Université Libre de Bruxelles
Actualités en médecine factuelle
Institut Bordet, Bruxelles, 24 février 2018

Comment adapter la recherche clinique aux différents niveaux de preuve ?

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Jacques Demotes
24 février 2018

Agenda

- Interventional / observational
- Evidence along the drug development : efficacy / safety
- Pragmatic trials, comparative effectiveness
- Personalised / stratified medicine : biomarker profiles, new trial designs
- Data reuse, data sharing

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Interventional / observational

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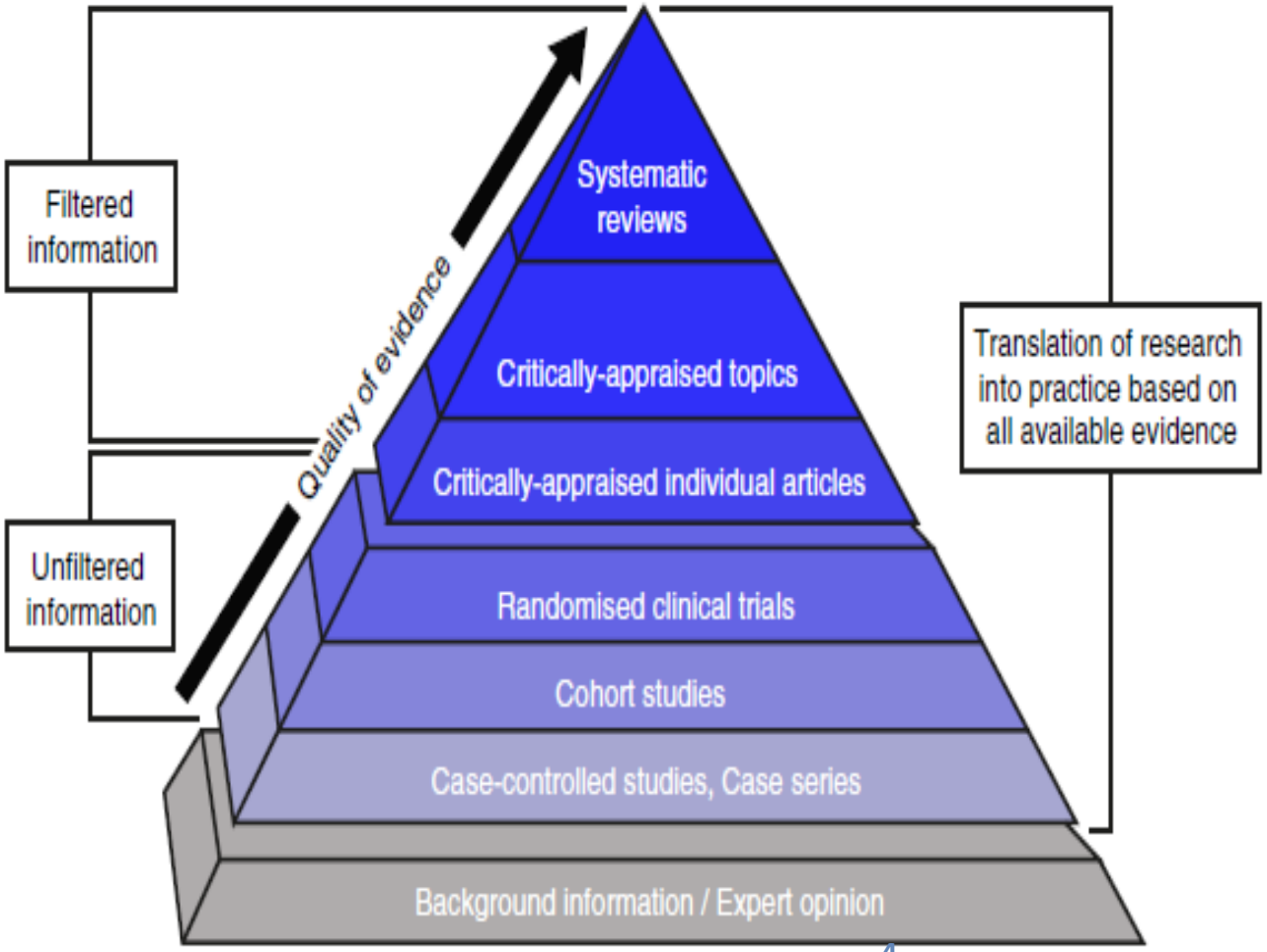
Levels of scientific evidence

