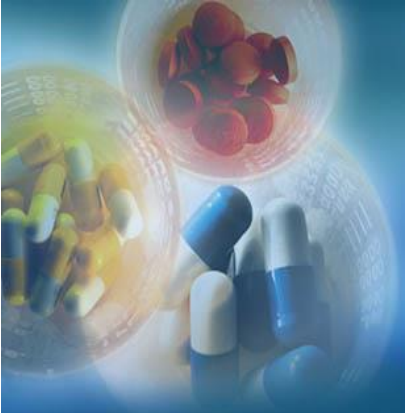




Lessons to be learned for an efficient execution of a clinical trial protocol with a multi-country, multi-center set-up

Sergey Kozhukhov

MD, PhD

**Head of Clinical Pharmacology Department
& Cardio-Oncology Unit**

SI «NSC «Institute of Cardiology by M.D.Strazhesko»

2019

Conflict of interest

Employment

- *SI “NSC “Institute of Cardiology n.a. M.D.Strazhesko”, Kyiv, Ukraine*
- *Expert Group “Cardiology. Rheumatology” of the State Expert Center*

Research support

- *Federal: European union*
- *Industry: Multiple clinical trials*

Consultant

- *Bayer, Dr. Reddy's, BCPP, Darnitsa, KRKA*

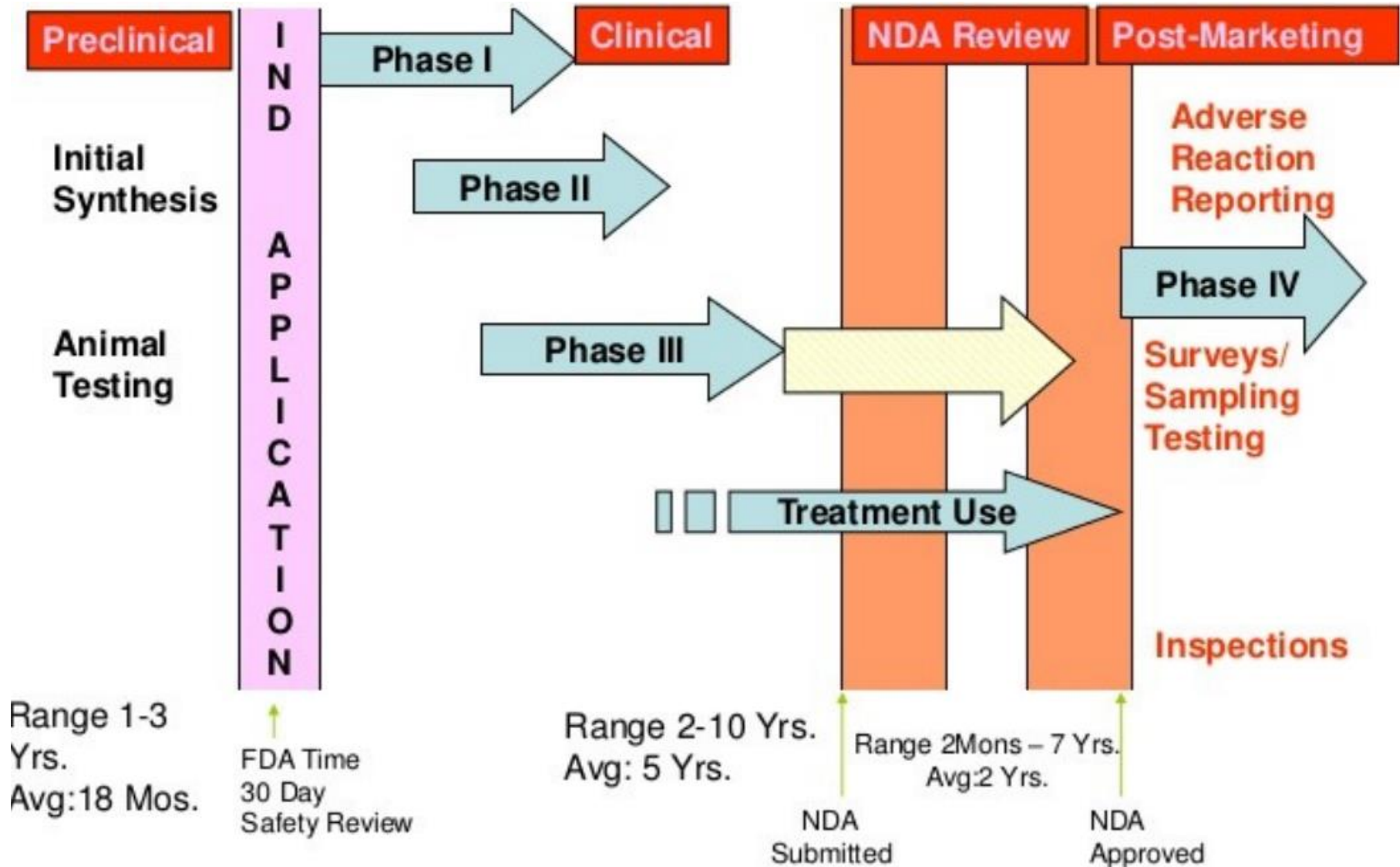
Editorial responsibility

- *Ukrainian Journal of Cardiology*
- *Journal Medical Research and Innovations*

Clinical Trial

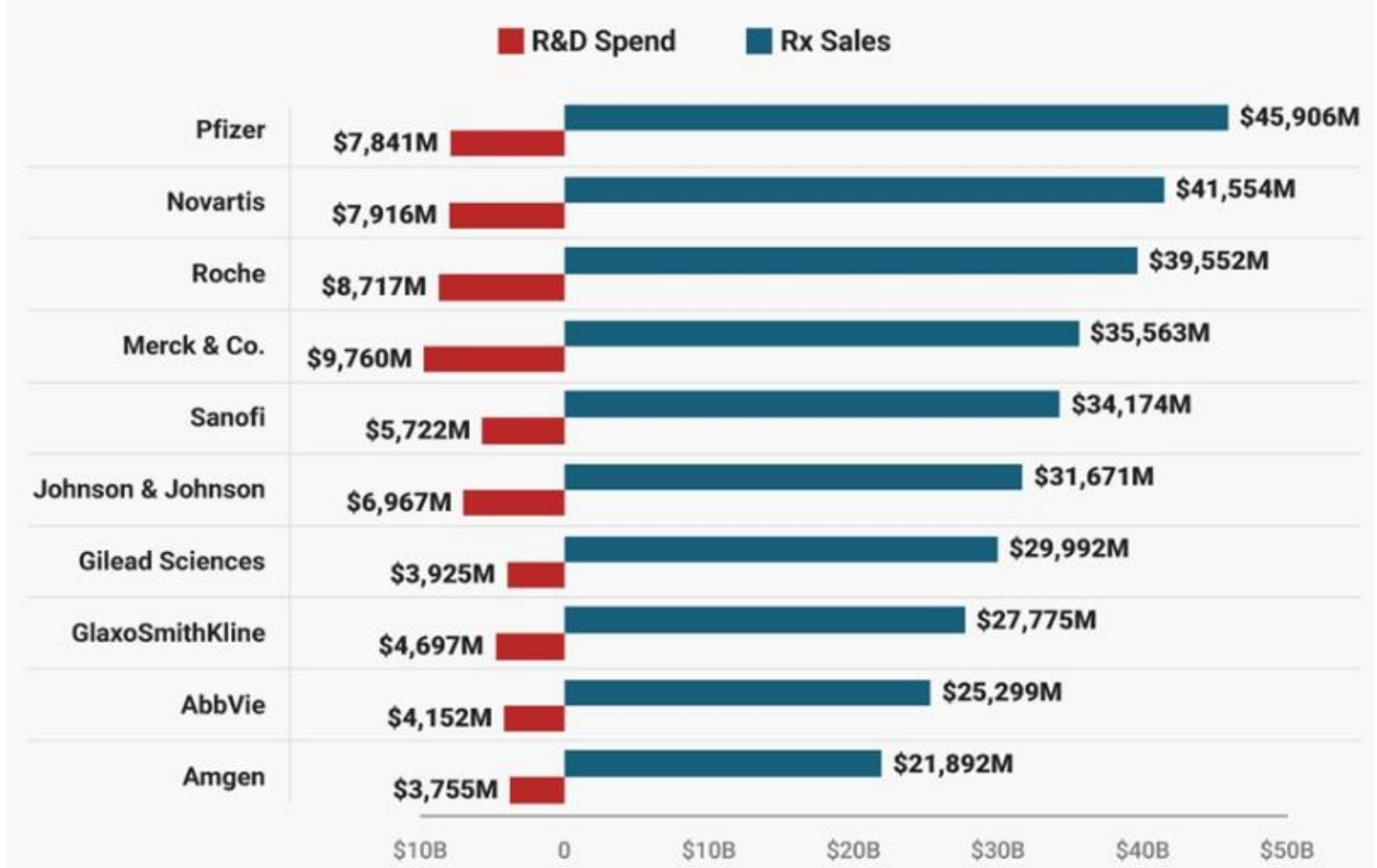
- scientific investigation that examine and **evaluate safety and efficacy** of different therapies in human subjects.
- **research** activity that involves administration of a test treatment to some experimental unit in order to evaluate the treatment.
- **experimental testing** of medical treatment on human subject.
- The Code of Federal Regulations (CFR) defines a clinical trial as the **clinical investigation** of a drug that is administered or dispensed to, or used involving one or more human subjects.

Drug Development Process



← Average of Approximately 100 Months From Initial Synthesis to Approval of NDA →

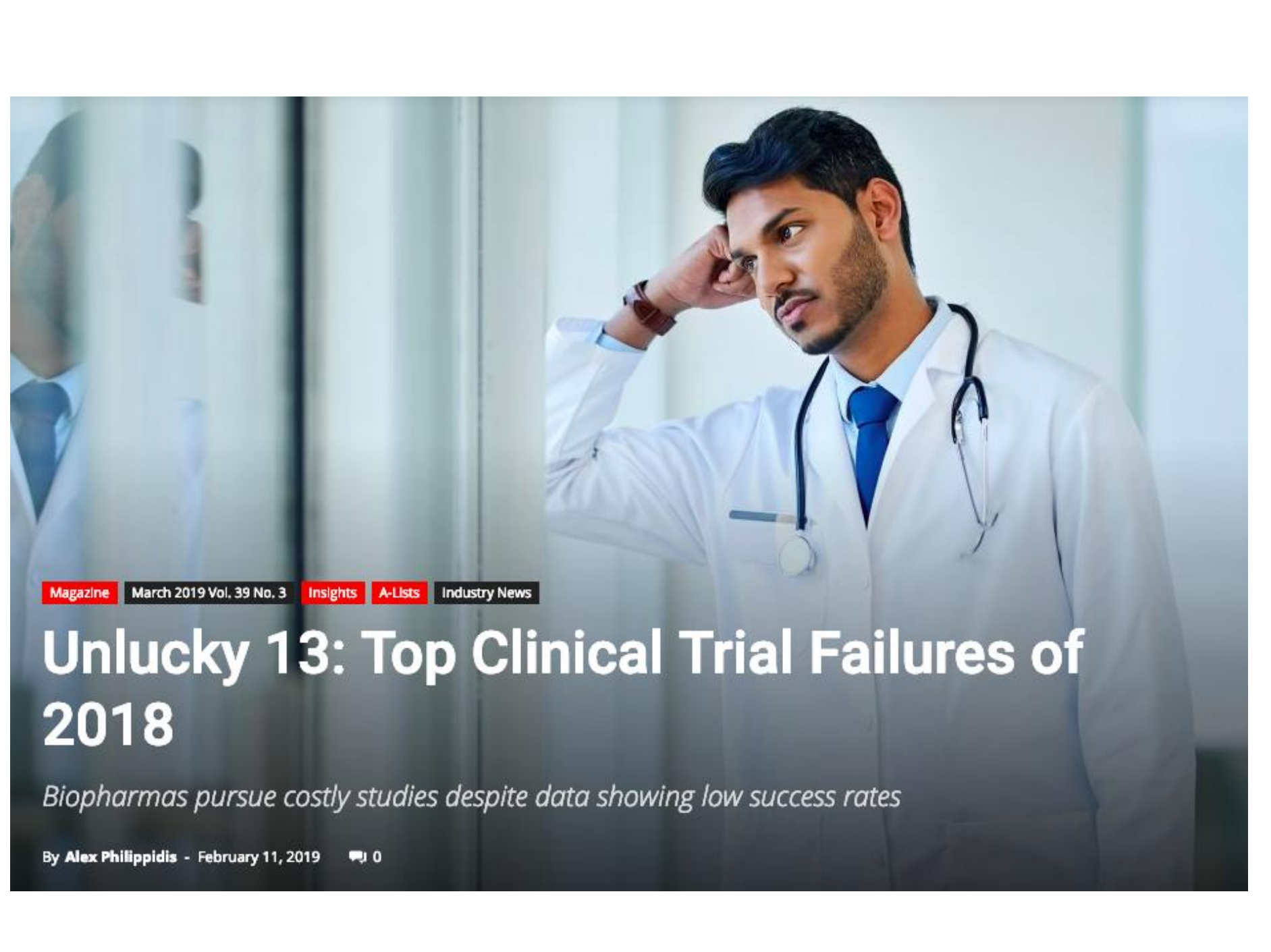
How much the 10 largest Big Pharma spend on R&D



Clinical trial success rates!?

- **sample of 406,038 entries of clinical trial data**
- **more than 21,143 compounds from January 1, 2000 to October 31, 2015**
- **32.6% for clinical studies of ophthalmology drug candidates**
- **25.5% for cardiovascular drug candidates**
- **25.2% for infectious disease products**

The lowest percentage came from oncology trials, at just 3.4%



Magazine March 2019 Vol. 39 No. 3 Insights A-Lists Industry News

Unlucky 13: Top Clinical Trial Failures of 2018

Biopharmas pursue costly studies despite data showing low success rates

By **Alex Philippidis** - February 11, 2019  0

Unlucky 13

Top Clinical Trial Failures of 2018

Each drug candidate is listed alphabetically. Also shown is each drug's sponsor(s), the indication for which the drug failed, the type of drug, and a brief account of how the drug failed.

1 Atabecestat (JNJ-54861911)
Janssen (Johnson & Johnson)
Alzheimer's disease
BACE inhibitor

Janssen halted clinical development of Atabecestat, ending a Phase I/II trial and a Phase II European long-term safety study after citing "serious" elevations of liver enzymes in some study participants who received the drug.

2 Axalimogene filolisbac
Advaaxis
Cervical + head and neck cancer
Targeted Lm-based immunotherapy

A Phase II combination trial with AstraZeneca's imfinzi[®] was halted in March after a patient death, then resumed in July after C-level overhaul. In November, Advaaxis said it would halt enrollment in the combination trial to maximize the efficient use of clinical funding resources.

