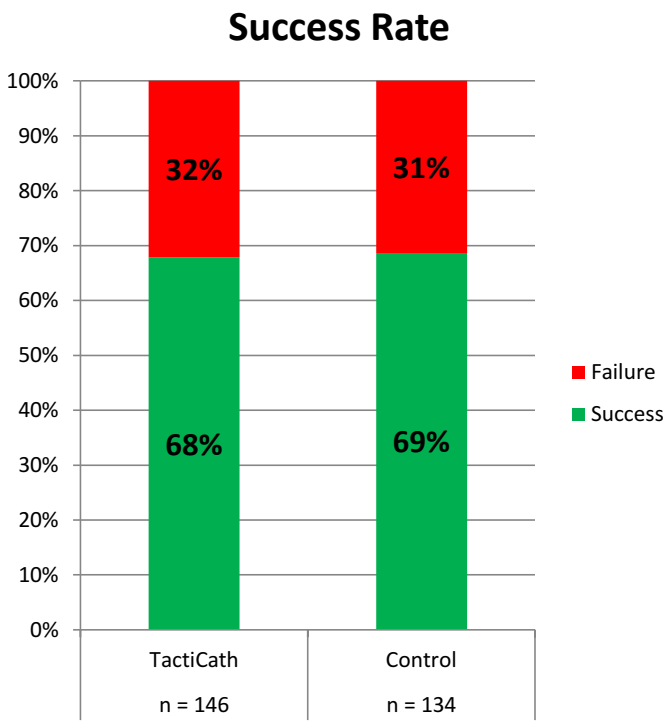


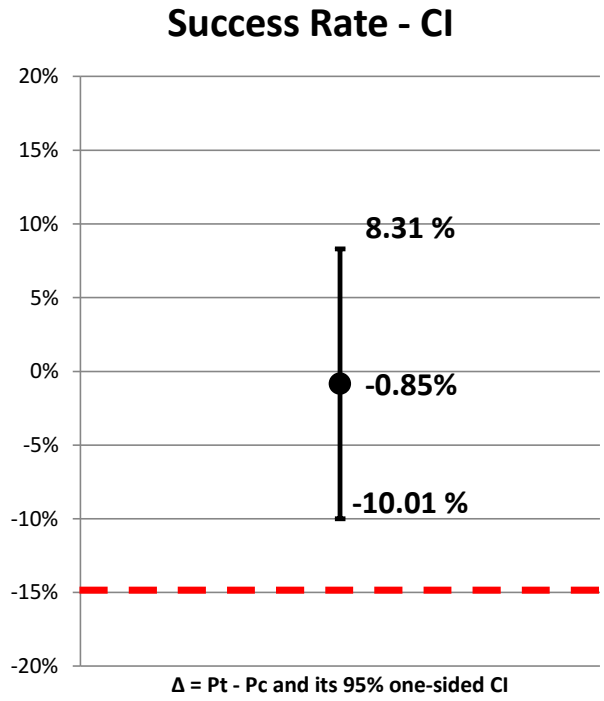
Definition of endpoints and statistical analysis

- Safety primary endpoint
  - Device and procedure related Serious Adverse Events (SAE)
- Effectiveness primary endpoints
  - Acute electrical isolation of all pulmonary veins
  - Freedom from symptomatic atrial arrhythmia off all anti-arrhythmic drugs during 12 months follow-up
- Prospective statistics – non-inferiority
  - Boundary of 95% Confidence Interval (CI) should not cross the pre-defined non-inferiority margin (prospective definition of endpoint)
- Secondary endpoints: Retrospective analysis
  - Did the operator use the Contact Force information following recommendations (>10g during ablation) ?
  - Subgroup analysis to define ‘optimal contact force’
  - Formulate hypothesis for potential future clinical trials

Primary Effectiveness Endpoint – Protocol Defined Endpoint Met

- Per-Protocol (**PP**) Population: **280** patients (146 TactiCath® - 134 Control)
- Success Rate: TactiCath® (P_t) **67.81%** - Control (P_c) **68.66%**
  - $\Delta = P_t - P_c$ = **-0.85%** → one-sided 95% Confidence Interval = **[-10.01%, 8.31%]**





