


# Integrating RWE and RCT within patient-journey studies

Francesco Perrone, MD

Istituto Nazionale Tumori
Napoli, Italy

# Disclosure of conflicts of interest (last 2 years)

- No personal payment from industry
- Grants and drug support to my Institute/Department for phase 1 activities:
  - Bayer, Sutro Biopharmaceuticals, Exelisis, MSD, Incyte Corporation, Boehringer-Ingelheim, Aileron Therapeutics,  K-Group Beta, Janssen Cilag, Roche, Kartos Therapeutics, HiFiBiO, Gilead Sciences, AstraZeneca, Byondis BV, Relay Therapeutics
- President of AIOM (Foundation)

# Agenda

- Do we need randomised clinical trials (RCT) and real world evidence (RWE)?

- Can we integrate (and improve) RCT and RWE?

# Agenda

- **Do we need randomised clinical trials (RCT) and real world evidence (RWE)?**
  - Limitations of trials (pharma &academia)
  - Limitations of RWE

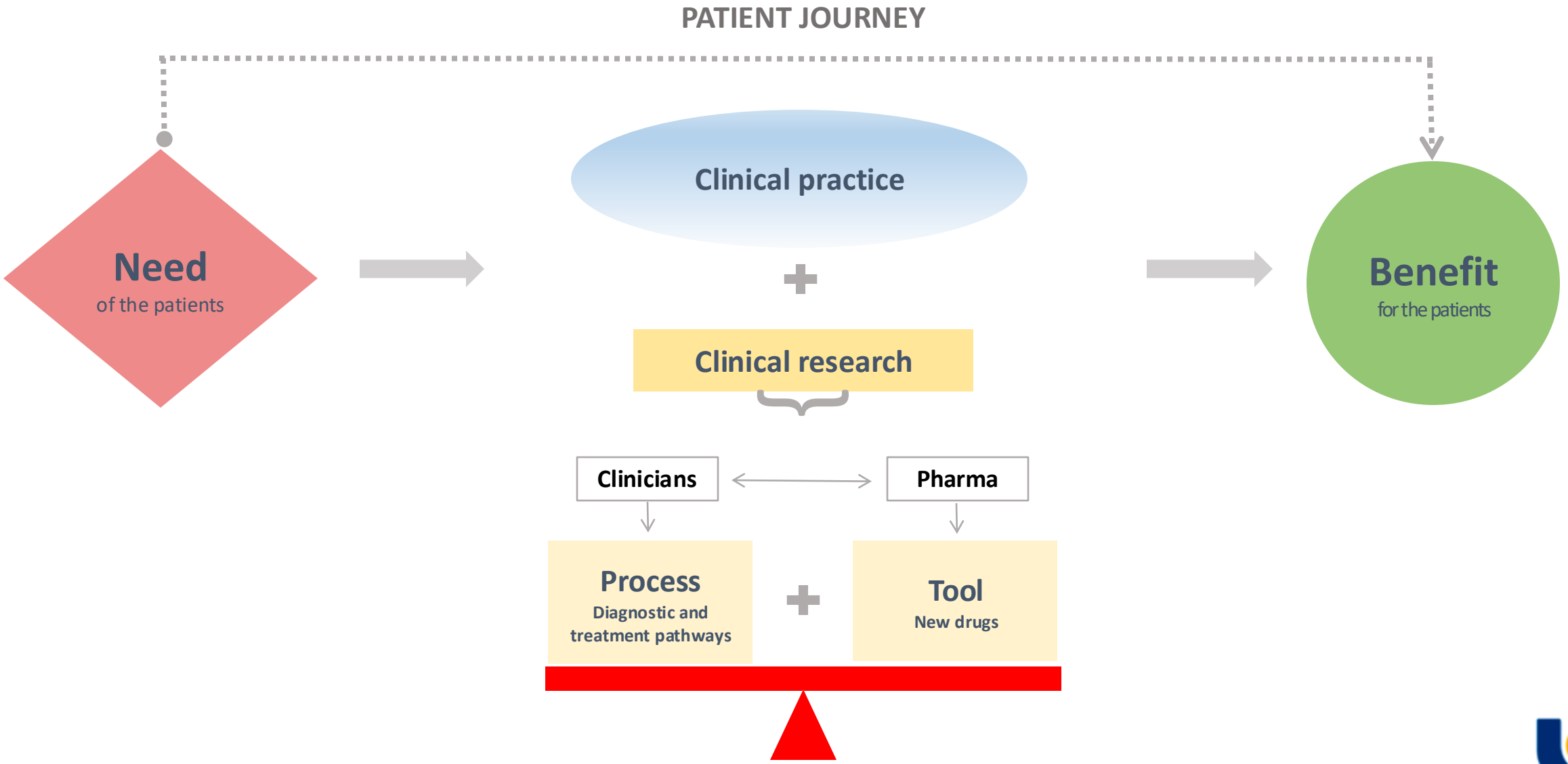
- Can we integrate (and improve) RCT and RWE?

# The equilibrium point

***Which comes first: the medication or the treatment plan?***

**forward #33** — VALUTAZIONE — 1 / 2024

**Francesco Perrone**
*Presidente*
*Associazione italiana oncologia medica*



# Patient Enrollment to Industry-Sponsored Versus Federally Sponsored Cancer Clinical Trials

Joseph M. Unger, PhD[1]; Hong Xiao, PhD[1]; Riha Vaidya, PhD[1]; and Michael LeBlanc, PhD[1]

DOI https://doi.org/10.1200/JCO.24.00843

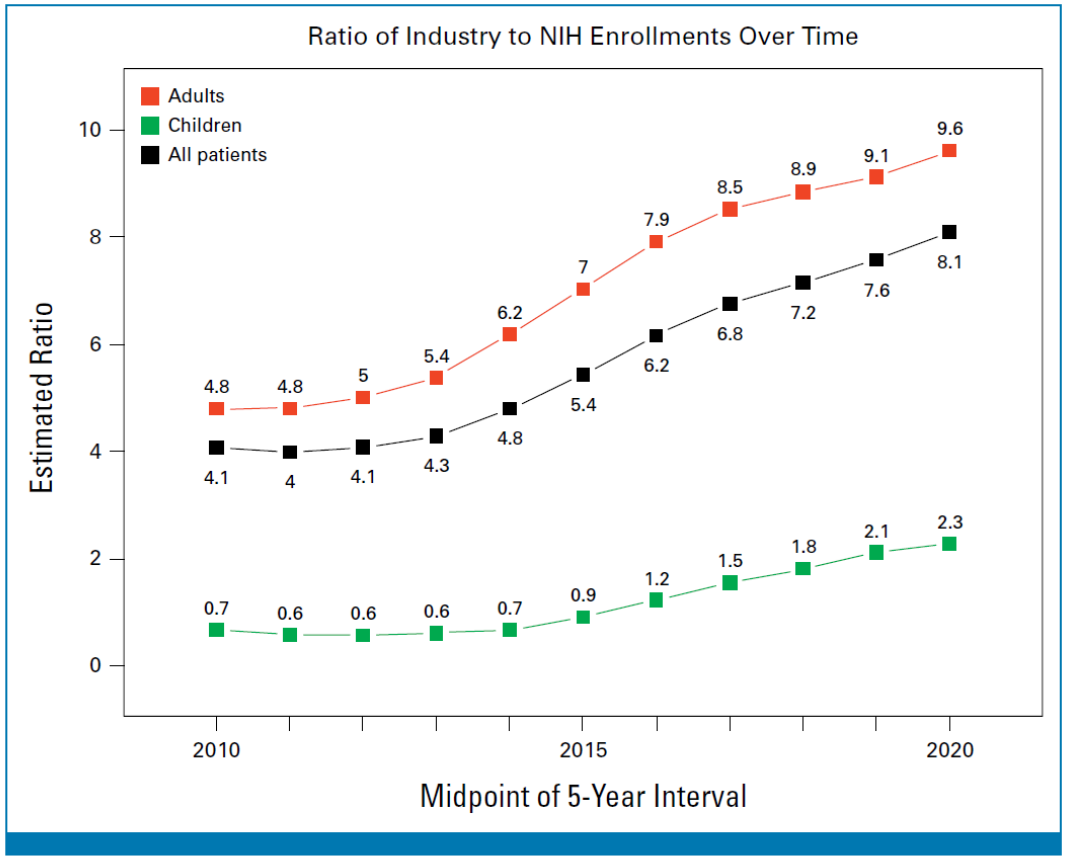



**FIG 2.** Ratio of industry to NIH enrollments over time. A 5-year rolling average was used. NIH, National Institutes of Health.

