The Medical Device Regulation (MDR) and its implications for (your own) medical hard and software

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MAASTRO, Maastricht, NL

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The Pelvic Mesh Mess

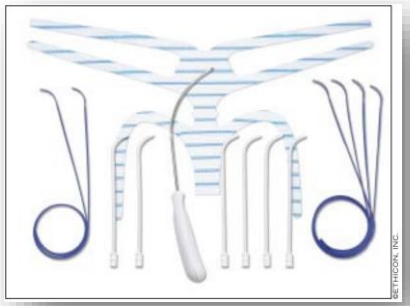
Critchfield/Duke Health, The Guardian

Pelvic mesh rise and fall

- ~2000: transvaginal tape for stress urinal incontinence, FDA approved
- 2002: introduced for pelvic organ prolapse
- 2010: 25% for prolapse
- ~2012: Bad results (vaginal scarring, perforation/erosion, return of prolapse, urinary problems)

  Withdrawn products, notably ProLift, Ethicon Inc. (J&J)

Lemperle G, doi:10.36876/smggr.1005

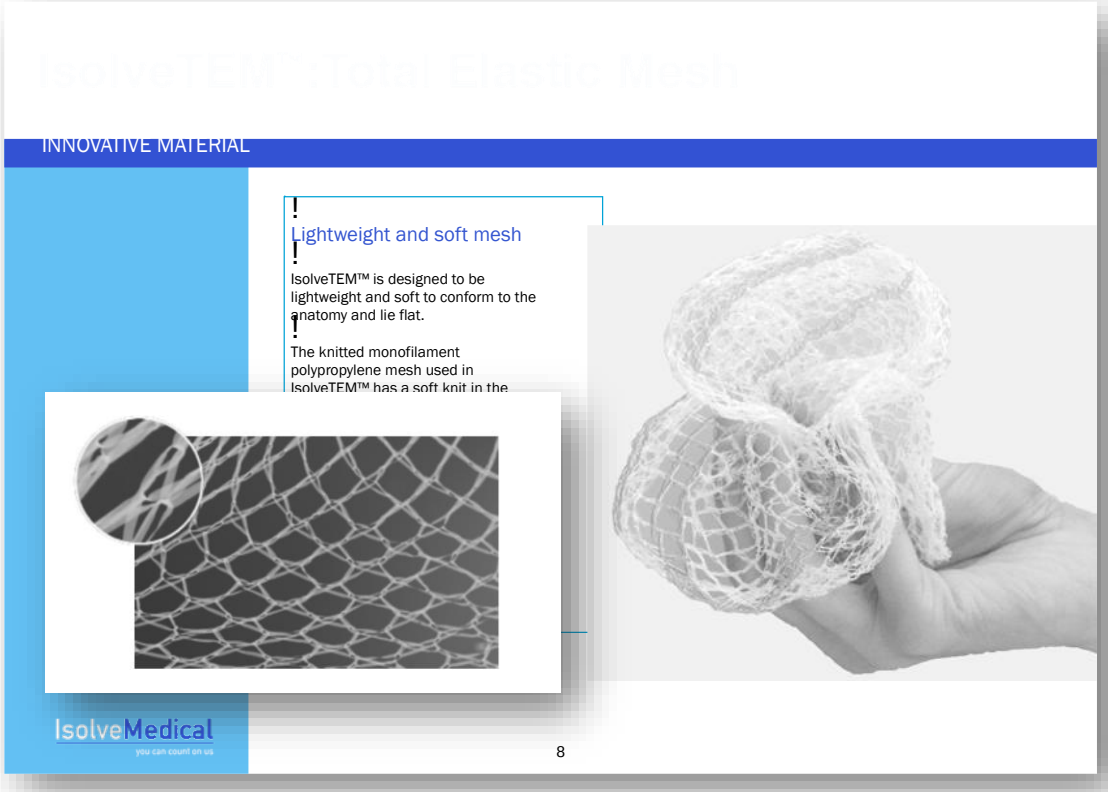


Ob.Gyn.News, 2009-02-01

Marco Verch © CC BY 2.0 via Flickr

2014: IsolveMedical introduces IsolveTEM™

- Despite dozens of issues reported!
- Flawed design:
  - Full-size mesh
  - 8 straps (‘arms’)
  - “soft elastic synthetic mesh”
  - uses *non-elastic* Polypropylene



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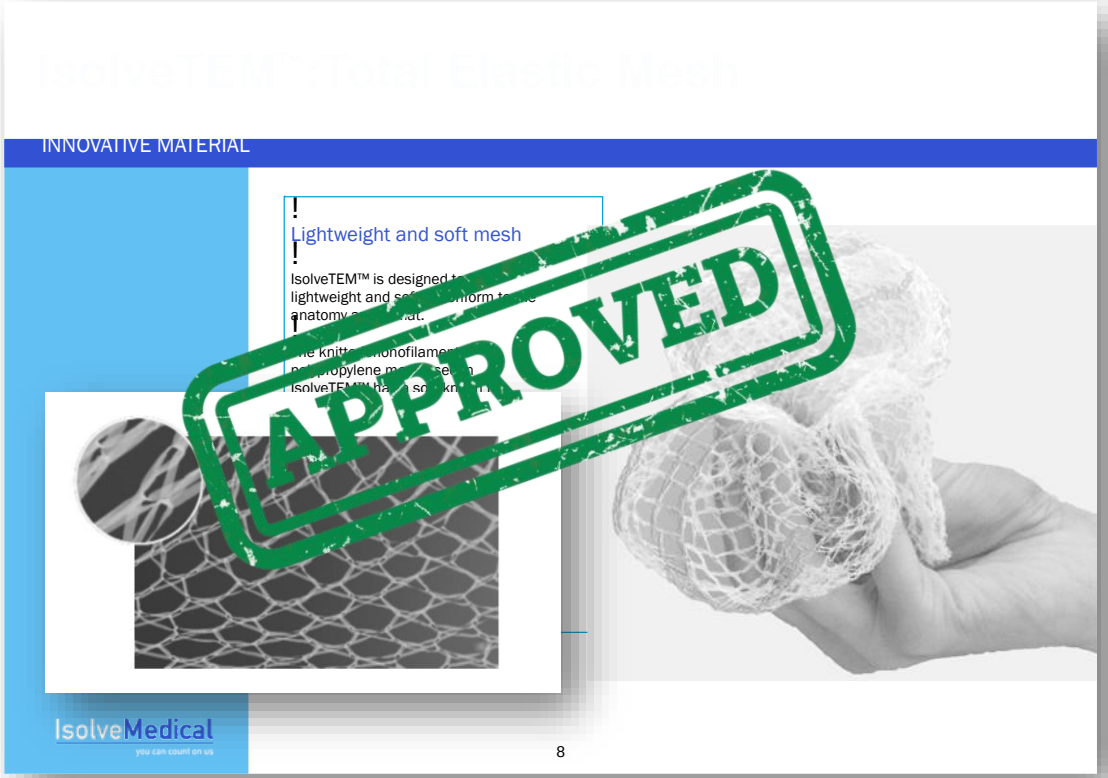
- GETS CE MARKED !!

CE



So, what happened...?