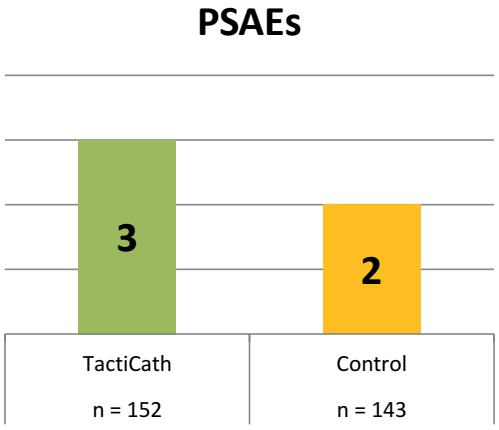
One-sided 95% lower confidence limit > -15%

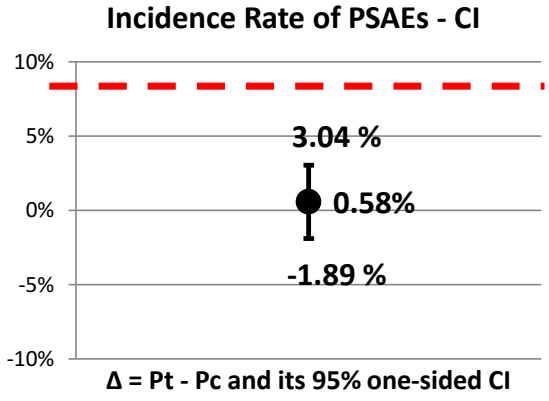
-> ENDPOINT MET

Primary Safety Endpoint – Endpoint Met

- Safety (**SAF**) Population: **295** patients (152 TactiCath® - 143 Control)
- Incidence Rate of PSAEs: TactiCath® (P_t) **1.98%** - Control (P_c) **1.40%**
  - $\Delta = P_t - P_c$ = **0.58%** → one-sided 95% Confidence Interval = **[-1.89%, 3.04%]**

Primary Serious Adverse Event	TactiCath patients (%)	Control patients (%)
Cardiac Tamponade / Cardiac Perforation	1 (0.66 %)	1 (0.70 %)
Pericarditis	2 (1.32 %)	0 (0 %)
PV Stenosis	0 (0 %)	1 (0.70 %)
Total	**3 (2.0 %)**	**2 (1.4 %)**