Interventional
(causality)

Observational
(correlation)



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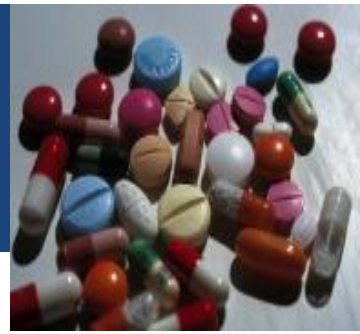
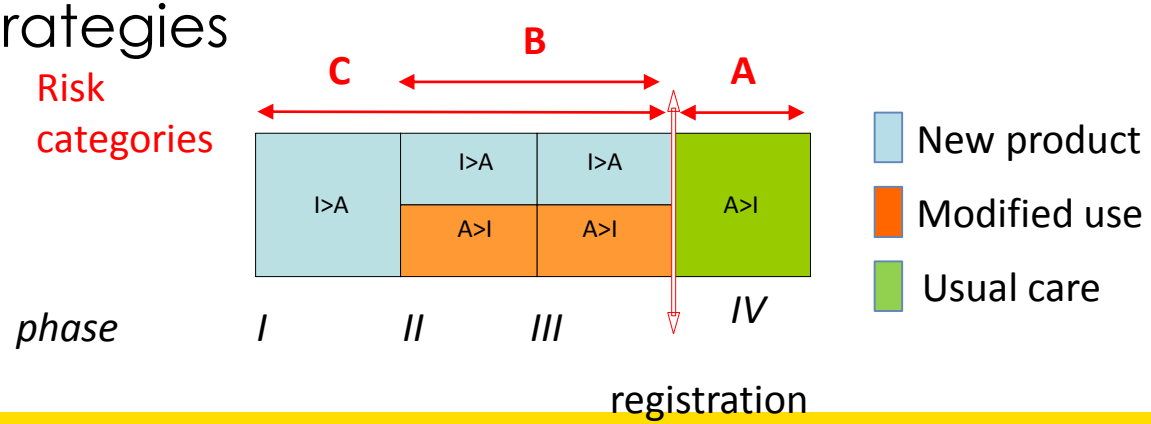
Need for clinical trials



- **1 - Development of innovative health products**
  - registration trials
  - phase I – II – III
- **2 - Repurposing trials**
  - exploring new indications for authorised products
  - phase II – III
- **3 - Comparative efficacy/ safety / effectiveness trials**
  - compare efficacy and safety of authorised healthcare strategies
  - phase IV



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Methodology and design

European Journal of Internal Medicine 32 (2016) 13–21

Contents lists available at ScienceDirect

European Journal of Internal Medicine

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

Review Article

Evidence-based clinical practice: Overview of threats to the validity of evidence and how to minimise them

Silvio Garattini [a], Janus C. Jakobsen [b,c], Jørn Wetterslev [b], Vittorio Bertelé [a], Rita Banzi [a], Ana Rath [d], Edmund A.M. Neugebauer [e], Martine Laville [f], Yvonne Masson [f], Virginie Hivert [f], Michaela Eikermann [g], Burc Aydin [h], Sandra Ngwabyt [d], Cecilia Martinho [i], Chiara Gerardi [a], Cezary A. Szmigielski [j], Jacques Demotes-Mainard [k], Christian Gluud [b,*]

Djurisic et al. Trials (2017) 18:360
DOI 10.1186/s13063-017-2099-9

Trials

REVIEW Open Access

Barriers to the conduct of randomised clinical trials within all disease areas

Snezana Djurisic[1*], Ana Rath[2], Sabrina Gaber[3], Silvio Garattini[4], Vittorio Bertele[4], Sandra-Nadia Ngwabyt[2], Virginie Hivert[5], Edmund A. M. Neugebauer[6], Martine Laville[7], Michael Hiesmayr[8], Jacques Demotes-Mainard[3], Christine Kubiak[3], Janus C. Jakobsen[1,9] and Christian Gluud[1*]

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Methodology and design

Rath et al. Trials (2017) 18:556
DOI 10.1186/s13063-017-2287-7

Trials

REVIEW Open Access

A systematic literature review of evidence-based clinical practice for rare diseases: what are the perceived and real barriers for improving the evidence and how can they be overcome?

