In Silico Regulatory Science for the Digital Era

Safer, Faster, and More Sustainable Medical Devices for Better and More Equitable Care

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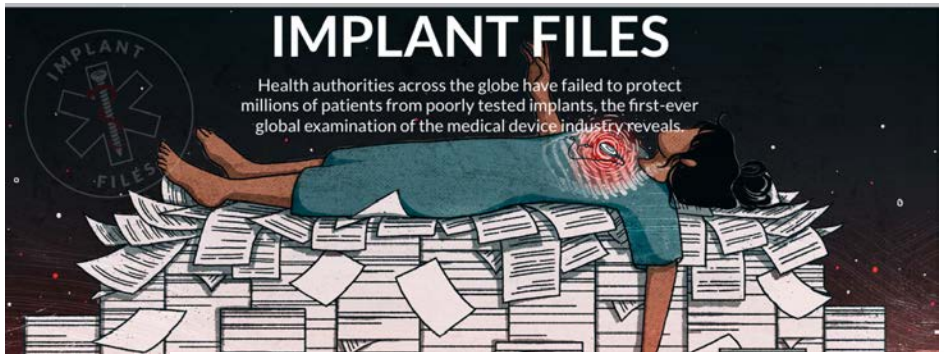
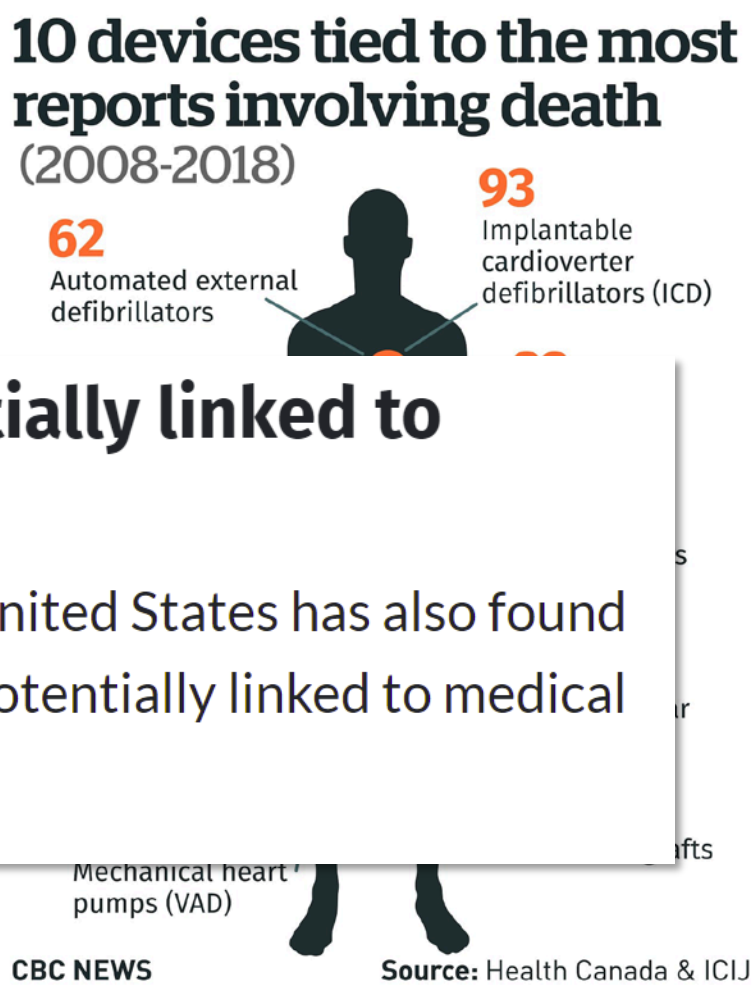
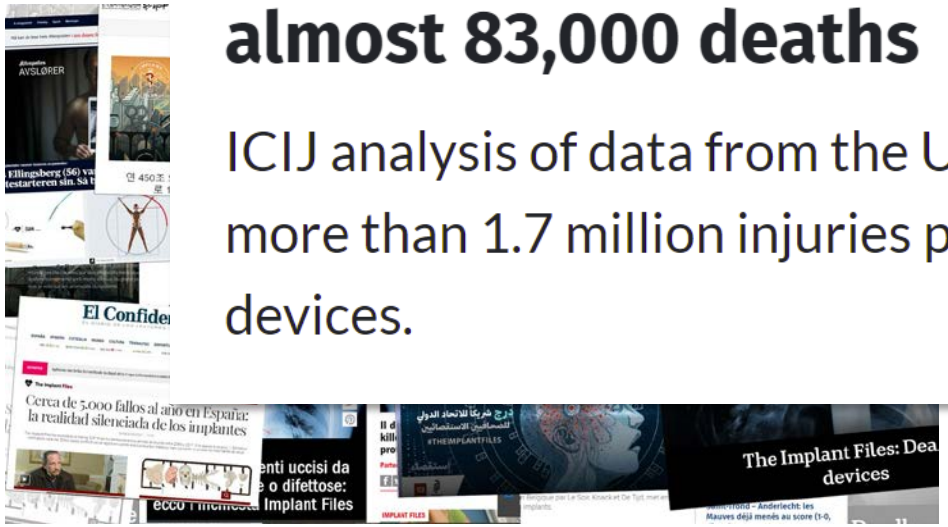
Euro-CASE


