Training course: All About Clinical Trials

December 12th, Stockholm

TRADITIONAL VERSUS NOVEL CLINICAL TRIALS

(New types of CTs: Smaller, faster, cheaper)

Juan Tamargo, MD, PhD, FESC

Dpt. of Pharmacology, School of Medicine

University Complutense, Madrid, Spain

Declaration of Conflict Of Interest

The existence of potential conflicts of interest does not necessarily indicate a bias. However it is our ethical obligation to inform organisers and participants so that they are made aware of any relationship that might cause unintentional bias. A potential conflict of interest may arise from various relationships, past or present, such as employment, consultancy, investments and stock ownerships, funding for research, family relationship etc.

□ xxx I have no potential conflict of interest to report

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Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports:	
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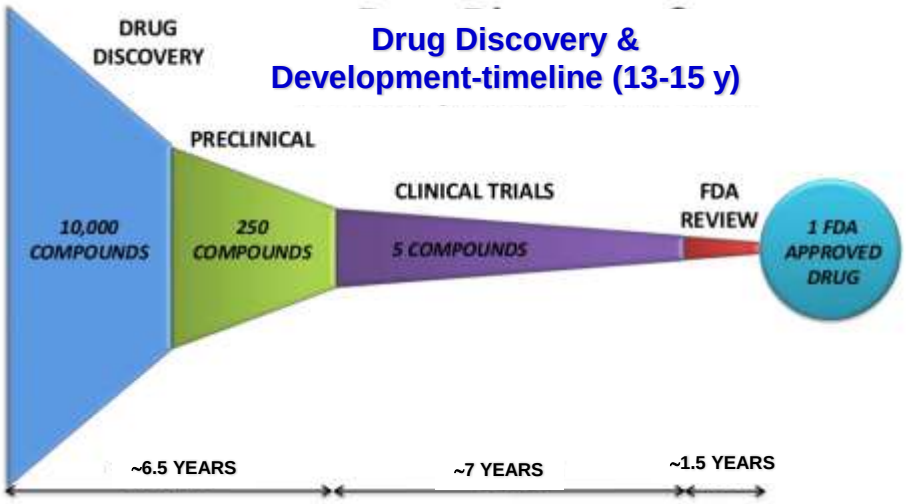
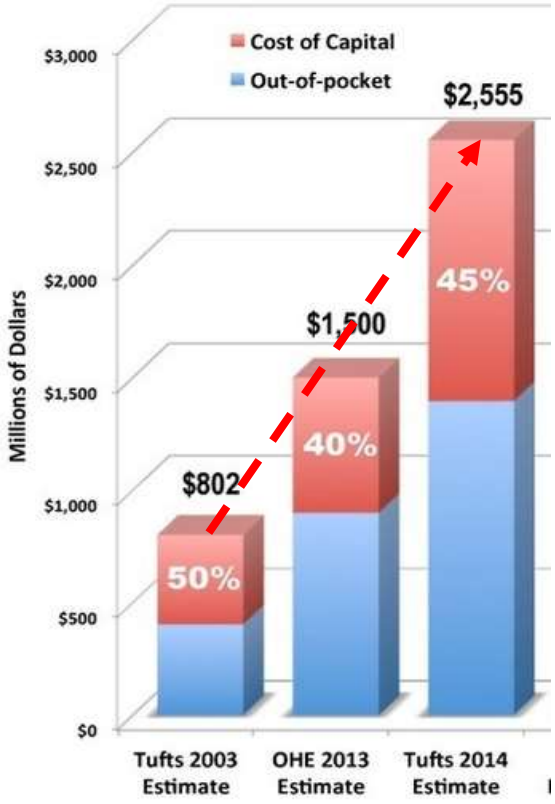
To develop a new drug is a complex, slow, costly and inefficient process

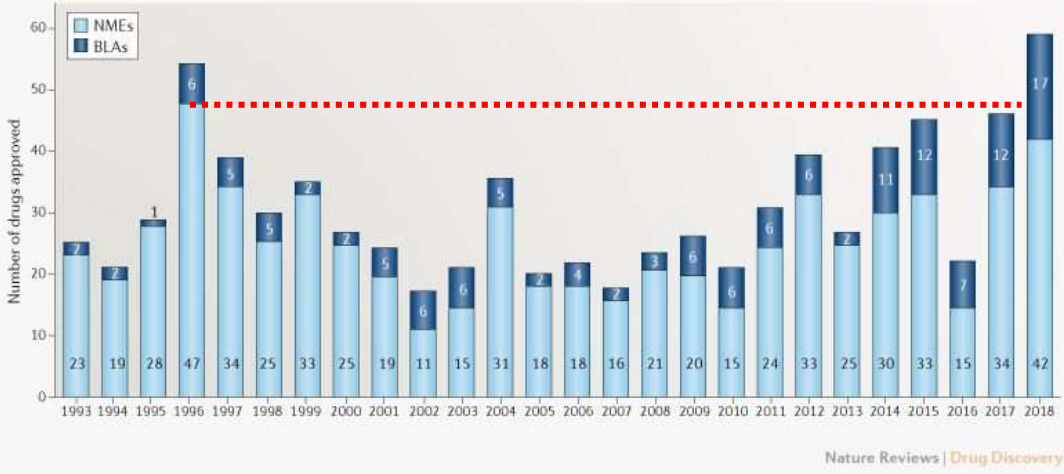


Drug Discovery & Development-timeline (13-15 y)



Estimates of costs to bring a drug to market

FDA approvals of new molecular entities (NME) and biologicals



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Reasons for the higher cost of drug development for cardiovascular as compared with other diseases

- **Drug therapy requires long-term treatment (years) to effectively modulate CVDs**
- **Many CV development programs involve event-driven studies where the annual incidence of events is small but the population at risk is large (e.g. stroke prevention in AF**)
- **CTs are conducted in patients receiving multiple evidence-based therapies**
- **Demonstrating incremental risk reduction requires very large sample sizes**
- **CV mortality and other major CV outcomes have declined in recent years**
- **CV trials are performed in large, unselected groups of patients (e.g. HF, AF, CAD) in whom a diverse range of disease mechanisms may be active**
  - **Not all are likely to be influenced by the agent under studied**
  - **It is difficult to identify patients more likely to benefit**
- **Complex infrastructure to conduct clinical trials**
  - **Event adjudication, data protection**
  - **A lot of burocracy, complex/contradictory national/local regulations**

Jackson et al. Eur Heart J 2016;37:757-54

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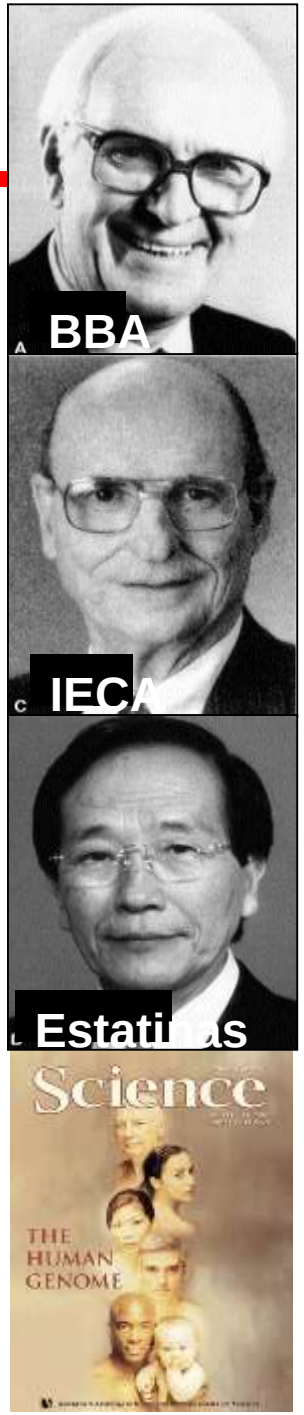
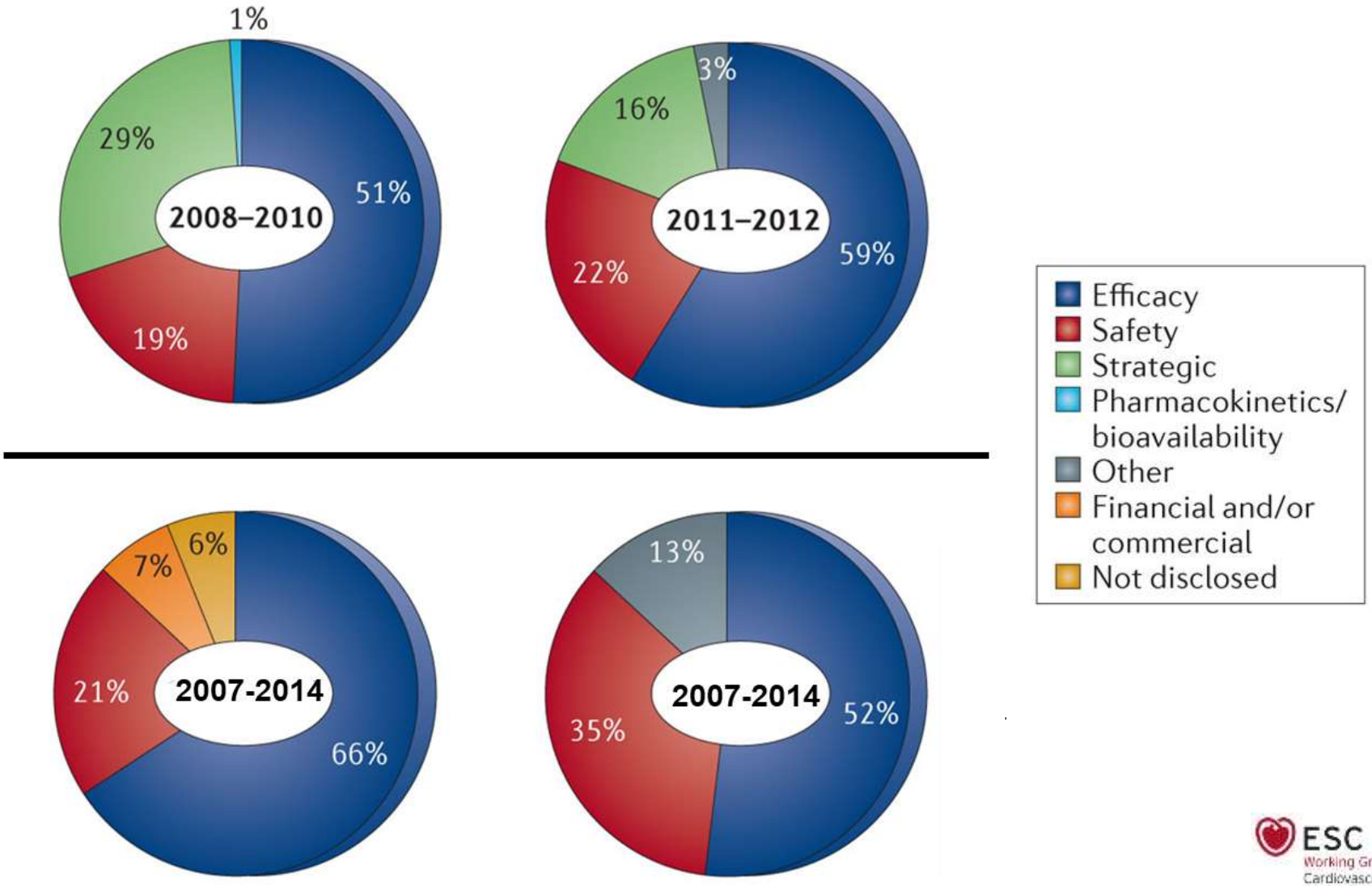
Adverse effects of great success