The (*burden of the*) MDR and how it might affect your work

- Background / Disclosures
  - Dr. ir. Erik Roelofs, a.k.a. *ER(ik)*, MAASTRO, NL
    - Qualified Medical Physicist (in Radiotherapy)
    - Medical Technology Supervisor
    - Chief Medical Information Officer (CMIO)
  - Medical Devices Expert, Medical Research Ethical Committee (MREC), MUMC+, NL
  - MD Expert Panel, Central Committee on Research Involving Human Subjects (CCMO), NL

The ProTones (MAASTRO), ESTRO 37, Razzmatazz, Barcelona, 2018

RADAR critisises CE certificartion process

2014: ~~IsolveMedical introduces~~ IsolveTEM™

- Popular Dutch TV show RADAR
- Consumer's rights program
- Started fake company : *IsolveMedical*

- Compiled Technical Documentation
  - 10 ‘Boobytraps’
  - full mesh
  - non- vs. elastic material
  - ‘easter-egged’ literature

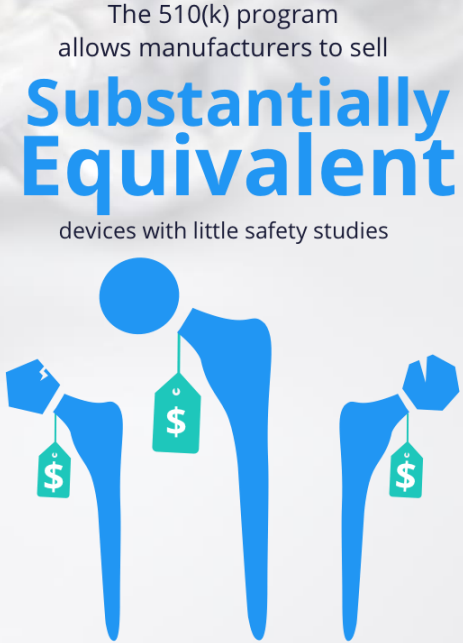
- Filed at 3 Notified Bodies

- Hidden camera visits:
  - “100% you’ll get your CE mark”

“IsolveMedical”, Avro/Tros

CE certification process

- Fast-track certification, based on “equivalent performance”
- FDA 510(k) : “safe and effective, -> substantially equivalent, to a legally marketed device”
- No limit in ‘chaining’ of predicate devices
- Refer to previous product Clinical Evaluation
- Note: literature, not Clinical Trial evidence!



References; find the ‘easter eggs’…

Reisenauer C, Kirschniak A, Drews U, Wallwiener D, Anatomical Conditions for pelvic floor reconstruction with polypropolyne implant and its application for the treatment of vaginal prolapse. Eur. J. Obstet. Gynecol. Repor. Biol. 2007 Apr; 131 (2): 214-25

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Cobb. et al. The argument for lightwieght polypropyle mesh in hernia repair. Surg Innov. 12 (1):63-69. (2005)

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Biocompatible: monocryl layer reduce inflammatory response and tissue l’integration. Reduces Shrinkage effect]

Pascual et al. Surgery. (2008) 144 (3). Junge et al. Hernia (2005) 9:212. Ethicon Inc.

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B. Fatton, J. Amblard, P. Debodinance, M. Cosson, B. Jacquetin, Transvaginal repair of genital prolapse: preliminary results of a new tension-free vaginal mesh (Prolift TM technicque) a case series multicentric study. Int/ Urogynecol J (2007) 18:743:752

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Reaction Notified Body: Tüv Austria

- “The article did not clarify the continuous misunderstanding that the conversations only related to your flawed product documentation.”
- “Despite multiple requests, no product sample was provided.”
- “At 21:45 of the video the TÜV AUSTRIA expert explained that ‘non-conformities' had been found in the documentation *(14)*”
- “These 14 important objections were however not taken up by the narrator. Your broadcast creates the impression that your team has accompanied the whole certification process.”
- “Therefore, Radar TV's assertion that the product presented in the broadcast could ever receive a CE mark is incorrect.”

Critical ‘Non-Conformities’

- **The clinical evaluation report is not in line with the requirements of MedDev 2.7.1 Rev3. A systematic approach is missing.**
  The clinical evaluation did not even meet the formal requirements required to start a review of the contents with the involvement of medical experts.
- **There is no document available proofing the fulfilment of the Essential Requirements.**
  This essential document required for the CE marking was missing. Among other aspects, these essential requirements also pertain to the biocompatibility of the material used and the aspect of sterility.
- **The complete risk management dossier is missing.**
  A fundamental analysis of the product risks is missing, which must be drafted as a risk management file.

- *As stated after the fact…*

Call for action

- Many, many more lawsuits:
  - 100,000 worldwide on mesh implants
  - + PIP breast implants
  - + metal-on-metal hip implants
  - + surgical staplers
- 2011: Institute of Medicine, ‘after 35 yrs 510(k)’ -> develop a new regulatory framework*
- 2012: FDA -> *postmarket surveillance studies:* -> address safety and effectiveness of mesh kits (prolapse and single-incision slings)
- 2016 : EU MEDDEV 2.7/1 revision 4 -> demonstration of conformity with Essential Requirements must include a clinical evaluation
- April 2019: FDA orders full stop of pelvic mesh sales

* Institute of Medicine. 2011. *Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years*. Washington, DC: The National Academies Press. doi:10.17226/13150.

Upgrading MDD to MDR: Sep 2007 → May 2020/2021

12. 7. 93 Official Journal of the European Communities No L 169/1

II

(Acts whose publication is not obligatory)

COUNCIL

COUNCIL DIRECTIVE 93/42/EEC

of 14 June 1993

concerning medical devices

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 100a thereof,

States to manage the fund
sickness insurance schemes re
to such devices; whereas, ther
affect the ability of the Meml
abovementioned measures pr
complied with;

5.5.2017 EN Official Journal of the European Union L 117/1

I

(Legislative acts)

REGULATIONS

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)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 114 and Article 168(4)(c) thereof,

Global comparison

- No longer a *directive* with national implementations
- Full-fledged *law* in all EU member states

	MDD	MDR
Name	Council Directive 93/42/EEC	Regulation (EU) 2017/745
Effective date	14 June 1993	26 May 2021
# Articles	23	123
# Annexes	12	17
# Pages	~60	~175

from 'Comparison of the articles of the MDD and MDR', BSI group

Big impact… for you?

“Epilobium hirsutum - Seed head - Triptych” by © User:Colin / Wikimedia Commons

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Vendor viewpoint

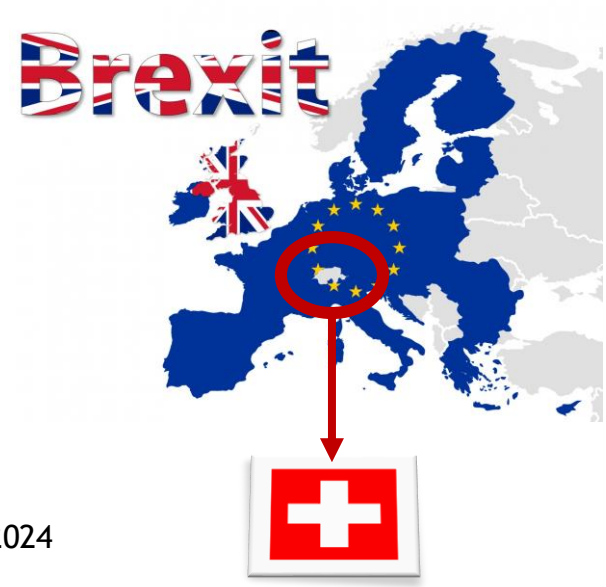
- Grace period for MedDev under MDD, expires 25 May 2024
- EU law -> facilitates sales in whole of Europe (?)
- Additional administration — Design, risk analyses, testing, verification, validation, …
- Post Market Surveillance (MDR Art.2) — A proactive and systematic process .. to take Corrective And Preventive Action (CAPA) in accordance with information on medical devices and their performance.
- Post Market Clinical Follow-up — A continuous process that updates the clinical evaluation .. addressed in PMS plan.
- Central database EUDAMED — + update *Summary of Safety and Clinical Performance*
- Unique Device Identification — EU/Global labelling *device, packaging, manufacturer*
- Appoint or have direct access to a — Person Responsible for Regulatory Compliance (PRRC)