Ana Rath[1], Valérie Salamon[1], Sandra Peixoto[1], Virginie Hivert[2], Martine Laville[3], Berenice Segrestin[3], Edmund A. M. Neugebauer[4], Michaela Eikermann[5], Vittorio Bertele[6], Silvio Garattini[6], Jann Wetterslev[7], Rita Banzi[8], Janus C. Jakobsen[7,8], Snezana Djurisic[7*], Christine Kubiak[9], Jacques Demotes-Mainard[9] and Christian Gluud[7*]

Neugebauer et al. Trials (2017) 18:427
DOI 10.1186/s13063-017-2168-0

Trials

REVIEW Open Access

Specific barriers to the conduct of randomised clinical trials on medical devices

Edmund A. M. Neugebauer[1], Ana Rath[2], Sunya-Lee Antoine[3], Michaela Eikermann[3], Doerthe Seidel[3], Carsten Koenen[3], Esther Jacobs[3], Dawid Pieper[3], Martine Laville[4], Séverine Pitel[5], Cecilia Martinho[6], Snezana Djurisic[7*], Jacques Demotes-Mainard[8], Christine Kubiak[8], Vittorio Bertele[9], Janus C. Jakobsen[7,10], Silvio Garattini[9] and Christian Gluud[7*]

Laville et al. Trials (2017) 18:425
DOI 10.1186/s13063-017-2160-8

Trials

REVIEW Open Access

Evidence-based practice within nutrition: what are the barriers for improving the evidence and how can they be dealt with?

Martine Laville[1], Berenice Segrestin[1], Maud Alligier[1], Cristina Ruano-Rodríguez[2,3], Lluís Serra-Majem[2,3], Michael Hiesmayr[4], Annemie Schols[5], Carlo La Vecchia[6], Yves Boirie[7], Ana Rath[8], Edmund A. M. Neugebauer[9], Silvio Garattini[10], Vittorio Bertele[10], Christine Kubiak[11], Jacques Demotes-Mainard[11], Janus C. Jakobsen[12,13], Snezana Djurisic[12*] and Christian Gluud[12*]

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Clinical trial design and methodology

- **Clinical trials :**
  - prospective experiment
  - compare randomised groups
  - no confounding factor, causality
- **Ideally :**
  - randomised
  - double-blind
  - controlled

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Challenges in randomized clinical trials

- **Controls**
  - placebo
  - active comparator
  - uncontrolled ? placebo effect, regression to the mean
  - historical control ? patient, treatment, evaluation may differ
  - ideally concurrent : same time period

- **Randomisation**
  - simple (unbalanced ?)
  - blocked (predictability ?)
  - stratified (balance sex, age)

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Challenges in randomized clinical trials

- **Outcome measures**
  - standardized, patient-relevant, avoid surrogate endpoints
  - statistical power calculated for primary endpoint
  - long-term outcome (device) : trial then registry

- **Blinding : avoid bias**
  - double blind : patients and investigators
  - single blind
  - open
  - blinded independent review

  - Similar treatments, or double-dummy
  - Surgery trials : sham ?
  - Psychotherapy, physiotherapy ?
    - make assessors blind

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Challenges in randomized clinical trials

- **Learning curve**
  - randomise the first patient, analyse 2 groups

- **Statistical analysis plan pre-specified (and registered)**
  - sample size calculation based on primary endpoint
  - avoid multiple tests and post-hoc analysis
    adjustment for multiplicity : Bonferroni, Hochberg

- **Sample size calculation**
  - more patients -> more chance to detect effect (if any)
  - large effect -> small sample size