Hypertension	• Diurétics, β-Bs, α-Ba, BCCs • IRAASIs: ACEIs, ARBs, MRAs
Angina	Nitrates, β-Bs, CCBs, ivabradine, ranolazine
Heat failure	• Digoxin, dopamine/dobutamine, levosimendan, milrinone • Diurétics, vasodilators • β-BAs, ACEIs, ARBs, MRAs, sacubitril/valsartan
Lipid disoreders	• Estatins, fibrats, resins, ezetimibe, PCSK9 inhibitors
Thrombosis	• Anticoagulants: heparins (UFH, LMWH), vitamine K antagonists, FIIa y Fxa inhibitors, fondaparinux • Antiplatelets: COX-1, TXA2, P2Y12, PAR-1, GPIIB/IIIA, and PDE inhibitors • Thrombolytics
Antiarrythmics	• Adenosina, amiodarone, β-Bs, digoxia, dronedarone, flecainide, lidocaine, propafenone, vernakalant……..
Otros	• Pulmonary hypertension: PGI2 analogs, ET-1/2R inhibitors y PDE-5 inhibitors • Multiple antidiabéticos: glitazones, DDP4 inhibitors, GLP-1R agonists, SGLT2 inhibitors



Many are excellent, easy to get and cheap generics

Reasons for termination the development programs of NCEs



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- **Half of phase 2 & 3 drug candidates failed for lack of efficacy**
- **A third failed because of safety issues (not predicted earlier in development)**

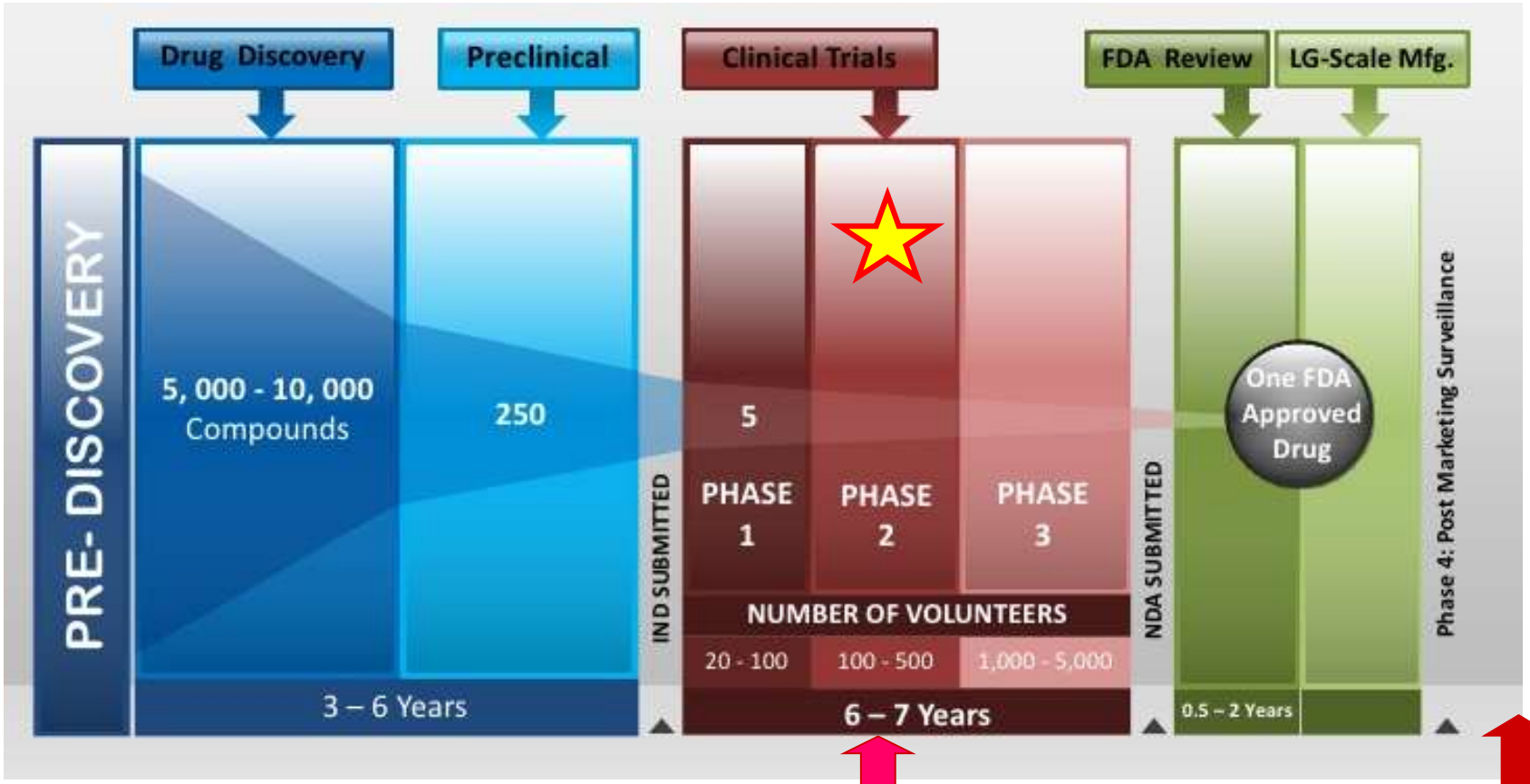
Recent “Failures” in AHF/CHA Treatment

« *Failure is simply the opportunity to begin again this time more intelligently* “

Drug	Mechanism (adverse effects)
Alagebrium	AGE breaker- Ineffective
Aliskiren	Direct renin inhibitor - Ineffective
Allopurinol, Oxypurinol	Xantino-oxidase inhibitors - Ineffective
Bardoxolone	Nuclear factor (erythroid-derived 2)-like 2 activator (higher rate of CV events)
Cinaciguat	GC activator (hypotension)
CLP-1001	Na-K-Cl symporter inhibitor - Ineffective
Darbopoetin	ESA - Increase thromboembolic events
Digoxin	Friend or enemy
DPP-4 inhibitors: - Alogliptin, Saxagliptin	They may increase the risk of HF, particularly in patients with heart or kidney disease (FDA, 2016)
ISMN	Nitrate – Ineffective in daily activity tests
PF-03882845	Nonsteroidal MRA –strategic reasons
Rolofylline	Adenosine A1R antagonist (seizures, stroke)
Rosuvastatin	HMG-CoA reductase inhibitor - ineffetive
Sildenafil	PDE5 inhibitor – May impair LV contractility
Tolvaptan	V2R antagonist (hepatotoxicity)
TRV120027	Biased ligand of AT1R - ineffective
Vericiguat	sGC stimulator - ineffective

Tamargo J et al. Expert Opin Investig Drugs. 2019;7:1-21

25 Years life-cycle of a drug



Animal models to determine drug efficacy and safety

Mice are not men, a cell is not a tissue

- **Dose-finding**
- **Confirm MOA**
- **PK/PD**
- **Dose, best time**
- **Comorbidities**

Patent expires

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1. Know the drug before pivotal trials are performed

1. Half of phase 2 & 3 drug candidates failed for lack of efficacy

- **Many drugs enter phase III RCTs without adequate proof-of-concept studies in humans**