Journal of Clinical Oncology

ACCOMPANYING CONTENT

Editorial, p. 3887

Appendix

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J Clin Oncol 42:3917-3925

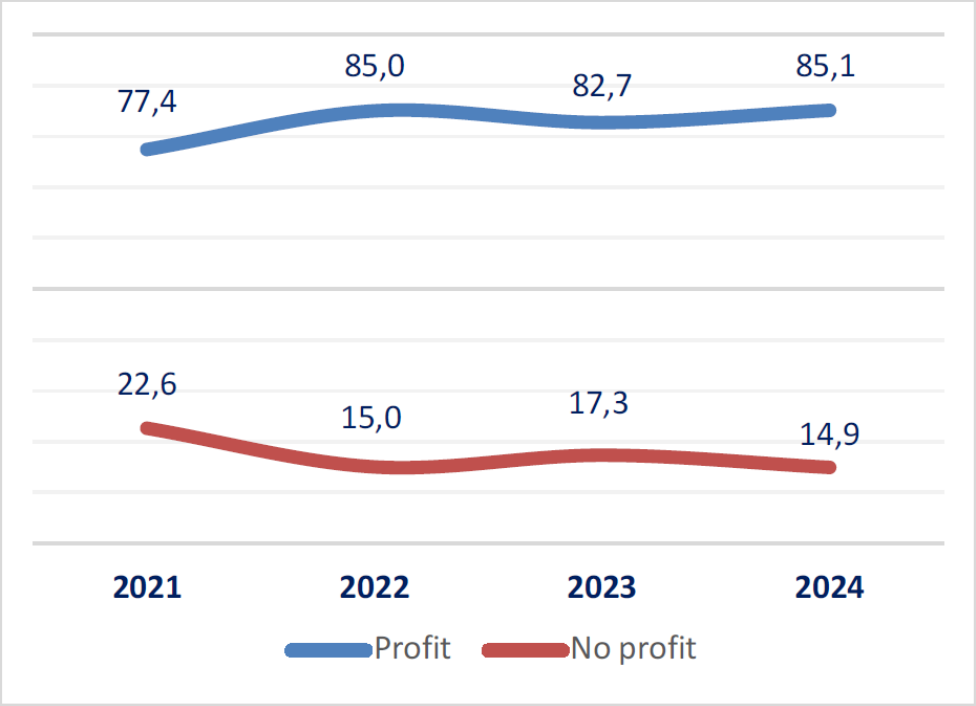
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View Online Article

AGENZIA ITALIANA DEL FARMACO

**Sperimentazioni per anno e promotore profit / no profit (%)**

SC autorizzate nel quadriennio: 2.777



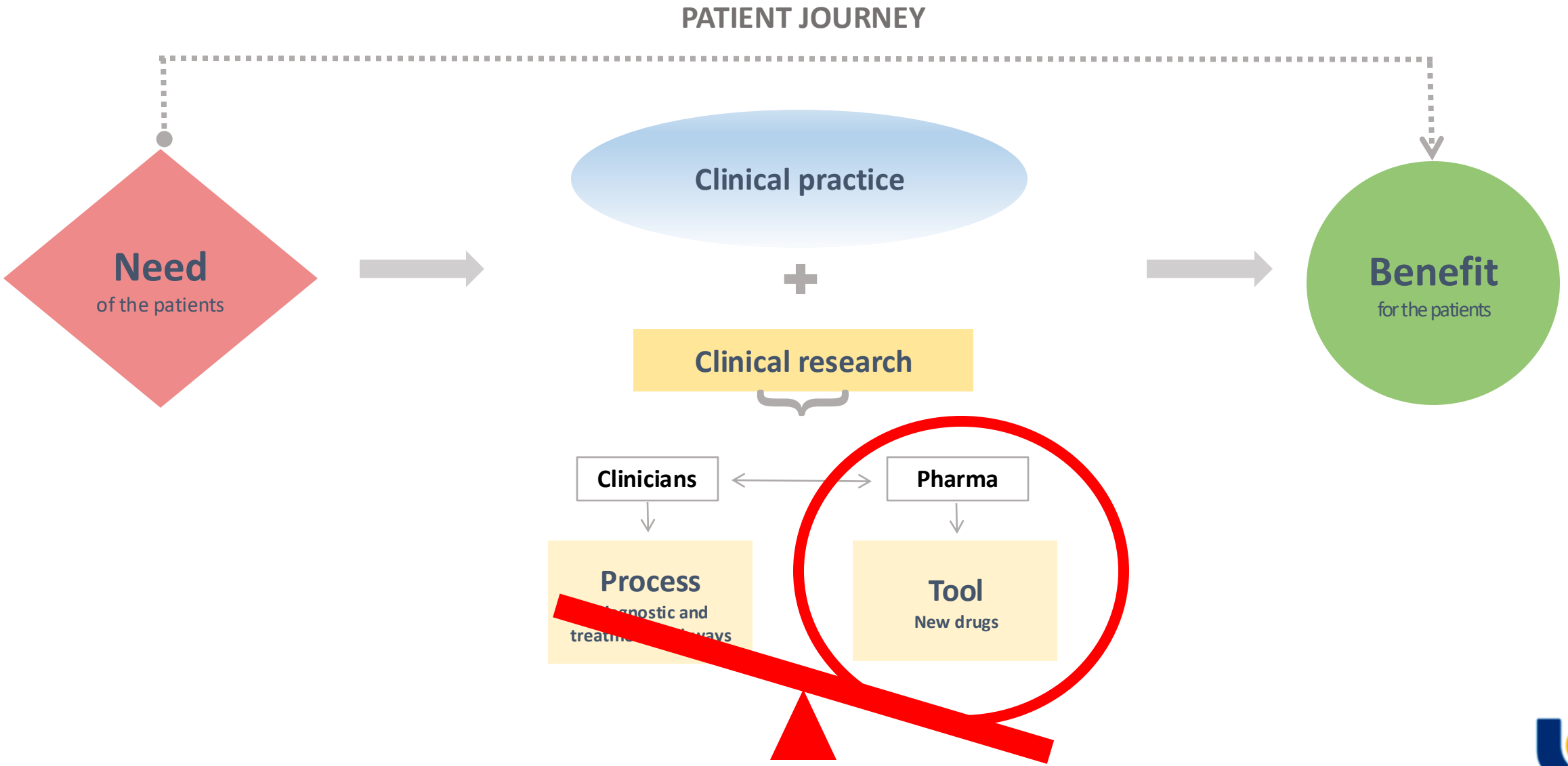

# Equilibrium?

# The equilibrium point

***Which comes first: the medication or the treatment plan?***

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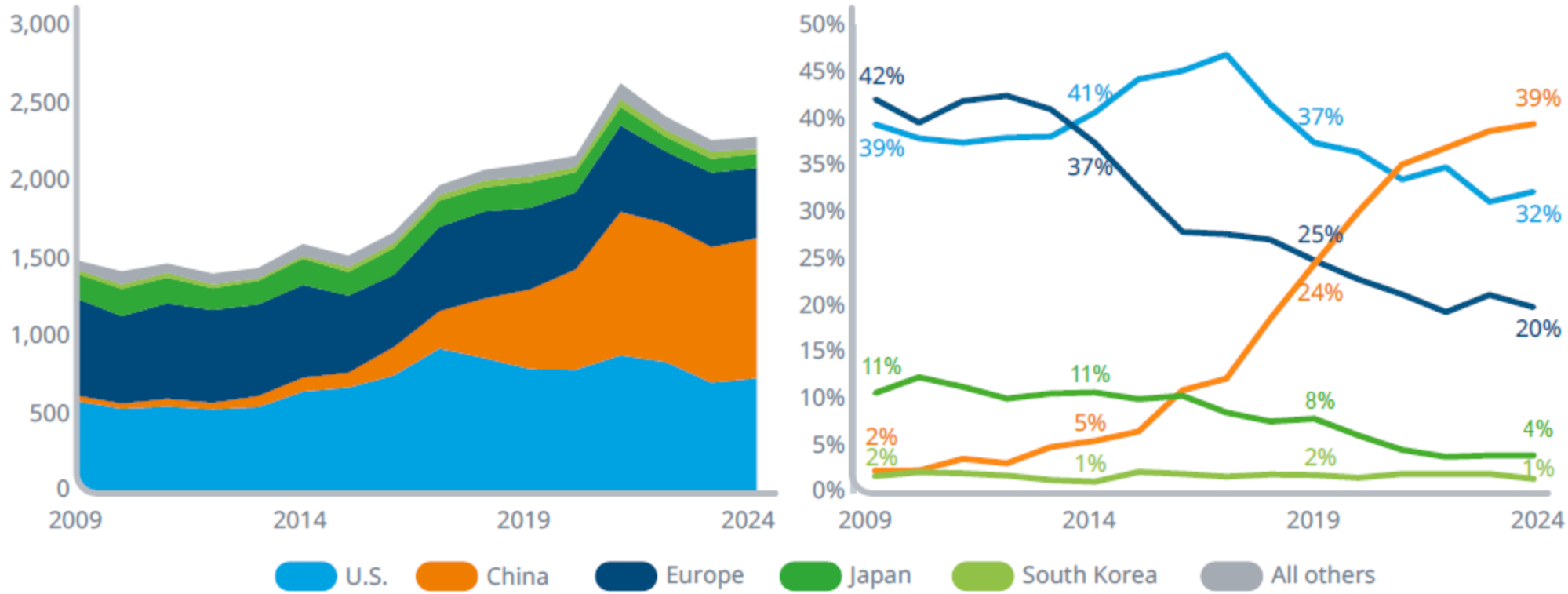
## Reflection #1

# Academic clinical research is not doing well

And it has been this way for a long time — though there are few of us who despair over it…

# Oncology trials from China-headquartered companies have risen to 39% of total starts, up from only 5% a decade ago

**Exhibit 3: Number and share of oncology trial starts by company headquarters location, 2009–2024**




Source: Citeline Trialtrove, Jan 2025; IQVIA Institute, Apr 2025.