No Intended Medical Purpose, but under MDR (Annex XVI)

- Coloured, non-corrective contact lenses or other items that are applied directly to the eye
- Products that must be inserted into the human body through surgical means to modify anatomy or fixate body parts. Ex. Cosmetic horn implants
- Substances, or items to be used for facial or nasal cosmetic purposes. Ex: dermal fillers.
- Equipment intended to aid in the reduction of adipose tissue. This equipment includes tools used for liposuction or lipolysis.
- High intensity electromagnetic radiation emitting equipment used on human skin, including tattoo or hair removal, skin resurfacing, or other skin treatment.
- Equipment used to penetrate the skull in order to modify neuronal activity using electrical currents or electromagnetic fields (transcranial magnetic stimulation)

And then there was the EXIT…

- Brexit:
  - MDR does not apply
  - UKCA (UK Conformity Assessed) mark
  - UK products need EU representatives
  - UK Notified Bodies no longer EU-qualified



- Swixit
  - Mutual Recognition Agreement (MRA) with 3rd countries
  - E.g. on good manufacturing practice (GMP), inspections, etc.
  - Modification: existing devices valid until 26 May 2024
  - Was not agreed upon… → Switzerland considered a "*third country*"
  - Swiss Authorized Representative (CH-REP) required for:
    - CE-marked medical devices under the new MDR
    - Legacy devices
  - CE-mark from Swiss-based Notified Bodies no longer valid after May 26, 2024

- When in doubt: ask your vendor/distributor!

Vendor -> Buyer

Created by Nociconist
from Noun Project

Created by Graphic Enginer
from Noun Project

Some consequences

- Extra documentation needed (e.g. Clinical Evidence)
- Not enough Notified Bodies
- Delay in devices becoming available
- Vendors withdrawing due to MDR burden
- UK/CH vendors not transitioning to EU

- Improving safety with MDR?

- Post-Market Surveillance

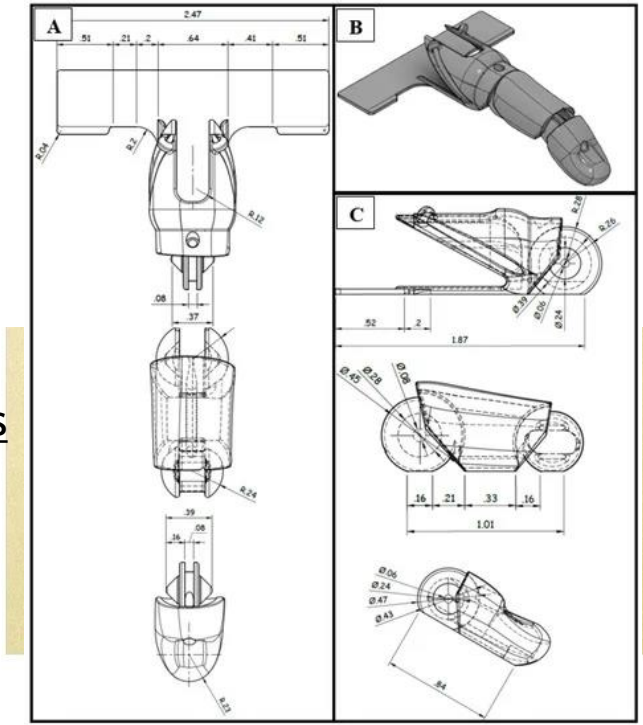
Buyer / Clinical User

- Only CE-marked medical devices allowed to “put into service”
  - *Showing* non-compliant devices is allowed (e.g. exhibitions, demonstrations)
- Unless:
  - ‘Custom-Made Device’ (CMD), no CE-mark
  - In-house development
  - As Investigational Device (clinical trial)

Custom-Made Device (CMD)

MDR Article 2(3):

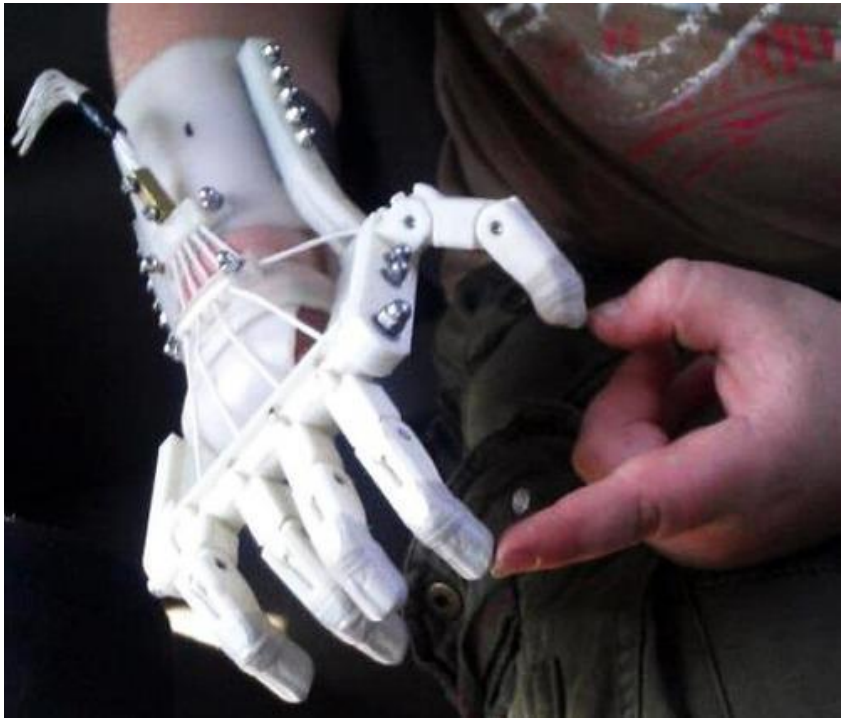
- Specifically made .. with a written prescription
- of any person authorised by *national law*
- by virtue of that person's professional qualifications ..
- which gives .. specific design characteristics,
- and is intended for the sole use of a particular patient
- exclusively to meet their individual conditions and needs



CMD - 3D Printing

“5. Does a 3D printed device (additive manufacturing) qualify as a CMD?”

- Not by default; needs assessment per case
- It is when:
  - written prescription, patient specific design, authorised person
  - sole use of a particular patient, individual conditions and needs,
  - not mass-produced.



MDCG 2021-3 - Questions and Answers on Custom-Made Devices
https://ec.europa.eu/health/system/files/2021-03/mdcg_2021-3_en_0.pdf

