DEFINITIONS AND PRACTICAL IMPLICATION OF UNMET NEEDS

Clinical trials and cardiovascular drugs: Are we lacking innovation and are we facing unmet needs?

Faiez Zannad, MD, PhD, FESC Emeritus Professor, Cardiology and Therapeutics,
Université de Lorraine and Inserm, France

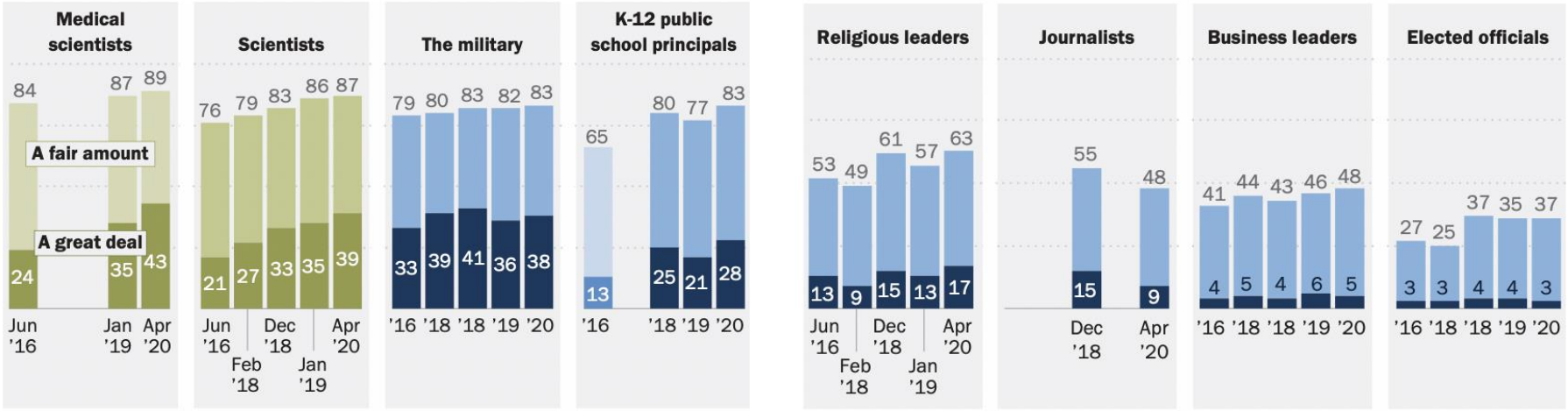
ESC-CRT Nov 22nd 2023

ESC
European Society of Cardiology

Disclosure

- Dr. Zannad reports personal fees for participation in advisory boards or clinical trials oversight committees from 89Bio, Applied Therapeutics, Bayer, Boehringer, BMS, CVRx, Cardior, Cereno pharmaceutical, Cellprothera, CEVA, KPB, Merck, Novartis, NovoNordisk, Owkin, Pfizer, Otsuka, Roche Diagnostics, Servier, US2.2 having stock options at Cardiorenal and Eshmoun Clinical research and being the founder of Cardiovascular Clinical Trialists Forum.