3 Azeliragon (TTP488)
vTv Therapeutics
Alzheimer's disease
BACE inhibitor

Shares plunged 71% after vTv halted azeliragon studies following an initial readout failure in Part A of the Phase III STEADFAST study. However, vTv identified a subpopulation (Alzheimer's patients with type 2 diabetes) showing statistically significant benefit.

4 BI 409306
Boehringer Ingelheim
Alzheimer's disease
PDE5 inhibitor

Boehringer Ingelheim shifted BI 409306's development focus to ongoing schizophrenia studies after missing efficacy endpoints in two Phase II trials in patients with cognitive impairment and memory dysfunction in Alzheimer's and schizophrenia.

5 EG-1962 (nimodipine microparticles)
Edge Therapeutics
Aneurysmal subarachnoid hemorrhage
Resorbable microparticle

Edge ended the Phase III NEWTON2 study after concluding EG-1962 was unlikely to meet the primary endpoint. Edge reviewed strategic alternatives, resulting in its planned reverse-merger with **PDS Biotechnology**, expected to close in Q1 2019.

6 Epacadostat (INC8024360)
Incyte
Unresectable or metastatic melanoma
IDO1 inhibitor

Incyte downsized its epacadostat clinical program after a combination with Merck & Co's Keytruda[®] (pembrolizumab) failed the Phase III ECHO-301/KEYNOTE-252 trial. Two pivotal lung cancer trials of the combo were converted to Phase II studies.

7 HTL0018318
Sosai Group and Allergan
Lewy body dementia
Muscarinic M1 receptor agonist

The companies said Phase II studies in Lewy body dementia and other dementias, including Alzheimer's, would be delayed at least 6 months. The companies cited the need to investigate an unexpected toxicology finding that occurred in a single animal study involving nonhuman primates.

8 Ingrezza[®] (valbenazine)
Neurocrine Biosciences
Tourette syndrome
Selective VMAT2 inhibitor

Neurocrine began 2019 assessing Ingrezza's future in Tourette syndrome after its third trial failure in that indication, missing the primary endpoint in the Phase III T-Force GOLD Study. Ingrezza generated an estimated \$400M in the treatment of tardive dyskinesia.

9 Keyzilen[®] (AM-101)
Auris Medical Holding
Acute inner ear tinnitus
NMDA receptor antagonist

Auris has been weighing Keyzilen's future since March 2018, when the drug missed its primary endpoint in the TACTT3 trial of significant Tinnitus Functional Score improvement vs. placebo—Keyzilen's second Phase III failure in 19 months.

10 MM-141 (lirastatimab)
Merrimack Pharmaceuticals
Pancreatic cancer
Tetavalent monoclonal antibody

Merrimack scrapped MM-141 after missing primary and secondary endpoints in the Phase II CARRIE trial, assessing the drug plus nab-paclitaxel in patients with previously untreated metastatic pancreatic cancer and high serum levels of free insulin-like growth factor-1.

11 Olumacostat glasaretil
Dermira
Acne vulgaris
Topical sebum inhibitor

Dermira effectively scrapped olumacostat glasaretil after it failed to reduce lesion counts or show 2+ grade IGA improvement in two Phase III trials. The drug was once projected to generate \$250M in annual sales.

12 Verubecestat (MK-8931)
Merck & Co.
Prodromal Alzheimer's disease
BACE1 inhibitor

Merck & Co. dropped verubecestat from its late-stage pipeline after the drug failed the Phase III APOCS study in February 2018—the drug's second late-stage failure. The first came in February 2017 in the EPOCH study.

13 VR475 (nebulized budesonide)
Vectura Group
Asthma
Drug-device combo with jet nebulizer

Vectura ended VR475 development in November after it failed a Phase II trial in adults and adolescents with severe uncontrolled asthma. Vectura added VR475 to its pipeline in 2014 by acquiring **Activase** for €130M (\$147.6M).

5 of the 13 drug

...for Alzheimer's treatments

...next largest category was cancer

When Good Trials Go Bad

Beyond these biological considerations, a number of other factors can also derail a clinical trial. These may include:

- Inadequate Study Design**
- Improper Dose Selection**
- Non-optimal Assessment Schedules**
- Inappropriate Efficacy Metrics/Markers**
- Issues with how the data are analyzed**

PRE-CLINICAL FAILURE

- Model does not reflect human disease biology
- Drug does not target biology relevant to human application
- Lack of appreciation of human disease **Mechanism is all Important**
- Dogma & overstating effect **Relevance of Slight Delay of a Few Days, Slight Diminution**
- Model used in a way that does not reflect human indication
Prophylactic/Therapy
- Drug doses are not used in at physiological doses **“Building Site Effect”**
- Drugs are not delivered in a way appropriate to how used in humans
“Route & Timing”
- Studies are not transparent & not reproducible (Ineffective Study Design) **Reporting Issues**

TRANSLATING FROM BENCH TO BEDSIDE



Animal model!

Even if we give a new medicine to some human cells, this cannot tell us how it will affect the whole body. We also need to know if the medicine will reach the part of the body it needs to.

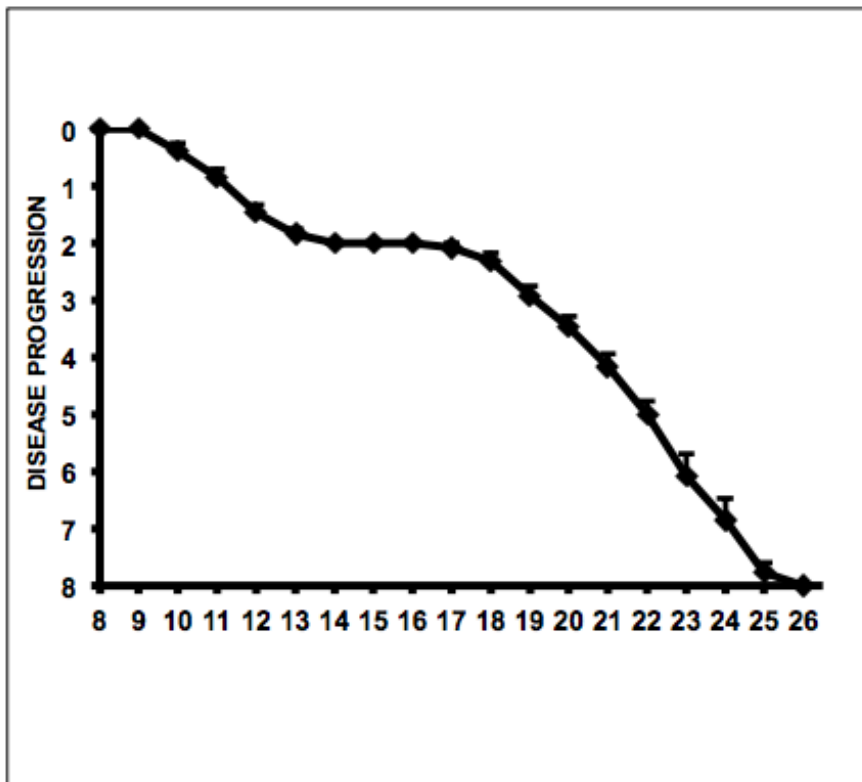
Living animals, most commonly mice, rats and fish, are used to see how a medicine affects a whole body. It can tell us about the toxicity and will also indicate what dosage is necessary for humans.



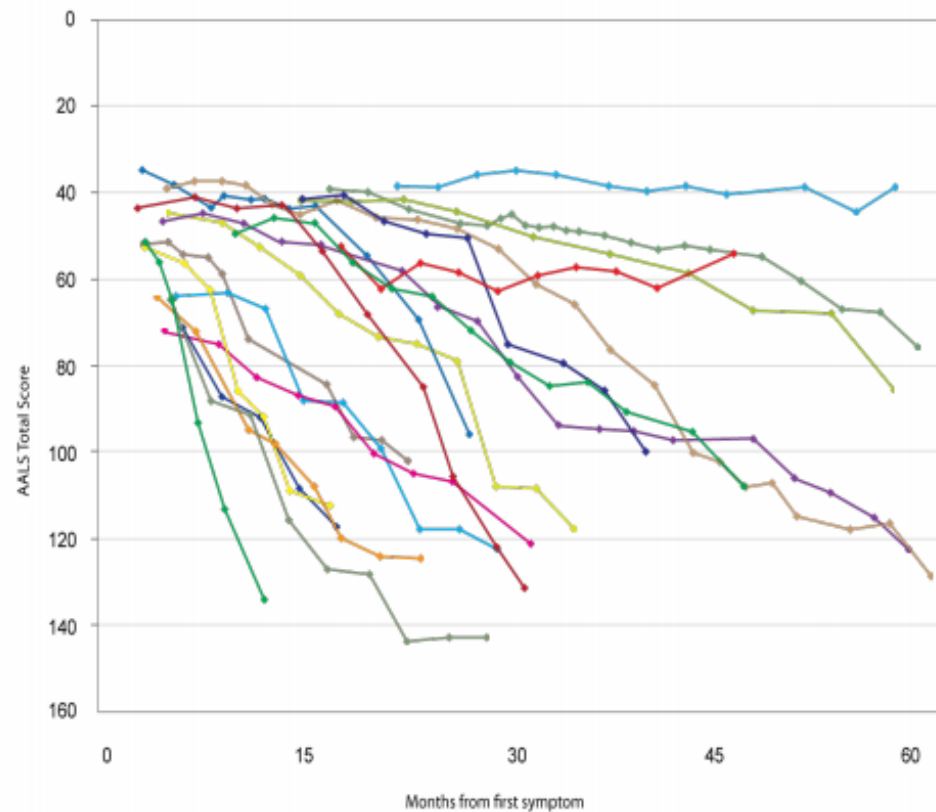
The government requires new medicines to be tested on two species. Why do you think this is?

MICE AND MEN: HOMOGENEITY VERSUS HETEROGENEITY

ALS mSOD1 Transgenic Mice



Human ALS Patients



CLINICAL FAILURE

- Lack of clear understanding of human pathology **Immune (T/B cell) or Neurodegeneration**
- Drug is seldom investigated by scientists developing the Idea **Professional Trialists**
- Over-interpretation of significance of pre-clinical studies
- Drug is not used at a dose relevant to the pre-clinical studies
- Population does not respond as predicted. (Ineffective Trial Design) **“Placebo Effect”**
- Dose-limiting side-effects **Less Circuitry so Less Compens Capacity**
- Study Underpowered, too short or unrealistic expectations
- Measurement Instruments Inadequate Clinical Outcomes and Surrogate Markers
- Wrong Group of studied (Ineffective Trial Design) **Non-Responders**
- Commercial Interests

Scientific model!

Models are used in scientific research when we cannot study the real thing. They help us to predict what will happen.

There are 3 kinds of models used in developing a new medicine:

- Non-animal/non-human
- Living humans
- Living animals



Human model!

Stage I

Testing at low doses on healthy volunteers. Usually young males



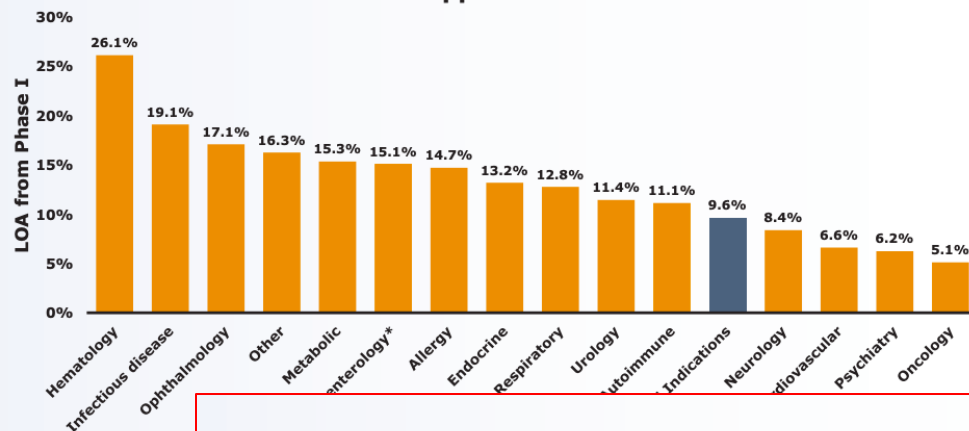
Stage II

Testing on ill patients to test efficacy of drug and calculate appropriate dosages

Stage III

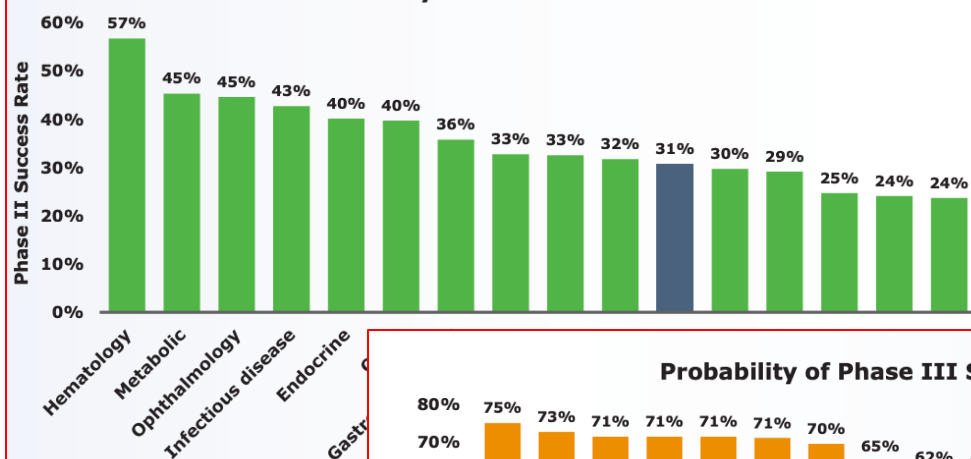
Testing on a large number of patients to gather data from larger populations

Likelihood of Approval from Phase I



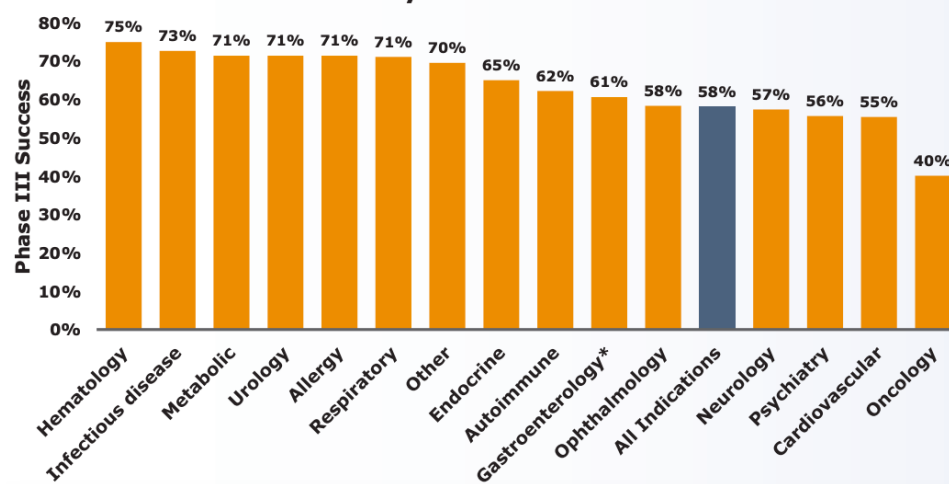
9.6%

Probability of Phase II Success



31.0%

Probability of Phase III Success



58.0%

from phase II to phase III CT... (chance 1 of 10)

The High Price Of Failed Clinical Trials: Time To Rethink The Model

*By Ralf Huss, MD, Chief Medical Officer,
Definiens*

Back in 2014, a [study](#) in Nature Biotech showed that only 32% of drugs have a probability of making it to Phase 3 trials, and only one in 10 drugs overall actually makes it to market. Things haven't improved since then.