$$n = 2\,(Z\alpha + Z\,[1-\beta])^2 \times SD^2 / d^2$$

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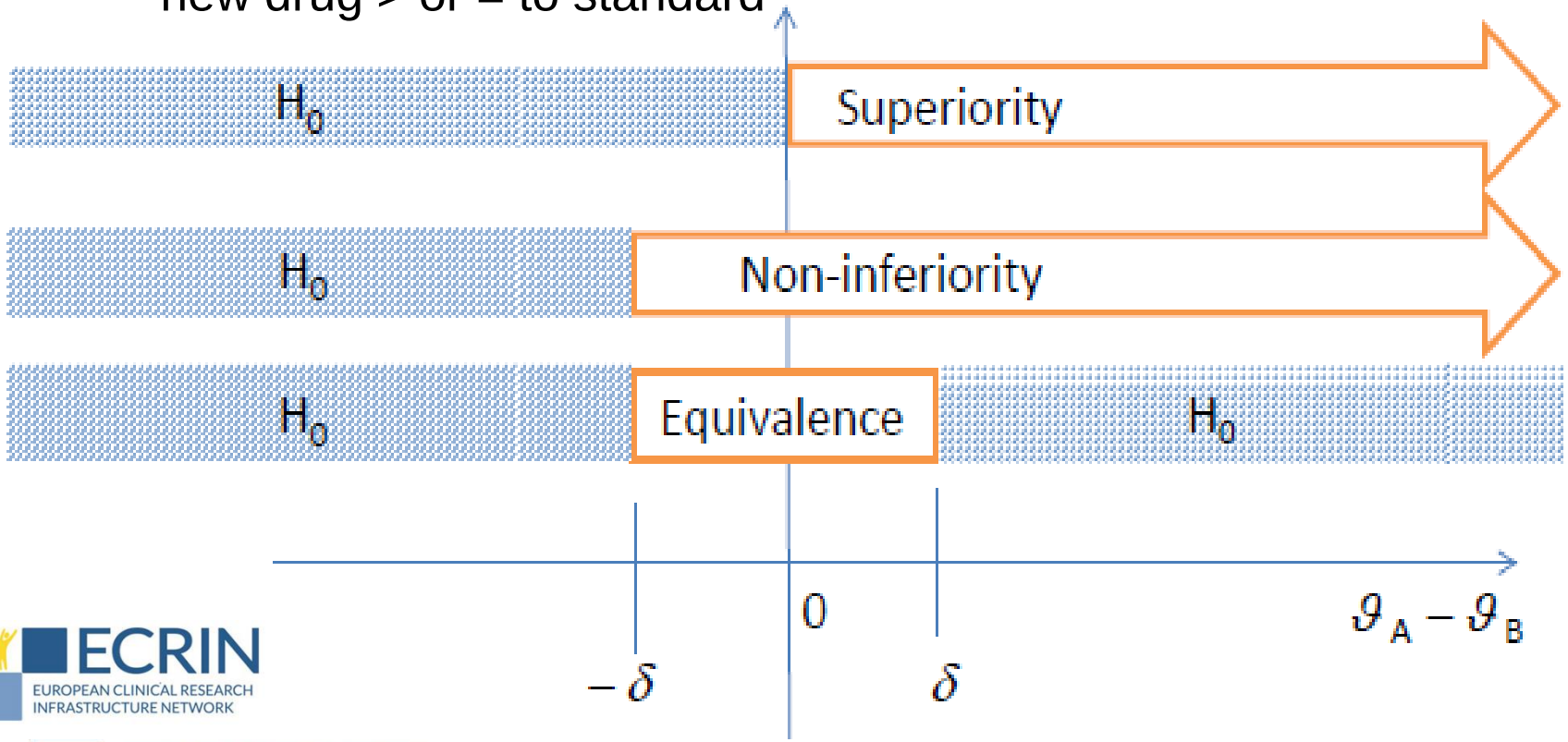
Superiority, non-inferiority, equivalence

- **Design : based on question**
  - new drug > placebo
  - new drug + standard > standard
  - new drug > or = to standard