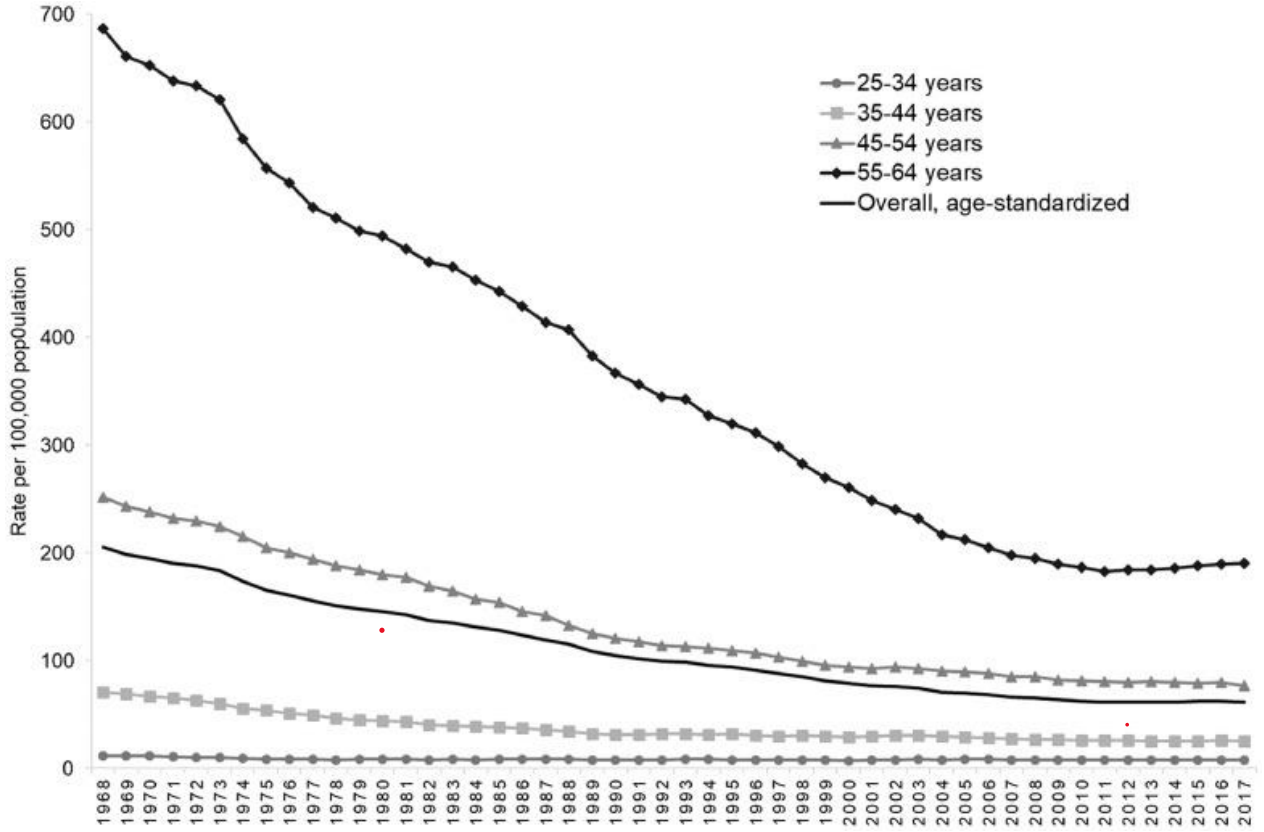
Medical Scientists are Most Trusted



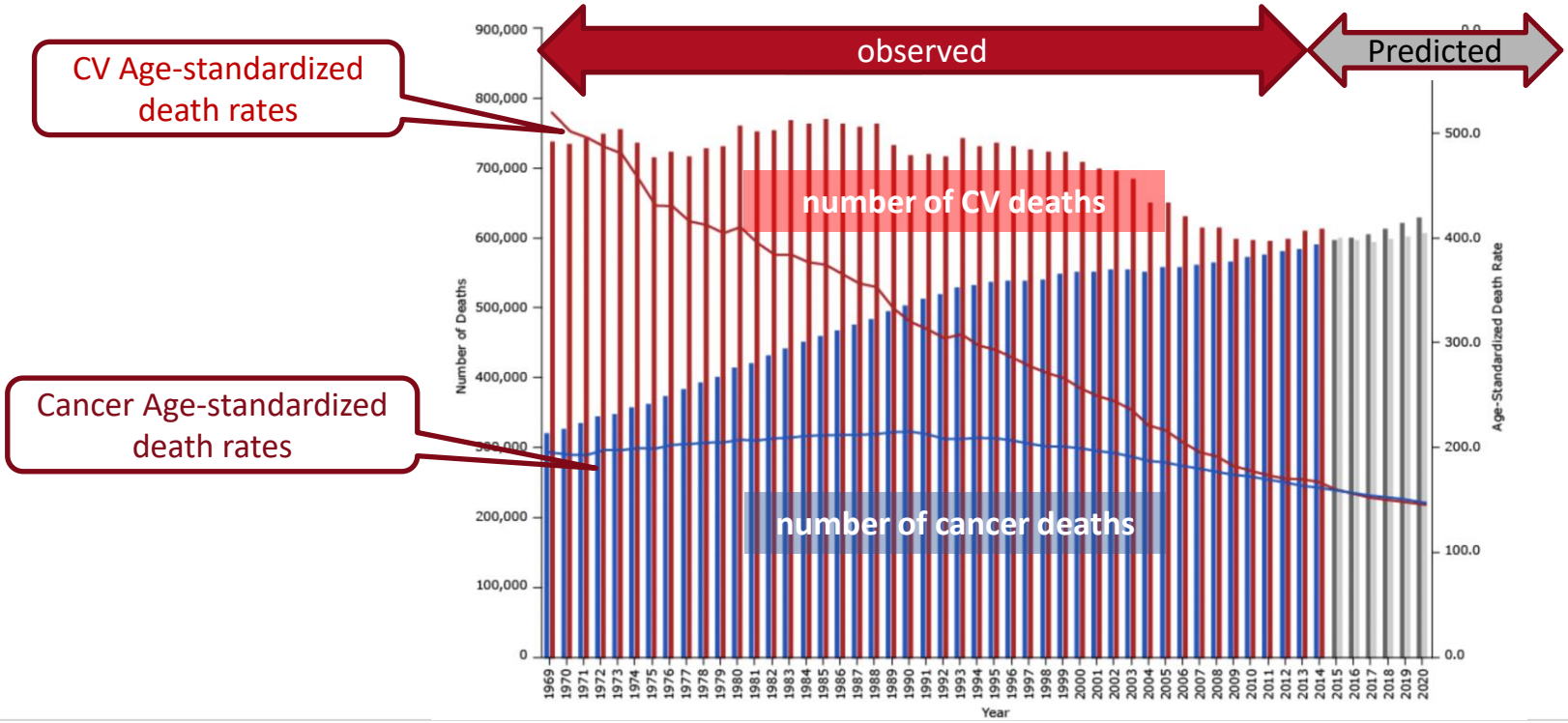
https://www.pewresearch.org/science

Trends in cardiovascular-related deaths

(Trends in Cardiovascular Medicine, August, 2020)



CV vs. Cancer moratlity
1969 - 2020 for men and women combined

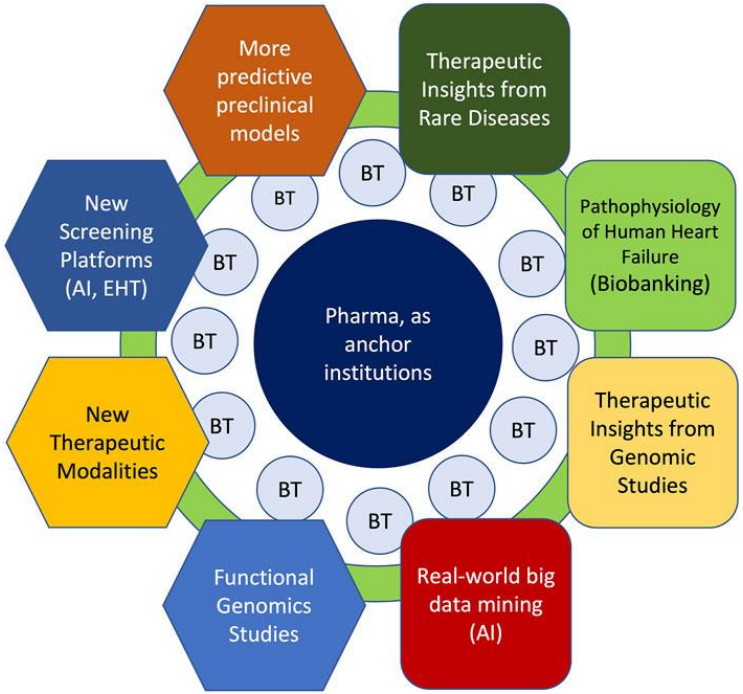


Unmet Medical Needs

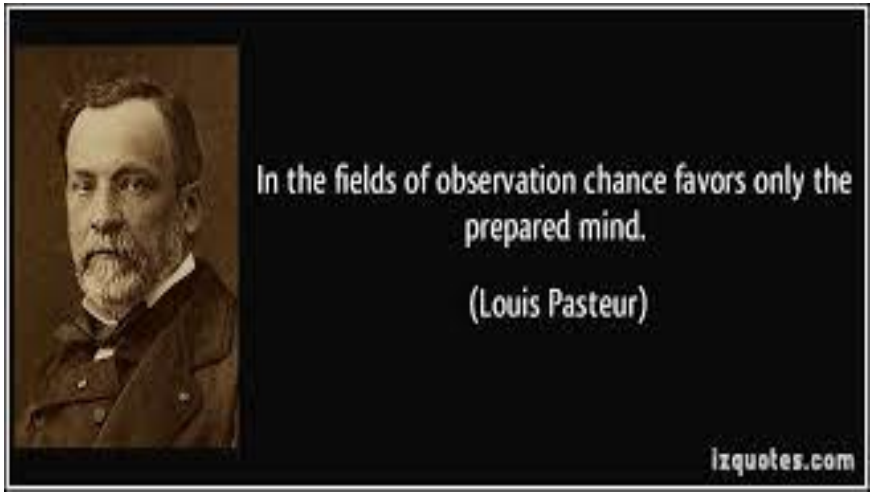
- **Do we lack innovative approved drugs?**
  - We can do a better job, but progress is tangible : New Lipid lowering (PCSK9), NOACS, ARNi, NS-MRAs, SGLT2is, GLP1RA, Iron, sGC ..)
  - We are doing a good job repurposing metabolic drugs
- **How is the pipeline?**
  - Not too bad: IL-6, Anti-inflammatory, Lp(a), XIa, Self Injecting with P2Y12 Inhibition ANGPTL3, ANGPTL4, PPAR-alpha A, Apolipoprotein C3 inhibitors, Lerodalcibep , FGF21, Gene editing, ASO/siRNA therapies for PCSK9 , mRNA, GIP, antiNPR1, CETP inhibition, Antisense Inhibition-angiotensinogen, aldosynthase inhibitors, Myotropes, HDAC, PAH disease modifiers…