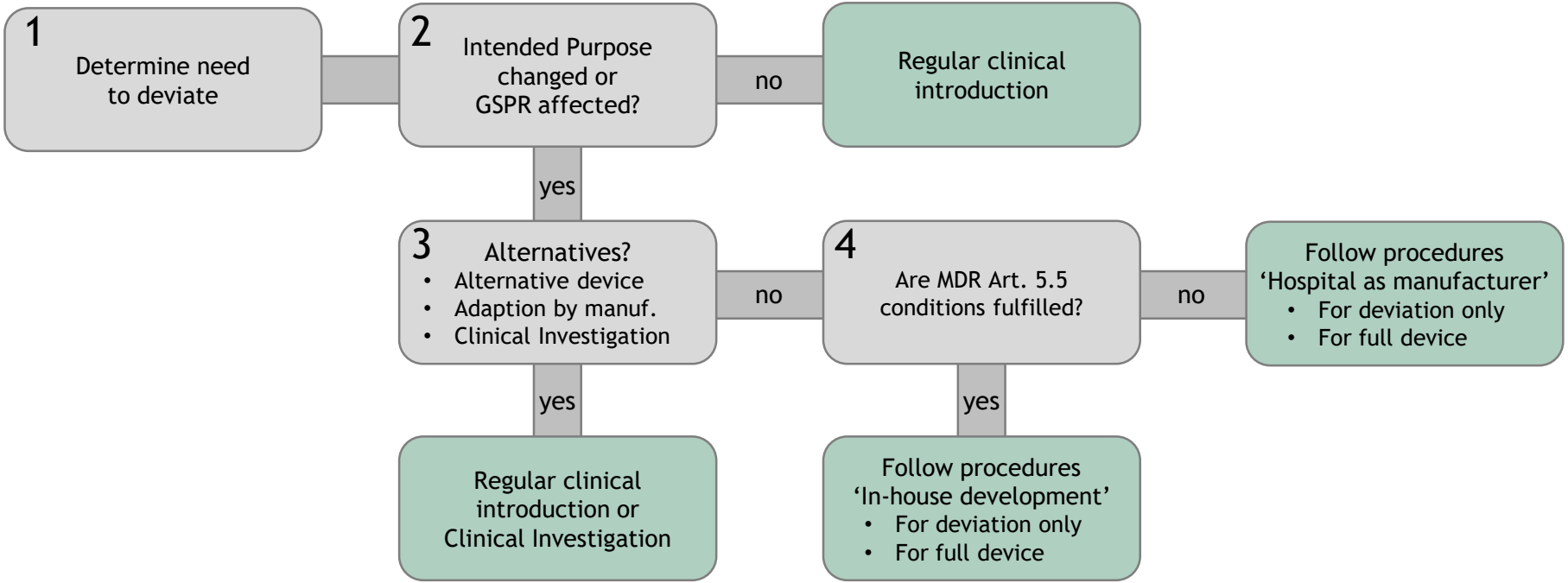
CMD - prescription

“6. What defines a written prescription containing patient specific design characteristics?”

- At minimum, it should contain:
  - the name of the patient (or pseudonym if relevant),
  - specific design characteristics, unique to the patient’s anatomic-physiological features and/or pathological condition.
- additions can accompany and constitute specific design characteristics:
  - models (physical or 3D model data),
  - moulds (e.g. for dental or orthotic purposes),
  - dental impressions, ++
- Note: dimensions, geometric parameters (eg. DICOM CTs) alone not specific design characteristics. Additional measured data/information needed to be CMD.

MDCG 2021-3 - Questions and Answers on Custom-Made Devices
https://ec.europa.eu/health/system/files/2021-03/mdcg_2021-3_en_0.pdf

Deviate from instructions manufacturer



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In-house development…
Radiotherapy's Playground

- 'Tinkering' to fix stuff common in RT.
- For single patient? No? → 'development'
- But allowed according to MDR (30):

> "Health institutions should have the possibility of manufacturing, modifying and using devices in-house…"

- However, you're shifting from *user* to *manufacturer*…!

MDR Art. 5.5 : non-CE-marked MD

Only when:

- within own institution (legal entity)
- developed under appropriate Quality Management System
- no equivalent device available on the market
- make details publicly available
  - checklist General Safety and Performance Requirements (Annex I, 23 items, 14 pages!)
- design, performance, manufacturing, etc. (i.e. ‘Technical Documentation’)
- review clinical use, take corrective actions (‘Postmarket Surveillance’)

But is it a Medical Device?

MDR: ‘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 (→ IVDR)

… and ‘devices for the control or support of conception’

… and ‘products specifically intended for the cleaning, disinfection or sterilisation’ of MDs

ER(ik):

A Medical Thing...

… and then some

‘accessory for a medical device’

- means an article which, whilst not being itself a medical device, is intended by its manufacturer
- to be used together with one or several particular medical device(s)
- to specifically enable the medical device(s) to be used in accordance with its/their intended purpose(s)
- or to specifically and directly assist the medical functionality of the medical device(s) in terms of its/their intended purpose(s);

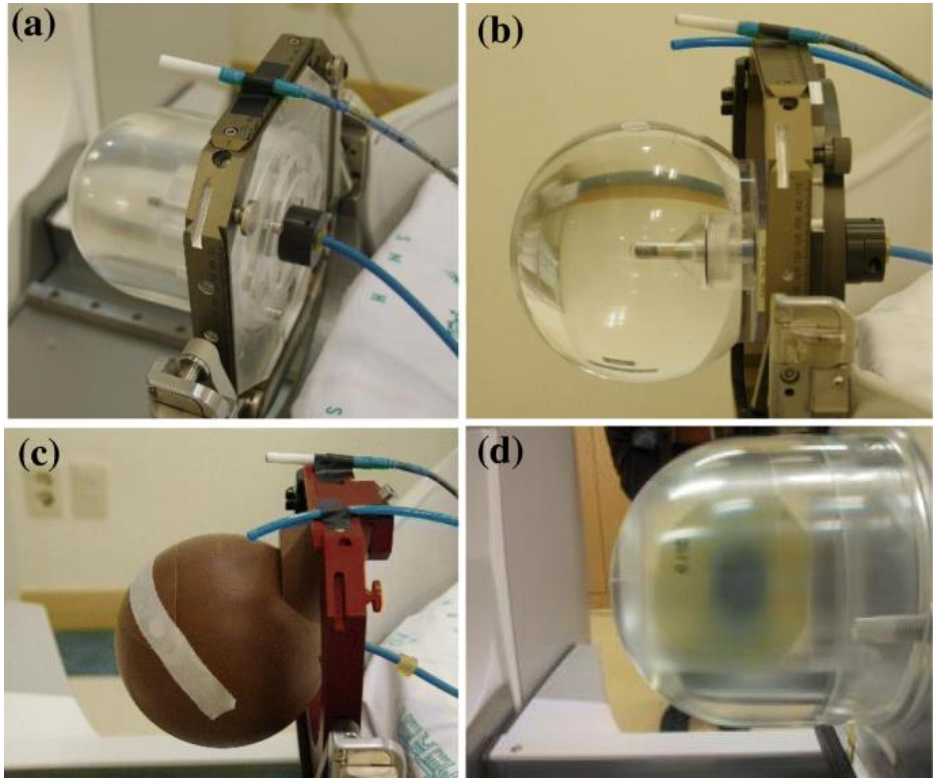
MDR applies to
accessories as well.

… and then some more

What about QA phantoms?
- Used for commissioning, not for treatment
- Not provided by manufacturer (e.g. of linac)
- Not an accessory either…

Equivalent to ‘Tool’ ?
- In software development
- ISO 13485, ISO/TR 80002-2
- Needs ‘Tool validation’…

‘Good Manufacturing Practice’



Chung JP., et al., Radiation Oncology, 2018, doi:10.1186/s13014-018-1117-8

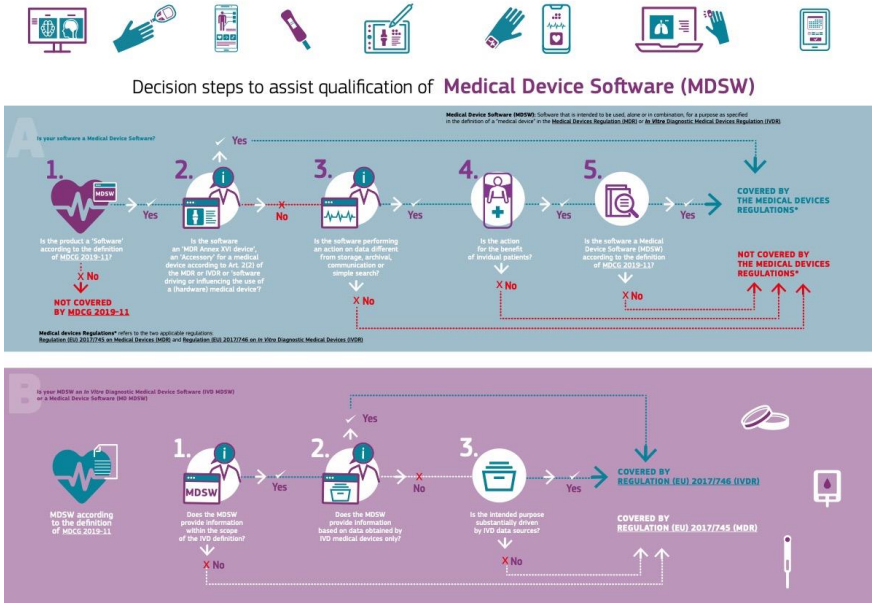
Guidance documents

- Medical Device Coordination Group (MDCG)
  - https://ec.europa.eu/health/md_sector/new_regulations/guidance_en