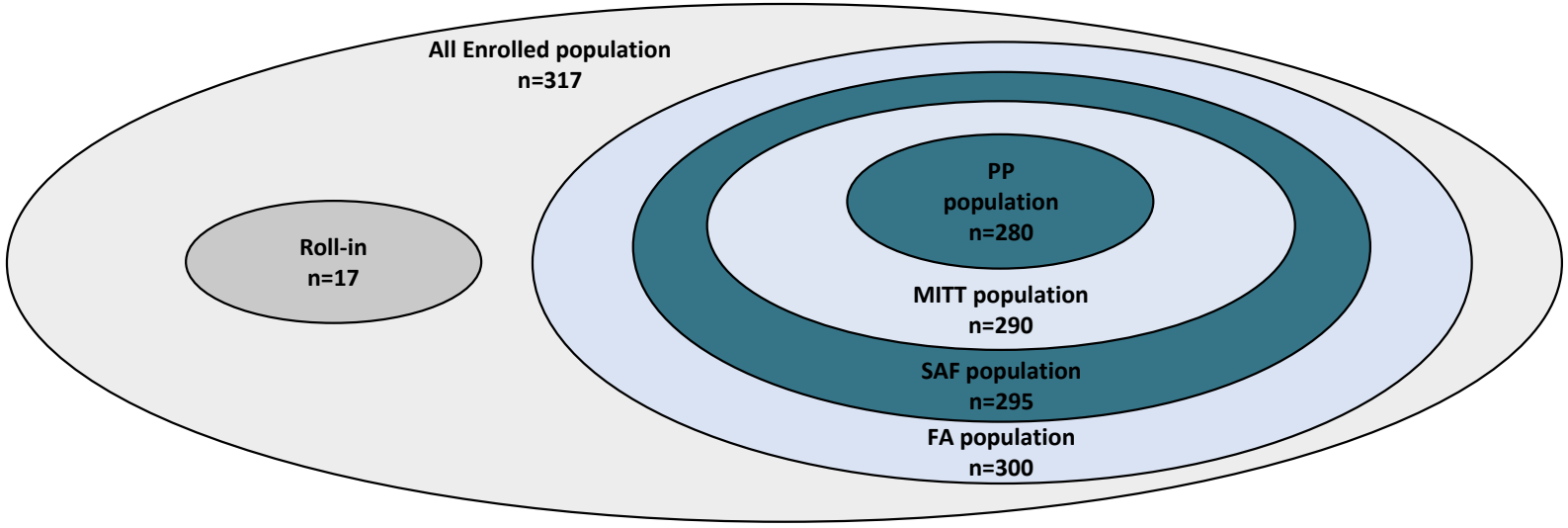




One-sided 95% upper confidence limit < 9%

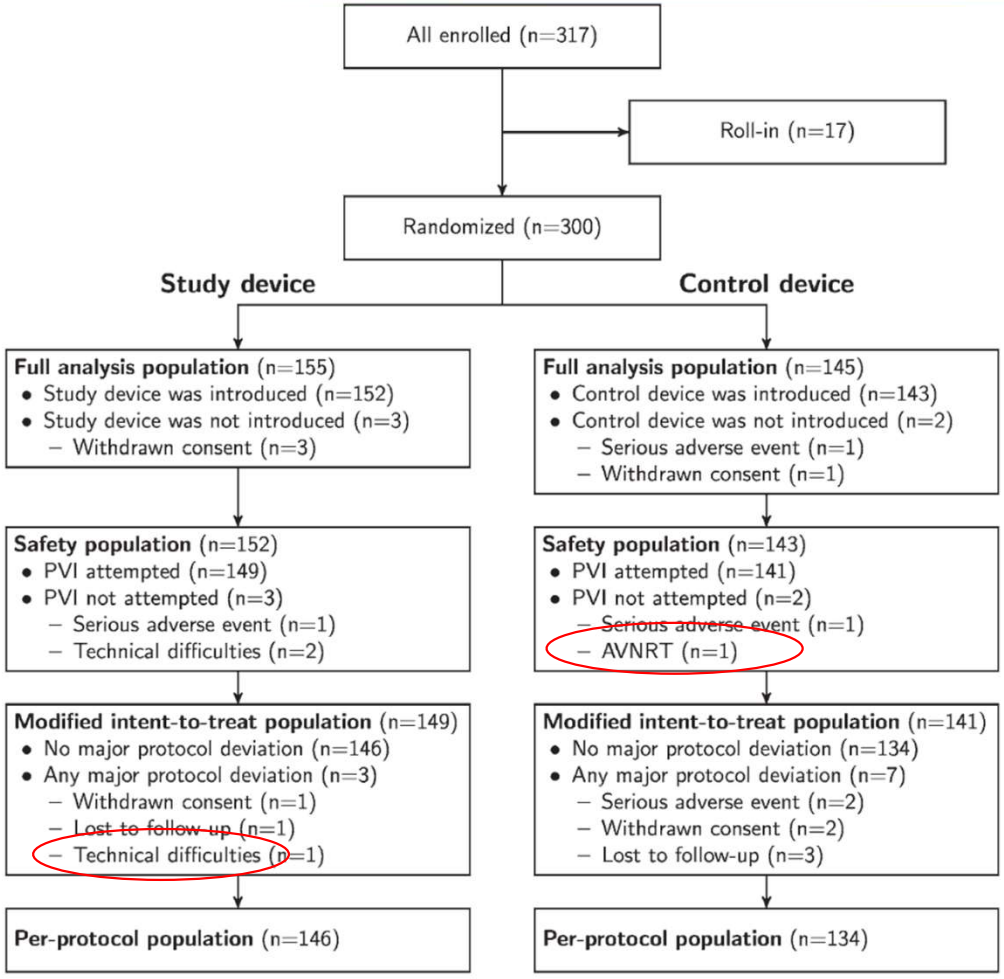
-> ENDPOINT MET

Analysis Populations



Analysis Population	Total	TactiCath®	Control
All Enrolled	317	-	-
Roll-in	17	-	-
FA (Full analysis)	300	155	145
SAF (Safety)	**295**	**152**	**143**
MITT (Modified Intent-To-Treat)	290	149	141
PP (Per-Protocol)	**280**	**146**	**134**

Patient populations for different analysis



Randomized, Controlled Trial of the Safety and Effectiveness of a Contact Force–Sensing Irrigated Catheter for Ablation of Paroxysmal Atrial Fibrillation

Results of the TactiCath Contact Force Ablation Catheter Study for Atrial Fibrillation (TOCCASTAR) Study