Innovation is vibrant

Key Areas for Cardiovascular Drug Discovery Within the Context of Academia-Biotech-Pharma Ecosystem



Serendipity
« accident and sagacity while in pursuit of something else »

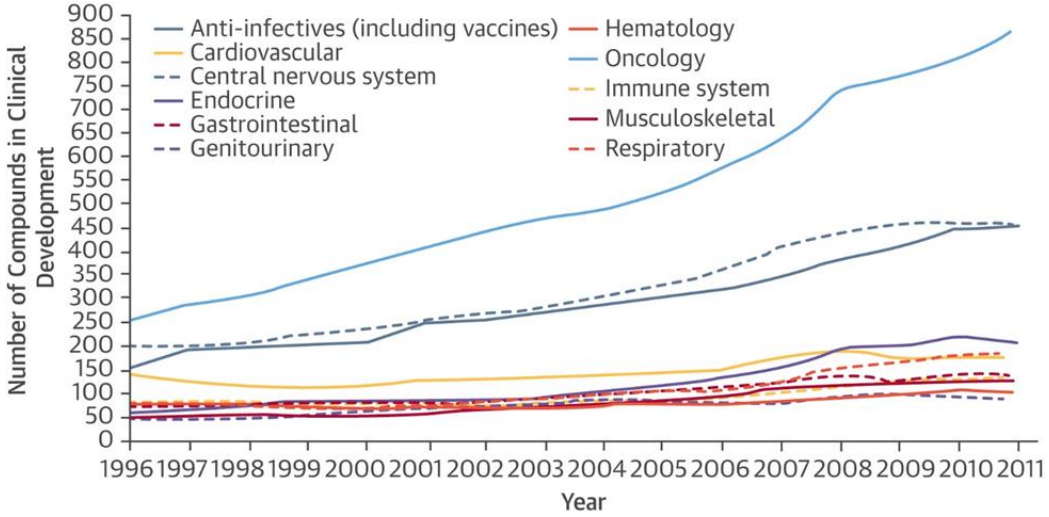


Unmet Medical Needs

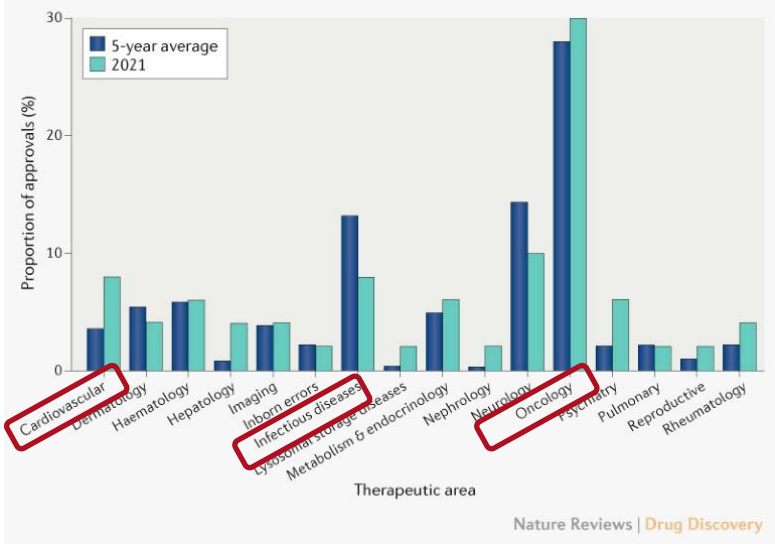
- **Is the rate of CV drug approval declining?**
  - Yes, comparatively to ”more rewarding” disease areas (Oncology, Orphan diseases)
- **Is the clinical trial enterprise less efficient?**
  - Yes : ISIS-2/GUSTO large, cheap, transformative, vs. costly trials for limited efficacy increments
- **Are the approved drugs being used?**
  - Many are not accessible to patients: Major problem with HTAs pricing policy
  - When accessible, poor implementation, Physicians inertia, and risk aversion

Drug products by specialty

Development

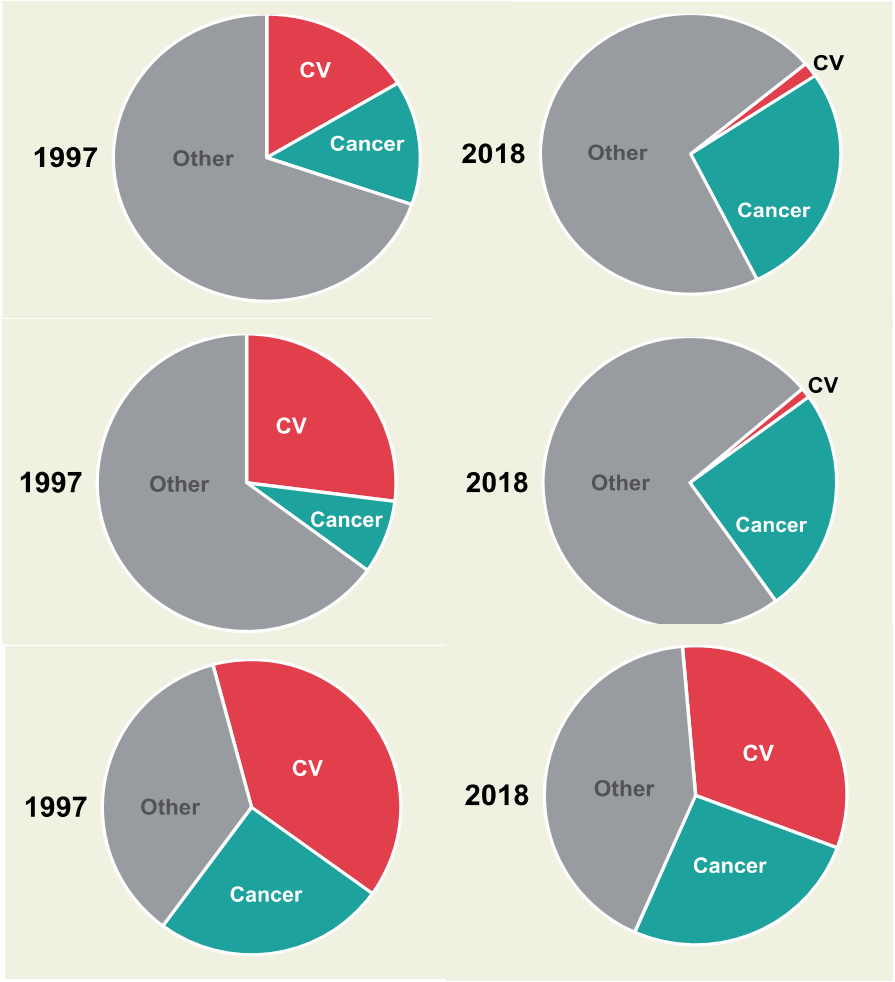


Approvals



Journal of the American College of Cardiology
Volume 65, Issue 15, 21 April 2015, Pages 1567-1582