# Reflection #2

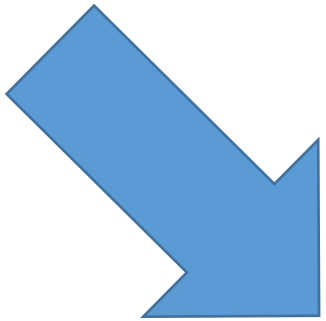
## In Europe… for-profit clinical research isn't doing well either…

And it's almost certain to get worse

# Is this a problem?
# Perhaps not…

Innovative drugs reach our clinical practice thanks to studies sponsored by pharmaceutical companies with an explicit regulatory intent.

**Trials with regulatory aim**



Innovative drugs reach our clinical practice thanks to studies sponsored by pharmaceutical companies with an explicit regulatory intent.

# Trials with regulatory aim



Registration studies sponsored by pharmaceutical companies are often insufficient to define the **value** and "**place in therapy**" of drugs

The FDA and EMA approve a new drug if there is convincing evidence regarding its safety and efficacy (risk/benefit ratio).

## Snapshots… focused on drugs

(Super-)selected patients
"Outdated" control arms
Few or no head-to-head comparisons
Over-reliance on surrogate endpoints
Therapeutic sequences ignored
…

# Comparison of baseline patient characteristics in Italian oncology drug monitoring registries and clinical trials: a real-world cross-sectional study

Maria Lucia Iacovino,[a,j] Simone Celant,[b,j] Luca Tomassini,[b] Laura Arenare,[a] Andrea Caglio,[c] Andrea Canciello,[a] Flavio Salerno,[c] Pier Paolo Olimpieri,[b] Susanna Di Segni,[b] Antonella Sferrazza,[b] Maria Carmela Piccirillo,[a] Giordano Domenico Beretta,[d] Carmine Pinto,[e] Livio Blasi,[f] Saverio Cinieri,[g] Luigi Cavanna,[h] Massimo Di Maio,[i] Pierluigi Russo,[b,k] and Francesco Perrone[a,k,*]

The Lancet Regional Health - Europe
2024;41: 100912

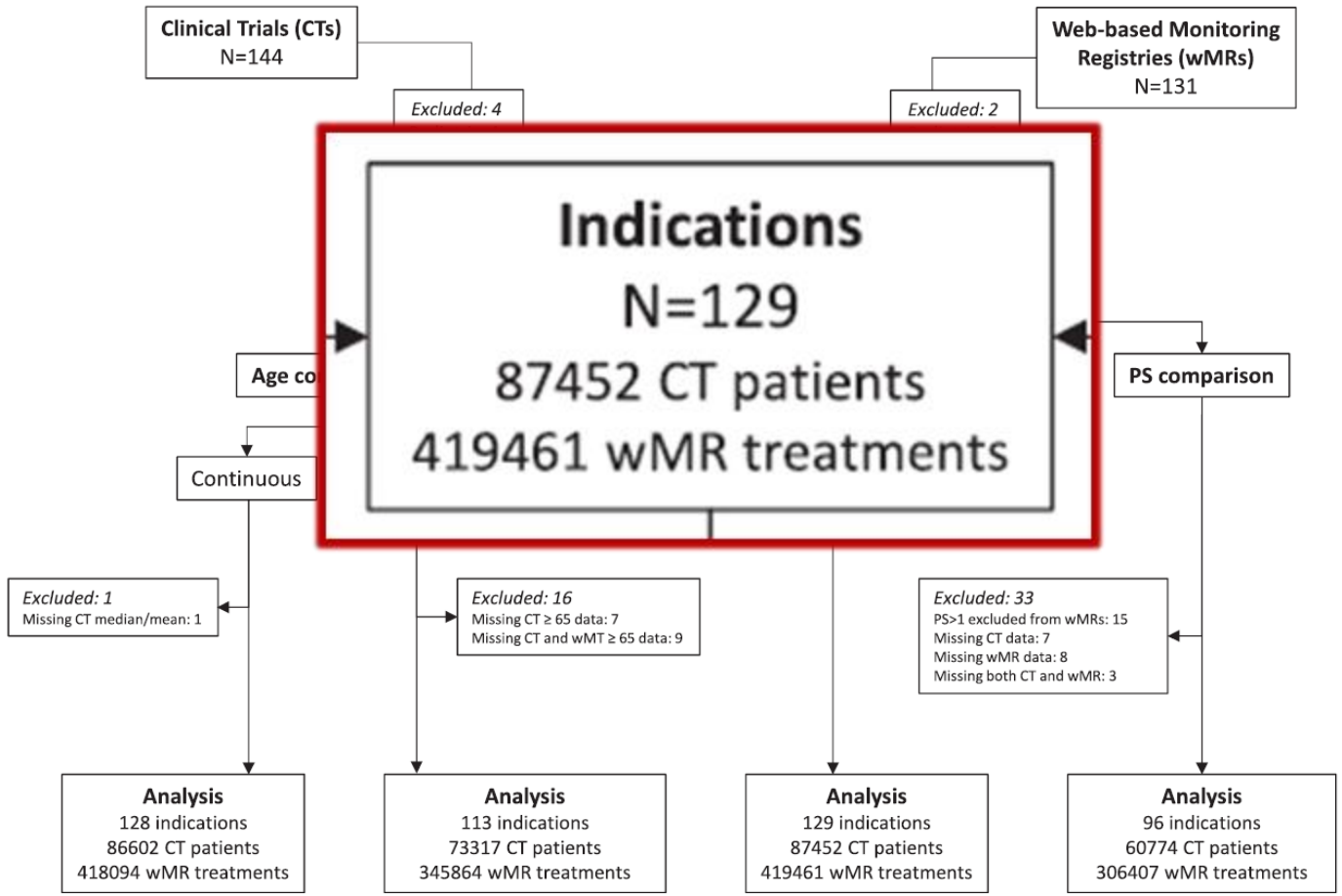



*Fig. 1:* Flow chart of the study.

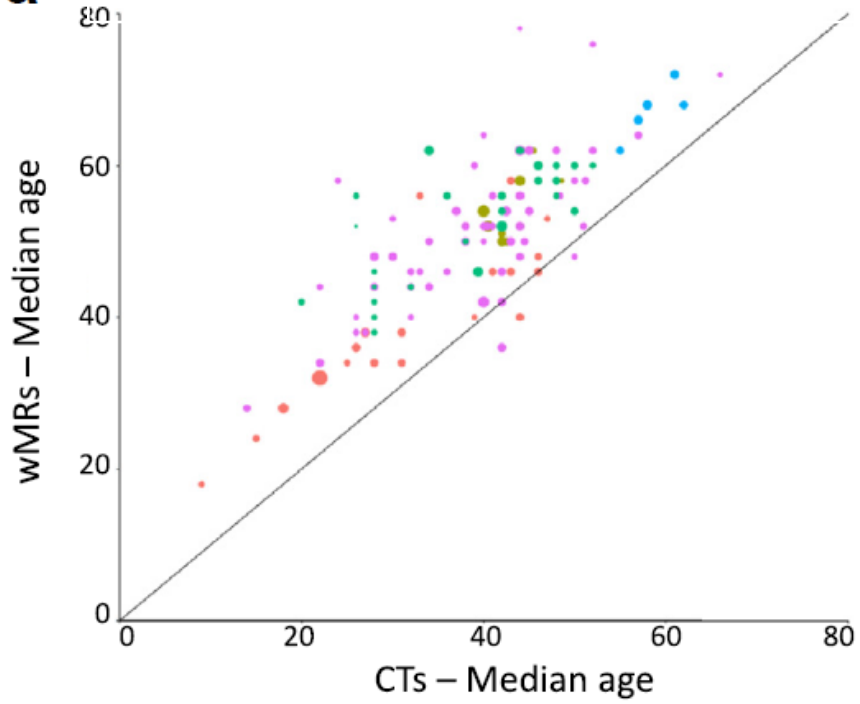
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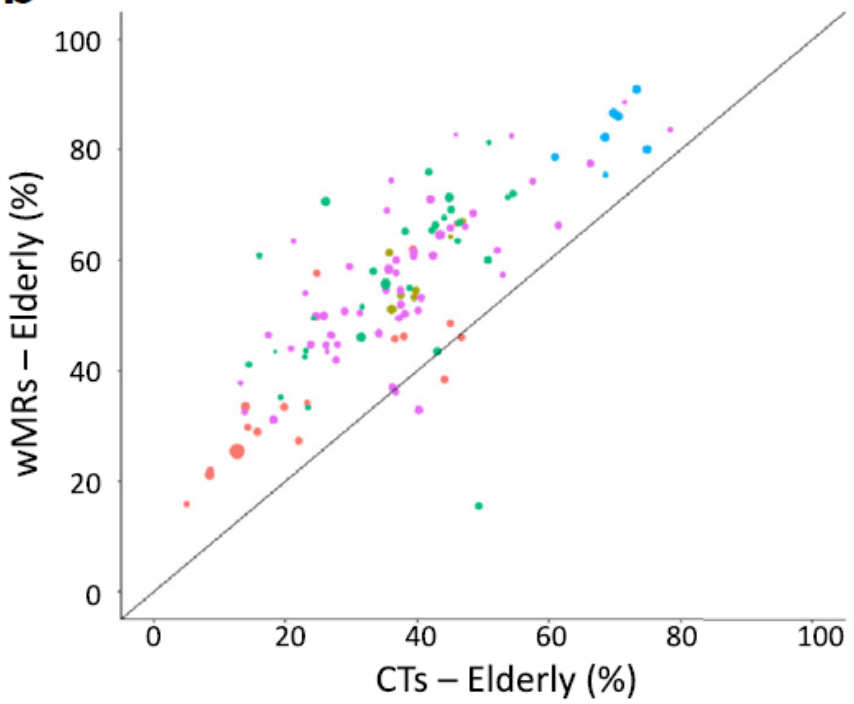
Maria Lucia Iacovino,[a,j] Simone Celant,[b,j] Luca Tomassini,[b] Laura Arenare,[a] Andrea Caglio,[c] Andrea Canciello,[a] Flavio Salerno,[c] Pier Paolo Olimpieri,[b] Susanna Di Segni,[b] Antonella Sferrazza,[b] Maria Carmela Piccirillo,[a] Giordano Domenico Beretta,[d] Carmine Pinto,[e] Livio Blasi,[f] Saverio Cinieri,[g] Luigi Cavanna,[h] Massimo Di Maio,[i] Pierluigi Russo,[b,k] and Francesco Perrone[a,k,*]