- International Medical Device Regulators Forum (IMDRF)
  - https://www.imdrf.org/

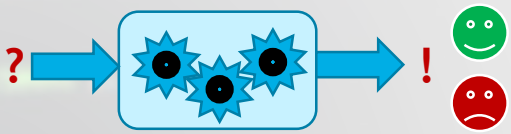
- E.g. is this a Medical Device? What (risk) class is it?
- Custom-Made, Patient-matched, Intermediate Devices,
- Clinical Evaluation, Equivalence, Significant changes…

Is it a Medical Software Device ?



How about Excel sheets, scripting?

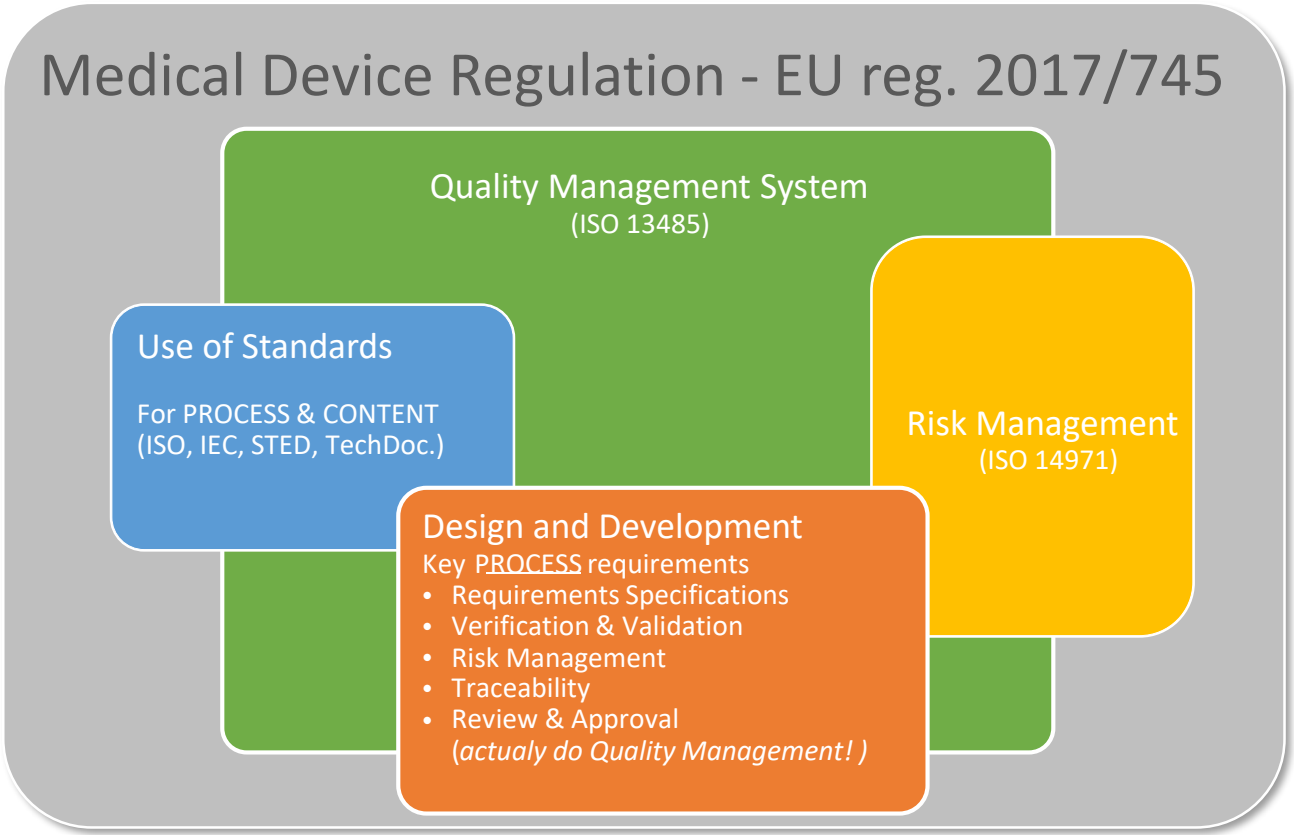
- That is Software per definition of MDCG
  - *"**Software** is defined as a set of instructions that processes input data and creates output data."*
- What is done with the results?
- Used in medical decision making? -> medical purpose…