Rule #1
Do No Harm

First Do not Harm - revisiting patient safety







www.icij.org/investigations/implant-files/

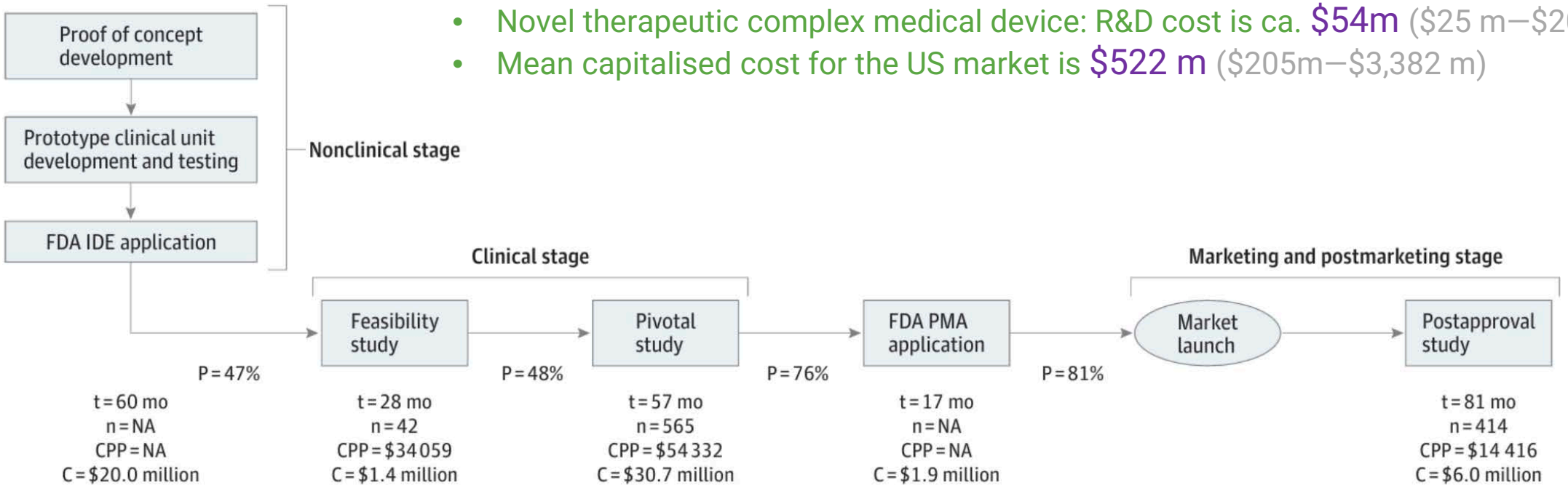
www.immdsreview.org.uk

Therapeutic Complex Medical Device

Development Stages

- Novel therapeutic complex medical device: R&D cost is ca. $54m ($25 m—$200 m)
- Mean capitalised cost for the US market is $522 m ($205m—$3,382 m)