Nature Reviews Drug Discovery 21, 83-88 (2022)
doi: https://doi.org/10.1038/d41573-022-00001-9



USA

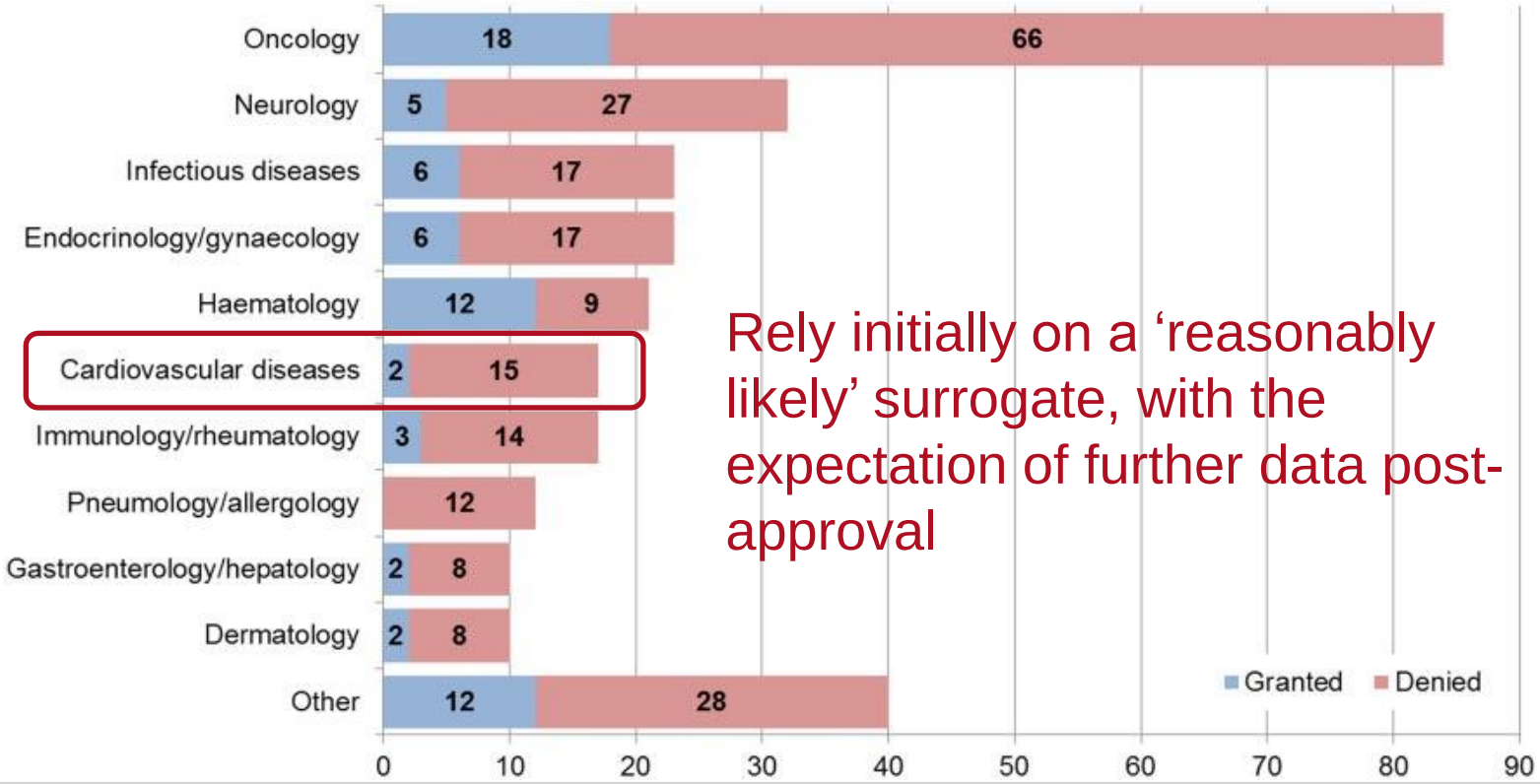
Drug approval by FDA

US drug Revenue

Proportion of deaths

https://www.ema.europa.eu/en/documents/report/human-medicines-highlights-2018_en.pdf

EMA PRIME priority medicines recommendations : 5 times more frequently activated for Cancer *vs.* CV

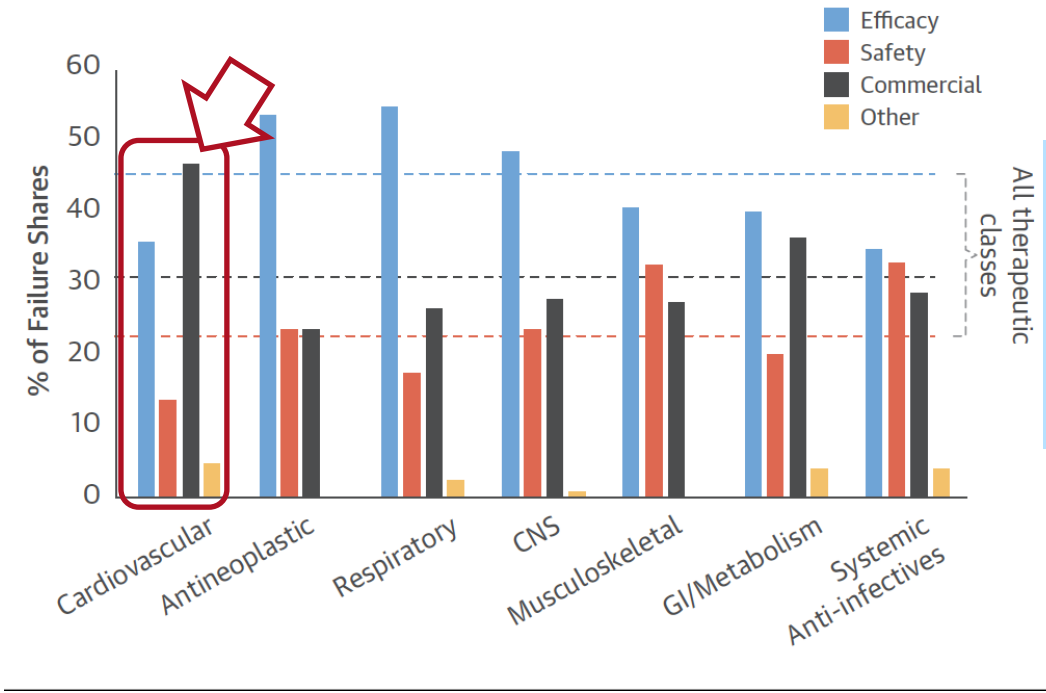


Rely initially on a ‘reasonably likely’ surrogate, with the expectation of further data post-approval

https:// www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines (14 September 2020).