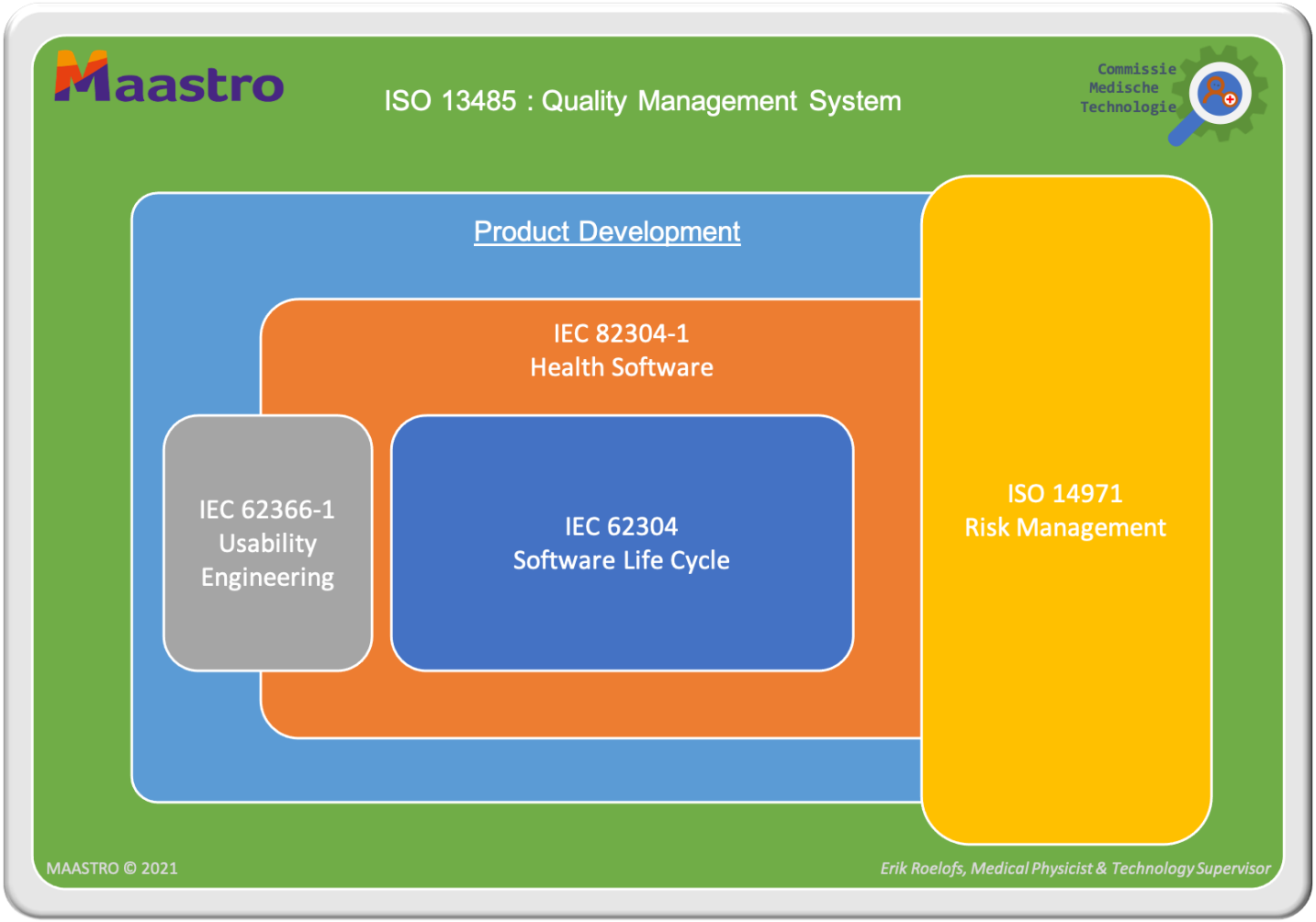


Quality Management System

- Standard: ISO 13485: not required, but good reference
- MDR Art. 5.5b suffices, but how different is it?
- Still needed to have
  - Proper coding practices -> instructions, SOPs
  - Design specifications
  - System Architecture
  - Build procedures
  - Verification
  - Validation
  - Risk assessment
  - Reports -> audit trail

‘Appropriate’ Quality Management System

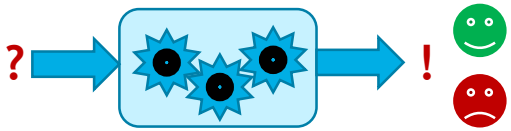




40
DSMF
Dansk Selskab for Medicinsk Fysik

Risk classification

- MDR: ‘Up-classified’ Class I -> Class IIa (++)
- Extra focus on Decision Support Systems
- Perform Design FMEA (not hFMEA → Processes)
- Multidisciplinary team
- Assign a Person Responsible for Regulatory Compliance (-like role)



RISK ANALYSIS					RISK CONTROL									
1. ID #	2. Hazard (source) What are the main hazard sources in the system / use / study? *Consider hazards for patients, users, bystanders, property and environment* See tab 'Examples of Hazards'.	2a. Initiating events & components What leads to the hazardous situation? Under which circumstances? *Include the root cause/component in the description and describe how it leads to the hazardous situation* See tab 'Examples of Initiating Events'.	3. Hazardous situation *Describe the situation just before actual harm or damage to the use environment occurs* See tab 'Examples of Hazards and Harm'	3a. Harm What may happen to the patient / user / others / property / environment? *Harm should be damage to the body/health or damage to the use environment* See tab 'Examples of Hazards and Harm'.	4. Initial Risk Probability	Severity	Risk (S&P)	5. Mitigation / risk control measures Describe the intended design changes or protective measures to lower harm probability and/or harm severity	6. Reference to the requirement specifications Document ID + Requirement Number that describes mitigation.	7. Reference to verification/validation reports Document ID + Test nr. of the verification/validation test report.	8. Residual risk Probability	Severity	Risk (S&P)	8a. Residual risk acceptable? Add rationale when residual risk level is unacceptable, but the risk/benefit ratio is deemed acceptable.
					Legend: 0 = Improbable 1 = Remote 2 = Occasional 3 = Probable 4 = Frequent		Legend: 1 = Negligible 2 = Marginal 3 = Critical 4 = Catastrophic							
Device / System Design														
Note:	Basic assumptions and exclusions for this risk analysis are: EXAMPLES 1. The system will not be connected to devices for patient treatment (e.g. LINAC system) 2. This study will not have an impact on the patient treatment itself (e.g. delivered dose or treatment planning) 3. Data output will not be used for diagnostic / therapeutic purposes 4. Data output will be checked or analyzed by a research specialist before it will be used for further research purposes													
1.00	Software													
1.01							?					?		
1.02							?					?		
							?					?		
2.00	Function / integration													
2.01							?					?		
2.02							?					?		
Usage related														
							?					?		
3.00	User error													
3.01							?					?		
3.02							?					?		
							?					?		
4.00	Labelling													
4.01														

QMS Documentation (~ISO 13485)

	Template	Document name	Type (abbr)	Tool*
4	**Quality Management System**			
	MTD-QM_04-01	Quality Manual	QM	
	MTD-SOP_04-01	Procedure Document and Record control	SOP-DRC	
	MTD-SOP_04-02	(Software) Tool Validation	SOP-TVL	
	MTD-SOP_04-03	Change Management	SOP-CM	
	MTD-TPL_04-01	Generic Document template	GEN-TPL	
	MTD-TPL_04-02	Qualification, Classification and Justification.	CE-QCJ	X
	MTD-FRM_04-01	General Safety and Performance Requirements checklist	CE-GSPR	
	MTD-FRM_04-02	IEC 62304 Checklist	CE-IEC	X
	MTD-FRM_04-03	(Software) tool validation level document	MTD_TVL-xx	X
	MTD-FRM_04-04	(Software) tool validation report	MTD_VLR-xx	X
	MTD-FRM_04-05	(Software) tool Asset form	MTD_STAF	
	MTD-FRM_04-06	Declaration of Conformity	CE-DOC	

*contributing to quality of medical device

Technical Documentation

7	**Product realization**		Type (abbr)	Tool
	MTD-TPL_07-01	User Requirement Document	URD	
	MTD-TPL_07-02	(Software) System Requirement Document	SRD	X
	MTD-TPL_07-03	(Software) Architectural Design Document	ADD	X
	MTD-TPL_07-04	Product Development plan	PDP	X
	MTD-TPL_07-05	Software Development Plan	SDP	X
	MTD-TPL_07-06	Risk Management Plan	RMP	
	MTD-TPL_07-07	SOUP Risk Assessment	RM-SRA	
	MTD-TPL_07-08	Legacy Risk Assessment	RM-LRA	
	MTD-TPL_07-09	Hazard Analysis Report	RM-HAR	X
	MTD-TPL_07-10	(Software) Test Case Specification (Unit, System)	TCS (-U, -S)	X
	MTD-TPL_07-11	(Software) Test Case Report (Unit, System)	TCR (-U, -S)	X
	MTD-TPL_07-12	Product Release Notes	PRN	X
	MTD-SOP_07-01	Product Development process	SOP-PD	
	MTD-SOP_07-02	Software Development process	SOP-SD	
	MTD-SOP_07-03	Risk Management process	SOP-RM	

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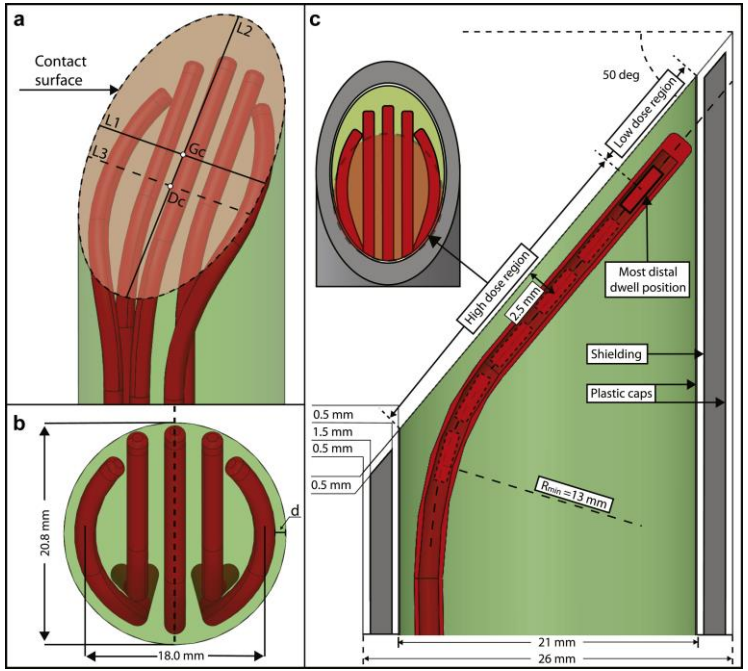
Example: the Maastricht Applicator (aka. ‘Flower’)