Figure 1. Stages of Therapeutic Complex Medical Device Development



In this flow, these are costs that do not incorporate the cost of capital or failure, or removing the phase probabilities. C indicates phase cost (in $ 2018); CPP, cost per patient (in $ 2018); n, number of patients; NA, not applicable; P, phase transition success probability (%); t, phase duration (in months).

Sertkaya A, DeVries R, Jessup A, Beleche T. Estimated Cost of Developing a Therapeutic Complex Medical Device in the US. JAMA Netw Open. 2022 Sep 1;5(9):e2231609.

FDA-Approved High-Risk Device Mods Linked to Recall Spike

- Safeguarding Patient Safety: Tackling Device Recall Risks Through Enhanced Testing and Vigilant Surveillance
- Design Flaws Drive 30% of Recalls, Over Half of Class 1 Recalls – Likely an Underestimate.

Table 3. Top 5 FDA-Determined Root Causes of Recall[a]

	Total, No. (%)	
FDA root cause	Recalls	Class 1 recalls
Total No.	193 (100)	43
Device design	56 (29.0)	23 (53.5)
Process control	22 (11.4)	5 (11.6)
Software design	21 (10.9)	2 (4.7)
Nonconforming material or component	15 (7.8)	1 (2.3)
Under investigation by firm	13 (6.7)	3 (7.0)
Other	66 (34.2)	9 (20.9)

Dubin JR, Enriquez JR, Cheng AL, Campbell H, Cil A. Risk of Recall Associated With Modifications to High-risk Medical Devices Approved Through US Food and Drug Administration Supplements. JAMA Netw Open. 2023 Apr 3;6(4):e237699.

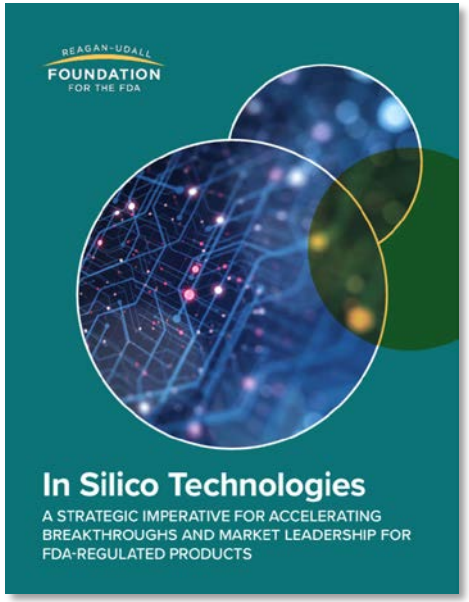
Computational Medicine – in silico trials/testing

Computational Medicine (aka in silico Medicine):
applying methods from engineering, mathematics and computational sciences to improve our understanding and treatment of human diseases Prof R Winslow, JHU.

In-silico testing/trials:

computer-based tests/trials using detailed prediction models on highly controlled virtual conditions or virtual cohorts

representing realistic operational conditions or target populations for the intended use