The Lancet Regional Health - Europe
2024;41: 100912

**Patients in clinical practice are significantly older than in clinical trials**

| | Monitoring Registries | Clinical Trials | ΔMR-CT |
|---|---|---|---|
| a | **65.1** | 59.8 | **+5.3yrs** |
| b | 53.9 | 36.8 | **+17.1%** |



European Journal of Cancer 189 (2023) 112920

# Analysis of the adequacy of control arms in oncology randomised clinical trials published between 2017 and 2021: a meta-research study

Alessandro Rossi [a], Giacomo Aimar [b,c], Marco Audisio [d], Maristella Bungaro [e], Andrea Caglio [f], Raimondo Di Liello [g], Teresa Gamba [f], Piera Gargiulo [h], Eleonora Ghisoni [i], Pasquale Lombardi [j], Laura Marandino [k], Annapaola Mariniello [l,m], Chiara Paratore [d], Maria Lucia Reale [n], Federica Trastu [f], Valentina Tuninetti [f], Fabio Turco [m,o], Alessandra Fabi [a], Francesco Perrone [h], Massimo Di Maio [p,*,1,2]



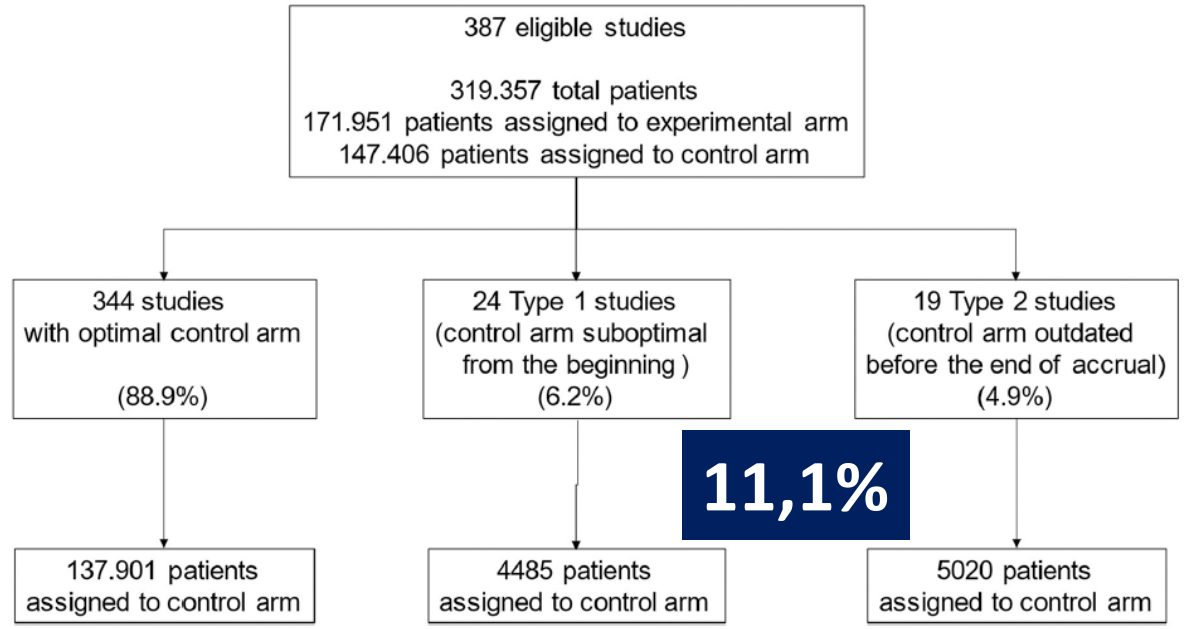




Fig. 2. Number of studies and number of patients assigned to control arm for each subgroup (studies with optimal control arm, studies with control arm suboptimal from the beginning, studies with control arm outdated before the end of the accrual).

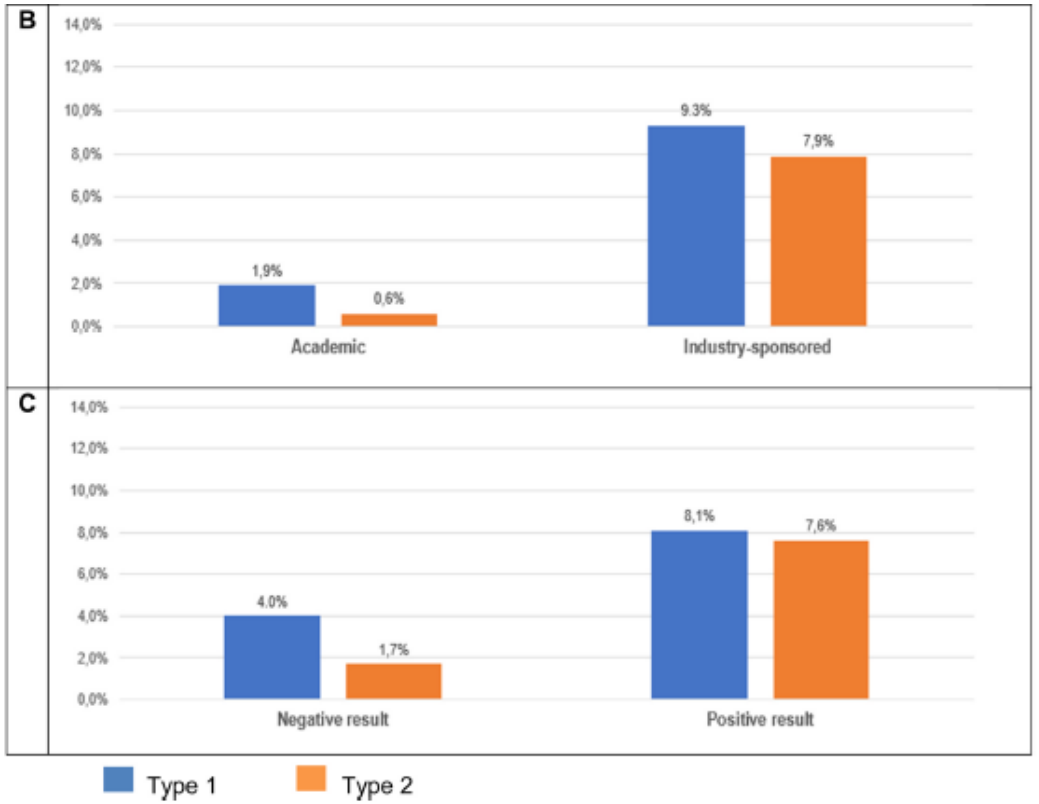



Fig. 3. Proportion of Type 1 studies (control arm suboptimal from the beginning) and Type 2 studies (control arm outdated before the end of the accrual) in the whole series of studies (panel A), in subgroups according to study sponsor (panel B), and in subgroups according to study results (panel C).

**Inadequate control arm is more frequently found in industry sponsored studies and in those with positive results**

JAMA Oncology | Original Investigation

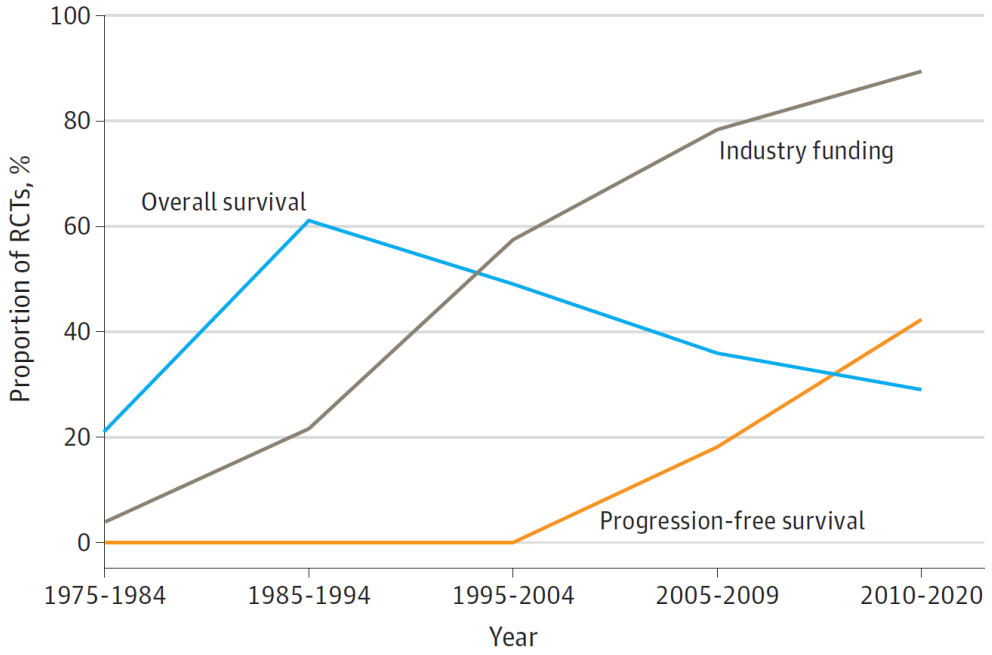
*JAMA Oncol*. doi:10.1001/jamaoncol.2021.0379
Published online March 25, 2021.