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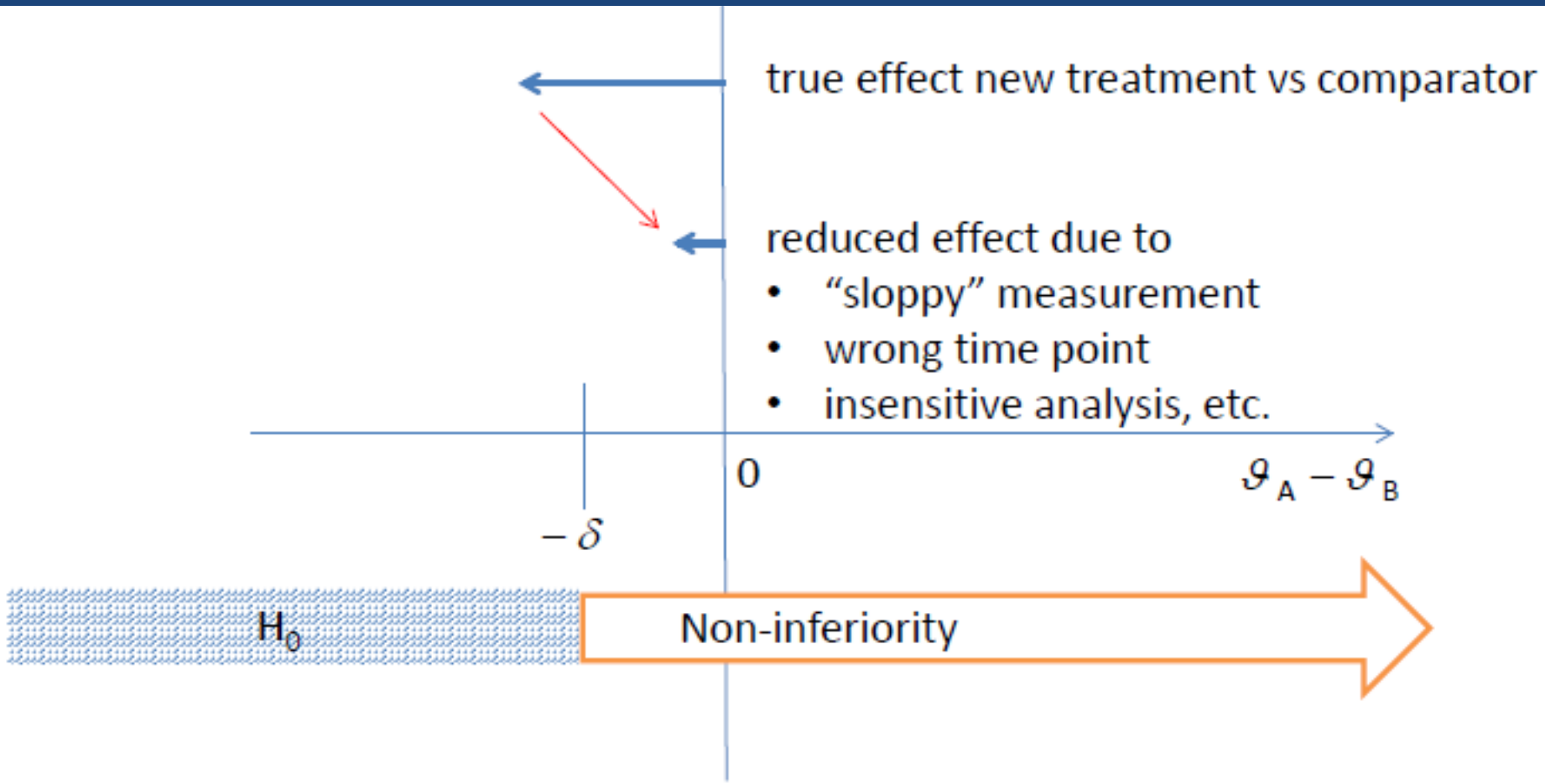
Insensitive non-inferiority trial



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Evidence along the drug development :