Vivek Y. Reddy, MD; Srinivas R. Dukkipati, MD; Petr Neuzil, MD; Andrea Natale, MD; Jean-Paul Albenque, MD; Josef Kautzner, MD; Dipen Shah, MD; Gregory Michaud, MD; Marcus Wharton, MD; David Harari, BS; Srijoy Mahapatra, MD; Hendrik Lambert, PhD; Moussa Mansour, MD

Background—Contact force (CF) is a major determinant of lesion size and transmurality and has the potential to improve efficacy of atrial fibrillation ablation. This study sought to evaluate the safety and effectiveness of a novel irrigated radiofrequency ablation catheter that measures real-time CF in the treatment of patients with paroxysmal atrial fibrillation.

Methods and Results—A total of 300 patients with symptomatic, drug-refractory, paroxysmal atrial fibrillation were enrolled in a prospective, multicenter, randomized, controlled trial and randomized to radiofrequency ablation with either a novel CF-sensing catheter or a non-CF catheter (control). The primary effectiveness end point consisted of acute electrical isolation of all pulmonary veins and freedom from recurrent symptomatic atrial arrhythmia off all antiarrhythmic drugs at 12 months. The primary safety end point included device-related serious adverse events. End points were powered to show noninferiority. All pulmonary veins were isolated in both groups. Effectiveness was achieved in 67.8% and 69.4% of subjects in the CF and control arms, respectively (absolute difference, −1.6%; lower limit of 1-sided 95% confidence interval, −10.7%; P=0.0073 for noninferiority). When the CF arm was stratified into optimal CF (≥90% ablations with ≥10 g) and nonoptimal CF groups, effectiveness was achieved in 75.9% versus 58.1%, respectively (P=0.018). The primary safety end point occurred in 1.97% and 1.40% of CF patients and control subjects, respectively (absolute difference, 0.57%; upper limit of 1-sided 95% confidence interval, 3.61%; P=0.0004 for noninferiority).

Conclusions—The CF ablation catheter met the primary safety and effectiveness end points. Additionally, optimal CF was associated with improved effectiveness.

Clinical Trial Registration—http://www.clinicaltrials.gov. Unique identifier: NCT01278953.

(*Circulation*. 2015;132:907-915. DOI: 10.1161/CIRCULATIONAHA.114.014092.)

Key Words: ablation techniques ■ atrial fibrillation ■ catheter ablation

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Retrospective analysis on 2nd Endpoints (1/2)

- Published positive outcomes are clinically relevant
- Becomes part of official labelling on FDA website

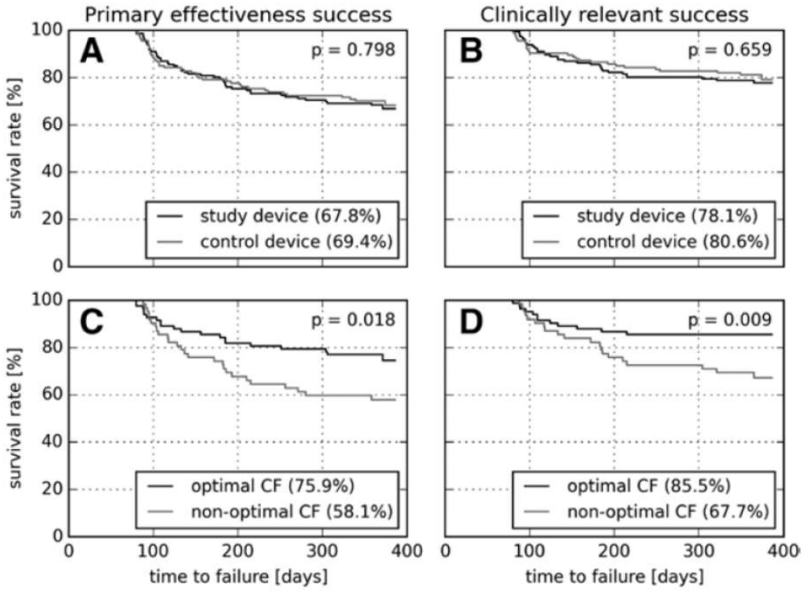


Figure 2. Kaplan–Meier survival curves with respect to protocol-defined and clinically relevant success. **A**, Primary effectiveness success for contact force (CF; study device) and control catheters (control device). **B**, Clinically relevant success for the 2 groups. **C**, Primary effectiveness success for the optimal and nonoptimal CF groups. **D**, Clinically relevant success for the optimal and nonoptimal CF groups.