BIO recently [put out](#) a study reporting that the average overall likelihood of approval (LOA) by FDA from Phase I was 9.6 percent – a 1 in 10 chance. The rate is even lower for major disease areas like oncology. Phase II clinical programs continue to experience low success rates as well, with only 30.7 percent of candidates advancing to Phase III, a slightly worse rate than it was a few years ago.



**CLINICAL
LEADER**

Steps Reducing the Rate of Failure

There are several important steps the industry can take to reduce the failure rate of clinical trials:

- **Prioritize Biomarkers**
- **Leverage Big Data**
- **Diversify Research**

With Pain Comes Gain

Failed clinical trials result in wasted money and resources, lost jobs and a setback in research. The only silver lining to this cycle of failures is that it will facilitate a change in the industry.

Important steps to reduce the rate of unsuccessful CT

1. Priority to biomarkers

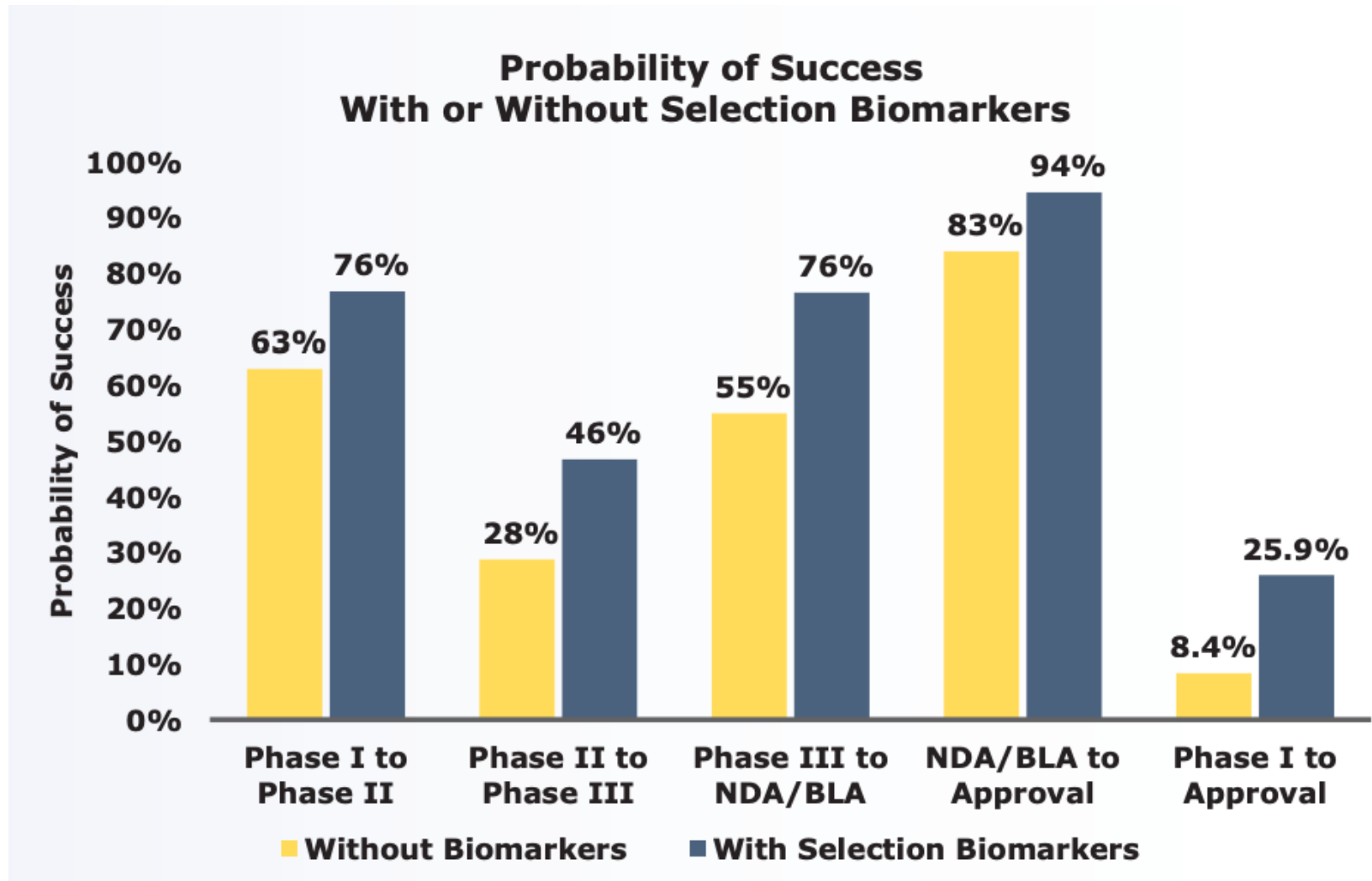
- Personalized medicine is the right choice of patients for the right medicine at the right time and in the right dose.
- Identify a drug that may be unsuccessful ...
- 50% of drugs failed in phase III - due to lack of effectiveness.
- To stratify patients and improve diagnosis
- Select patients who will benefit from treatment.

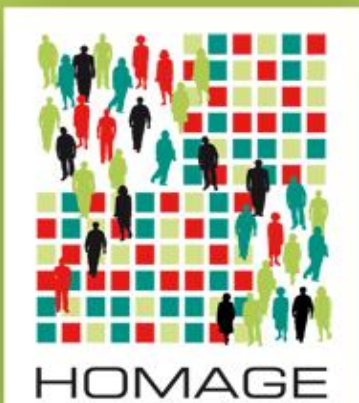
Industry:

- Lack of attention to biomarkers
- The initial reason? Is expensive and ambiguous ...

Biomarker programs should be incorporated into clinical studies in order to avoid the loss of finances!!!

Biomarkers in Clinical Trials





HOMAGE (Heart OMics in AGEing) is a ‘bench to bedside’ project which aims to identify and validate specific biomarkers of heart failure in order to prevent the development of the disease affecting elderly population.

FIBRO TARGETS

[Home](#) [About us](#) [The project](#) [Work program](#) [Achievements](#) [News & Events](#) [Usefull links](#) [Contact us](#) [Extranet](#)

Welcome to FIBROTARGETS website

The Fibro-Targets (Targeting cardiac fibrosis for heart failure treatment) project is a multi-disciplinary program involving 11 partners ambitioning “the identification, characterisation and validation of in vitro and in vivo models of novel therapeutically relevant targets” for myocardial interstitial fibrosis (MIF) in heart failure.



MYOCARDIAL INTERSTITIAL FIBROSIS

TGF- β pro-fibrotic pathways

TGF- β -related cytokines: Cardiotrophin-1 (CT-1), Apelin
NADPH oxidases (NOX)

Genetic and environmental
factors

Other factors

MIF

Pro-fibrotic miRs

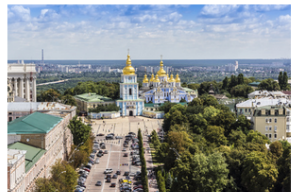
miR-21, miR-21*,
miR-24, miR-212/132

Aldosterone-related targets

CT-1, NGAL, Galectin 3

Matricellular proteins

SPARC Thrombosponin (TSP-2) Osteoglycin OGN



National Scientific Center

Institute of cardiology was established 75 years ago as the largest clinical and research institution in Ukraine. Currently, we employ 720 persons, most of them researchers, teachers and professors. The institute has 340 beds and offers degrees in general and interventional cardiology, electrophysiology, clinical pharmacology, vascular biology. We have nearly 132 PhD and 32 physician scientists of Sciences.

Emergency Cardiology Department, as a sub-unit of the Institute of Cardiology, has about 900 patients/year with different acute cardiovascular disorders – acute coronary syndromes, decompensated heart failure, arrhythmias, complicated hypertensive crisis. Department has involved in molecular cardiology translational studies and genomic long-term collaboration with National Academy of Sciences institutions, in 25 multicenter randomized clinical trials with TIMI group (Boston, USA), Duke Research Institute (USA), PHRI (Hamilton, Canada), Oxford University (UK), Thrombosis Research Institute (London, UK) etc.

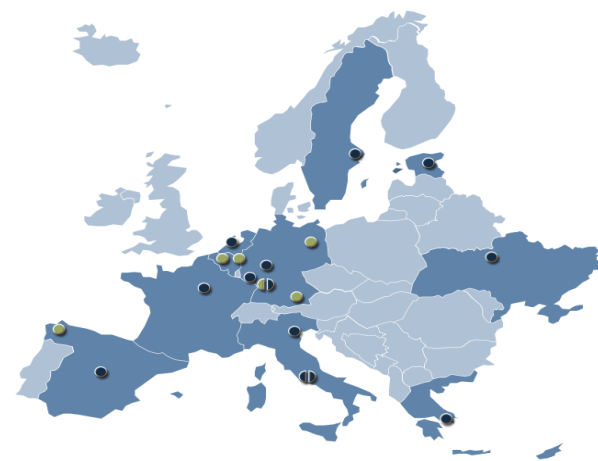


Contact:
Prof. Dr. Alexander
Parkhomenko
Head of Department
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Institute of Cardiology
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Ukraine

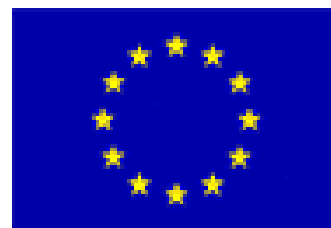


Partner

- University Hospital Heidelberg
- Comprehensive Biomarker Center GmbH
- Saarland University
- Tartu University
- University Hospital of Padova
- metanomics GmbH
- Uppsala University
- Goethe University Frankfurt
- Hôpital Pitié-Salpêtrière



In 2014-2018 our department participated in project EC - Seventh Framework Programme (FP-7) "Biomarker Research Alliance for Diagnostics Heart Disease in the Ageing European Population" – «Альянс по дослідженню біомаркерів для діагностики захворювань серця у різних вікових групах європейської популяції», проект FP-7-HEALTH-2012-INNOVATION-1. Grant Agreement Number 305031



**Clinical Pharmacology Department
SI «NSC «Institute of Cardiology by
M.D.Strazhesko»**

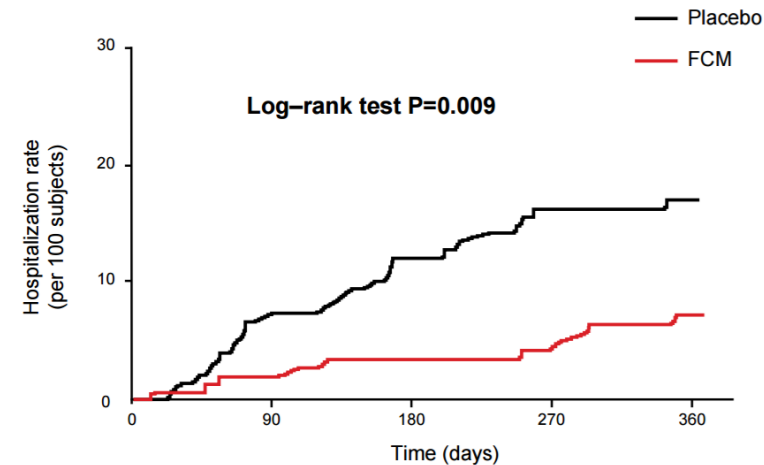
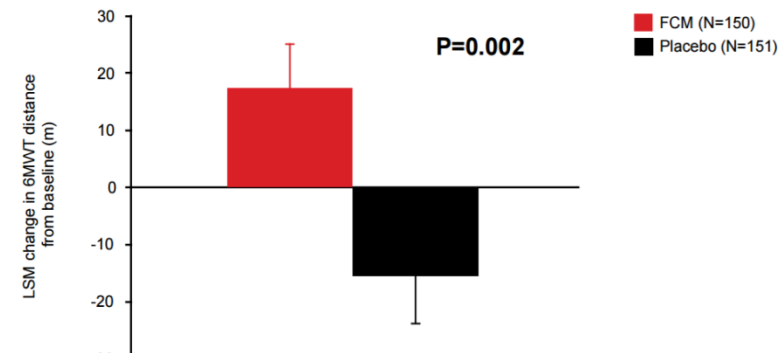
CONFIRM-HF protocol FER-CARS 05

(304 patients, 41 sites)

- Measurement LV EF <45%
- Hb < 15 g/dL
- BNP > 100 pg/ml
- NT-proBNP > pg/ml
- Ferritin < 100 ng/ml
- Transferrin saturations < 20%
- Vit B12/acid folic deficits

FCM improved 6MWT at week 24

FCM vs placebo: 33 ± 11 m (*least squares mean $\pm$ SE*)



No. of subjects at risk

Placebo	151	138	127	117	78
FCM	150	140	131	126	77

Important steps to reduce the rate of unsuccessful CTs

2. Use available data

- Large amounts of data
- No completed data
- The lack of publication of the results of CT (especially unsuccessful)

3. Pilot study

1 farm company for 10 years,

- only **6** of 26 molecules in the development of new molecules were approved

- unsuccessful investments amounted to **\$ 290 million**.