efficacy / safety

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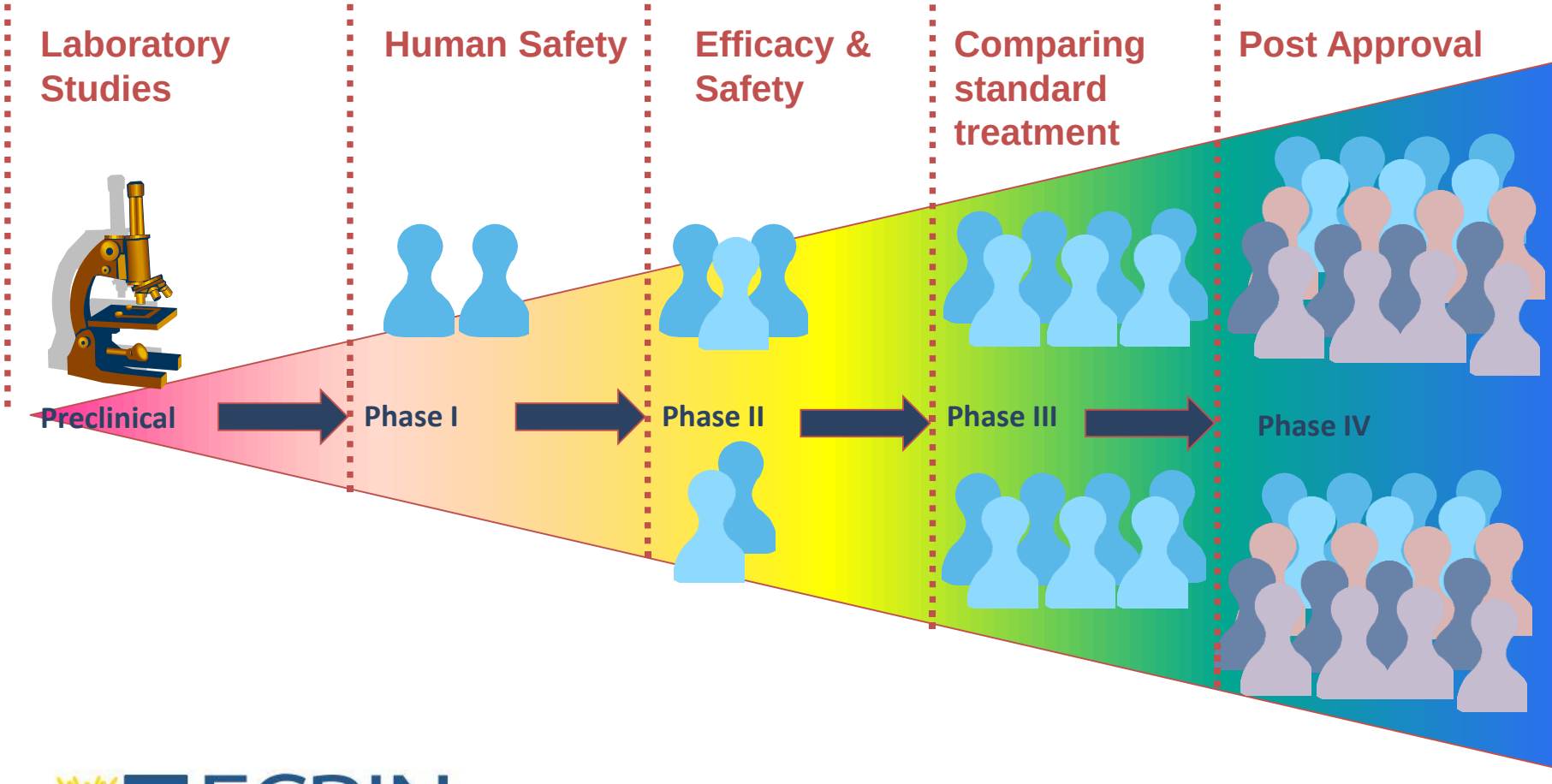
Stages of clinical development



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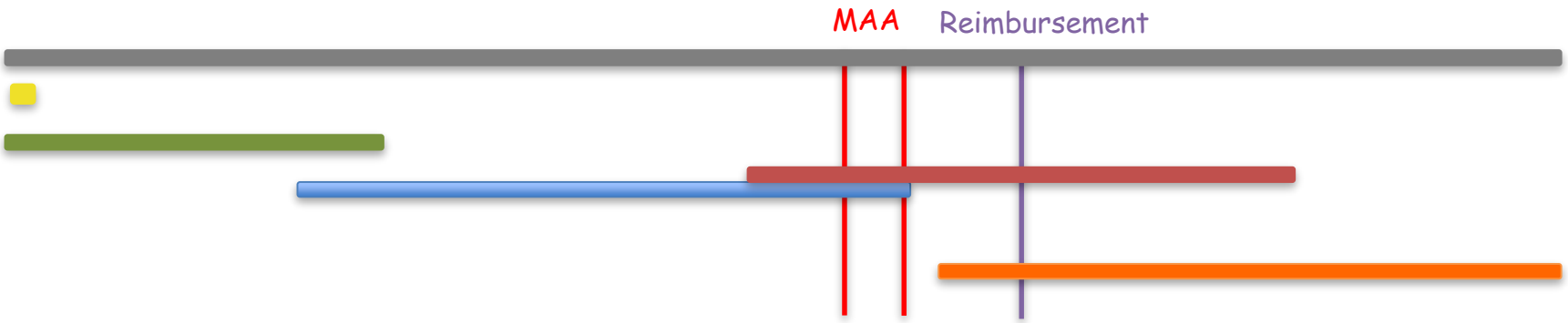
Evidence along the drug development process