Phase 2 CTs play a key role

- **Understand drug properties (MOA, PD/PK)**
  - **Confirm the MOA in humans ("target validation") and pharmacokinetics (phase 1 in healthy people)**
  - **Define dose range, time of administration**
  - **Define Off-target effects (Cancer chemotherapy)**
- **Identify the right population - most likely benefit (all vs specific subsets)**
  - **Imaging and biomarkers as surrogates to predict clinical efficacy/safety**
- **Incorporate primary endpoints based on MOA and right population**
- **Obtain safety data and possible drug-drug interactions (not analyzed in preclinical developmental programs)**

MOA: mechanism of action

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CV events in the DALCETRAPIB and placebo arms in the dal-OUTCOMES trial according to the genotypes at rs1967309 in the ADCY9 (adenylate cyclase type 9) gene

Targeting those patients most likely to benefit from modification of receptor targets might be a more direct, efficient approach to generate robust scientific evidence and decrease the cost of failure in terms of resources and time

(Jackson et al. Eur Heart J 2016;37:757-54)

Dalcetrapib 'failed', but a post-hoc genomic analysis identified a genetic variant in ADCY9 (rs1967309) was associated with positive effects of dalcetrapib on intima-media thickness in dal-PLAQUE-2 and events in dal-OUTCOMES

Dalcetrapib	978	914	864	822	648	373	118		1379	1308	1255	1225	1003	570	186		485	475	458	449	378	223	74
Placebo	1006	947	916	880	698	388	124		1417	1326	1284	1243	1019	577	192		476	459	438	424	353	208	55

Events: Composite of CHD death, resuscitated cardiac arrest, non-fatal myocardial infarction, unstable angina with objective evidence of ischemia, atherothrombotic stroke and unanticipated coronary revascularization

Tardif et al. Arterioscler Thromb Vasc Biol. 2017;37:396-400 and Circ Cardiovasc Genet. 2016;9:340-348.

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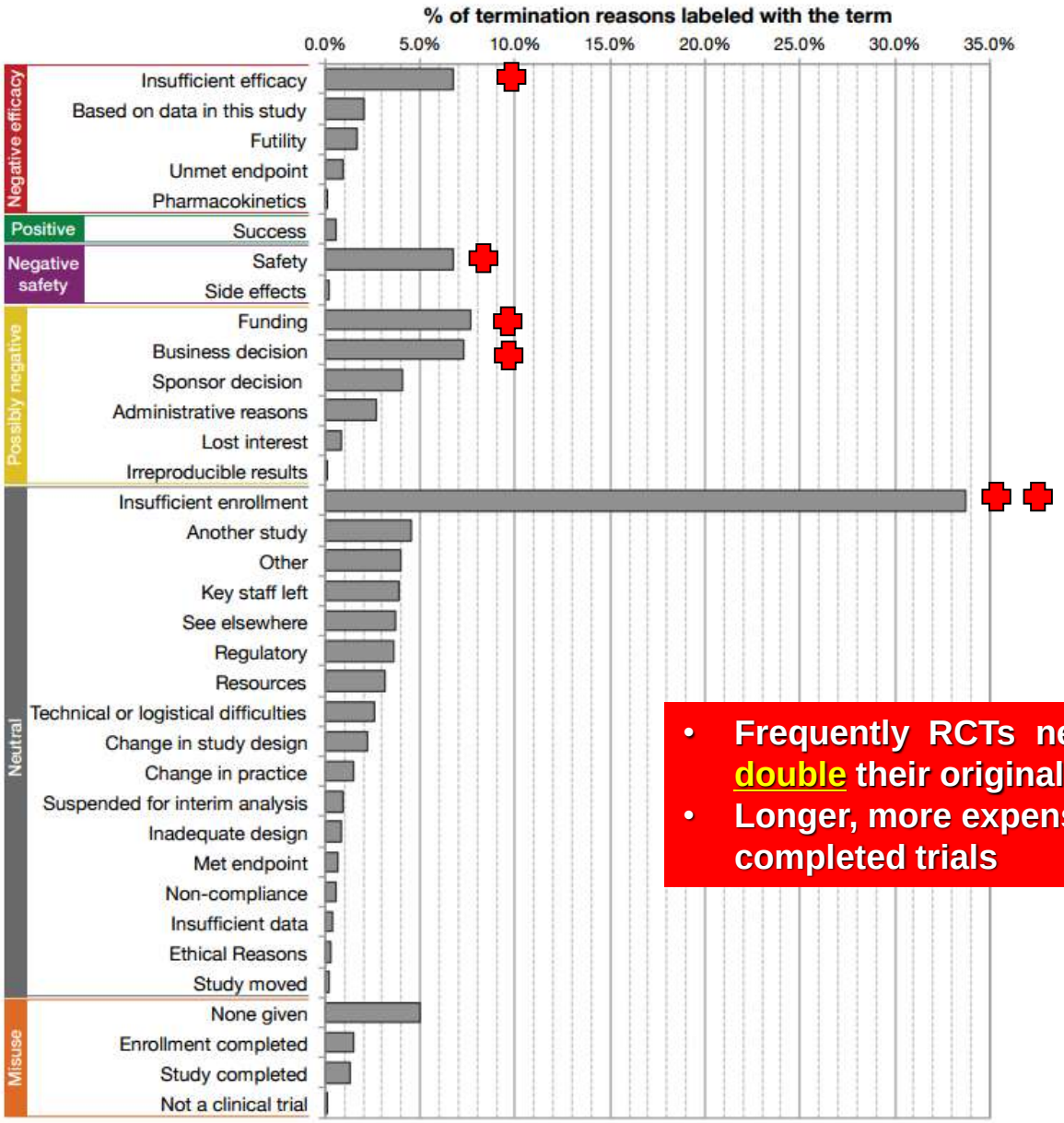
Percentage of termination reasons labeled with each ontology term (N=3122)

July 2, 2015; doi: http://dx.doi.org/10.1101/021543



- **Frequently RCTs need to nearly double their original timelines**
- **Longer, more expensive or never completed trials**

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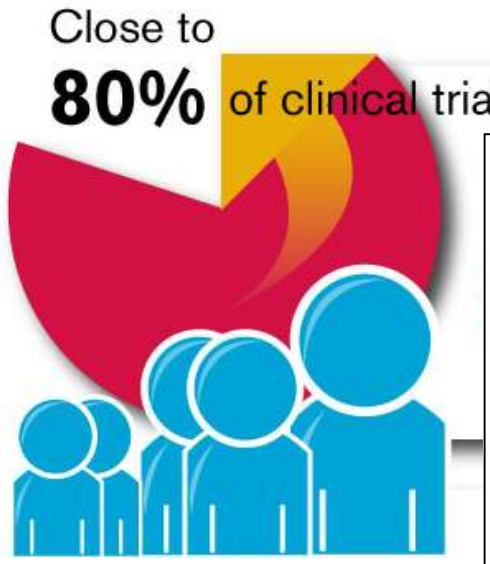
2. Patient enrollment challenge is the leading cause of missed CT deadlines



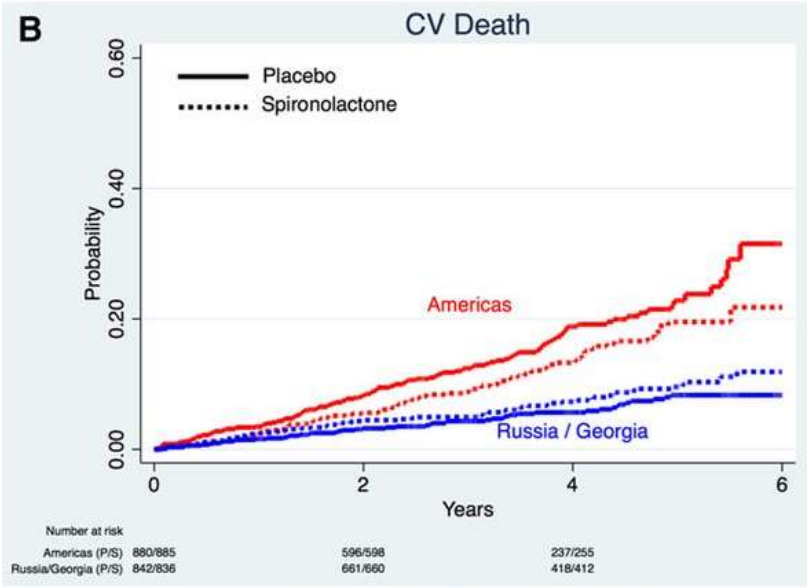
Sponsors and CROs rely on traditional recruitment and retention tactics:

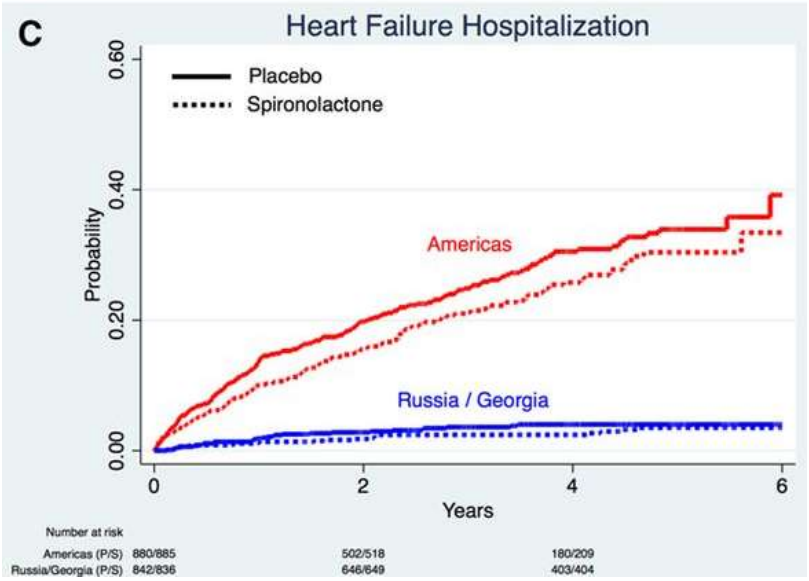
- **Physician referrals**
- **Consumer data (from pharmacy services)**
- **Site selection and support - making site more able to recruit all the patients available**
- **Advertising - increases the patient pool with access to the trial**
- **They must embrace non-traditional approaches**

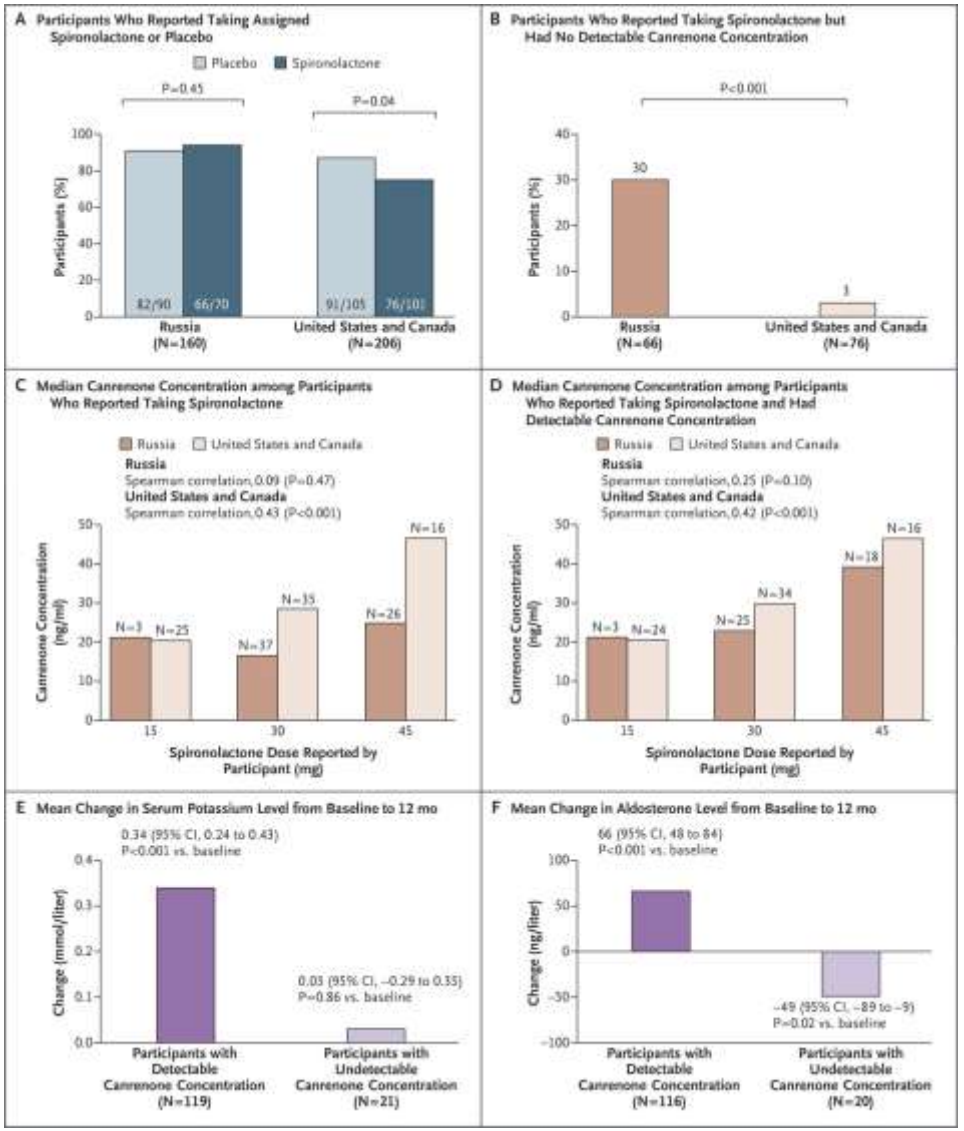
Enrolment rates

- **Asia/Pacific and Latin America achieve the highest rates**
  - Can we extrapolate the data to our population?
- **11% of sites fail to enrol a single patient**
- **37% under-enrol**
- **39% meet their enrolment targets**
- **13% exceed their targets**

Regional Discrepancies in the TOPCAT Trial







De Denus et al. N Engl J Med 2017

Individuals with Hepatitis C are needed!

The Rockefeller University Hospital is looking for individuals who have Hepatitis C to participate in a study to enhance our understanding of immune function in chronic disease.

HEALTHY VOLUNTEERS NEEDED FOR CLINICAL TRIALS

If you are aged 18-50 and in good health, contact us or visit our website to receive more information.

Participants will be compensated for time, inconvenience and travel expenses.

THE JENNER INSTITUTE

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01865 857406
www.jenner.ac.uk/recruiting-trials

A response to this advert will be recorded but carries no obligation to participate. You can withdraw at any time. Your GP will be informed if you take part.

General Mini Ad V2.0 13th March 2014

New ASTHMA research studies

Research studies testing investigational medications for asthma.

- Compensation up to $900
- No-cost study medication

www.MyTrialForAsthma.com

Type II Diabetes Research

If you have been diagnosed with Type II Diabetes, you may be eligible to participate in a clinical research study.

In order to be considered for the study, you must be:
• Generally healthy • 18 to 80 years of age And you must be able to answer yes to one of the following:

- ***Do you have type 2 diabetes mellitus not adequately controlled with diet and excercise alone?***

OR

- ***Do you have type 2 diabetes mellitus not adequately controlled with metformin alone?***

This study includes 11 clinical visits across a 13 - 14 week period. If you qualify, you will receive all study-related care and study medication at no cost to you.

Compensation may be available for time and travel.

CCR COMPREHENSIVE CLINICAL RESEARCH

For more information, please contact:
Comprehensive Clinical Research • Berlin, NJ
1-877-CCR-TX4U (ext. 337) • 1-877-227-8948 ext. 337

2. New ways of patient recruitment and retention

- **Internet scraping – People publish millions of data every day about themselves**
  - **A hugh database: geographical distribution of possible patients and high-quality sites**
  - **No direct contact with patients (confidentiality, coercion)**
  - **Software analysis (natural language capability) - patient´s attitude about CTs**

- **Brokerage Companies - match sponsors and patients interested in CTs**

- **Patients' organizations offer the potential to interact with individual patients**
  - **Based on trust and unbiased information (PIs are poorly trusted sources)**

- **Marketing campaigns (Google AdWords, Twitter hashtags) that potential patients follow, paid Twitter banners based on keywords and banner advertising**
  - **Faster recruitment of interested patients and reduced costs**

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3. Burocracy - a major stumbling block

1. **Replace Sites by Consortium**

- **A group of hospitals with unified databases, large banking and genetic information for present and future CTs**
- **High-quality/secure integrated information systems among hospitals**
- **Accreditation (ISO; CE) to reduce multiple inspections**

3. **Standardization of trial design:**

- **A single Review Board Committee (RBC) per project**
- **Develop patient-consent and standarized forms to record CT data**
- **High-quality/secure integrated information systems among hospitals**

3. **It's not simple (Centers are reluctant)**

- **"Each Institution brings its own values, preferences and interpretation of the privacy laws to the table"**
- **"To set up a system requires enormous trust"**

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4. Use secure web-based technologies

1. **CTs generate a huge amount of data**
- **Too much “written (many errors)**
- **Use of unsecured e-mail (67%)**
- **More than 3 h/week hunting for CT-related documents**
- **Data monitoring &and record keeping comprise a 30-66% of total costs**
- **Regulatory reporting requirements are rising**

2. **Exchanging information via traditional non-secure, inefficient, and not reliable audit methods is costly and time-consuming**
- **As CTs becomes more complicated is unsustainable**
- **Regulatory requirements create more urgency to exchange regulatory documents in a secure and auditable fashion**