Failures of CV drugs are mainly for commercial reasons

FIGURE 5 Drug Failures by Therapeutic Class, 2000 to 2009



UNMET NEED

- Access to market
- Drug valuation and pricing
- Implementation in clinical practice - Therapeutic Inertia

International Journal of Cardiology 365 (2022) 61–68

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

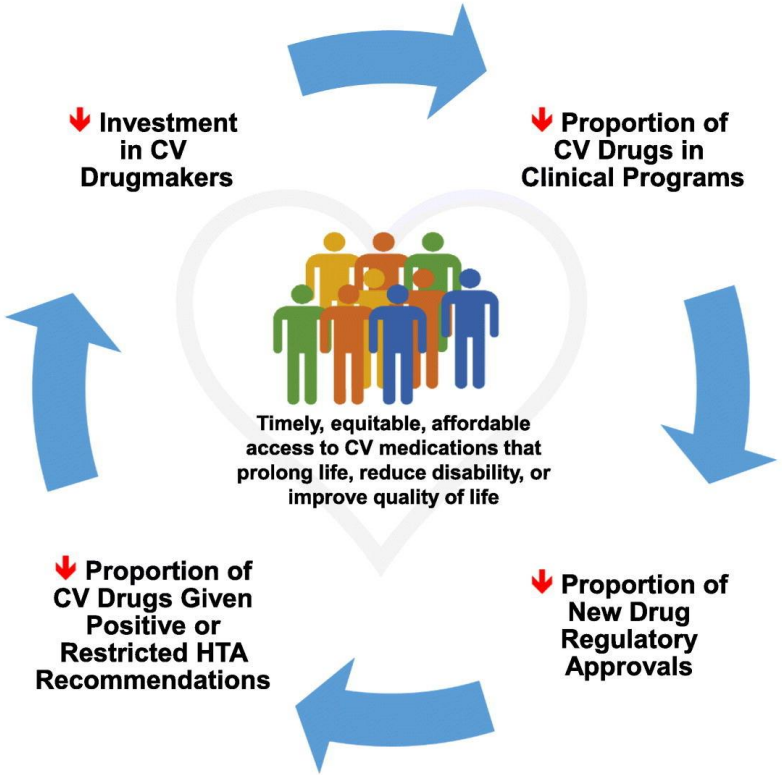
Review

How can we optimise health technology assessment and reimbursement decisions to accelerate access to new cardiovascular medicines?

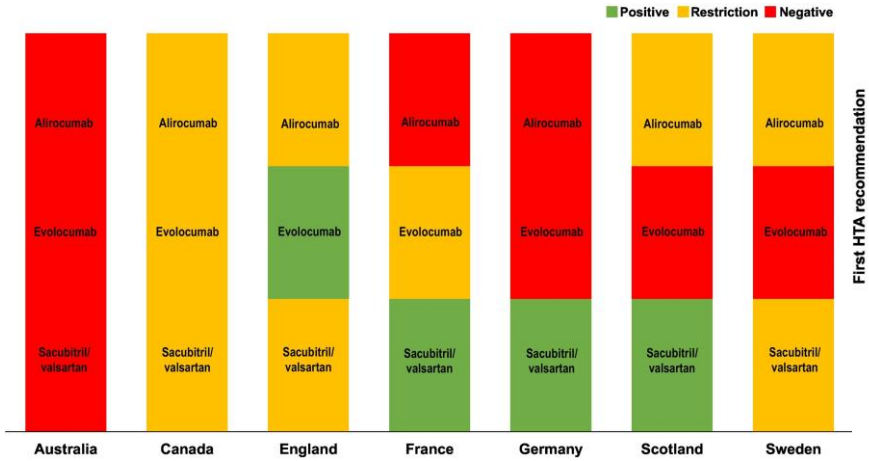
Martin R. Cowie [a,*], Biykem Bozkurt [b], Javed Butler [c], Andrew Briggs [d], Maria Kubin [e], Adrian Jonas [f], Amanda I. Adler [g], Bray Patrick-Lake [h], Faiez Zannad [i]

UNMET NEEDS

- **Education, Lobbying of HTA regulatory bodies about evidentiary requirements**
- **Alignement of HTAs and EMA regulatory bodies is key**

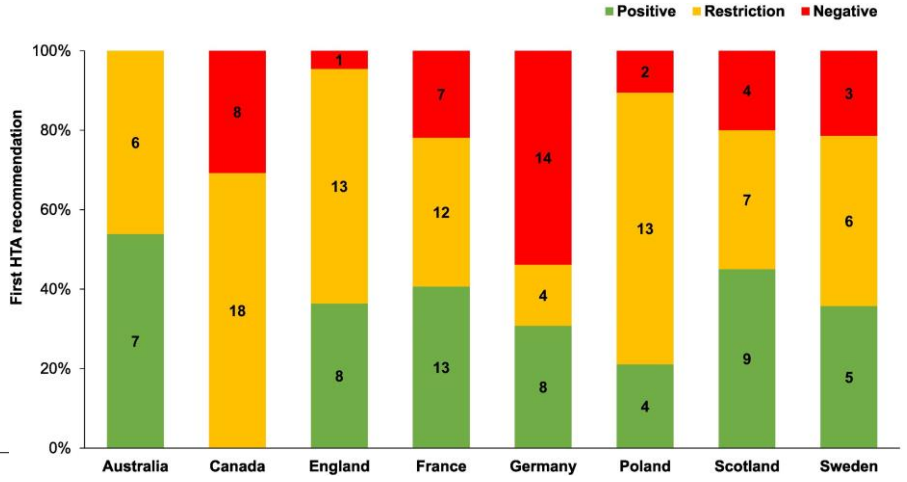


Reimbursement
Second obstacle, may be toughest



Misalignment

in recommendations from HTA bodies



Low rate

of recommandations for access to new drugs

Cowie M … Zannad F. International Journal of Cardiology 2022

CARDIOVASCULAR MEDICINE & SOCIETY

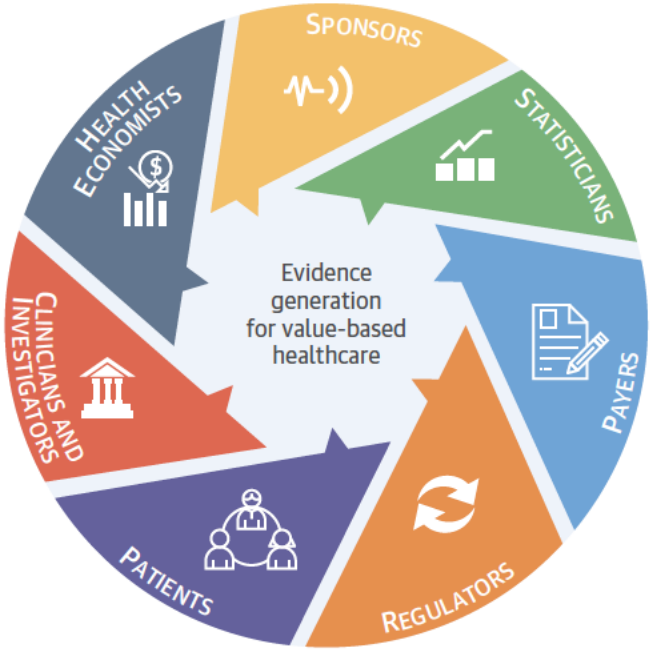
Role of Payers in the Development of Cardiovascular Therapeutics