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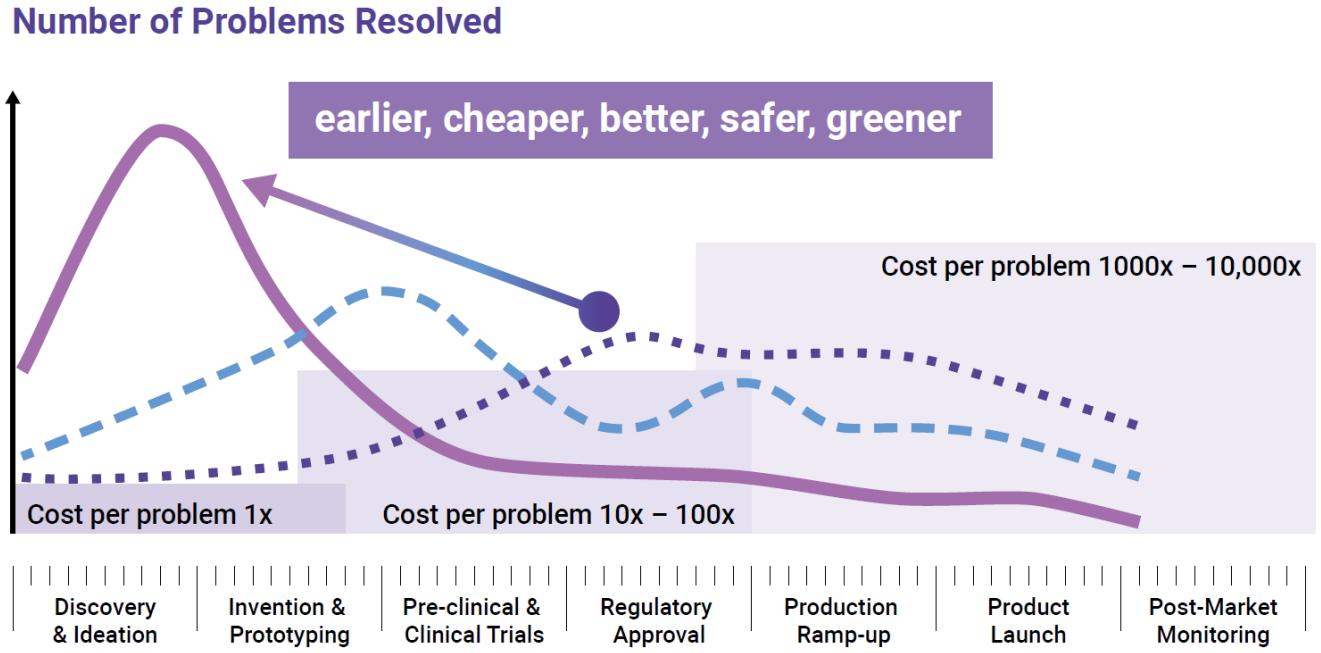
In Silico Technologies: A Strategic Imperative for Accelerating Breakthroughs and Market Leadership for FDA-Regulated Products. Reagan-Udall Foundation for the FDA, 2024 https://reaganudall.org/regulatory-science-accelerator-computational-modeling-simulation-cms-fda-regulated-products

First Do Not Harm ⇢ Simulation First?

The International Air Transport Association (IATA) estimates there was about a one-in-ten-million chance of dying in a commercial plane crash globally in 2022, or 0.00001% [1]

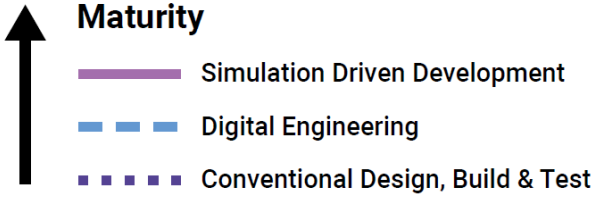
Analysis and reporting of adverse effects (AE) in randomised controlled trials (RCTs):

Recent RCT reports in high-impact medical journals often lack sufficient and consistent information, making it difficult to comprehensively analyse AE data and establish a clear safety profile [2]



Source: Adapted from J Lemon, ITI Global

The use of *in silico* methods can yield better results more quickly and economically.



1. Rodrigue J-P et al. (2020) The Geography of Transport Systems, Hofstra University, Department of Global Studies & Geography www.transportgeography.org
2. Phillips R et al. (2019) Analysis and reporting of adverse events in randomised controlled trials: a review. BMJ Open. 2019 Mar 1;9(2):e024537. doi: 10.1136/bmjopen-2018-024537.