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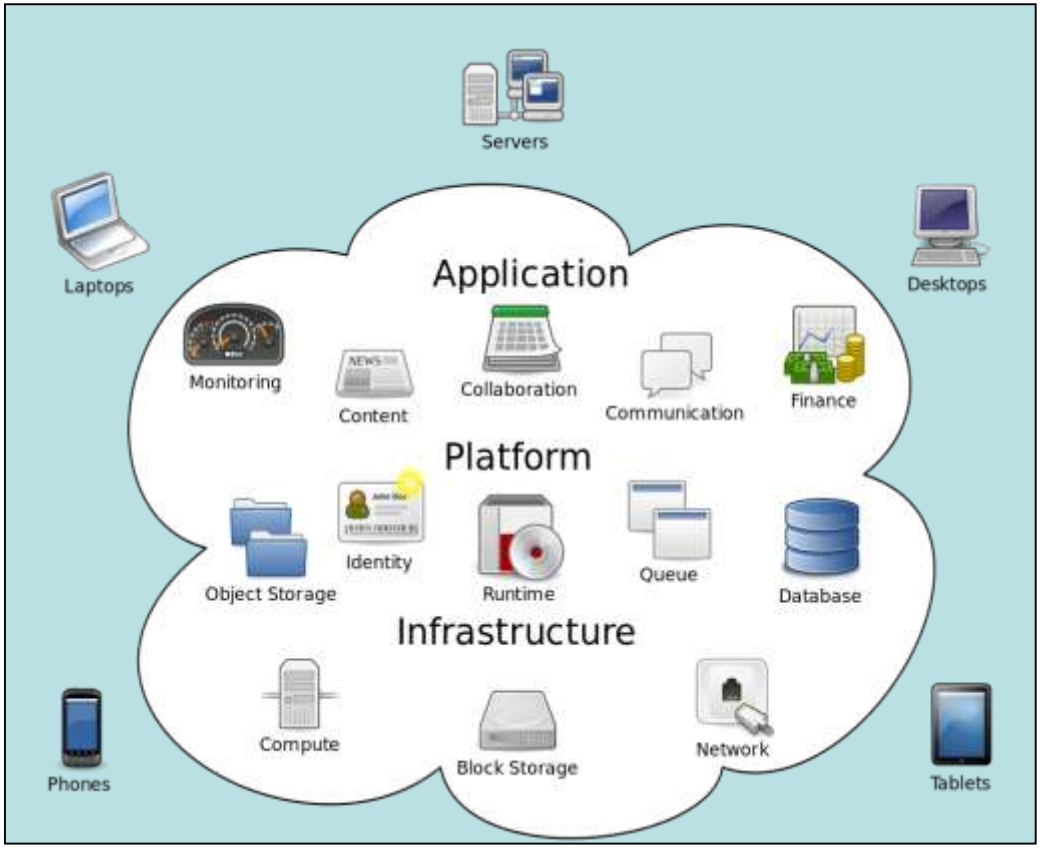
4. Use secure web-based technologies (Cloud)

1. **The IMPROVE-IT trial (Ezetimibe)**
- **Enrolled 18,144 patients**
- **Entailed 300,000 patient visits**
- **2.7 M case report forms completed**
- **Over 15,000 serious adverse effects processed**
- **14,709 events sent for adjudication**
- **Over 30,000 monitoring visits**
- **33 investigator meetings**
- **9 Data Monitoring Committee Reviews**

2. **A recent conventional trial of more than 14,000 diabetic patients enrolled at 660 sites from 2008–2012 with follow-up through 2015 cost nearly $250 million**
- **Monitoring represents more than $56 million (23%).**



Improve communications among stakeholders, while complying with the constantly tightening regulatory scene in an auditable fashion

(1) Cannon et al. N Engl J Med. 2015;372:2387–97. (2) Mentz RJ et al. Circulation. 2016;133:872–80

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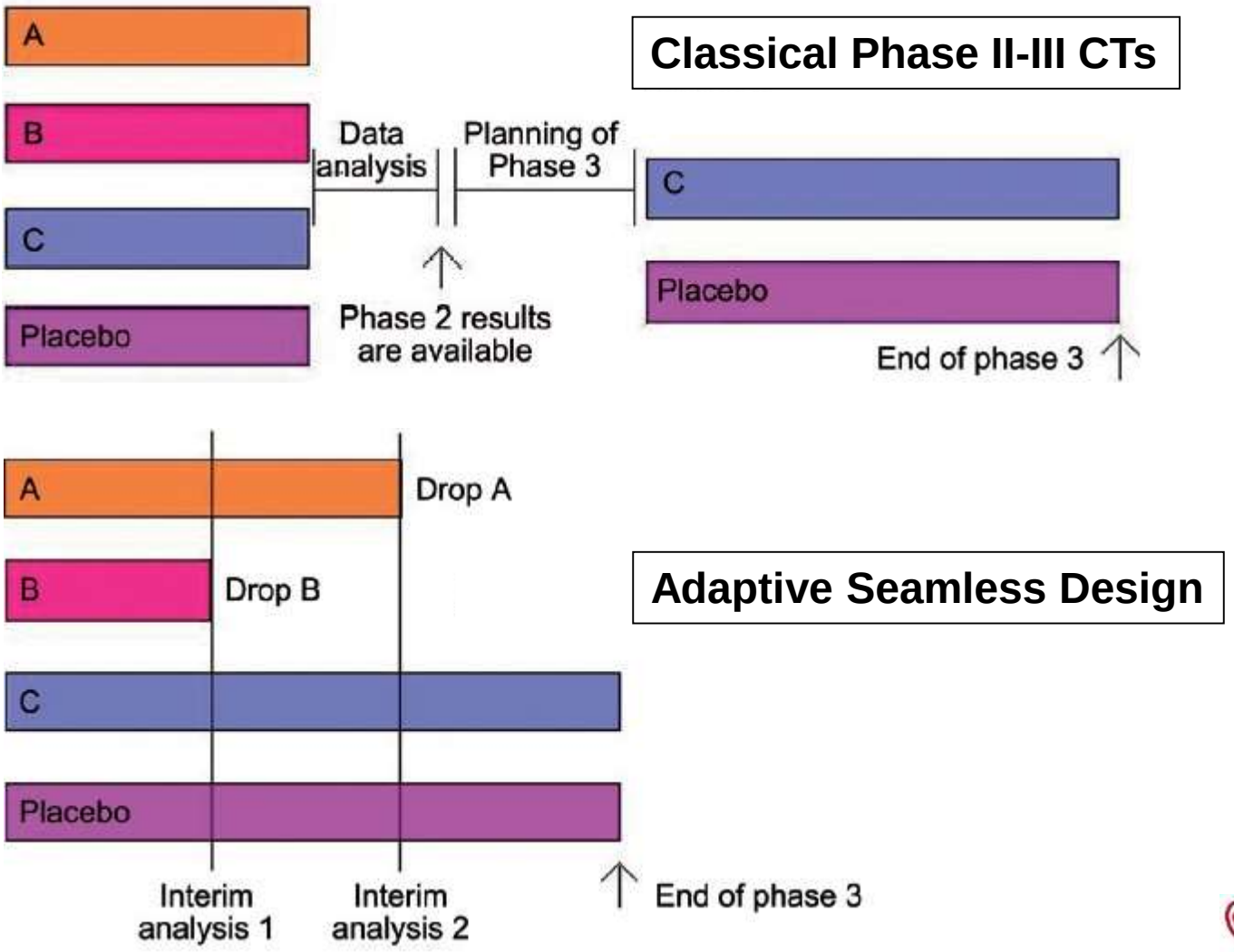
5. Replace the phase II/III design by adaptive trials



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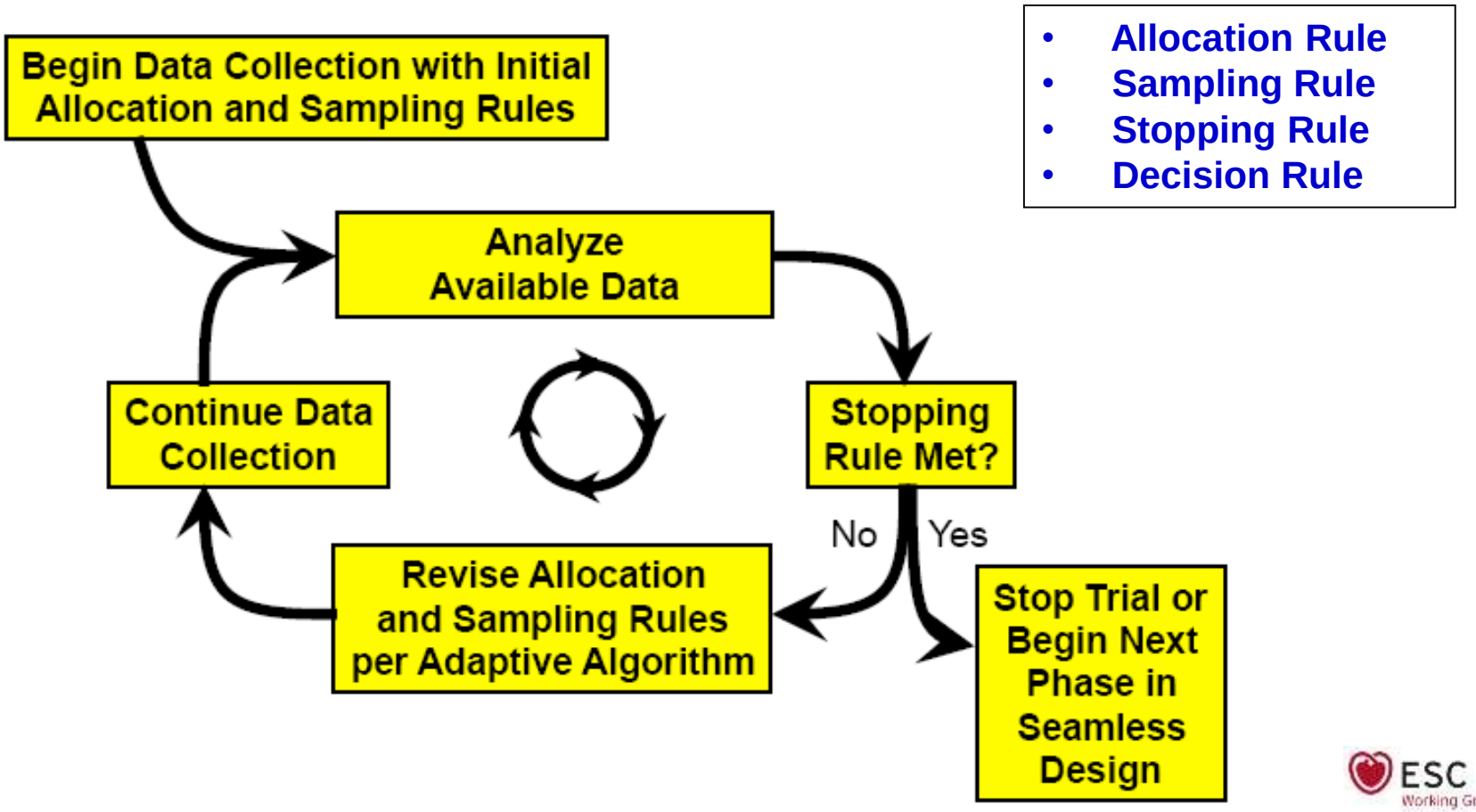
5. Adaptive designs for clinical trials