Misalignment Between Approval and Reimbursement

Faiez Zannad, MD, PhD,[a,b,c] Maria de los Angeles Alonso Garcia, MD,[d,e] Jeffrey S. Borer, MD,[f] Wendy Gattis Stough, PharmD,[g] Thomas Clutton-Brock, MD,[h] Yves Rosenberg, MD, MPH,[i] Milton Packer, MD[j]

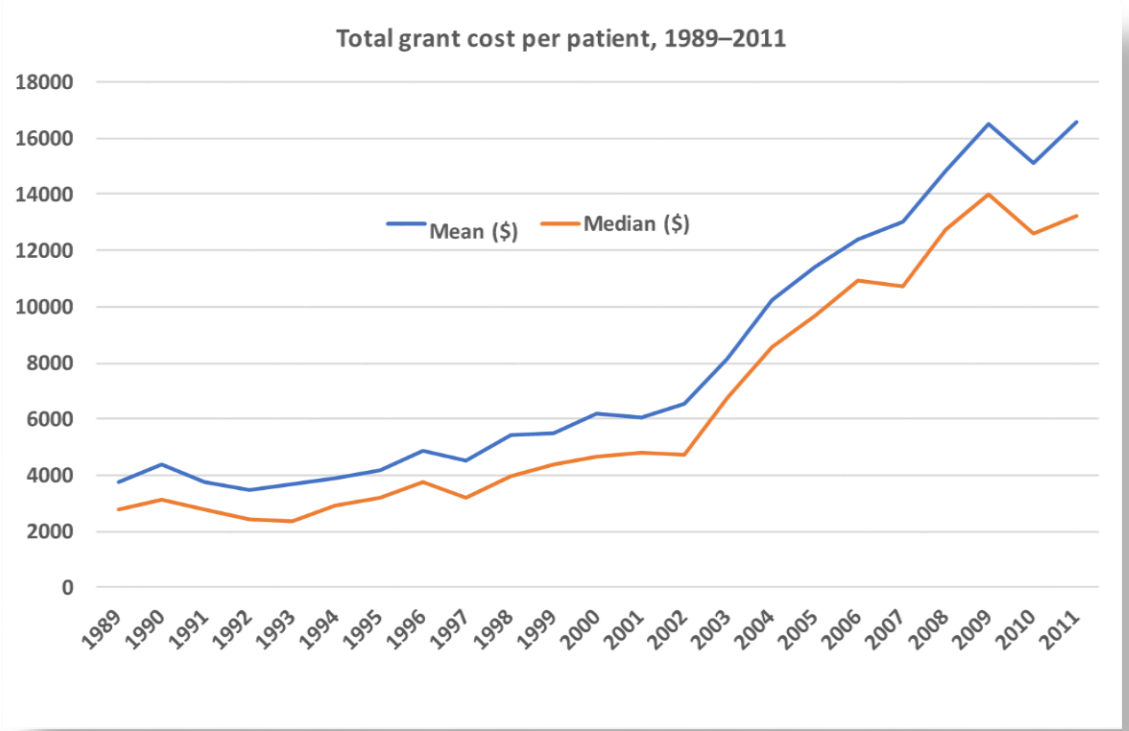
UNMET NEED: Delays in patient access to new therapies

- Payers' decision-making processes are not necessarily evidence based or cannot be reliably predicted
- Regulators and payers have contrasting priorities that can lead to divergent decisions and delays in patient access to new treatments.
- Payers are not routinely integrated in the drug development process.



J Am Coll Cardiol 2017;70:2822–30

Cost of Clinical Trials



Berndt and Cockburn, *Monthly Labor Review,* U.S. Bureau of Labor Statistics, 2014.

Needs being met: Innovation in trials design

- Outcomes such as prevention of hospitalization, length of hospital stay, improvements in quality of life and PROs could demonstrate benefits of a treatment in a shorter length of time compared to morbidity/mortality.
- Changes in biomarkers, or imaging tests can also demonstrate potential benefits of a new treatment.
- However, contrary to oncology and other disciplines approval of CV drugs based on surrogate endpoints is not recommended.
- Lessons learned from the development programs for devices, such as the FDA Expedited Access Pathway, followed by post approval confirmation.
- Multi-organ Composite endpoints:
  - trials enrolling patients with multiple comorbid conditions rather than excluding them.
  - paradigm shift from a siloed disease approach to the recognition of cardiorenal-metabolic multi-organ conditions

Pushing Forward A Changing Landscape

Traditional Randomized Trial

- RWD to assess enrollment criteria / trial feasibility
- eCRF + selected outcomes identified using EHR data
- RWD to support site selection
- Rare mobile technology use for data

Hybridization of Trials Clinical to Home Settings

- Pragmatic RCT using eCRF (+/- EHR data)
- Embedded RCT using EHR, Claims, Digital
- Single arm study using external control

Mobile to any-digital tech to capture data

- *A large, simple trial*
- *Platform Networked Trials*

Hybrid Trials

Observational to Implementation

- Registry
- Implementation
- Prospective Study
- AI Health
- Retrospective Study
- Learning Health

Common Data to Data Lakes/Science

- *Outcomes & Quality Improvement*
- *Real time, real-action Platforms*

Increasing reliance on multiple data streams
Healthsystem to Home

Adapted 2019 RWE Margolis/FDA Public Workshop

Needs being met: Innovation in trials execution

- Risk-based data collection and monitoring
- Pragmatic trials
- Randomised Registry based trials
- Post COVID lessons
  - simplified electronic consent
  - single, centralized Institutional Review Board (IRB)
  - Using registries and electronic health records with artificial intelligence
  - Remote monitoring and data collection..
- *(Contract (CROs) and Academic Research Organizations do not necessarily help).*

Needs being met: Innovation in trials results analyses

- New statistical methods (recurrent events, win ratio, hierarchical analyses, alpha borrowing, Bayesian methods)
- Totality of evidence, beyond reliance solely on p-values.
- Open data-sharing to ensure maximum knowledge gain

FDA Uses the ”Totality of Evidence” Approach

Emphasis on “formal findings”, rather than primary endpoint

- Enalapril approved for asymptomatic LV systolic dysfunction, although SOLVD-Prevention missed on its primary endpoint.
- Carvedilol for post-myocardial infarction LV dysfunction, even though CAPRICORN missed on all 4 prespecified endpoints.
- Sacubitril-valsartan for heart failure, regardless of ejection fraction, even though $P > 0.05$ for primary endpoint of the PARAGON-HF trial.