- Endoluminal brachytherapy boost
- MAASTRO R&D, Varian picked up
- Facing long delays, thanks to MDR (+Corona)
- Marketing under 510(k) -> equivalence
- Perform Clinical Trial (MAASTRO)
- Biocompatibility testing issues (*labs*)

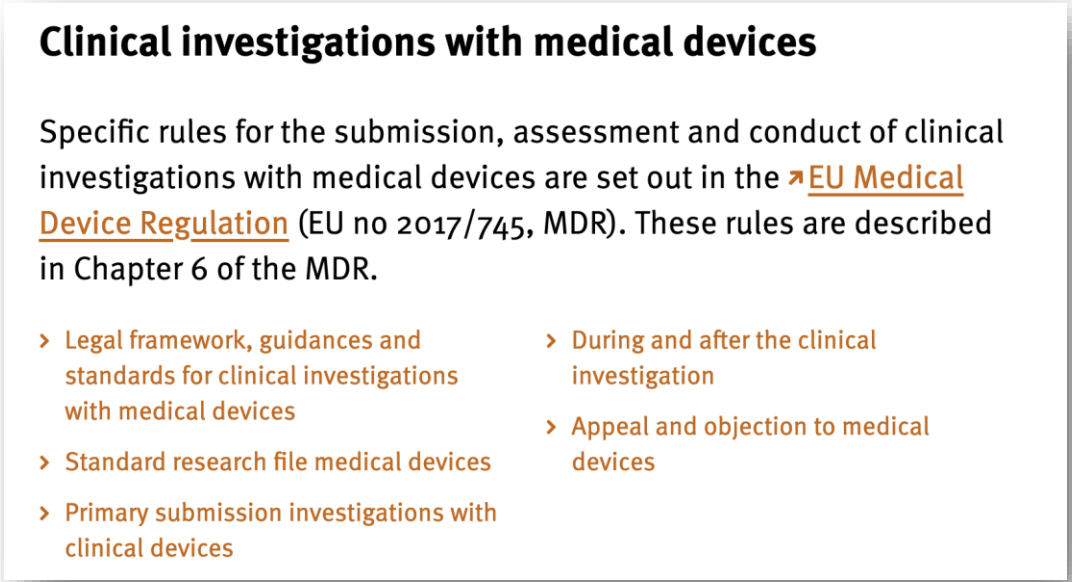
- MDR: Time-to-market increases…



Murrillo, B, et al., Brachytherapy, 2020, doi:10.1016/j.brachy.2020.03.009
Berbée M, et al., Future Medicine, 2019, doi:10.2217/crc-2019-0006
Bellezzo M., et al., Brachytherapy, 2018, doi:10.1016/j.brachy.2018.07.012
Poon E., Med Phys, 2006, doi:10.1118/1.2364054

Medical Research Ethical Committee

- Require Investigational Medical Device Dossier (IMDD)
- By vendor with clinical investigator
- Looks a lot like ‘CE-marking’
- Except for the Clinical Trial
- MREC’s stalled decisions until MDR
- Newly installed MedDev Experts
- Grey areas: e.g. wearables, apps



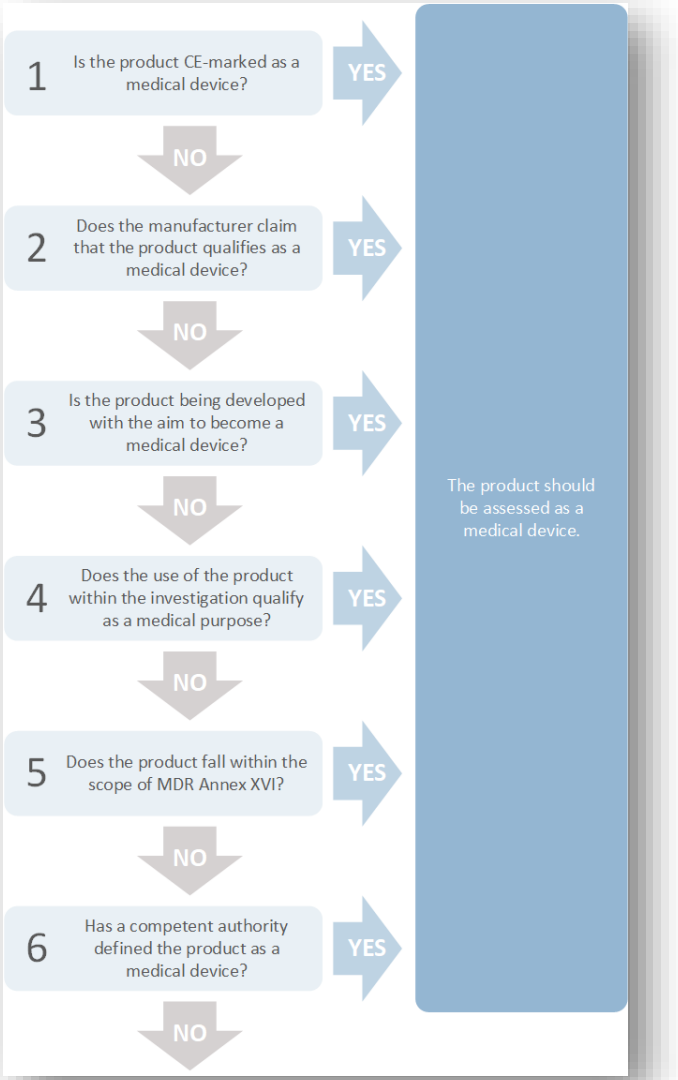
Clinical investigations with medical devices

Specific rules for the submission, assessment and conduct of clinical investigations with medical devices are set out in the EU Medical Device Regulation (EU no 2017/745, MDR). These rules are described in Chapter 6 of the MDR.

- Legal framework, guidances and standards for clinical investigations with medical devices
- Standard research file medical devices
- Primary submission investigations with clinical devices
- During and after the clinical investigation
- Appeal and objection to medical devices

https://english.ccmo.nl/investigators/clinical-investigations-with-medical-devices

Flowchart CCMO



https://english.ccmo.nl/investigators/clinical-investigations-with-medical-devices