Retrospective analysis on 2nd Endpoints (2/2)

- Published positive outcomes are clinically relevant
- Becomes part of official labelling on FDA website

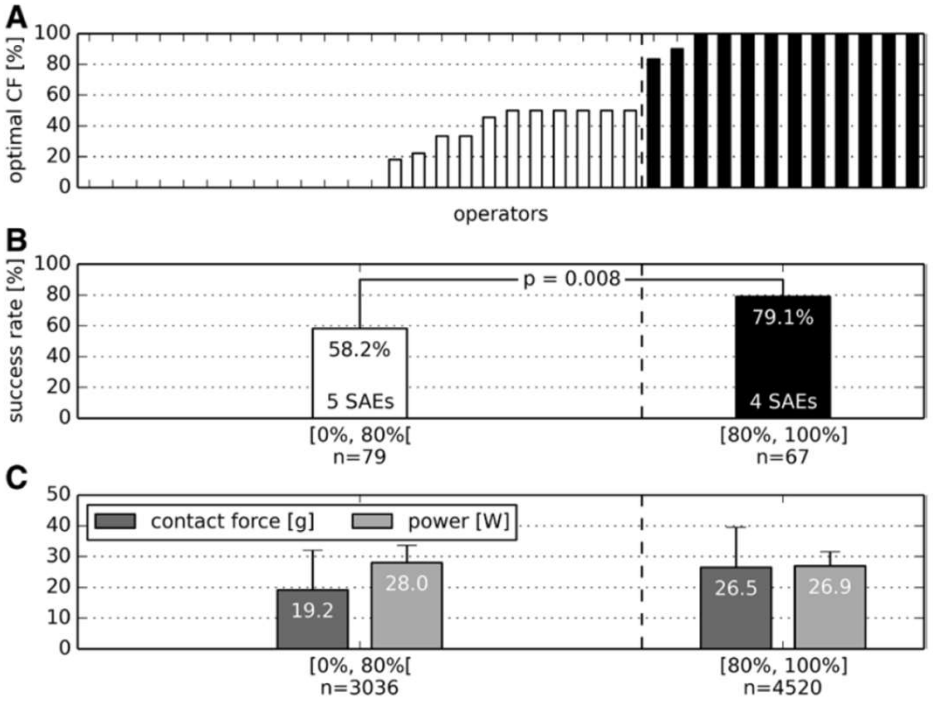


Figure 3. Analysis of optimal vs nonoptimal contact force (CF) by operator. **A**, Operator ranking based on the percentage of patients in whom an optimal CF was achieved (36 operators). The dashed vertical line separates the operators who achieved optimal CF in ≤80% of their patients (white bars, 24 operators, 13 with no optimally treated patients) from the operators who achieved optimal CF in >80% of their patients (black bars, 12 operators, 10 with all patients treated optimally). **B**, Treatment success achieved by operators with optimal CF in >80% of their patients procedures compared with other operators. **C**, Mean CF in at least and radiofrequency power for operators with optimal CF in >80% of the patients compared with other operators. Both variables were significantly different between the 2 groups (P<0.001). Subjects treated by operators using optimal CF required lower radiofrequency power while achieving a better outcome. SAE indicates serious adverse event.

Retrospective analysis part of FDA labeling

SSED* is available on FDA website for each approved device

*Summary of Safety and Effectiveness Data
https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130026B.pdf

A post hoc analysis of treatment success for all TactiCath™ subjects in the PP population who were treated with greater than 10 g of contact force (CF) in at least 90% of all lesions (n=83) is presented in **Table 18**.