- An ADCT is a study design planned <u>prospectively</u> that uses accumulating data from subjects in the study to decide how to modify aspects of an ongoing study
- At any stage, data are analyzed and next stages redesigned taking into account all data from the trial, based on predefined rules



Bhatt and Mehta. N Engl J Med 2016;375:65-74

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The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS
Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Adaptive Designs for Clinical Trials

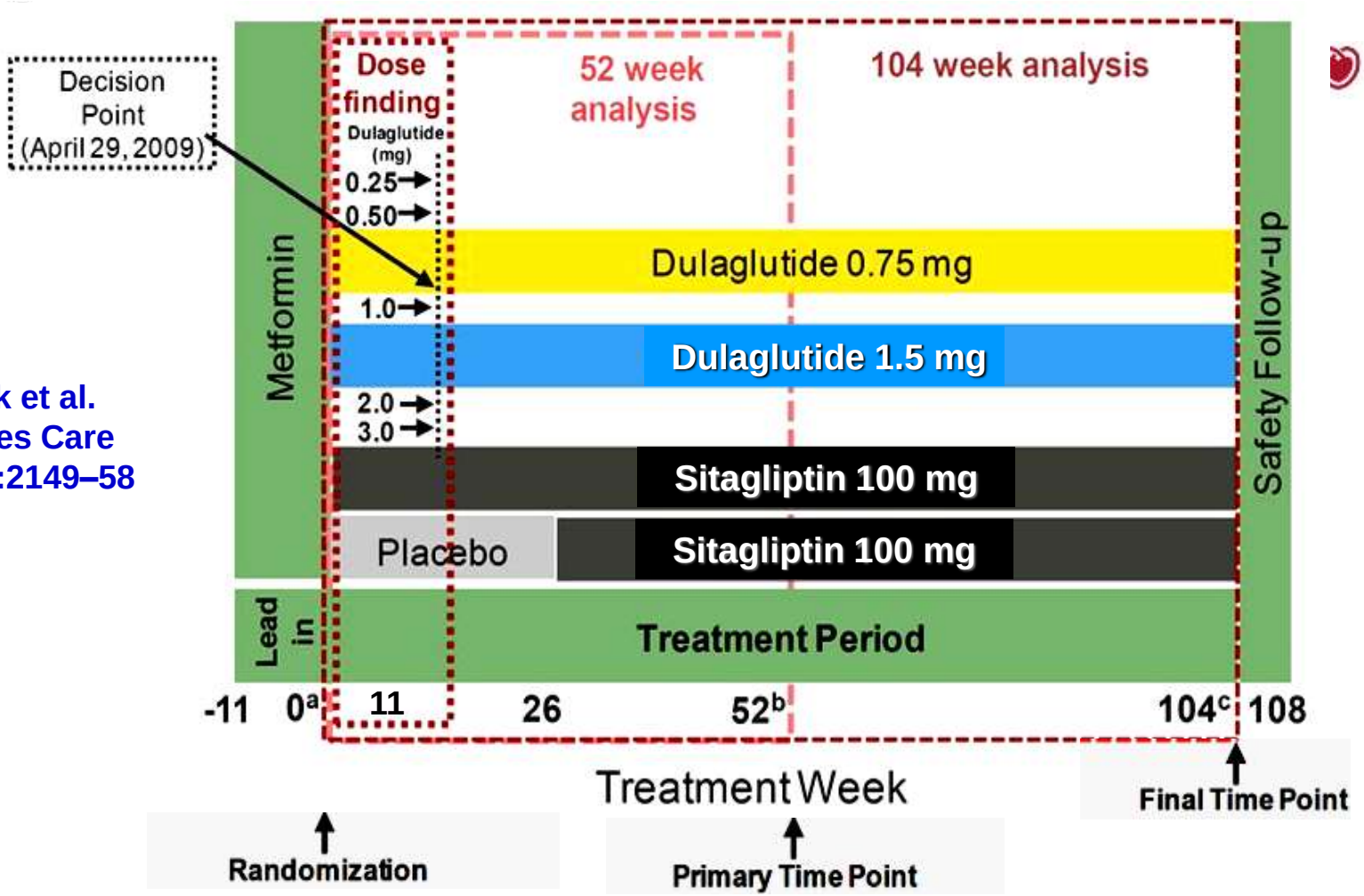
Deepak L. Bhatt, M.D., M.P.H., and Cyrus Mehta, Ph.D.

RANDOMIZED CLINICAL TRIALS SERVE AS THE STANDARD FOR CLINICAL research and have contributed immensely to advances in patient care. Nevertheless, several shortcomings of randomized clinical trials have been noted, including the need for a large sample size and long study duration, the lack of power to evaluate efficacy overall or in important subgroups, and cost. These and other limitations have been widely acknowledged as limiting medical innovation.[1] Adaptive trial design has been proposed as a means to increase the efficiency of randomized clinical trials, potentially benefiting trial participants and future patients while reducing costs and enhancing the likelihood of finding a true benefit, if one exists, of the therapy being studied.[2]

From Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School (D.L.B.) and Harvard T.H. Chan School of Public Health (C.M.), Boston, and Cytel, Cambridge (C.M.) — all in Massachusetts. Address reprint requests to Dr. Bhatt at Brigham and Women's Hospital Heart and Vascular Center, 75 Francis St., Boston, MA 02115, or at dlbhattmd@post.harvard.edu.

N Engl J Med 2016;375:65-74.
DOI: 10.1056/NEJMra1510061

Dose-finding results in an adaptive, seamless, randomized trial of once-weekly dulaglutide combined with metformin in type 2 diabetes patients (AWARD-5)



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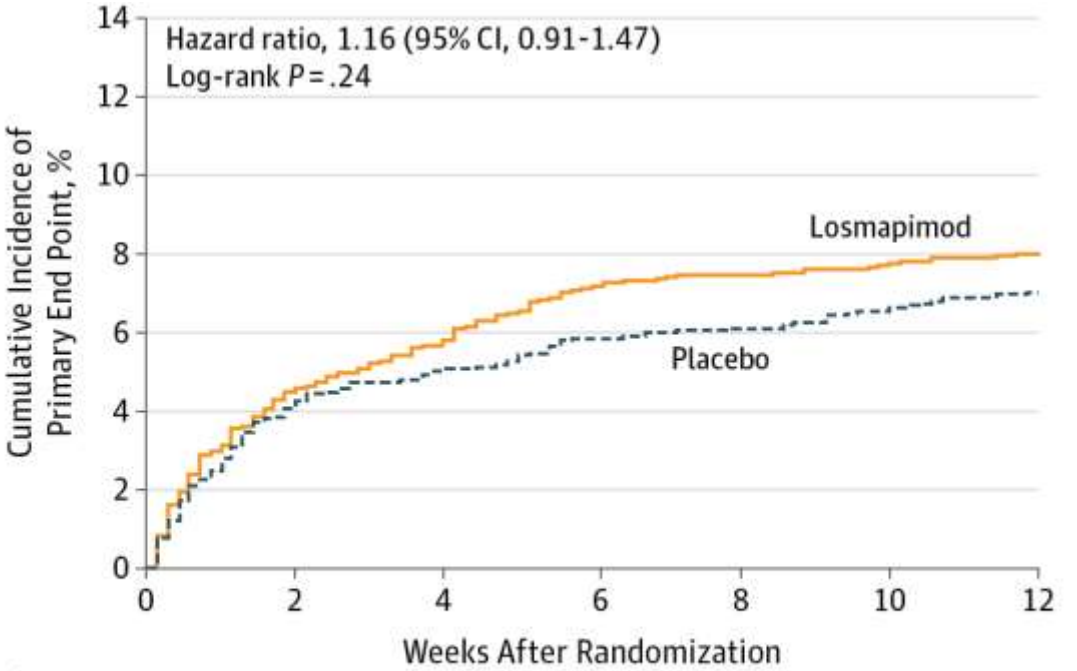
Nauck et al. Diabetes Care 2014;37:2149–58