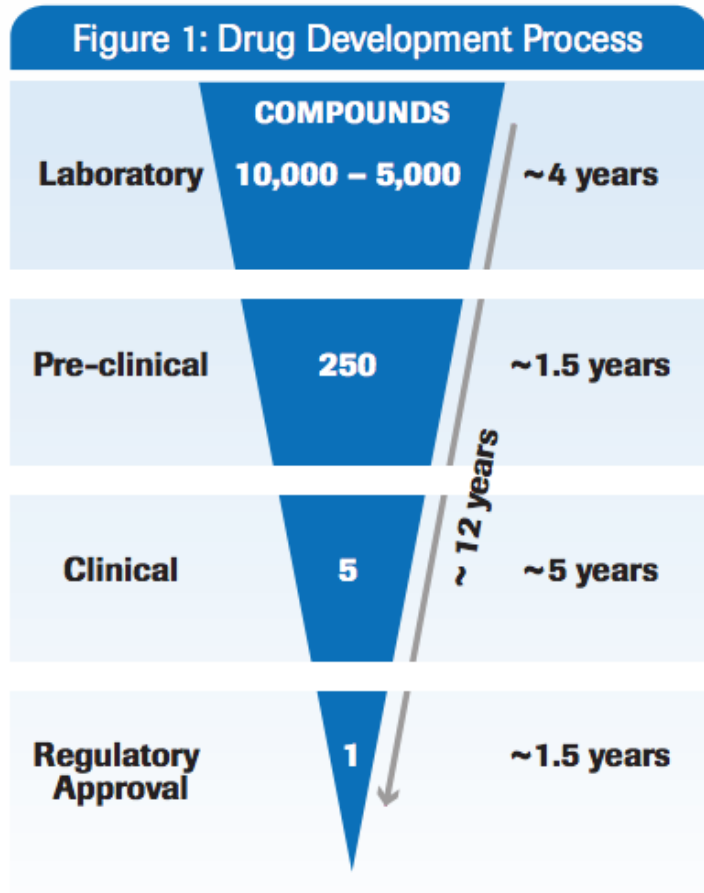
- **\$ 110 - \$ 170 million** is spent on the development of a single molecule.

Results of RCTs: publications...



Is it important?

Publication of failed CT



Publications of failed clinical studies, the causes - is a difficult task. If they publish "negative" results, then there is no exact data. They are either not published at all, or are published with a significant delay.

Even when studies are published, key research elements, such as statistical design, are often missing.

For researchers in any field, it is necessary to look for new research schemes and new endpoints, after a significant number of promising drugs research, if they have failed.

¹(Pharmaceutical Industries and Associations (EFPIA). A Highly Regulated Industry. Accessed November 2012. Available at: <http://62.102.106.100/Content/Default.asp?PageID=361>)

«black list...»

A black and white photograph of the Memorial Sloan Kettering Cancer Center building, a large multi-story glass and steel structure with many windows and rooftop HVAC units. The building is the background for the text overlays.

Memorial Sloan Kettering Cancer Center

Trials: **39**

Late/No Results: **39**

% Late/No Results: **100%**

Days late on average: **651**

«black list...»





\$10,000

Daily penalty for failure to report results within twelve months of trial completion under the FDA Amendments Act.

iversity

als: **82**

Late/No Results: **78**

% Late/No Results: **95%**

Days late on average: **629**

The UK is calling for greater CT transparency after a government committee released a report that indicates that data from about half of all CT in that country are not published

Commons Select Committee



Failing to publish data from clinical trials presents risk to human health



30 October 2018

The Science and Technology Committee has expressed concern that nearly half of clinical trials fail to publish their results. The Committee is calling for increased transparency today, as it releases a new Report.



House of Commons
Science and Technology
Committee

Research integrity: clinical trials transparency

Tenth Report of Session 2017–19

Report, together with formal minutes relating to the report

Ordered by the House of Commons to be printed 23 October 2018

...negative result - is also result...



Why it's time to publish research “failures”

Elsevier.com /connect/scientists-we-want-your-negative-results-too

Publishing bias favors positive results; now there's a movement to change that

Who's not sharing their trial results?

Trials registered on [ClinicalTrials.gov](https://clinicaltrials.gov) should share results on the site shortly after completing, or publish in a journal. But many organisations [fail to report the results of clinical trials](#). We think [this should change](#). Explore our data (last updated October 2016) to see the universities, government bodies and pharmaceutical companies that aren't sharing their clinical trial results.

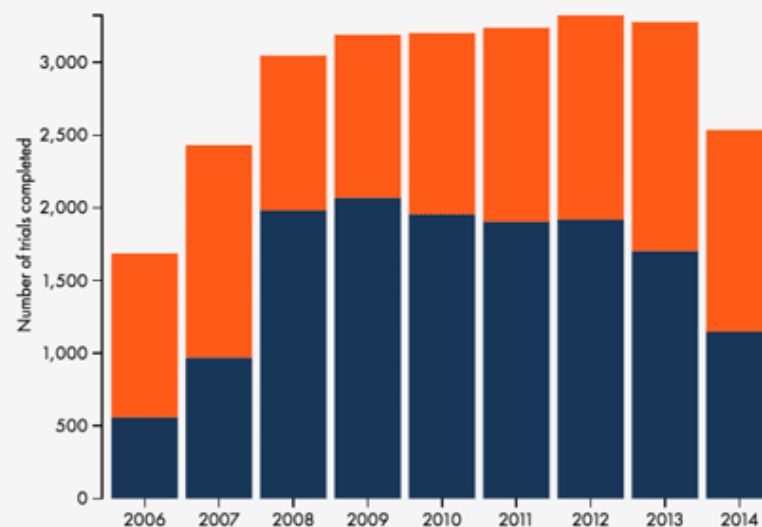
Trial sponsors

We've ranked the major trial sponsors with the most unreported trials registered on [ClinicalTrials.gov](https://clinicaltrials.gov). Click on a sponsor's name to find out whether it's getting better at reporting completed trials - or worse.

	Name of sponsor	Trials missing results	Total eligible trials	Percent missing
1	Sanofi	285	435	65.5%
2	Novartis Pharmaceuticals	201	534	37.6%
3	National Cancer Institute (NCI)	194	558	34.8%
4	Assistance Publique - Hôpitaux de Paris	186	292	63.7%
5	GlaxoSmithKline	183	809	22.6%
6	Mayo Clinic	157	312	50.3%
7	Yonsei University	139	194	71.6%
8	Seoul National University Hospital	131	207	63.3%

Trials by year

Since Jan 2006, **all major trial sponsors** completed 25,927 eligible trials and **haven't published results for 11,714 trials**. That means 45.2% of their trials are missing results.



Important steps to reduce the rate of failed CT

3 main reasons for failed CTs:

- ❖ molecule problems
- ❖ logistics problems
- ❖ design problems

Molecule mismatch:

- 1) Non-appropriate activity
- 2) Non-toxic (associated with biological activity)

Types of toxicity:

- ✓ Severe or generalized toxicity
- ✓ Severe unsuspected toxicity
- ✓ Suspected toxicity (cumulative toxicity, toxicity associated with renal failure...)

Predicting Successes and Failures of Clinical Trials: Time To Rethink The Model

Gayvert et al/ Publication



Please cite this article as: Gayvert et al., A Data-Driven Approach to Predicting Successes and Failures of Clinical Trials, Cell Chemical Biology (2016), <http://dx.doi.org/10.1016/j.chembiol.2016.07.023>

Cell Chemical Biology
Resource

A Data-Driven Approach to Predicting Successes and Failures of Clinical Trials

Kaitlyn M. Gayvert,^{1,2,3} Neel S. Madhukar,^{1,2,3} and Olivier Elemento^{1,2,4,*}

¹Department of Physiology and Biophysics, Institute for Computational Biomedicine, Weill Cornell Medicine, New York, NY 10021, USA

²Institute for Precision Medicine, Weill Cornell Medicine, 1305 York Avenue, New York, NY 10021, USA

³Tri-Institutional Graduate Program on Computational Biology and Medicine (Cornell University in Ithaca, Weill Medical College of Cornell University, and Memorial Sloan-Kettering Cancer Center), New York, NY 10065, USA

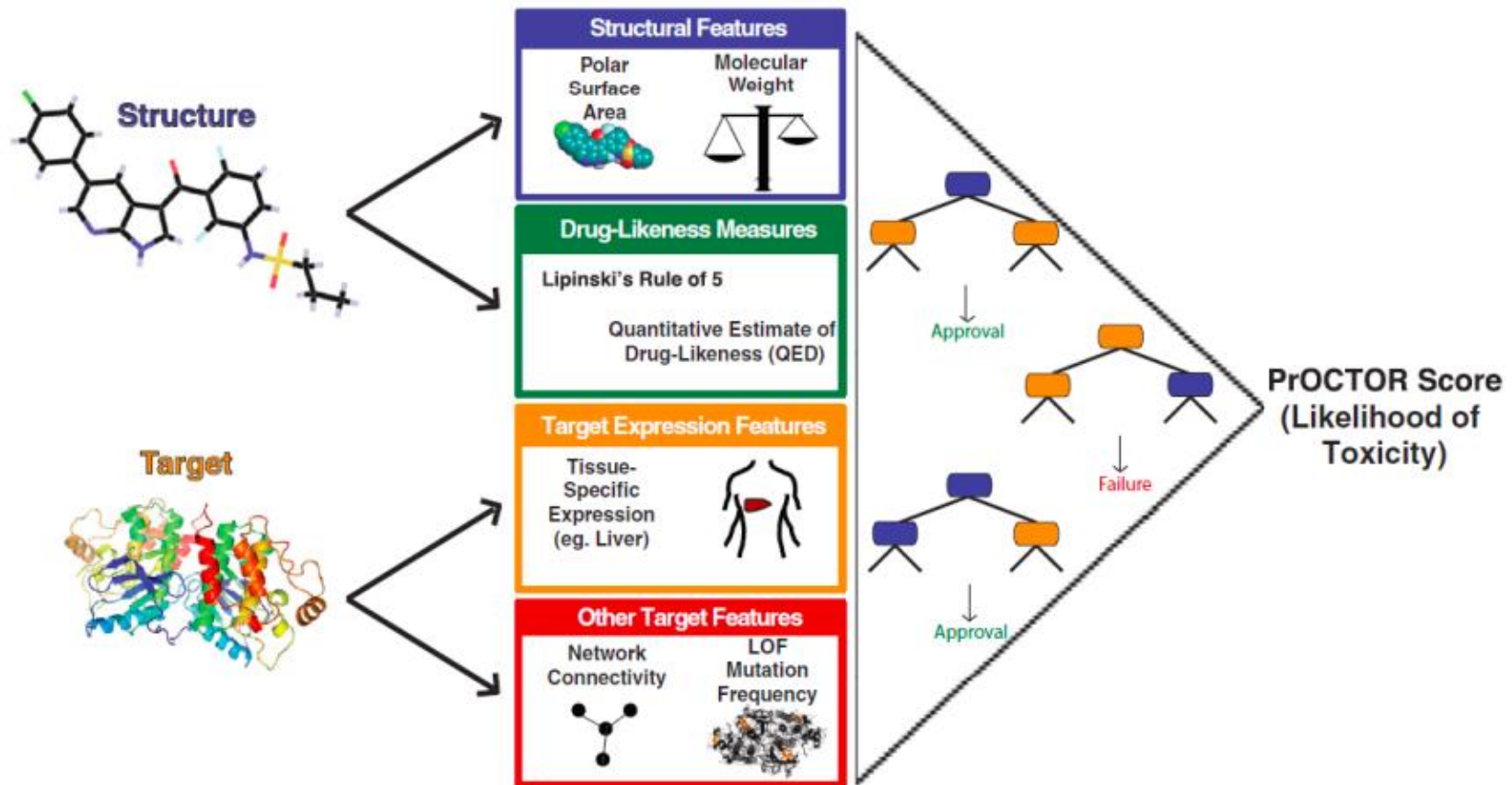
⁴Lead Contact

*Correspondence: ole2001@med.cornell.edu

<http://dx.doi.org/10.1016/j.chembiol.2016.07.023>

This paper introduced a data-driven approach (PrOCTOR) that directly predicts the likelihood of toxicity in clinical trials.

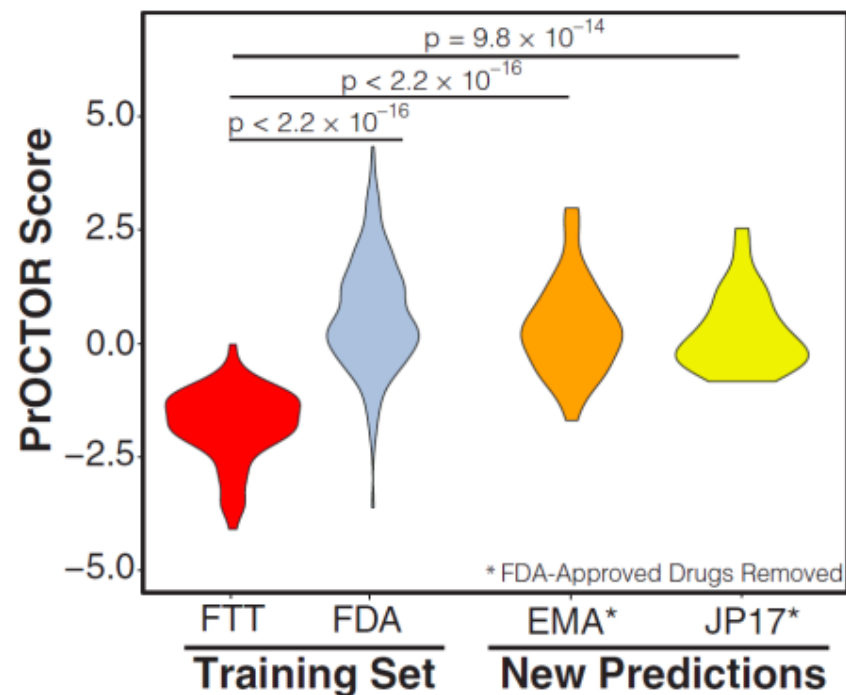
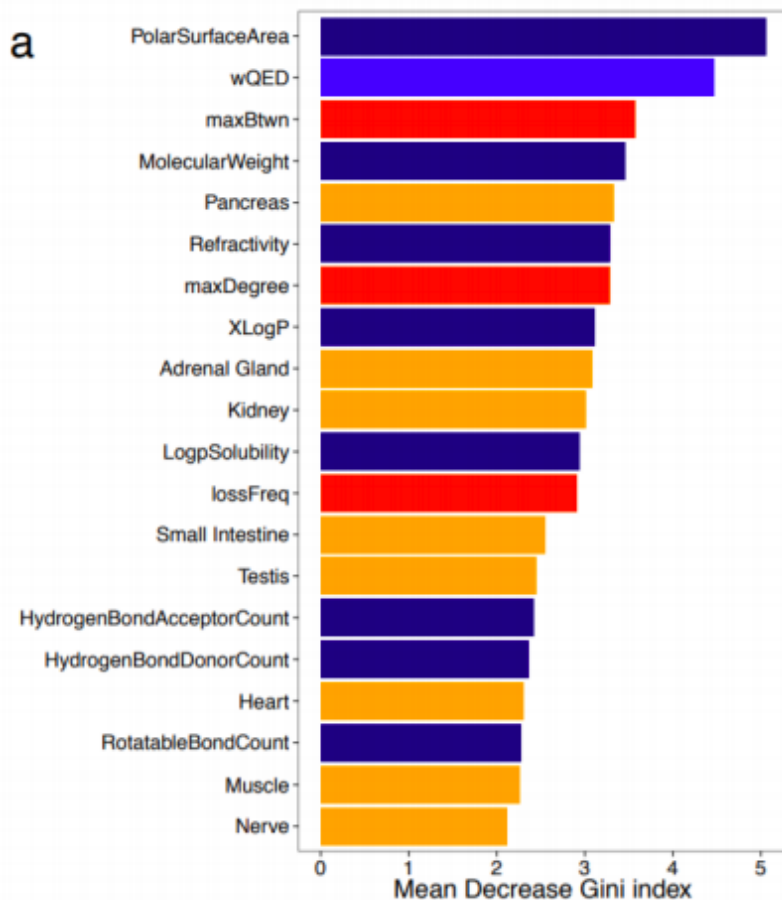
Modelling, Random Forest, Performance, Validation