EU framework for RWD/RWE

One of the core recommendations of the EMA Regulatory Science Strategy to 2025

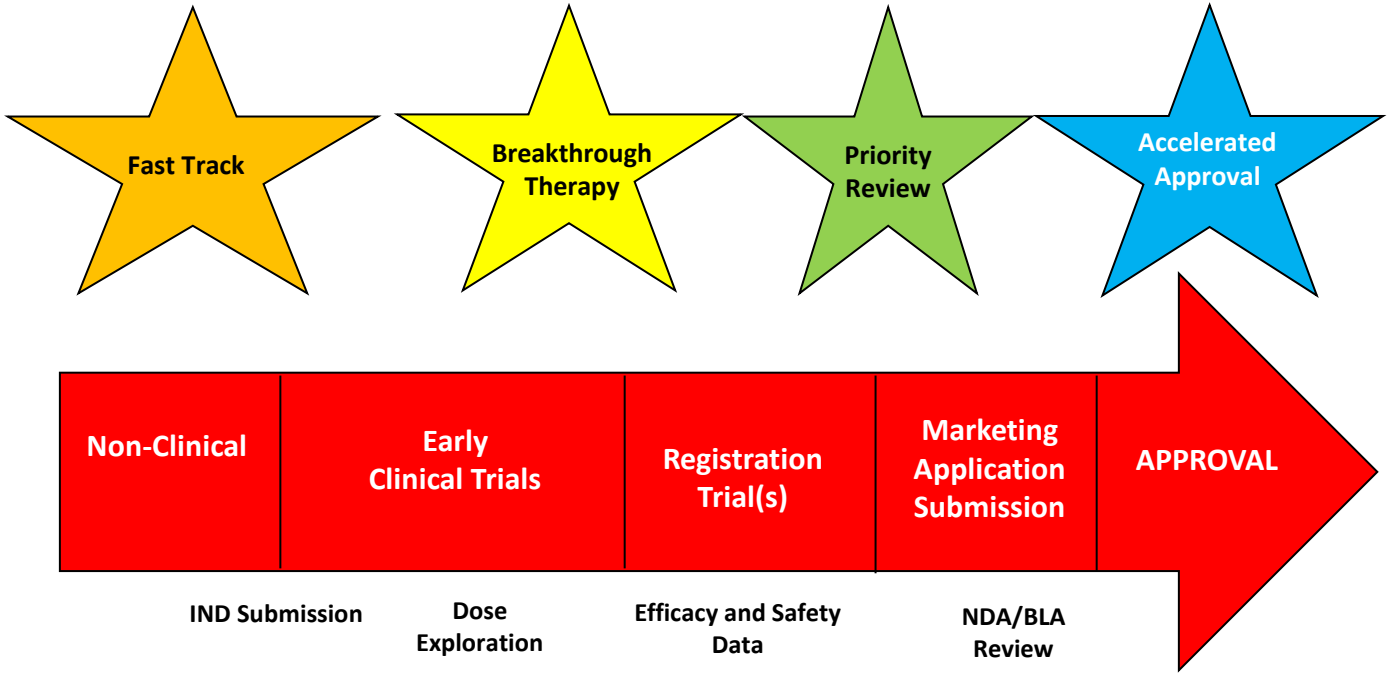
"Promote use of high-quality real-world data (RWD) in decision making"

Big data | European Medicines Agency (europa.eu)

Is the CV Device and oncology approval model a good benchmark?

- Smaller trials
- Greater reliance on biomarkers
- Greater reliance on surrogates
- Expedited access pathway - Breakthrough designation
- Reliance on post approval data

FDA Expedited Programs (FDA CV Device, and Oncology)



➢ to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition

British Journal of Cancer

ESC

REVIEW ARTICLE OPEN

An urgent call to raise the bar in oncology

John-John B. Schnog [1,2]✉, Michael J. Samson[3], Rijk O. B. Gans[4] and Ashley J. Duits [2,5,6]

« many oncological treatments approved by regulatory agencies are of low value and do not contribute significantly to cancer mortality reduction, but lead to unrealistic patient expectations and push even affluent societies to unsustainable health care costs.»

Investors want to know…

WHAT IT'S WORTH IF IT WORKS

HIGHER IS BETTER

- larger market
- higher diagnosis and treatment rate
- higher gross margin
- fewer competitors
- long patent life
- symptomatic relief drives higher adherence
- higher price

×

PROBABILITY OF SUCCESS

HIGHER IS BETTER

- validated target
- known/safe modality
- low placebo effect
- biomarkers
- high unmet need
- multiple shots on goal

×

HOW UNDERSTANDABLE (PERCEIVABLE) THIS ALL IS

SIMPLER IS BETTER

OR ELSE TOO FEW INVESTORS WILL UNDERSTAND AND RAISING MONEY WILL BE HARDER

HOW MUCH TIME (T) AND MONEY ($) IT WILL TAKE TO CREATE VALUE

LESS TIME IS BETTER

- shorter, smaller, adaptive trials
- many patients means faster enrollment
- FDA fast track
- high patient need means faster uptake

LESS MONEY IS BETTER

- smaller/ fewer/shorter trials
- inexpensive manufacturing
- fewer people
- no platform
- focused
- high patient need means cheaper marketing

KNOWN COMPARABLES:

- both companies and products,
- POC data,
- controlled trials,
- objective endpoints
- dose responses,
- many KOLs,
- smart investors,
- credible executives
- publications

SUMMARY (1/4)
MET AND UNMET NEEDS – Key messages for sponsors

- **Investors**
  - Vibrant pharmacology innovation
  - Busy pipeline
  - CV is still killer N°1
- **Industry**
  - CT can be streamlined
  - Opportunities with the changing landscape in trial design, execution and interpretation
  - Reliance on CROs is counterproductive
  - Data sharing may maximize knowledge

SUMMARY (2/4)
MET AND UNMET NEEDS – Key messages for regulators

- **EMA**
  - Declining CV drug approvals is alarming
  - Adoption of PROs, “living better” vs only “living longer” endpoints is claimed by patients (and doctors)
  - Conditional approval may help, obsession with $p<0.05$ must stop.
  - Harmonization with FDA is desired
  - No compromise with surrogates
- **HTAs**
  - EU expertise is better than USA (CMS, only coverage, not HTA!)
  - Tough pricing policy, mainly driven by economic reasons is limiting drug access
  - Hiring more expertise in evidence evaluation and valuation is desirable
  - Aligning with EMA is important
  - Double standards with CV vs. Oncology must be questioned

SUMMARY (3/4)
MET AND UNMET NEEDS – Key messages for HCPs

- We are not doing a good job with our life saving therapies

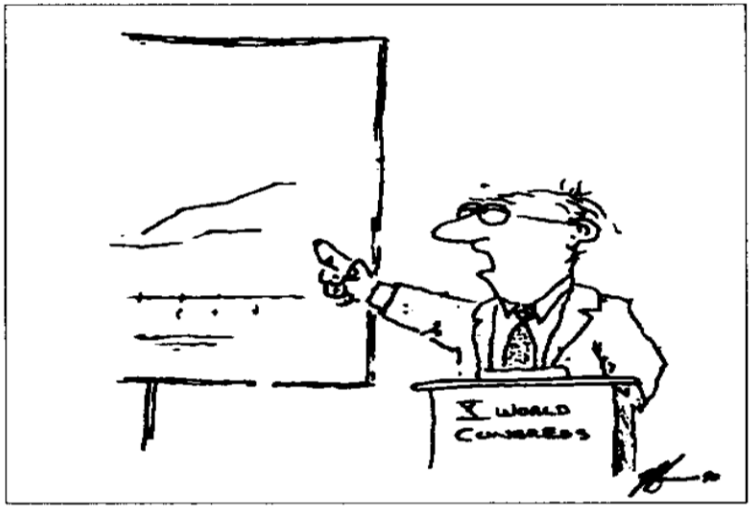
- “Drugs work only if they are taken”:
  - Improve Implementation (Ignorance, Incredulity, Inaction/inertia)
  - Creative implementation strategies (STRONG-HF, Disease management programs…)
  - Risk aversion and self censoring : Learn from oncologist colleagues