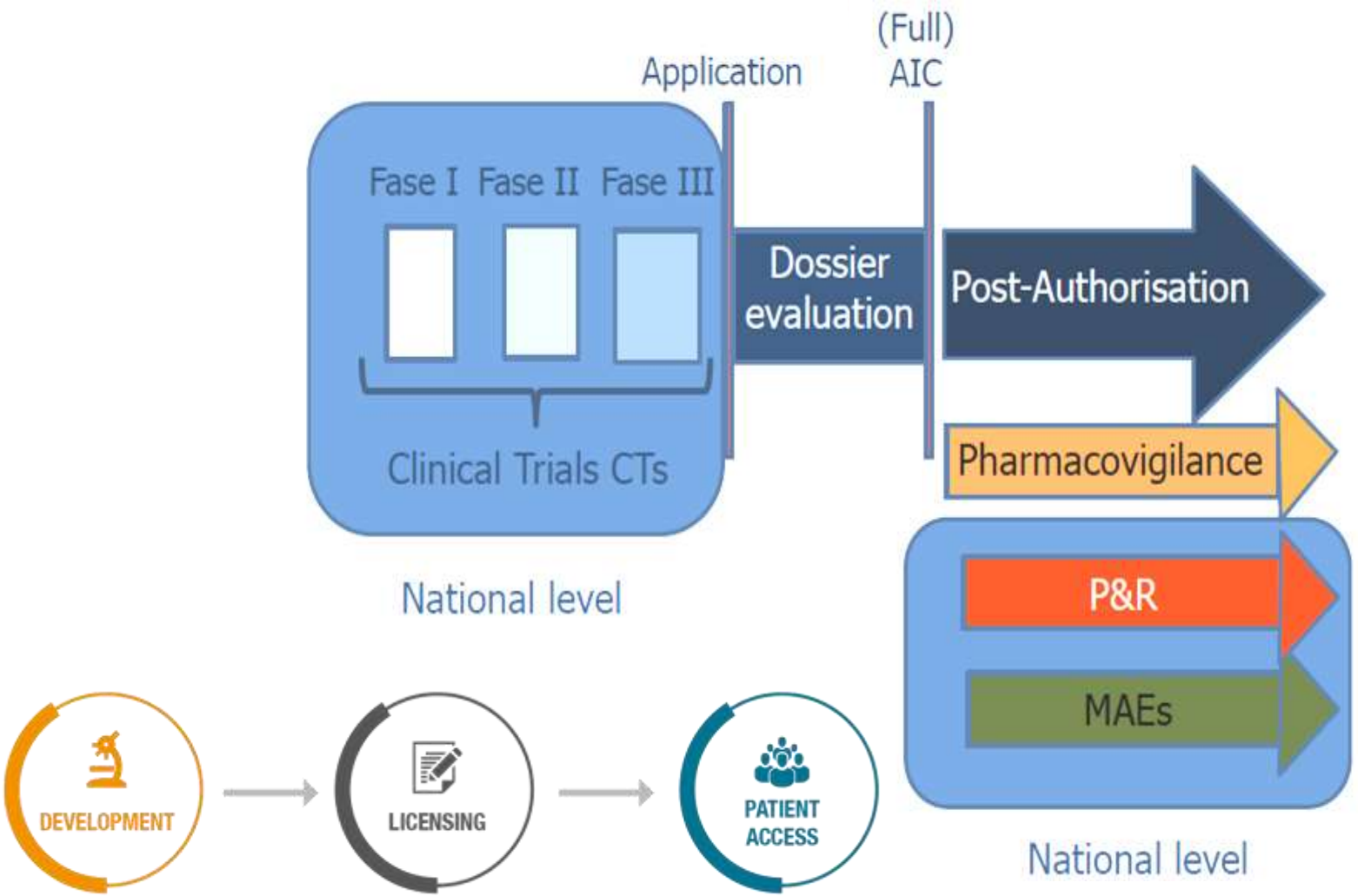
- 1098 patients, 2-stage adaptive, dose-finding (7 doses), seamless phase II/III
- Early phase: HbA1c, weight, HR and DBP
- Late phase: Mean change in HbA1c from baseline to 52 weeks, HbA1c<7.0% or ≤6.5%; body weight, FPG, fasting insulin; β-cell function and insulin sensitivity indices (HOMA2) and lipids

LATITUDE-TIMI 60 trial (O´Donoghue et al. JAMA 2016;315:1591-99)

- **Pilot data in a phase 2 trial in NSTEMI indicated that the p38 MAPK inhibitor Losmapimod attenuates inflammation and may improve outcomes**
- **Part A: a leading cohort (n = 3503) to provide an initial assessment of safety and exploratory efficacy before progression to part B (~22,000 patients)**
- **PEP - CV death, MI, or severe recurrent ischemia requiring urgent coronary revascularization at week 12**
- **Results did not justify proceeding to a larger efficacy trial in the existing patient population**



6. Today, marketing authorisation is a "yes/no" decision after completing a research program ≥ 10 years



P&R: pricing and reimbursement. MAES: medically-attended adverse events

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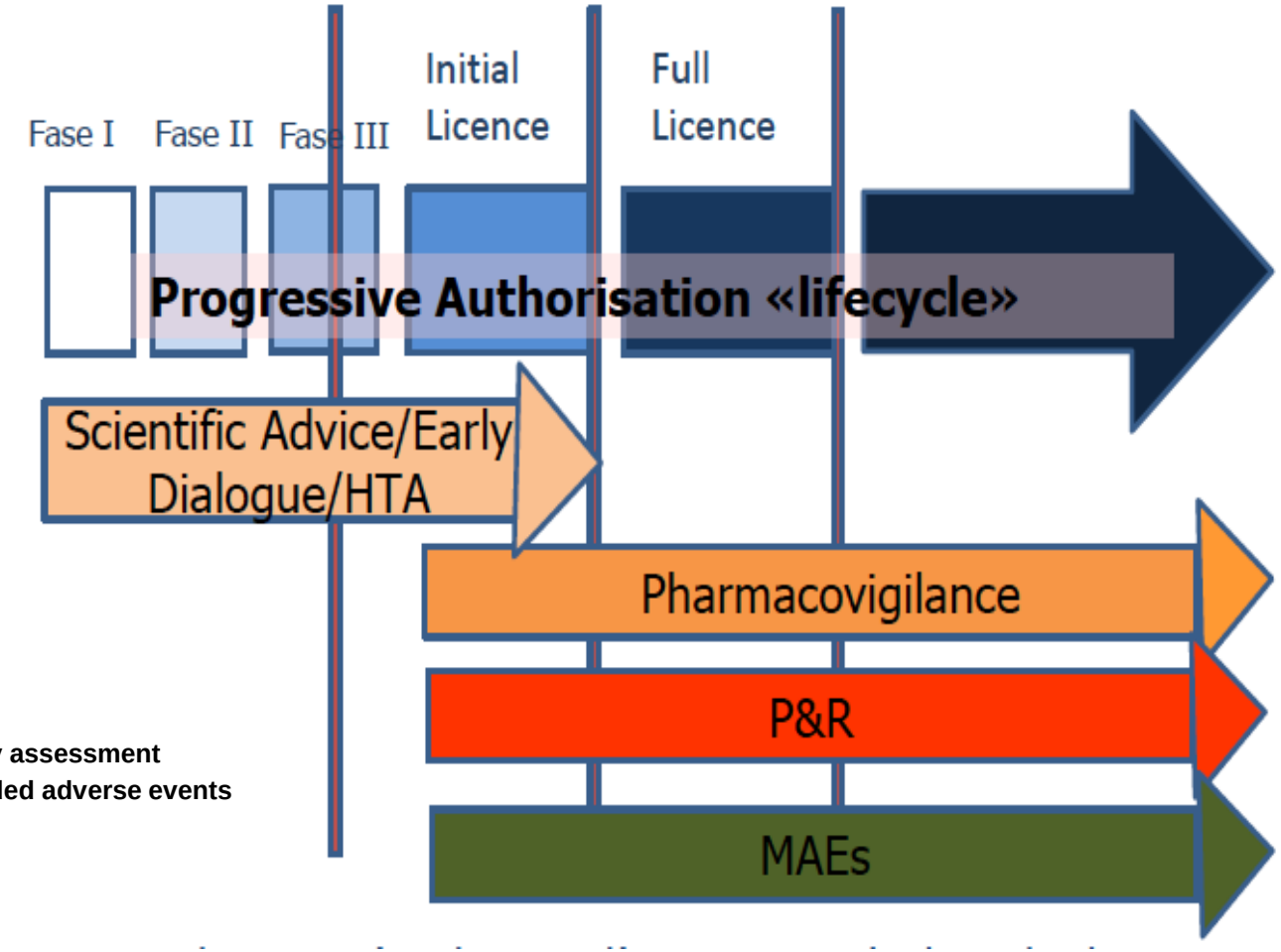
7. Tomorrow – Adaptive licencing