# Evolution of the Randomized Clinical Trial in the Era of Precision Oncology

Joseph C. Del Paggio, MD; John S. Berry; Wilma M. Hopman, MA; Elizabeth A. Eisenhauer, MD; Vinay Prasad, MD; Bishal Gyawali, MD, PhD; Christopher M. Booth, MD

**Use of surrogate end-points is growing parallel to the growth of industry funding**

Figure 2. Temporal Trends in Primary End Point and Industry Funding of Randomized Clinical Trials (RCTs) of Breast, Colorectal, and Non–Small Cell Lung Cancer Published in Major Journals Over 5 Decades, 1975-2020



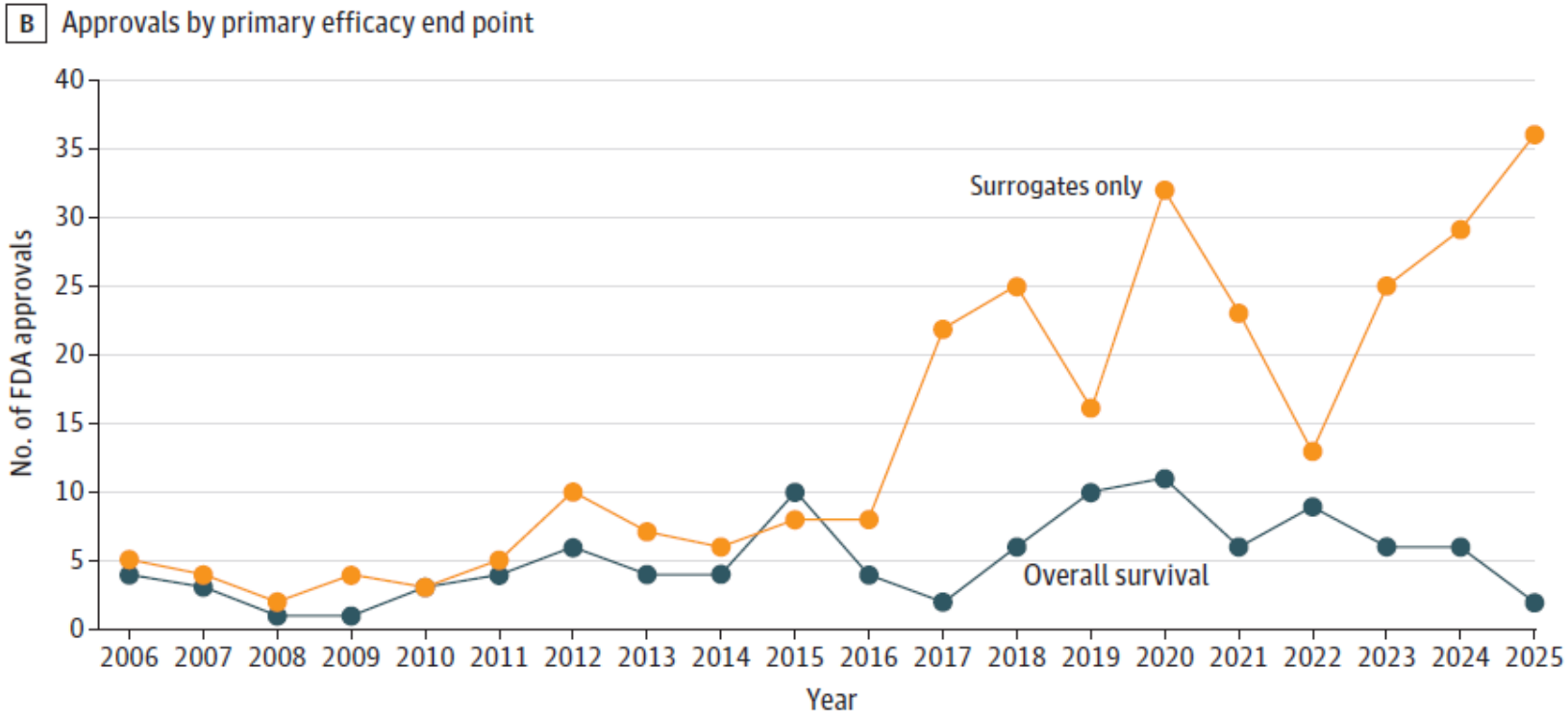
RESEARCH LETTER

JAMA August 25, 2026 Volume 336, Number 8

# Cancer Medicine Approvals in the US

Brian Shkabari, BHSc
Nicole I. Vorko, BHSc
Wesley M. Geerlinks, BHSc
Elizaveta Purh, BHSc
Claire M. Diana-Gonsalves, BHSc
Svasti Sutaria, BSc
Bishal Gyawali, MD, PhD

**Use of surrogate end-points is growing parallel to the growth of industry funding**



Linee guida

# CARCINOMA MAMMARIO AVANZATO

Edizione 2023

In collaborazione con

Associazione Italiana Radioterapia e Oncologia clinica

AIMN

A.N.I.S.C.

SIAPEC-IAP

SIMG Società Italiana di Medicina Generale e delle Cure Primarie

Società Italiana di Radiologia Medica e Interventistica

**Existing evidence does not allow to solve unertainty among possibly equivalent treatment options**

## ALGORITMO 2: CARCINOMA MAMMARIO HER2-POSITIVO

**Carcinoma mammario localmente avanzato/metastatico HER2+**

- **Controindicazioni alla chemioterapia** → Trastuzumab + terapia endocrina se HR+
- **Non controindicazioni alla chemioterapia** → Pertuzumab-trastuzumab-taxano o trastuzumab deruxtecan (se DFI ≤6 mesi)

or..

Trastuzumab deruxtecan o T-DM1 o tucatinib-trastuzumab-capecitabina* (se metastasi cerebrali attive)

or..

or..

Tucatinib-trastuzumab-capecitabina o trastuzumab deruxtecan o T-DM1

or..

or..

Chemioterapia + trastuzumab o lapatinib-capecitabina

*Indicazione rimborsata se precedente ADC anti-HER2.

Invited Articles | Breast Cancer

# Decoding Clinical Trials in Metastatic Breast Cancer: Practical Insights for Optimal Therapy Sequencing

Chiara Corti, MD[1,2,3,4,5]; Hope S. Rugo, MD, FASCO[6,7]; and Sara M. Tolaney, MD, MPH, FASCO[1,2,3]

DOI https://doi.org/10.1200/EDBK-25-100053

## OVERVIEW

The art of sequencing therapy in the management of breast cancer is a multifaceted challenge that demands the careful integration of clinical trial data, real-world evidence, and individualized patient factors to guide treatment decisions. As the therapeutic landscape evolves rapidly with new agents and combinations, clinicians are confronted with critical decisions on how best to order treatments to maximize benefit, minimize toxicity, and preserve future options. For patients with estrogen receptor–positive (ER+) disease, this review discusses how emerging resistance patterns after cyclin-dependent kinase 4 and 6 inhibitors require careful re-evaluation of subsequent endocrine and targeted therapies, as well as chemotherapy, emphasizing the need for evidence-based