SUMMARY (4/4)
MET AND UNMET NEEDS – Key messages for patients

- CV is a specialty where drugs are safest, most efficient, most evidence-based, and cost-effective
- You deserve better drugs and faster access to innovation
- There are many opportunities for further progress.
- We need to synergise lobbying stakeholders

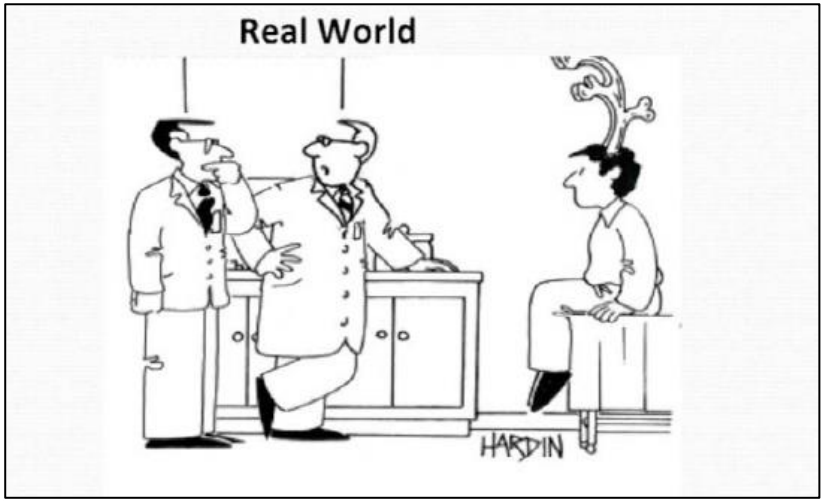
How can we integrate real world evidence alongside randomized trials

The “pros” RWE



“This randomized, double-blind trial involving over 20,000 patients was conducted over a 10 year period. Unfortunately we’ve forgotten why.”

The “anti” RWE



"In the computer model the only side effect was a dry mouth."

Current Challenges to Efficient Clinical Trials

Costs	Timelines	Patient Recruitment & Retention	Site & Investigator Selection	Regulatory Uncertainty
Clinical trials account for 60 – 80% of the $1.6 – $2.8B in development costs	Up to 8 years to bring a new drug from phase 1 to market	Difficulties in recruiting and retaining participants	Increasing competition for qualified investigators and sites with trial infrastructure and experience	Regarding use of RWE and AI in optimizing drug development program design and trial design
High costs have shifted priority from short-term conditions towards chronic conditions due to potential for longer revenue stream	Lengthy trials increase costs and decrease revenues	Eligibility screening yield based on complex inclusion and exclusion criteria can be low for some trials	Involvement of huge number of vendors in the studies	Acceptance of the use of RWD/E in regulatory submissions

80% of trials fail to meet enrollment deadlines
*Only 39% of trial sites meet enrollment targets; 11% fail to enroll a single patient**

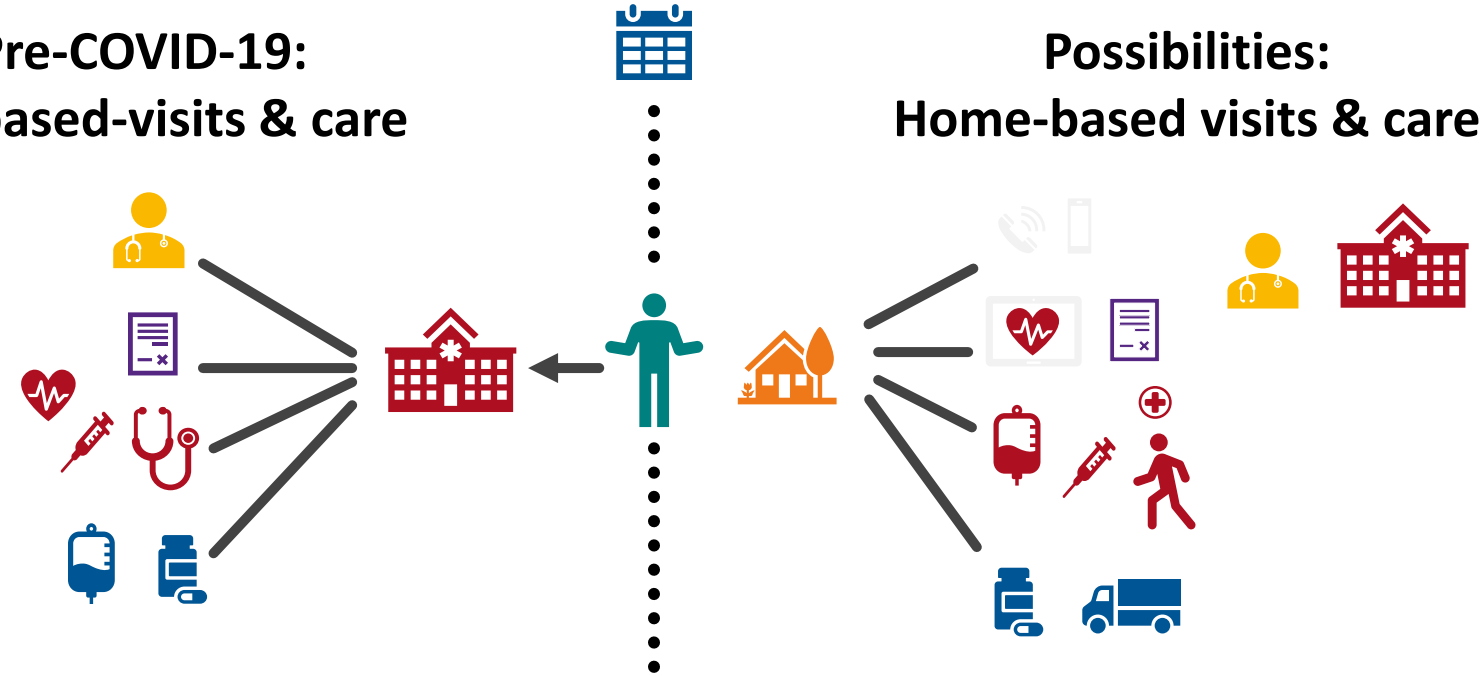
- *RWD/E – real-world data/evidence*
- *AI – artificial intelligence*

**Source: ESC Education Training Course All about Clinical Trials 12 December 2019 on Traditional vs Novel Clinical Trials by Dr. Juan Tamargo (Link)*

Going from Pre-COVID to Post-COVID Clinical Trial Visits

Pre-COVID-19:
Site based-visits & care

Possibilities:
Home-based visits & care



https://ctti-clinicaltrials.org/our-work/digital-health-trials/running-a-decentralized-trial/