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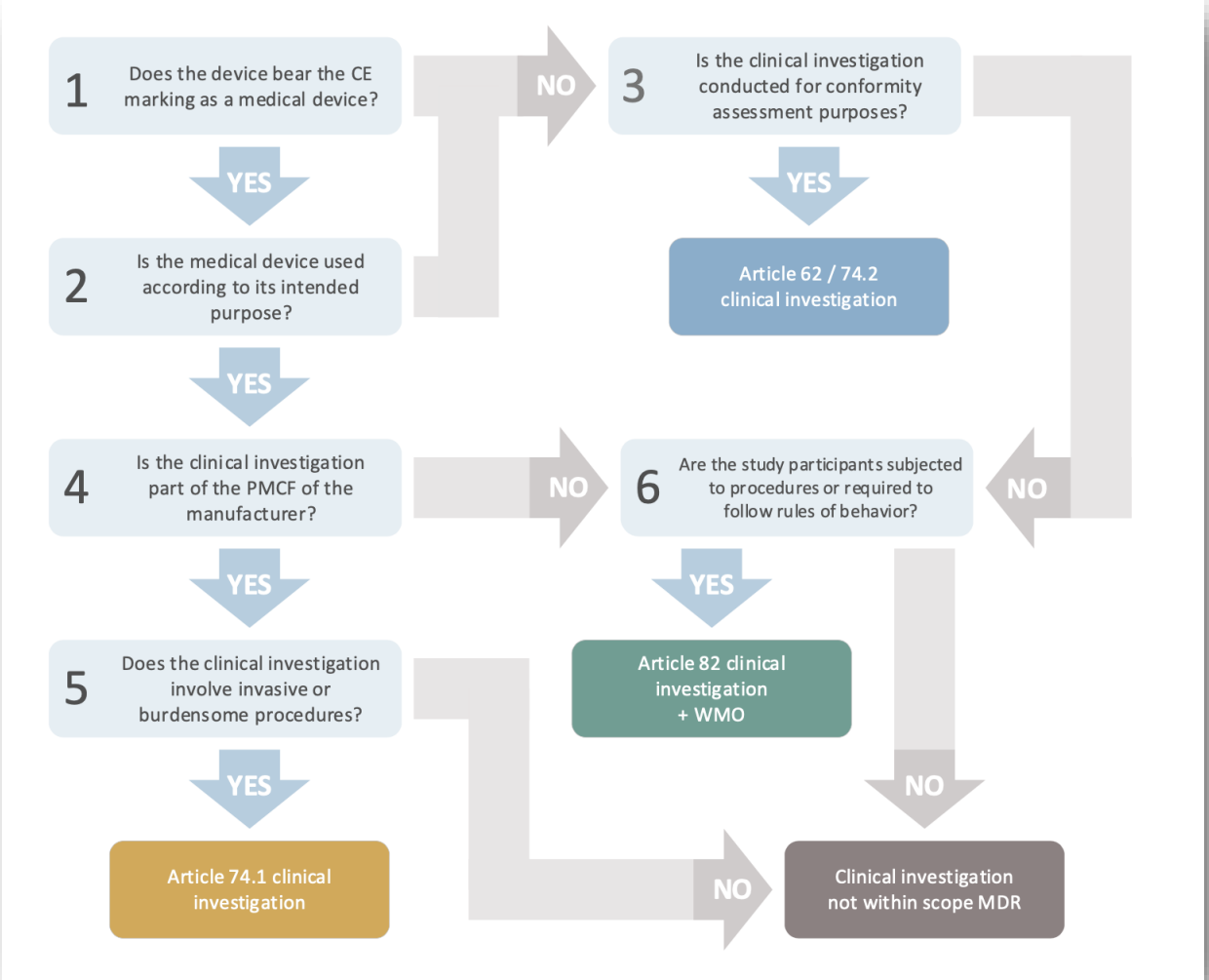


https://english.ccmo.nl/investigators/clinical-investigations-with-medical-devices

Article 62

A non-randomized feasibility study in which a prototype of a venipuncture device is tested. The primary outcome parameters are the feasibility (number of successful automated venipunctures) and the safety (number of adverse events and number of adverse device events).

A spin-off company developed an improved magnetic seed and detector for the localization of early stage (non-palpable) breast cancer. The objective of the clinical investigation is to show that the novel technology is safe and performs as intended.

Article 74.1

Consider a surgically invasive CE-marked medical device used within its intended purpose to fixate some thoracic vertebra in juvenile patients suffering from severe scoliosis. The manufacturer designs a clinical investigation as part of its PMCF plan to evaluate the medical device's performance in a real-life situation.

An extra CT-imaging (radiation exposure of 5 mSv) will be performed from the onset of the follow-up and repeated every two years for a period of six years. Clearly, the CT-imaging is considered an additional burdensome procedures additional to the normal conditions of use of the medical device.

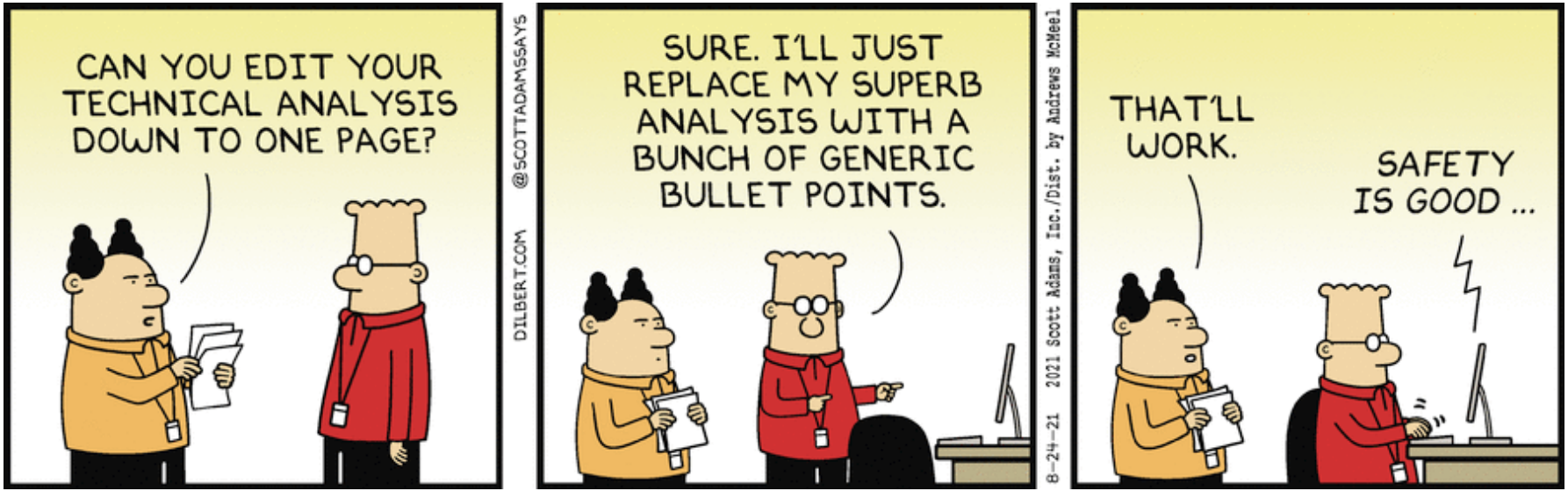
Article 74.2

The manufacturer of a “self-expandable metal stent” CE-marked to be used for the treatment of pancreatic pseudocysts wants to conduct a feasibility study to investigate the safety and technical performance of this stent used during endo-echoscopic gall bladder drainage in patients with acute cholecystitis.

Article 82

Clinical investigations for other purposes than the purposes mentioned in Article 62 or 74.

Article 82 investigations can for instance include clinical investigations with in-house medical devices, custom-made medical devices and investigator-initiated investigations with CE-marked medical devices.



https://dilbert.com/ Tuesday August 24,2021

Some useful links

- Regulation (EU) 2017/745 on medical devices (MDR): https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02017R0745-20200424
- MDCG endorsed documents and other guidance: https://ec.europa.eu/health/md_sector/new_regulations/guidance_en
- Quickscan: Medical Device or not? (in Dutch) : https://cetool.nl/medisch-hulpmiddel/quickscan/
- CCMO: research with medical devices:
  - https://english.ccmo.nl/investigators/clinical-investigations-with-medical-devices
  - https://english.ccmo.nl/investigators/clinical-investigations-with-medical-devices/legal-framework-guidances-and-standards-for-clinical-investigations-with-medical-devices/what-is-a-medical-device
- Medical Device Software or not? https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_mdcg_2021_mdsw_en.pdf

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