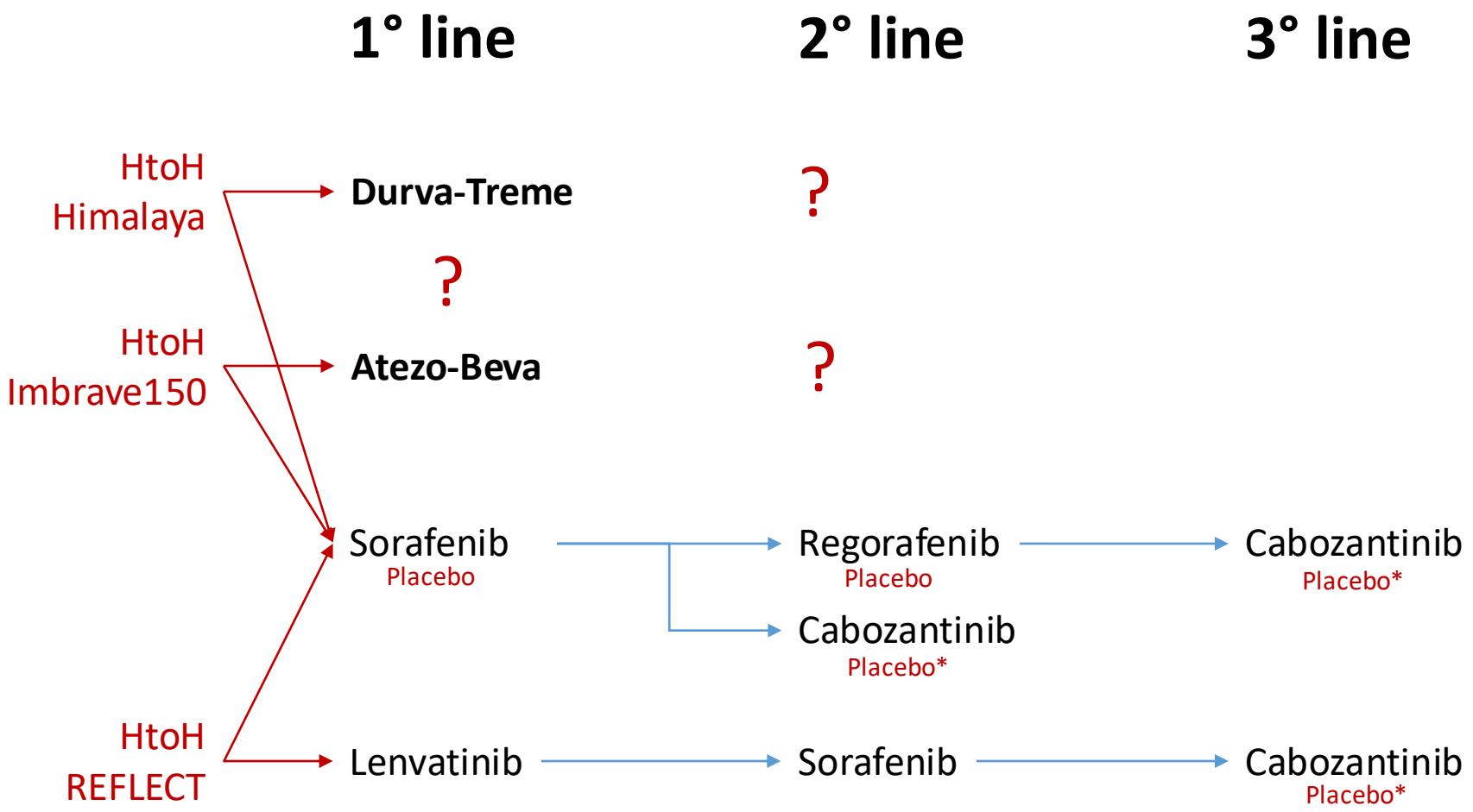
Accepted April 14, 2025
Published May 14, 2025

Am Soc Clin Oncol Educ Book 45:e100053
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**Art is wonderful… but science would be welcome too…**

# Advanced HCC
# Not eligible for LR treatment
# Child-A

**New more effective treatments may displace old ones and increase unertainty**



# Reflection #3

**Research conducted solely for registration purposes is not enough**

It creates opportunities,
but also uncertainties…

# academic research…



# The limitations of academic research…

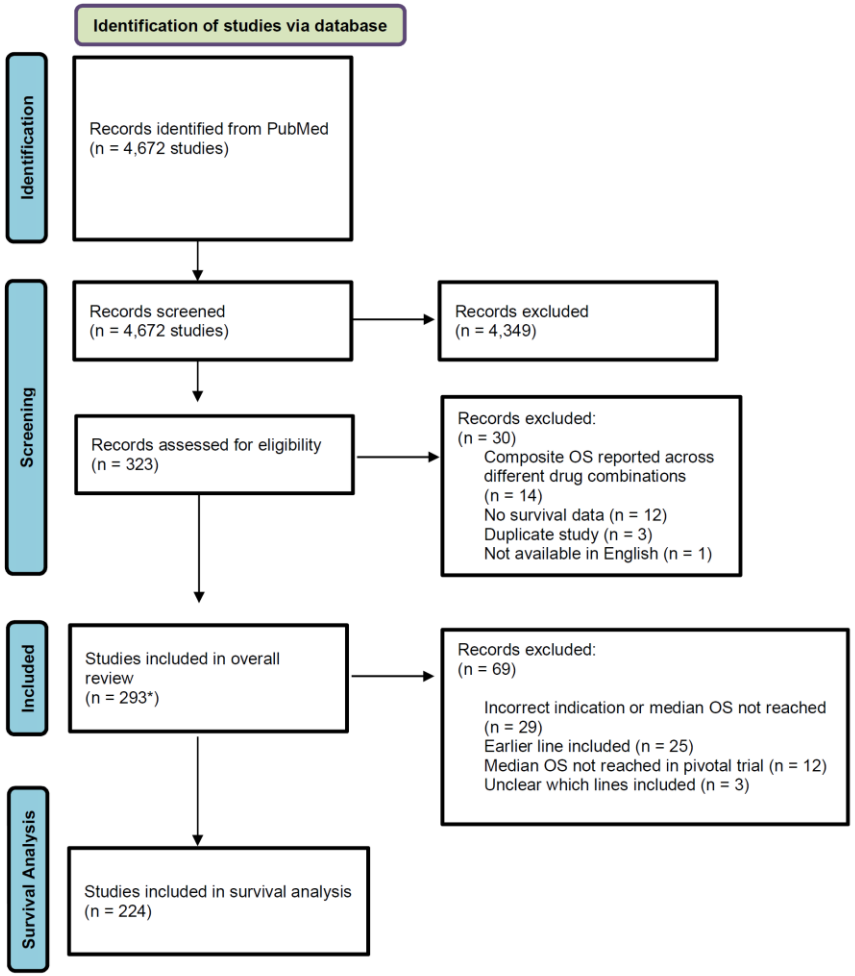
- **Too little** of it is conducted
- For the most part, it ends up producing **other snapshots** of drug effects (often with a significant **delay**)
- Much like research with regulatory aims…
  - it frequently employs **surrogate endpoints** to shorten timelines and reduce both the size and costs of studies
  - it rarely addresses the study of treatment **sequences**
- A great deal (perhaps too much?) of observational research is carried out, which does not necessarily constitute high-quality RWE

European Journal of Cancer 155 (2021) 136–144

# Real-world outcomes associated with new cancer medicines approved by the Food and Drug Administration and European Medicines Agency: A retrospective cohort study

Jemma M. Boyle [a,1], Gemma Hegarty [b,1], Christopher Frampton [c], Elizabeth Harvey-Jones [d], Joanna Dodkins [d], Katharina Beyer [e], Gincy George [e], Richard Sullivan [d,f], Christopher Booth [g,2], Ajay Aggarwal [a,d,f,*,2]

**Figure 1** – Flow diagram demonstrating selection of RWD studies included in the analysis.




**N=293**

| | Observational RWD Studies | | Observational RWD studies included in survival analyses | |
|---|---|---|---|---|
| | **No.** | **%** | **No.** | **%** |
| **Country** | | | | |
| Italy | 52 | 17.7 | 44 | 19.6 |
| Japan | 30 | 10.2 | 22 | 9.8 |
| China | 28 | 9.6 | 22 | 9.8 |
| USA | 26 | 8.9 | 16 | 7.1 |
| France | 22 | 7.5 | 18 | 8.0 |
| Spain | 15 | 5.1 | 12 | 5.4 |
| Canada | 14 | 4.8 | 9 | 4.0 |
| South Korea | 13 | 4.4 | 12 | 5.4 |
| UK | 8 | 2.7 | 6 | 2.7 |
| Netherlands | 8 | 2.7 | 8 | 3.6 |
| Poland | 7 | 2.4 | 5 | 2.2 |
| Multi-country | 14 | 4.8 | 9 | 4.0 |
| Other individual country | 56 | 19.1 | 41 | 18.3 |
| **Study Type** | | | | |
| Prospective | 50 | 17.1 | 39 | 17.4 |
| Retrospective | 242 | 82.6 | 184 | 82.1 |
| *Unknown* | 1 | 0·3 | 1 | 0·4 |