HTA: Health technology assessment
MAES: medically-attended adverse events

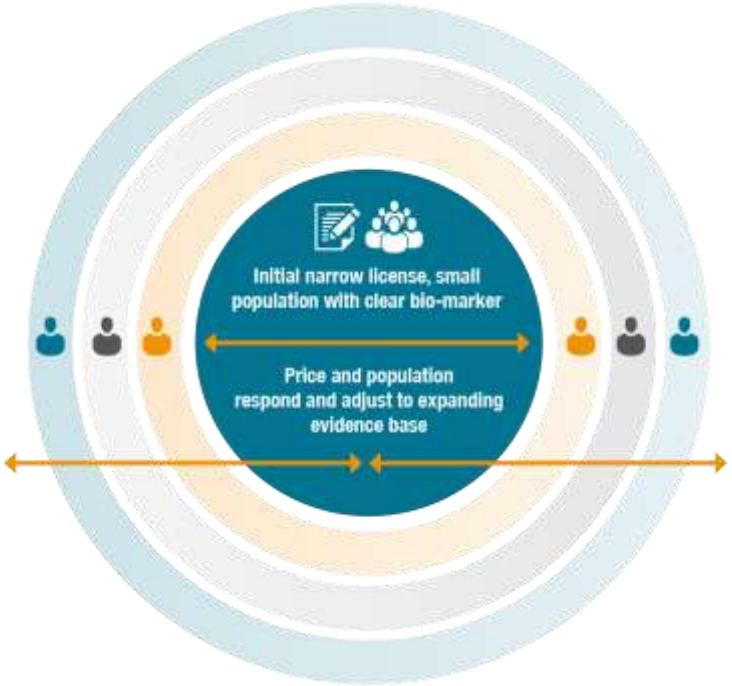
- **A <u>prospectively planned</u>, adaptative approach to bring more rapidly a promising new drugs for diseases where there is <u>an unmet medical need, orphan diseases or emergency threats to the market</u>**
- **Benefit for patients receiving earlier access to the product if benefit outweighs potential risk**
- **All patients exposed to the new drug will either be included in observational studies/registries, thereby contributing to real-word (effectiveness) information**

Adaptive Licensing (2014-17): Opdivo (Nivolumab)

- **Advanced unresectable or metastatic melanoma alone or plus ipilimumab**
- **BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent**
- **Unresectable or metastatic melanoma, plus ipilimumab**
- **Metastatic melanoma across BRA status**

- **Metastatic non-small lung cancer**
- **Advanced renal cell carcinoma who have received prior anti-angiogenic therapy**
- **Hodgkin lymphomanthat had relapsed or progressed after other treatments**
- **Recurrent or metastatic squamous cell carcinoma of the head and nec**
- **Hepatocellular carcinoma previously treated with Sorafenib**
- **Metastatic colorectal cancer**
- **Advences or metastatic urothelial carcinoma**

"no more one-size-fits-all"



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US National Institute of Health (NIH, 2015)

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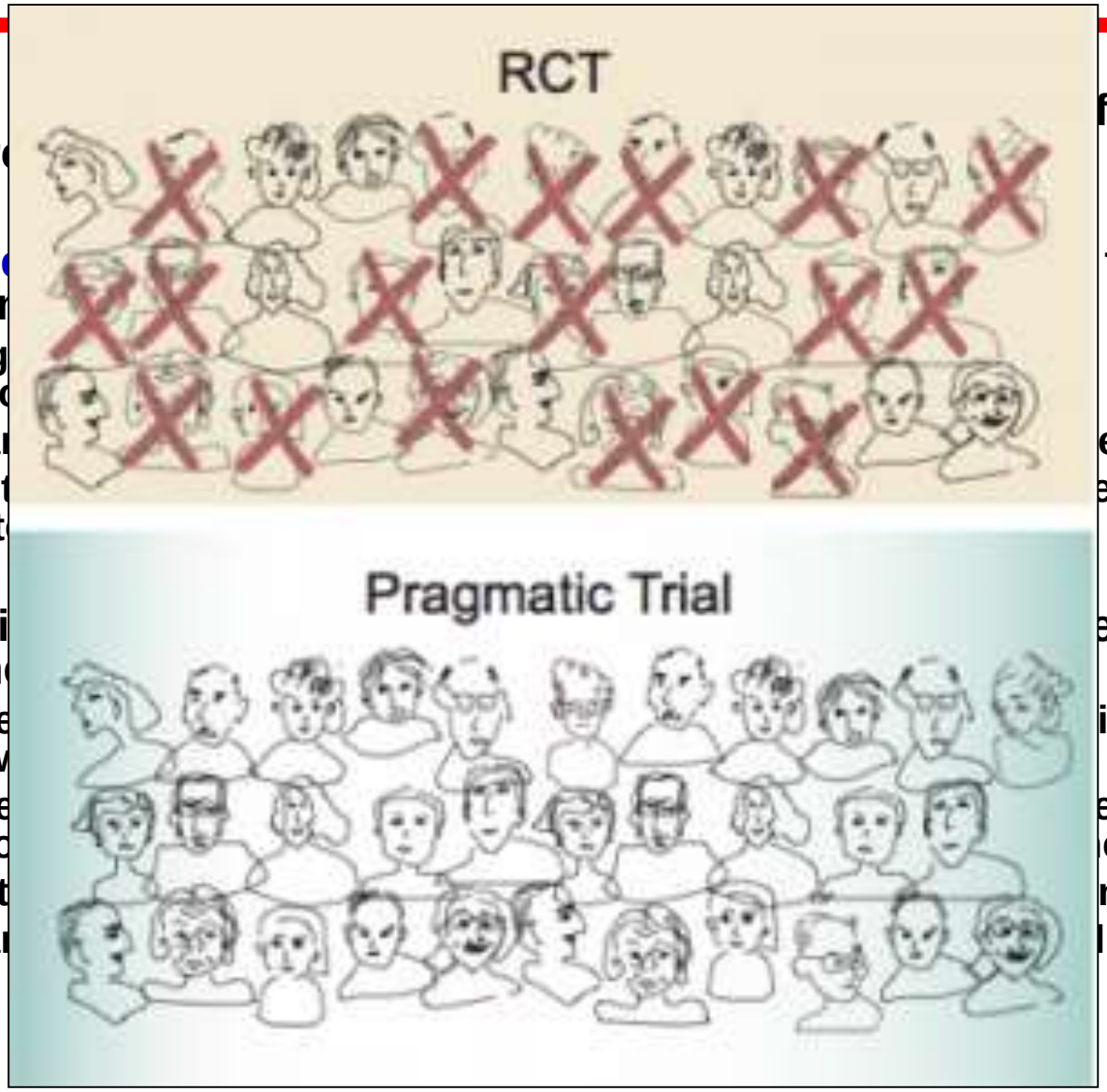

Pragmatic trials (NIH, 2018)

- **To counter these problems, many advocate a move to the so called Pragmatic clinical trials**

- **Designed NOT to study how treatments or interventions work in carefully controlled settings and study populations**

- ***The primary purpose of informing decision-makers regarding the comparative balance of benefits, burdens and risks of a biomedical or behavioral health intervention at the individual or population level*** **(Califf and Sugarmen. Clin Trials 2015)**
  - **Conducted in real-world settings to answer questions relevant for patients, providers and healthcare organizations**
  - **Questions may originate from academia, delivery systems, professional organizations, patient-clinician alliances, public health community or the general public**
  - **What interventions work for patients receving typical care**
  - **These intervencions are already used in clinical practice**

Pragmatic trials (NIH, 2018)

Must potentially add value to the healthcare system

- Results that decision makers might use to improve care and patient outcomes

- Integrated within daily clinical work flow
- Procesures should mimic normal clinical practice and use existing resources as much as possible
  - Use existing resources (electronic health records, registries and observational data already collected) for study design, participant recruitment, intervention implementation and data collection
- Clinics, hospitals, or clusters of facilities together to recruit large representative populations fostered by simple inclusion criteria and few exclusion criteria

- Frequently measure factors with practical value for the system such as costs

Johnson KE et al. BMJ 2014;349:g6826

Pragmatic clinical trials vs RCTs

Attribute	RCT	PCT
Who develops the study questions?	Researchers	Clinical decision makers (patients, clinicians, administrators, policy makers)
What is the purpose?	Determine causes and effects of treatments	Create generalizable knowledge, improve care locally, and inform clinical and policy decisions
What question does it answer?	Can this intervention work under ideal conditions?	Does this intervention work under usual conditions?
Who is enrolled?	A cohort of patients with explicitly defined inclusion/exclusion criteria	Diverse, representative populations. Inclusion/ exclusion criteria still apply, but tend to be broader
Who collects data?	Researchers. Data collection occurs outside of routine clinical care	Clinicians at the point of care in cooperation with researchers
What is studied?	A biological or mechanistic hypotheses	Comparative balance of benefits/risks of health intervention at the individual or population level
What is compared?	Treatment vs placebo	Comparative effectiveness of real-world alternatives
Is the study randomized to control for potential biases?	Yes. Usually at the individual level	May use randomization schemes: cluster randomization (by hospital or unit) or stepped wedge randomization (random crossover of clusters over time from control to intervention until all clusters are exposed)
What is the setting?	Medical centers - research sites	Multiple, heterogeneous settings
Outcomes	May be surrogates or process measures	Directly relevant to participants, funders, communities, and healthcare practitioners”

https://www.nihcollaboratory.org/Pages/default.aspx

Approaches to accelerate early clinical development

1. **Understand the MOA and PD/PK/safety before pivotal CTs**
- **Key phase II data – target validation, dose, best patients, efficacy/safety signals**

2. **Phase III:**
- **Incorporate primary endpoints based on MOA**
- **Focus on specific subsets of patients most likely to benefit (all vs niche)**
  - **Identified based on validated imaging and biomarkers**
- **Replace sites by Consortia with increasing harmonization**
- **Exchanging information in a secure and auditable fashion (cloud computing)**
- **Decrease burocracy:**
  - **Standardize trial design, single IRB and project management**
  - **Common data collection and processing, and sample banking**
  - **Identify safety signals**
3. **Became familiar new approaches for the design and analysis of CTs**
  - **Adaptative, Registry-based and Pragmatic Clinical Trials**

IRB: Institutional Review Board

ESC Working Group Cardiovascular Pharmacotherapy