- 48 features: 10 molecular properties, 24 target based features, 4 drug-

Model applied to European and Japanese approved drugs

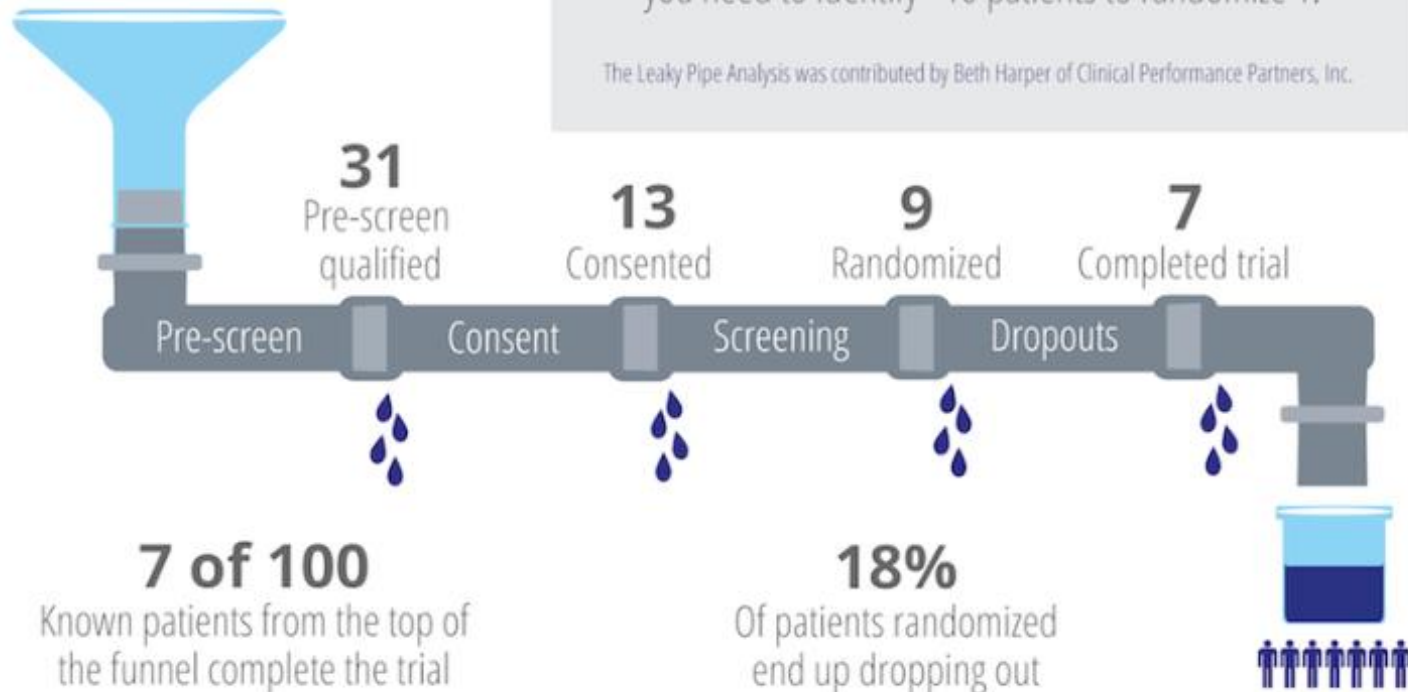
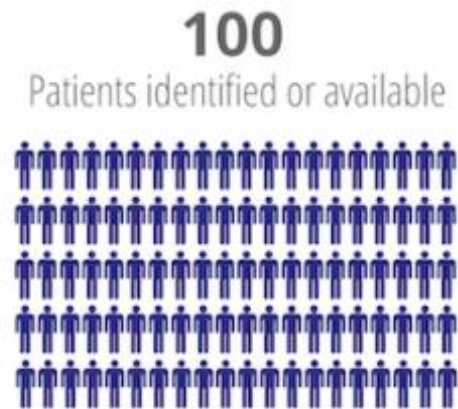
Feature importance in predicting FTT



Logistics:

- **Randomization**
- **Mistakes in software analysis (two independent teams)**
- **GCP violation of principles (human factor)**
- **Inadequate sample of patients (statistical power)**

How should we plan dropouts?



What we can be done for better retention?

Minimize burdens
during protocol design



Set expectations up-front
during ICF discussion



Explain importance
of their participation



Promptly respond
to inquiries



Send reminders for
upcoming visits



Provide a comfortable and
patient-friendly environment



Show appreciation
and recognition



Accommodate their schedule
as much as possible



**When possible, try to understand why participants withdraw,
and use that feedback to improve the patient experience.**

How do patients who have withdrawn from CT compare to those who have completed study?

Based on a survey asking study participants about their experiences

● Dropped out early
● Completed trial

It was difficult to understand the Informed Consent Form



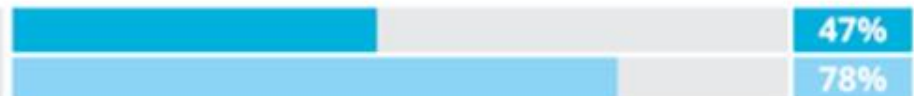
I'm satisfied that my questions were answered during the informed consent form discussion



The site visits were stressful



I was motivated by 'myself' to stay enrolled in the study



of CT fail to retain enough patients



average dropout rate across all CT

What motivates patients to continue their participation?

Based on a survey asking study participant about their experiences



Right patients:

Physiologically "non-responders to therapy" patients lead to failed CT.

"Moderately ill patients" are unlikely to demonstrate significant benefits.

Low frequency of events in the population (the risk is only 1% per year)

Exclude patients with very low risk events.

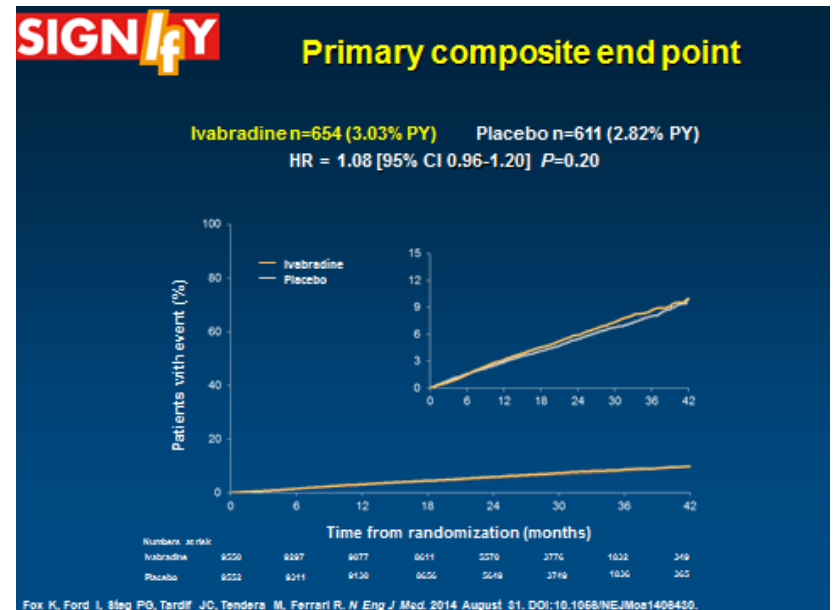
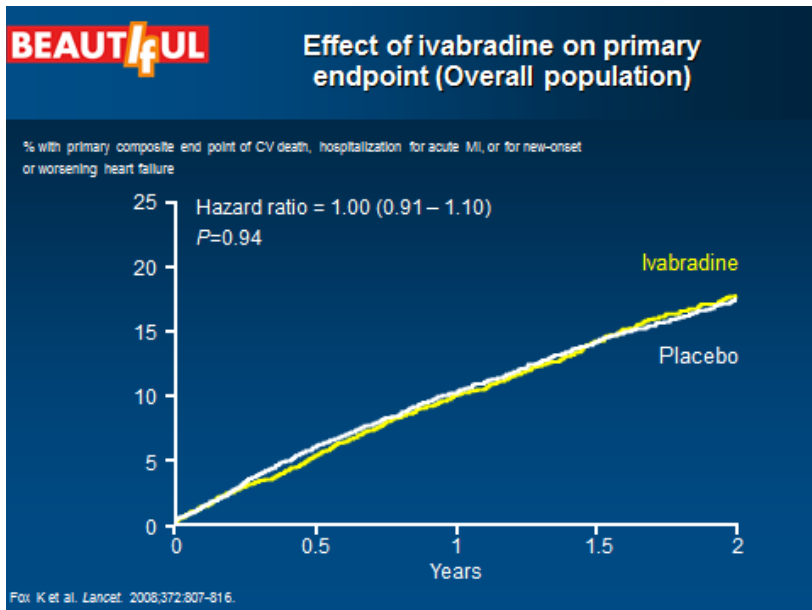
Do not follow only generally accepted patient selection criteria:

- ✓ *Histological changes*
- ✓ *Pathophysiological mechanisms*
- ✓ *Physical manifestations*
- ✓ *Symptoms and signs*
- ✓ *Parts of the body, organ or organ system*
- ✓ *Measurement thresholds*
- ✓ *Treatment response*

Patient's population selection

Why did the new treatment approach fail, was the patient population correctly chosen?

Example: two large trials of ivabradine involving patients with stable coronary artery disease - BEAUTIFUL and SIGNIFY - did not show any benefit ...!
But in the SHIFT study, which involved patients with CHF, the frequency of the primary endpoint (CV death or hospitalization for HF) was 26% lower with ivabradine compared with placebo ($p < 0.0001$).



Correct dose:

Dose:

- ❖ Less or much
- ❖ Depends on parameters (weight, GFR ...)
- ❖ Titration to obtain an adequate response (BP, HR)

Route of administration

Frequency and duration of use

Demografics (male-female, African Americans, Latinos ...).

EMIP-FR - a pioneer study

- Time from the onset of AMI - **up to 24 hours**
- Dose of the drug?
- Duration of therapy (**48 h**)?
- TMZ Application Point
- One center (12 patients) was excluded from all analyzes due to **withdrawal of consent by the researcher**.
- Acute myocardial infarction at the time of discharge was **confirmed in $92 \pm 0\%$**
- Lost to follow-up **2.6%**
- The analysis “according to the protocol” was carried out in 17 169 patients, with the exception of 2544 patients - with one or more **serious deviations from the protocol** or there was simply no data

Right endpoints:

Characteristics of a good endpoint:

- Clinically significant
- Closely and comprehensively reflects the disease in respect of which the treatment is carried out
- Enough endpoint information
- Sensitivity (discriminatory, with good distribution)
- Reliability (accurate, low variability and good reproducibility)
- Reliability with regard to dropouts and missing data
- Practical (implemented on different sites, applicable to all patients, economical and preferably non-invasive)

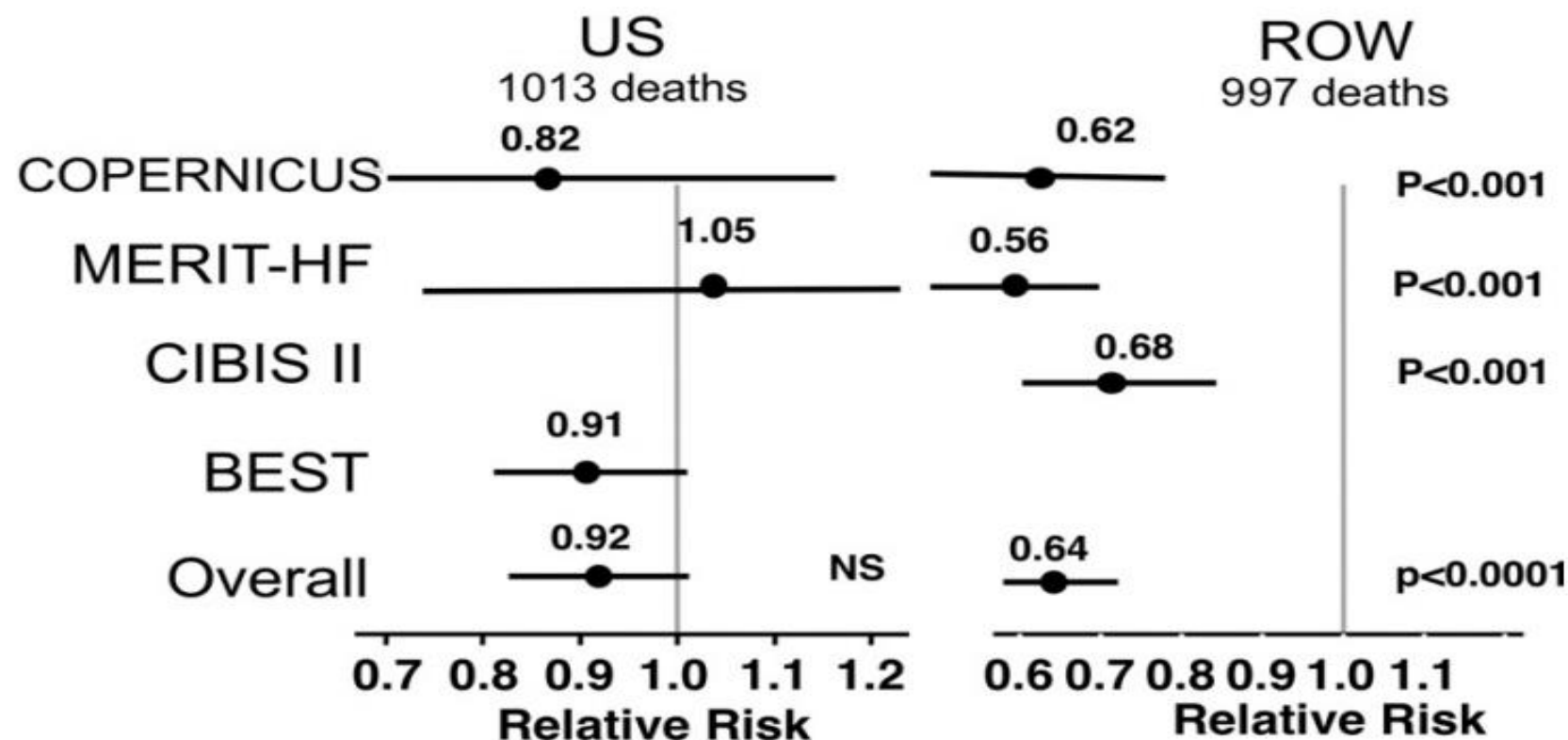
Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure

Adult Surrogate Endpoint Table

Disease or Use	Patient Population	Surrogate endpoint	Type of approval appropriate for	Drug mechanism of action
Alpha-1-antitrypsin deficiency	Patients with congenital alpha-1 antitrypsin deficiency	Plasma alpha-1 proteinase inhibitor	Traditional	Alpha-1 protease inhibitor augmentation
Acetylglutamate Synthase deficiency	Patients with hyperammonemia due to N-acetylglutamate synthase deficiency	Plasma ammonia	Traditional	Carbamoyl Phosphate Synthetase 1 (CPS 1) activator
Acromegaly	Patients with acromegaly who don't respond to or cannot undergo other standard therapies	Serum Insulin-like growth factor-I (IGF-1)	Traditional	Growth hormone receptor antagonist
Acromegaly	Patients with acromegaly who don't respond to or cannot undergo other standard therapies	Serum growth hormone and serum insulin-like growth factor-I (IGF-1)	Traditional	Somatostatin analog

Clinical Research

Influence of Global Region on Outcomes in Heart Failure Beta-Blocker Trials



Can Diseases be Different in China-Asia?