European Journal of Cancer 155 (2021) 136–144

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

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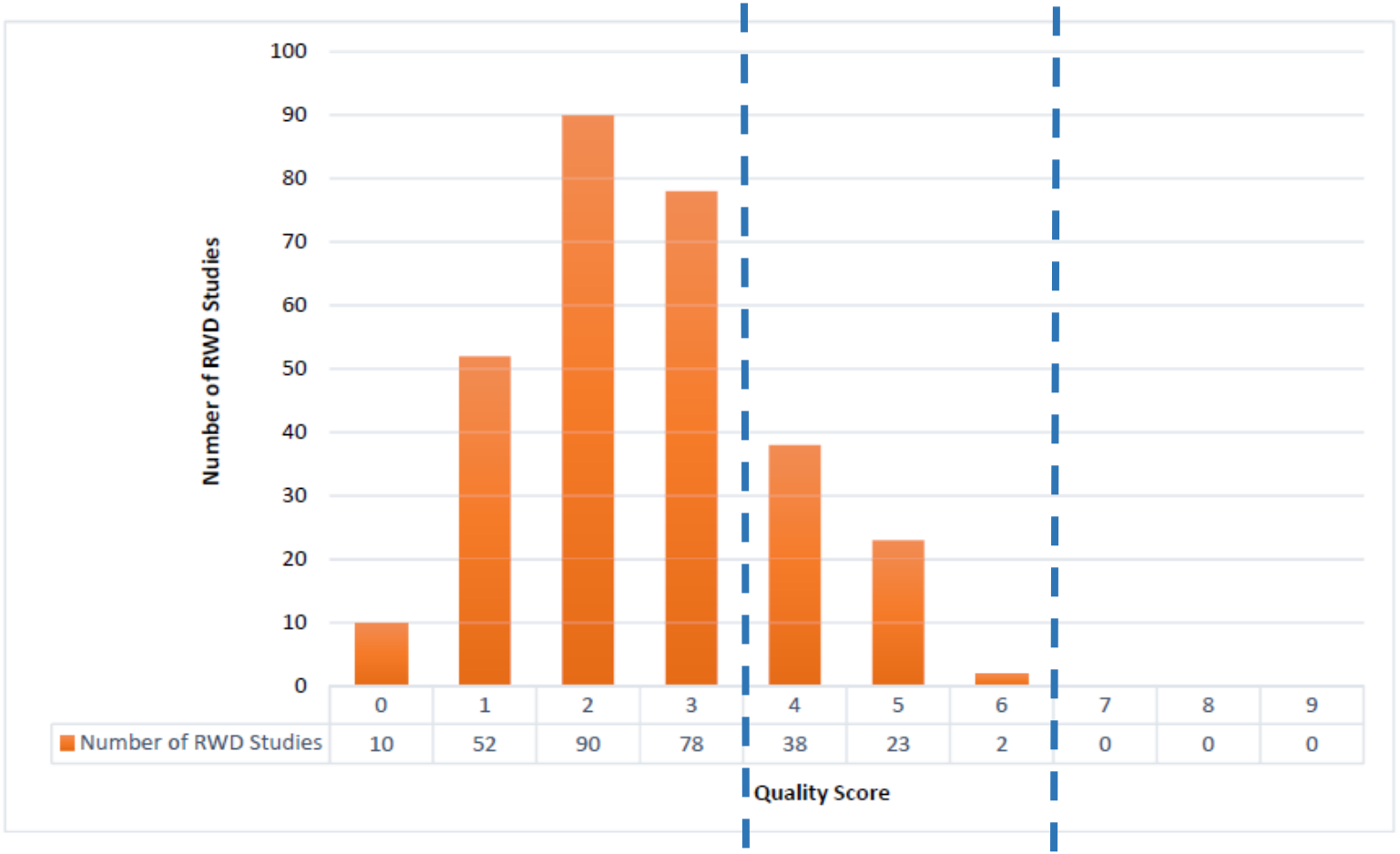



Fig. 1. Histogram of the distribution of total scores for RWD studies appraised using the Newcastle Ottawa Scale.

# Reflection #4

## Houston, we have a problem…

Something will have to be done…

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

# ESMO Guidance for Reporting Oncology real-World evidence (GROW)

L. Castelo-Branco[1*], A. Pellat[2,3†], D. Martins-Branco[1,4†], A. Valachis[5†], J. W. G. Derksen[6†], K. P. M. Suijkerbuijk[7], U. Dafni[8,9], T. Dellaporta[9], A. Vogel[10,11,12], A. Prelaj[13,14], R. H. H. Groenwold[15], H. Martins[16], R. Stahel[17], J. Bliss[18], J. Kather[19,20], N. Ribelles[21], F. Perrone[22], P. S. Hall[23], R. Dienstmann[24,25], C. M. Booth[26,27], G. Pentheroudakis[1‡], S. Delaloge[28‡] & M. Koopman[7‡]

**35 recommendations**

according to canonical paragraphs of a scientific article

**Annals of Oncology, 34 (12), 2023, 1097-1112**

# Agenda

- Do we need randomised clinical trials (RCT) and real world evidence (RWE)?
  - Limitations of trials (pharma &academia)
  - Limitations of RWE

- **Can we integrate (and improve) RCT and RWE?**
  - *Patient-journey study* model
  - A study case in hepatocellular carcinoma







# Patient-journey study model

Open access Communication

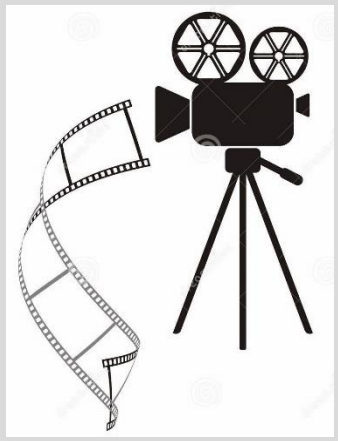
BMJ Open

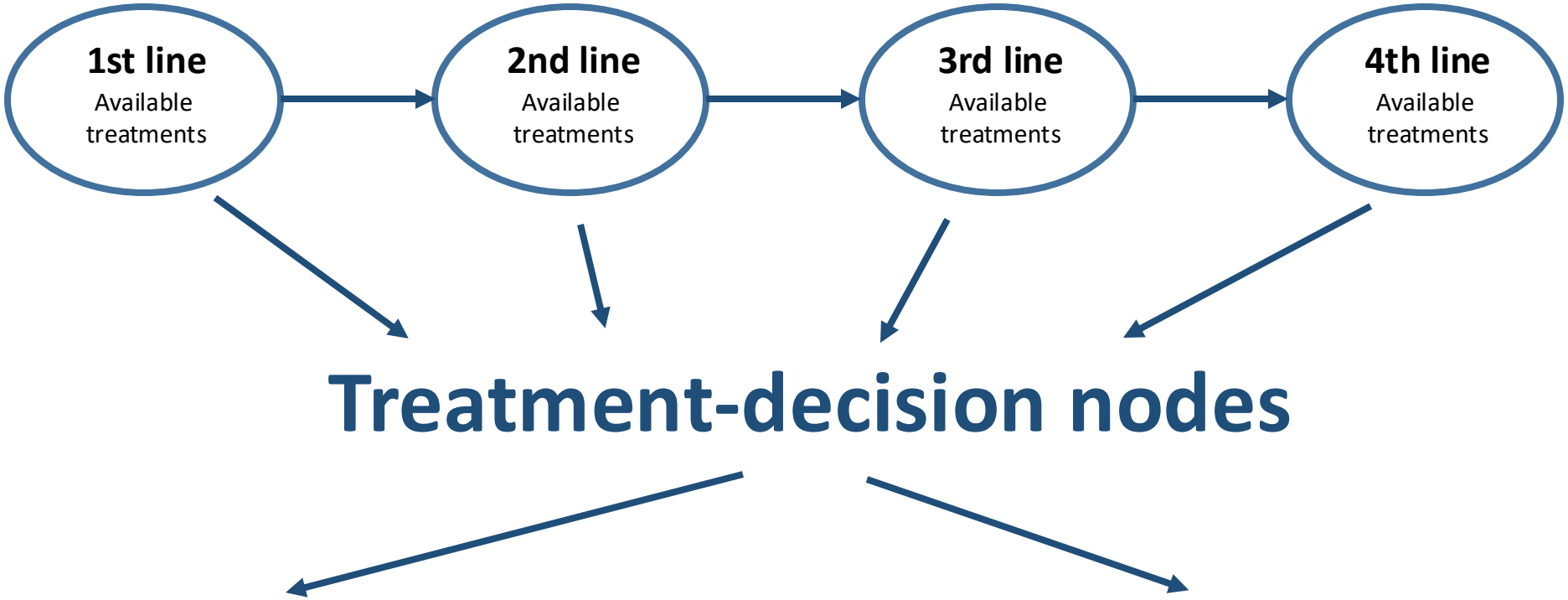
## The opportunity of patient-journey studies for academic clinical research in oncology

Francesco Perrone ,[1] Raimondo Di Liello ,[1] Piera Gargiulo,[1] Laura Arenare,[1] Lorenzo Guizzaro,[2,3] Paolo Chiodini ,[2] Ciro Gallo ,[2] Maria Carmela Piccirillo[1]

*BMJ Open* 2021;**11**:e052871. doi:10.1136/bmjopen-2021-052871

# In most cancers, we have >1 treatment option and >1 potential therapeutic line






**Clinical practice**

Share, discuss and

**choose**

**Patient-journey study (PJS)**

Share, discuss and

**choose or randomize if uncertain**

Editor's Note

INTEGRATING CLINICAL TRIALS AND PRACTICE

# Integrating Clinical Trials and Practice

## A New *JAMA* Series and Call for Papers

Gregory Curfman, MD

JAMA
**Published Online: June 3, 2024**
2024;332;(2):111. doi:10.1001/jama.2024.10266

*«Traditionally, clinical trialists and clinicians have worked independently, and,…, their separate missions, incentives, and infrastructures have been siloed. The result is inefficiency in the performance of trials and limitations in their scope and impact."*

# Pragmaticism in Cancer Clinical Trials

Kamya Sankar, MD[1]; Mary W. Redman, PhD[2,3]; Konstantin H. Dragnev, MD[4]; Brian S. Henick, MD[5]; Wade T. Iams, MD[6]; Charles D. Blanke, MD, FACP, FASCO[7]; Roy S. Herbst, MD, PhD[8]; Jhanelle E. Gray, MD[9]; and Karen L. Reckamp, MD[1]