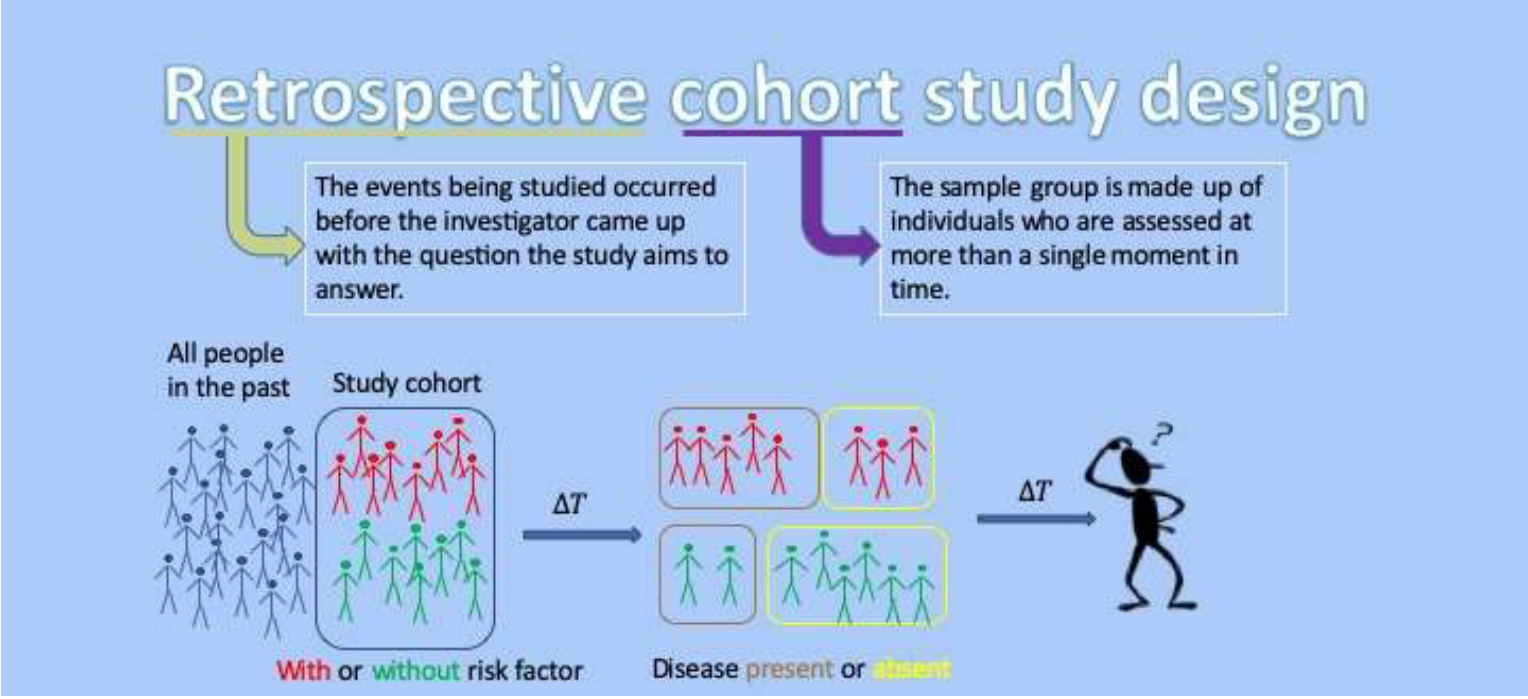
Table 18. Success Rates for TactiCath™ Subjects with a High and Low Percentage of Lesions Above 10g (PP Population)

Contact force	Subjects (n)	Success (%)	*P* value
Optimal (≥90% of lesions with CF >10 g)	83	75.9%	0.018
Suboptimal (<90% of lesions with CF >10 g)	62	58.1%	

Using protocol-defined criteria for success, TactiCath subjects who were treated with "optimal" contact force (≥90% of lesions with CF >10 g) were significantly more successful (75.9% vs 58.1%, P=0.018) than those treated with suboptimal contact force.

Control subjects had a higher failure rate due to reablation procedures after the blanking period compared to TactiCath subjects (12.7% vs 7.5%, respectively). Only 4 of the 83 (4.8%) subjects treated with optimal contact force required treatment with repeat ablation during the effectiveness assessment period compared to 17 of 134 (12.7%) subjects in the control arm (*P*=0.044).

Retrospective analysis, Good or Bad ?



Good

- Inexpensive and quick to do
- Identify new trends and observations in existing study cohorts
- The only way to identify new phenomena (e.g. Covid first diagnosis, trends of toxic polution, …

Caution

- Making subgroup analysis → reduced sample size and statistical power
- Too many analysis on the same data set → Increase likelihood of false positives (Type I error). For p=0.05 → 5% likelihood to make wrong conclusion)
- No control over the quality of data (incomplete, inaccurate, inadequate for this study question)

Acknowledgments

Thanks for the contribution to the slides !

Ragasudha Veerabathiran

Elisabeth Lambert

Anne Watrin


Questions?