- **Chinese-Asian known disease differences**
 - **Prevalence**
 - GI cancers ↑ (stomach, liver, bowel)
 - Hepatitis
 - Self inflicted injuries
 - **Disease biology**
 - NSCLC-EGFR+ 3-4x
 - Hepatitis B & C genotypes
 - **Phenotype**
 - Type 2 diabetes-Children – obese ↑ + Adults normal weight → ↑ Risk
 - Breast cancer- menopausal Pre > Post
 - **Criteria for diagnosis & assessment**
 - Depression & other diseases described by symptoms-behaviors

Are People Different?

(mean weight (kg))

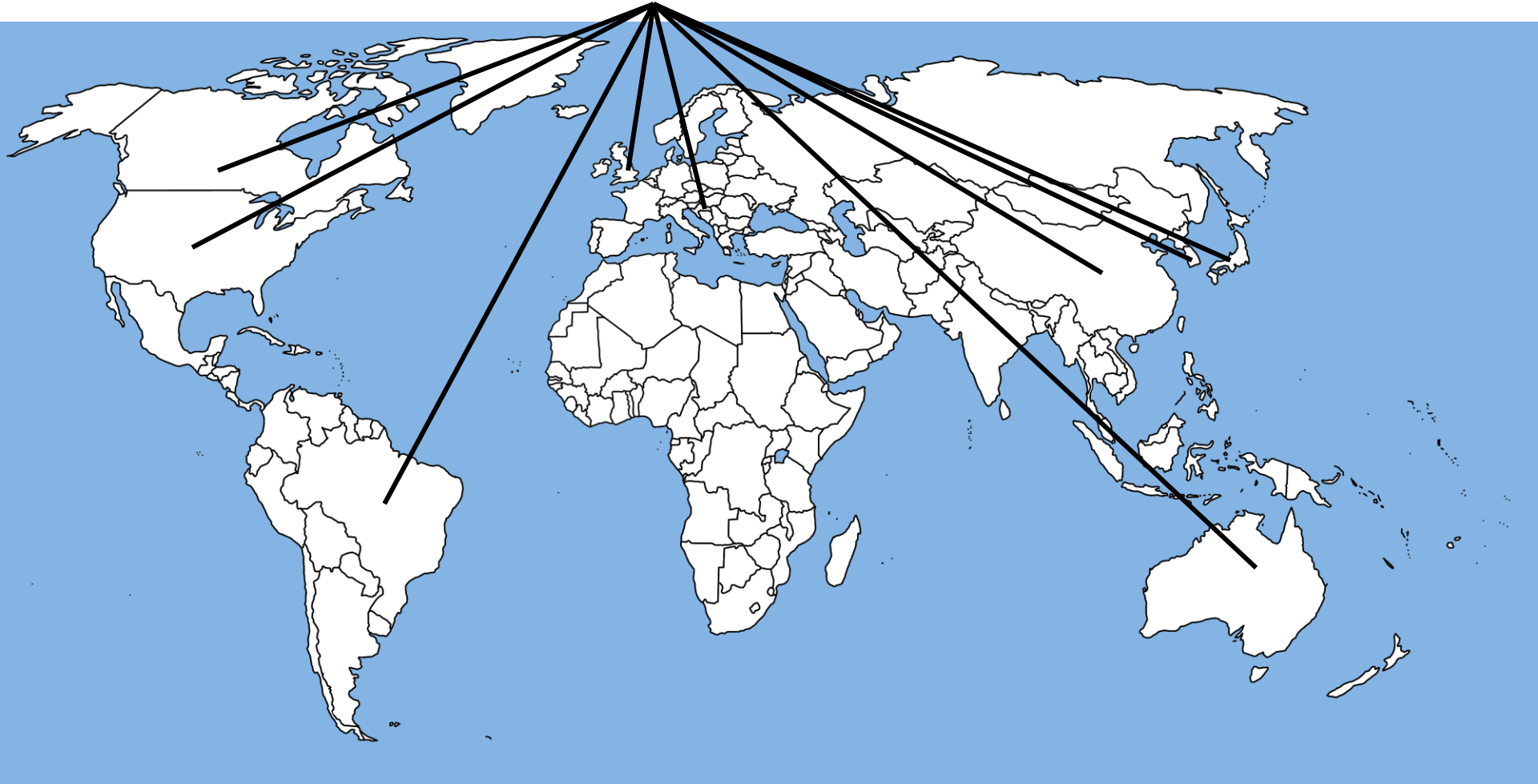
	USA¹ 2002 (50-59 years)	China 2002² (45-59 years)					
		Big City (>500k)	Town (200-500k)	Rural 1 (richer)	Rural 2	Rural 3	Rural 4 (poorest)
Males	88.8	68.9	66.6	63.0	60.5	63.6	57.9
Females	76.9	61.1	59.4	57.5	54.8	58.1	52.3

- Clcr (ml/min) estimated for 59 yo, 88.8 kg American ♂ versus 52.3 kg Chinese ♀ is 99.9 ml/min versus 50.0 ml/min.
- Might weight difference (amount, composition) lead to pharmacologic differences?
- Size differences not accounted for in clinical trial planning-rather post hoc analysis

1. CDC US mean body weight, height, bmi 1960-2002 <http://www.cdc.gov/nchs/data/ad/ad347.pdf>
 2. A Survey on Nutrition and Health in Chinese Citizens. Wang Longde

Global Development Paradigm 1

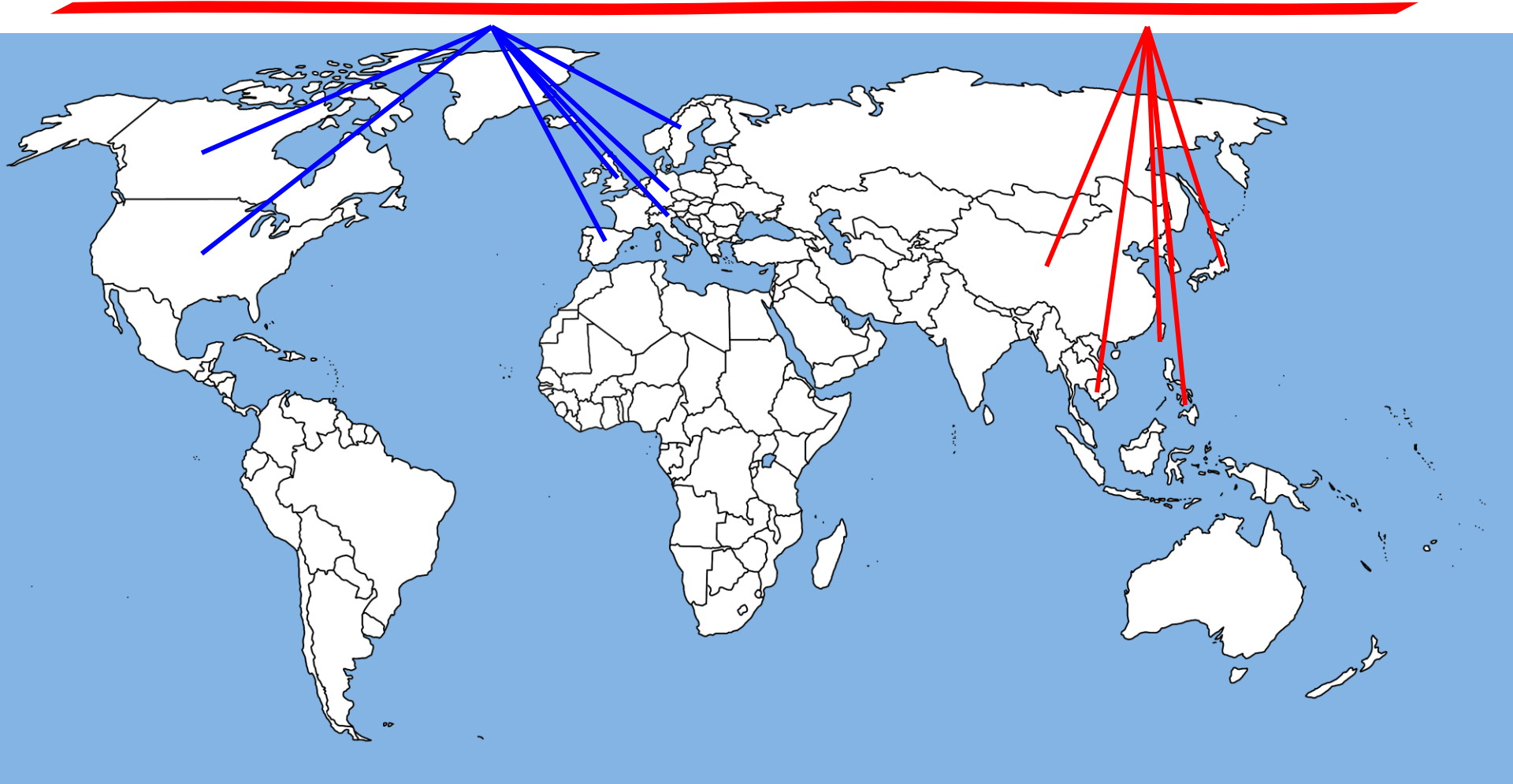
(Global Clinical Trials - Japanese Recommendation)



What if major ethnic differences exist in disease or pharmacology?

Global Development Paradigm 2

(Bi-Regional Multicenter Clinical Trials)



- Might this be more informative and lower risk than Global trials?
- Or.... designing trials based on patient comparability

Data Quality

Unskilled Project
Manager

Unproductive Team

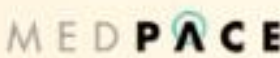
Complexity of
Protocol

Dilemma 'Project
completion targets'
vs. 'Eligibility of the
volunteers'