ASCO Educational Book

asco.org/edbook | Volume 44, Issue 3 | 1

American Society of Clinical Oncology Educational Book

Volume 44, Number 3

June 2024

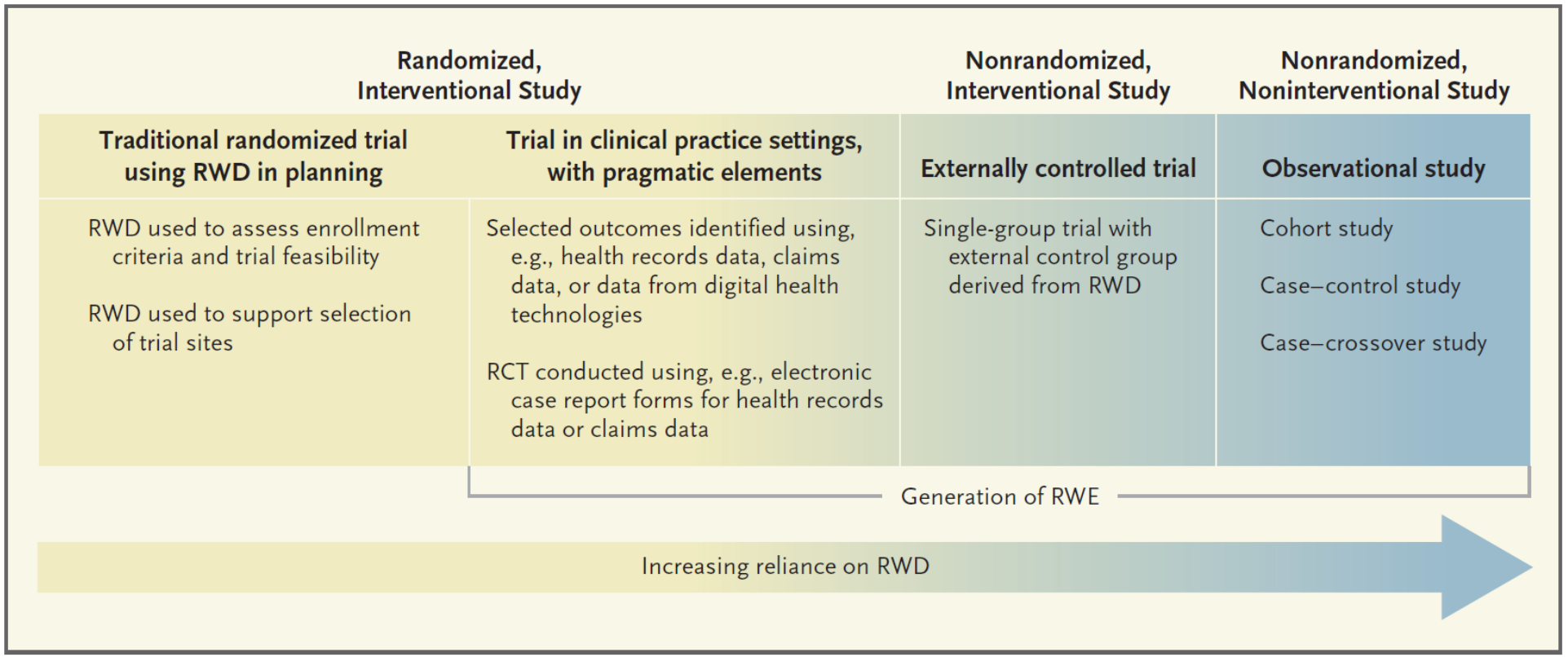
**TABLE 1.** Key Differences Between Trials With Explanatory and Pragmatic Features

| Trial Features | Explanatory | Pragmatic |
|---|---|---|
| Setting | Well resourced<br>Ideal setting | Everyday clinical practice |
| Participants | Highly selected patient populations with stringent inclusionary/exclusionary criteria | Clinical indication of interest, minimal selection criteria, ie, a patient who you would otherwise treat for this indication |
| Intervention | Strong adherence is enforced | Flexible, allows for modifications as would be the case in everyday practice |
| Outcomes | Often surrogates (eg, objective response rate, progression-free survival) | Relevant to participants, funders, communities, and health care providers (eg, overall survival, health-related quality of life) |
| Relevance to practice | Indirect—the trial does not match usual clinical practice where the intervention would be in use | Direct—trial is conducted in a simulated environment where the intervention would be implemented |

NOTE. Adapted from Zwarenstein et al.[18]

# Real-World Evidence — Where Are We Now?

John Concato, M.D., M.P.H., and Jacqueline Corrigan-Curay, J.D., M.D.




**Reliance on RWD in Representative Types of Study Design.**

RCT denotes randomized, controlled trial; RWD real-world data; and RWE real-world evidence.

N ENGL J MED 386;18 NEJM.ORG MAY 5, 2022

# April 2023




2023 AIFA CALL FOR INDEPENDENT RESEARCH

THERAPEUTIC SEQUENCING IN ONCOLOGY

**Awarding of Funding for Independent Research on Medicinal Products**

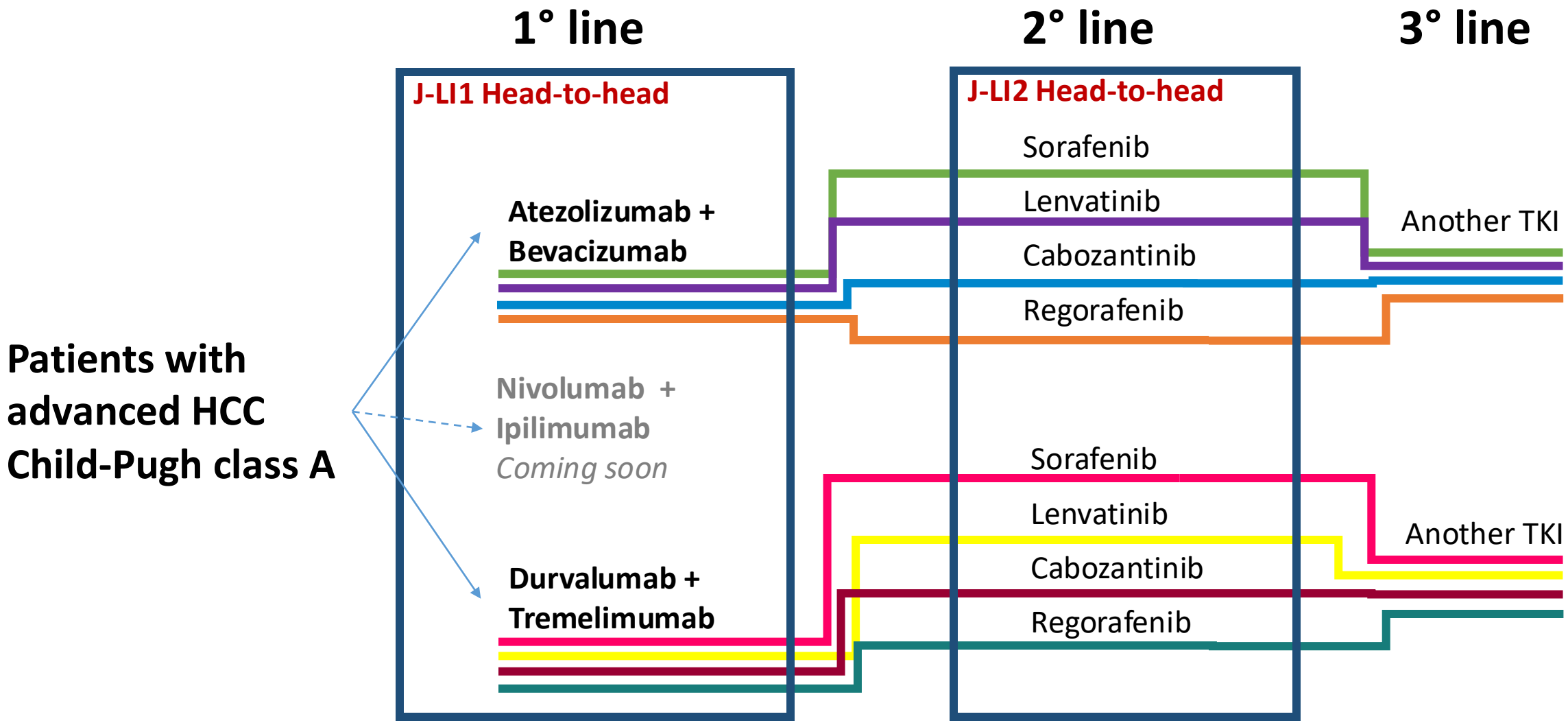
## Three areas

- NSCLC
- HCC
- Renal cancer

## Keywords

- Multicentric
- RCT and/or innovative models
- Adaptive design
- Sequencing

# J-LI - Which is the best treatment sequence?



# Pillars of a patient-journey study (PJS)

**Adaptive pragmatic master protocol …**

- **integrating** randomization at decision nodes where genuine uncertainty exists, within a prospective real-world-like cohort
- **combining** the rigour of RCT with the generalisability of prospective RWE
- **including** both head-to-head and sequence comparison
- **using** robust endpoints: OS, quality of life, toxicity, cost
- **leveraging** the potential of digital technology (EHR where available) and PROs (not only for QOL, FT…)

# Ongoing plans

- J-LI Italian going to enrol first patient by the end of 2026
- Attempt to scale to J-LI International
- Similar plans being discussed
  - Ovarian cancer setting within the MITO group (mid 2027?)
  - Advanced NSCLC setting
  - …
- Looking for cooperation!

# Agenda

- Do we need randomised clinical trials (RCT) and real world evidence (RWE)?
  - Limitations of trials (pharma &academia)
  - Limitations of RWE

- Can we integrate (and improve) RCT and RWE?
  - *Patient-journey study* model –
  - A study case in hepatocellular carcinoma

# Agenda

- Do we need randomised clinical trials (RCT) and real world evidence (RWE)? **Yes, and both need to be improved**
  - Limitations of trials (pharma &academia)
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# Thank you
# for your attention