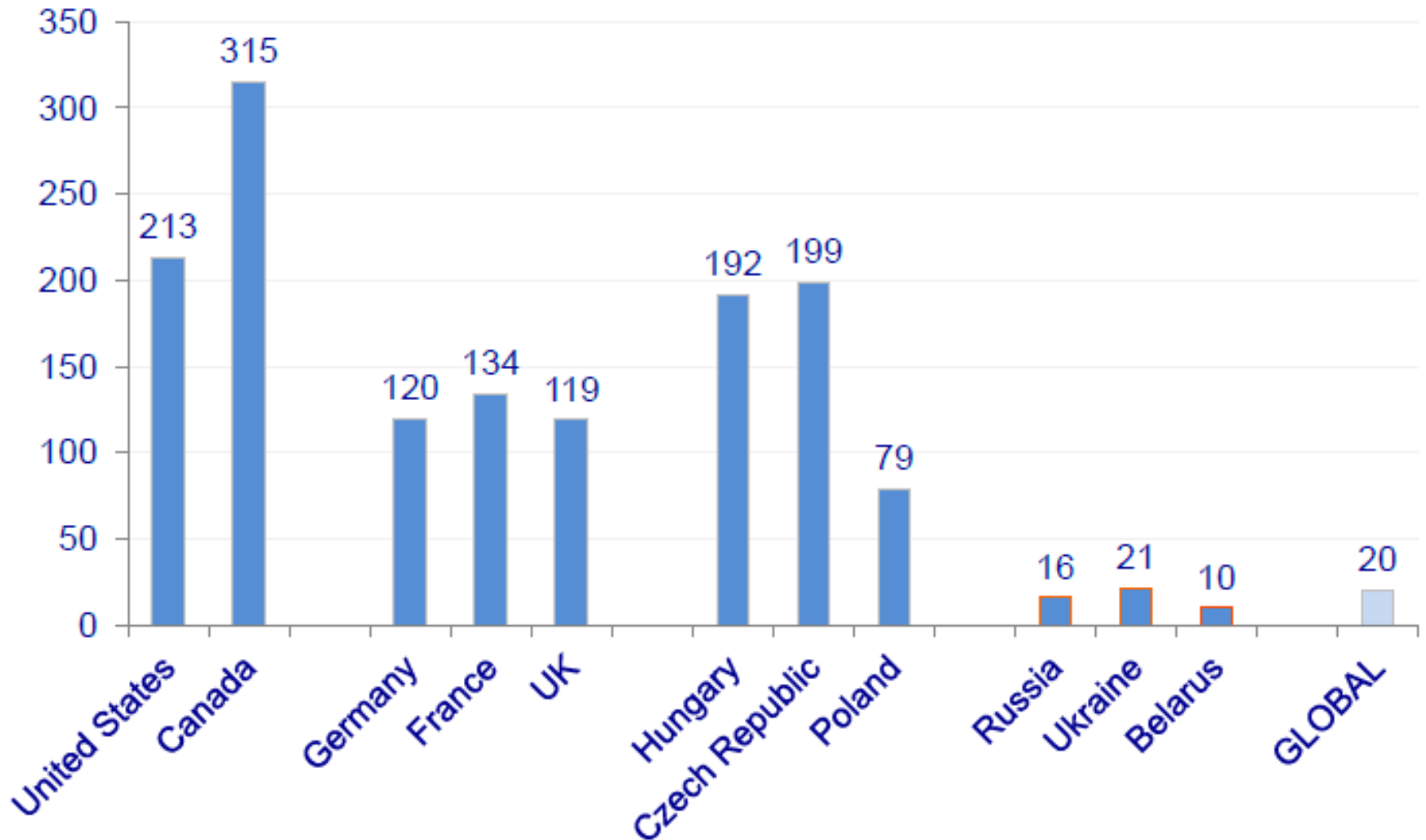
Poor training &
poor verification

Ethical Issues

Data Quality

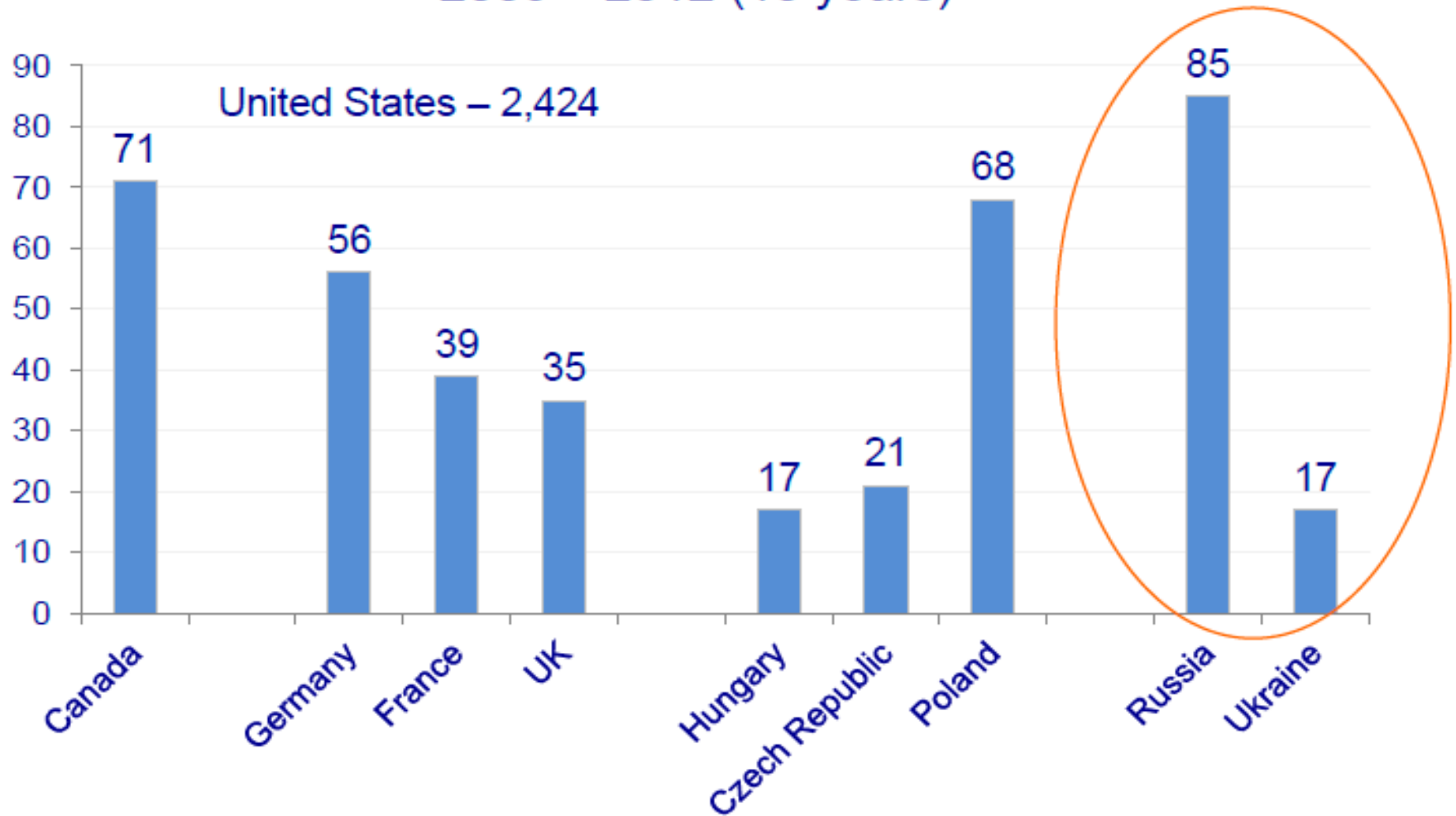
			Revenues, 2017 (USD billions)	Income Ratio, 2017	Expense Ratio, 2017	Service portfolio (units)
	01	Laboratory Corporation of America Holdings (Covance)	10,441	12,14%	87,86%	31
	02	Quintiles IMS Holdings, Inc	9,739	13,44%	86,56%	92
	03	Syneos Health	2,672	8,90%	91,10%	42
	04	Paraxel International Corporation	2,441	4,40%	95,60%	79
	05	PRA Health Sciences	2,259	9,69%	90,31%	27
	06	Pharmaceutical Product Development (PPD)	1,900	5,00%	95,00%	44
	07	Charles River Laboratories International Inc (CRL)	1,857	6,65%	93,34%	4
	08	ICON Public Limited Corporation	1,758	16,84%	83,16%	15
	09	Wuxi Apptec	1,011	12,00%	88,00%	5
	10	Medpace Holdings, Inc	0,436	8,96%	91,03%	2

Clinical Trials Quantity per 1 million



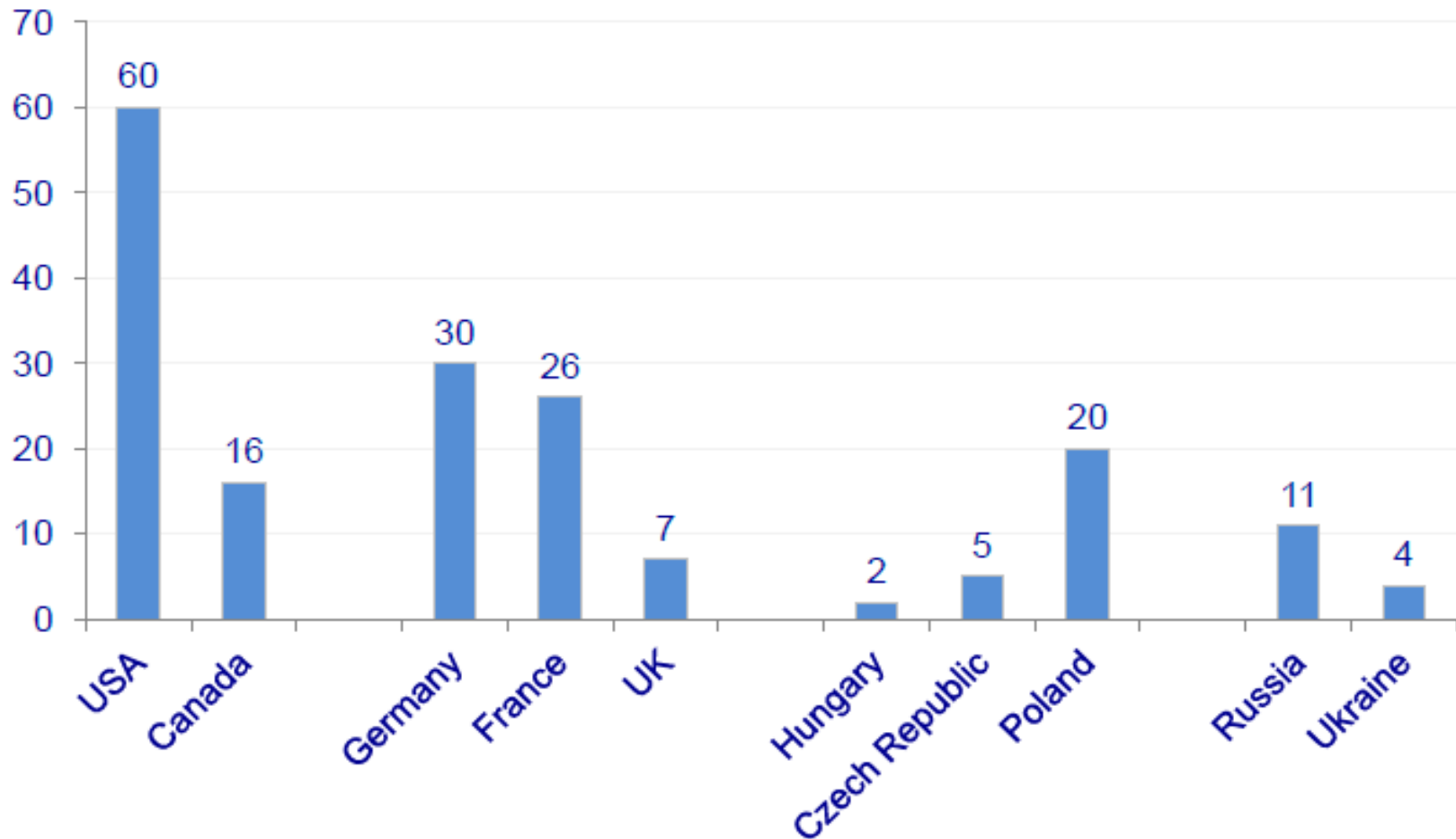
Number FDA inspection (10 years)

2003 – 2012 (10 years)



Number EMA inspection (10 years)

2002 – 2011 (10 years)



Regional differences in treatment and outcomes?

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS



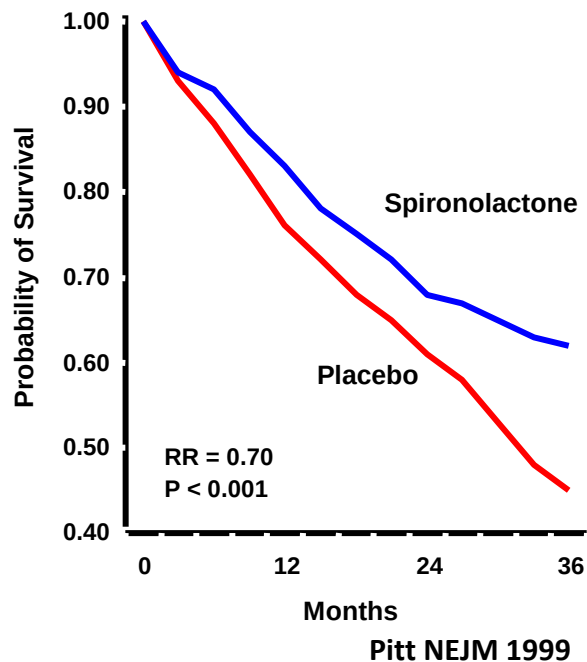
Lessons from the TOPCAT Trial

John J.V. McMurray, M.D., and Christopher O'Connor, M.D.

MRAs Beneficial in HFrEF and Post-MI LVD

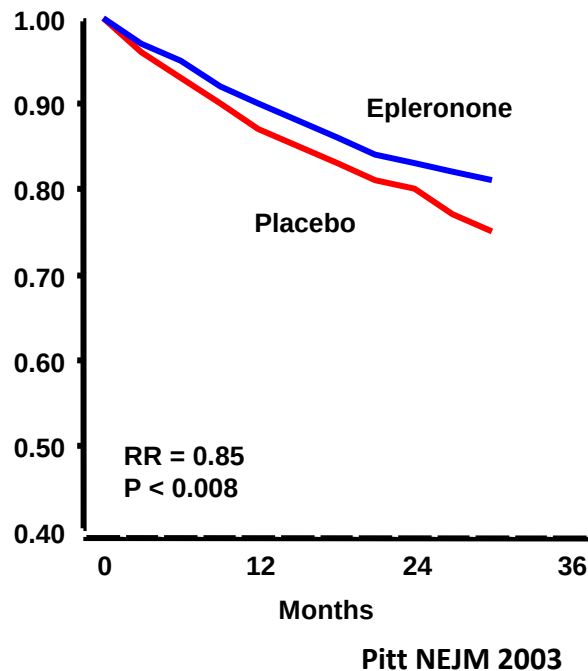
RALES (Severe HFrEF)

30% Risk Reduction



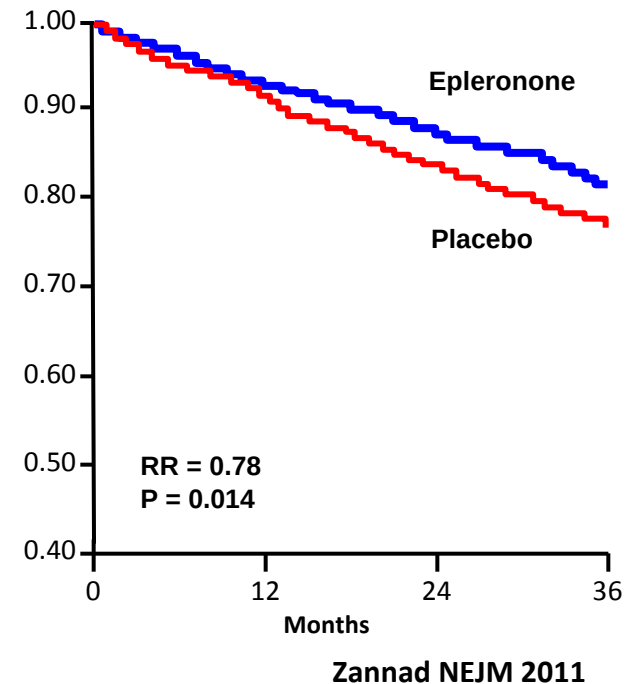
EPHESUS (Post-MI)

15% Risk Reduction



EMPHASIS (Mild HFrEF)

22% Risk Reduction



Patient Participation

Randomized: N=3445; **Mean follow-up:** 3.3 years

US (1,151); **Russia** (1,066); **Rep. of Georgia** (612);
Canada (326); **Brazil** (167); **Argentina** (123)

Mean Dose at 8 months: spironolactone 25 mg; placebo 28 mg

Spironolactone N=1,722

% discontinued study medication:

1 year: 17.0%

2 year: 25.1%

End: 34.3%

Vital status unknown: 67 (3.9%)

Placebo N=1,723

% discontinued study medication:

1 year: 13.5%

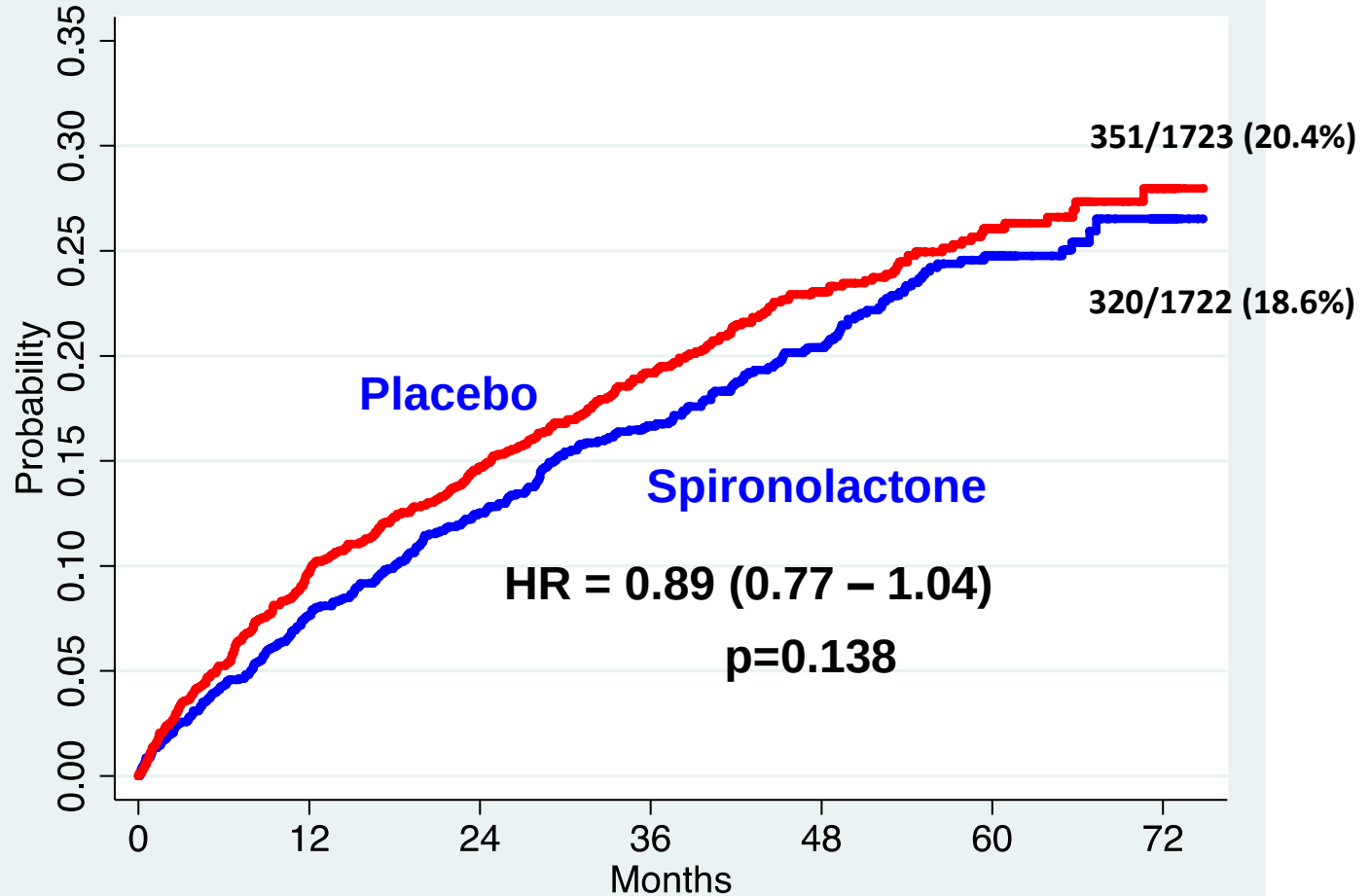
2 year: 20.1%

End: 31.4%

Vital status unknown: 65 (3.8%)

1° Outcome

(CV Death, HF Hosp, or Resuscitated Cardiac Arrest)

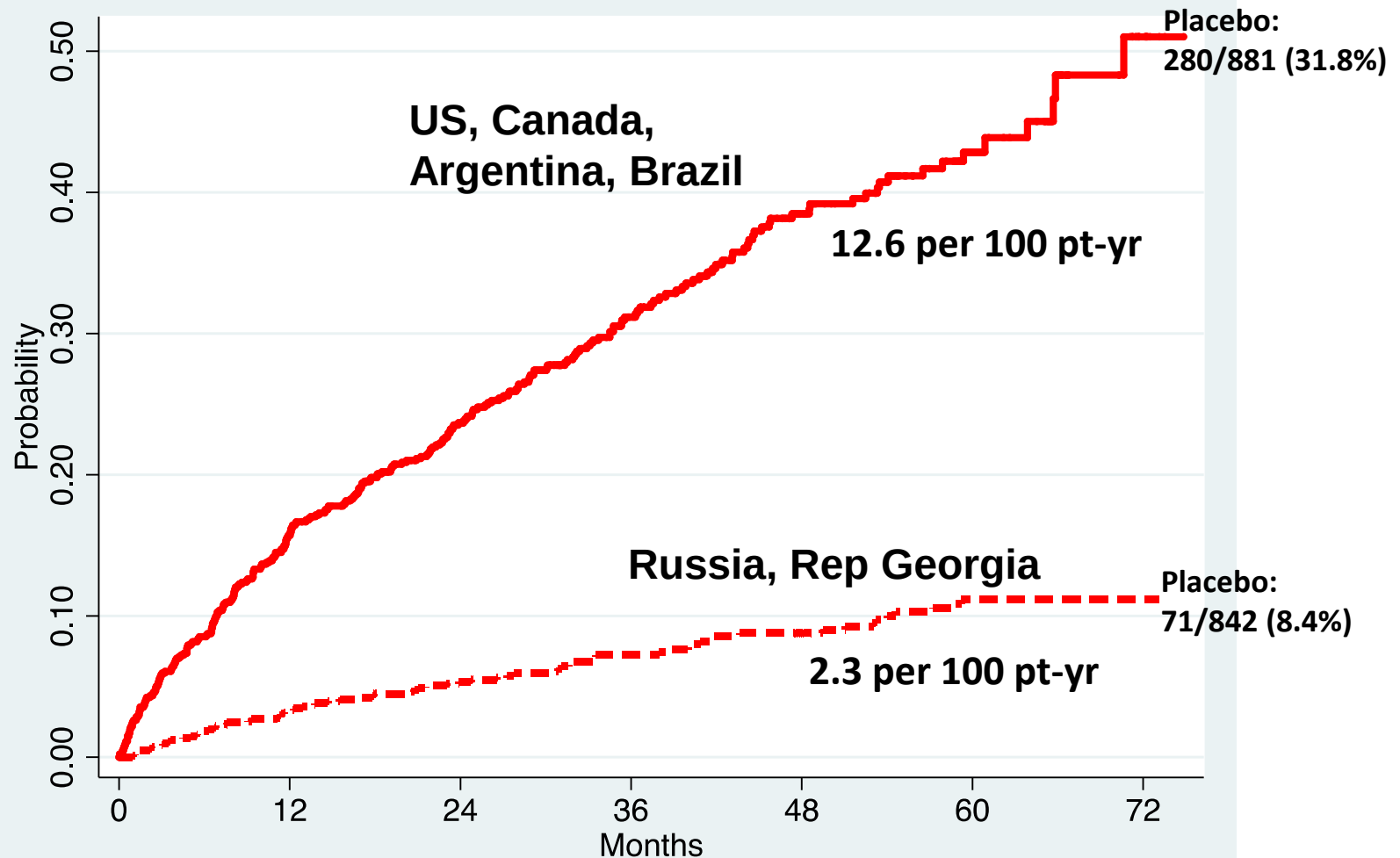


Number at risk

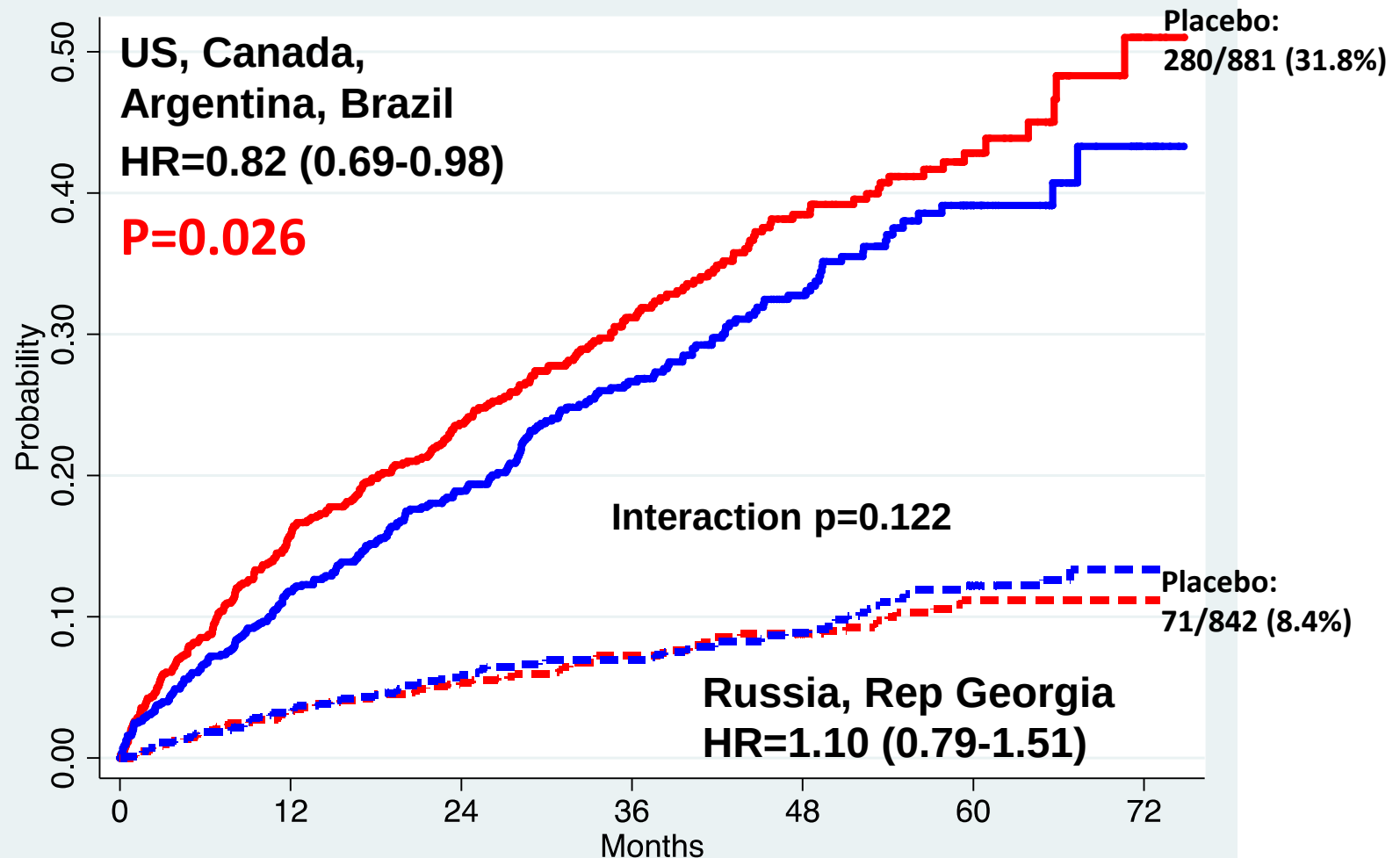
Spiro	1722	1502	1168	870	614	330	53
Placebo	1723	1462	1145	834	581	331	53

Placebo Rates:

Primary Outcome, by region



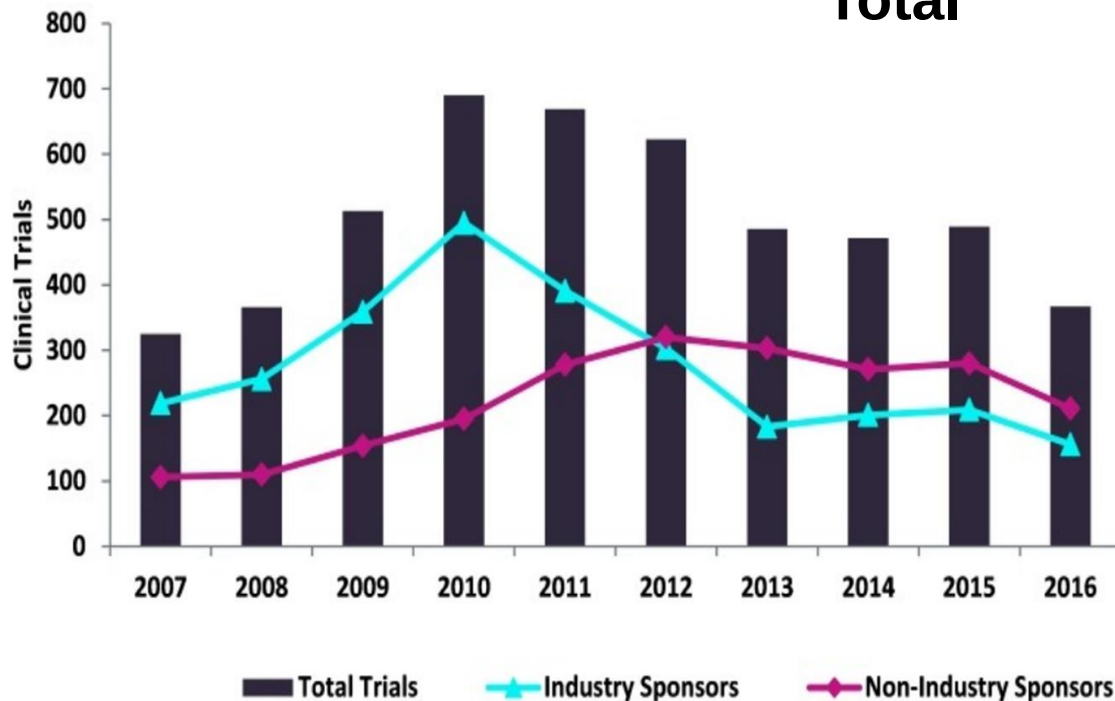
Exploratory (post-hoc): Placebo vs. Spiro by region



Sponsor for CT: Trials.gov statistics

Trials by Sponsor

US Federal (including NIH)	10,828	12%
Industry	29,233	32%
University, Other	50,076	55%
Total	90,137	



NDA: New Drug Application

NDA Refers to New Drug Application

Formal proposal for the FDA/DCGI to **approve a new drug for sale**

Sufficient evidences provided to FDA/DCGI to establish:

- *Drug is **safe and effective**.*
- ***Benefits** outweigh the risks.*
- *Proposed labeling is appropriate.*

NDA contains all of the information gathered during preclinical to phase III

NDA can be thousands of pages long

Can take 2-3 years for FDA to review

Instead of conclusion...

“Now this is not the end.
It is not even the beginning
of the end. But it is, perhaps,
the end of the beginning.”

— Winston Churchill