Non-clinical testing

Pre-MA
- Phase I
- Phase II
- Phase III
- Late phase III – LST

Post-MA
- Late phase III - LSS
- PASS (observational / interventional)
- PAES

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Pragmatic trials, comparative effectiveness

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Heterogeneity of patient population

Explanatory trials

Pragmatic trials

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N Engl J Med 2017;377:957-64.
DOI: 10.1056/NEJMra1510058

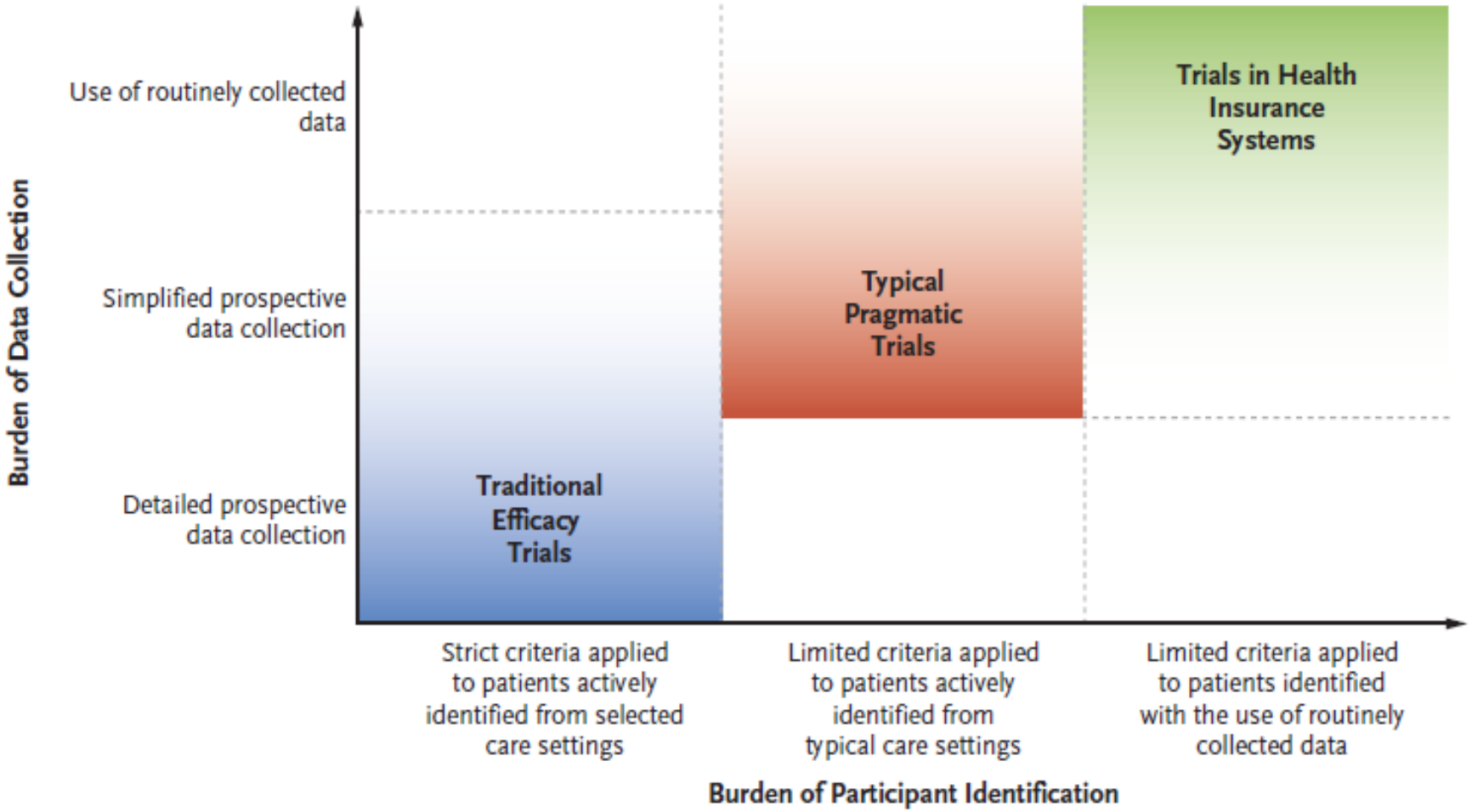

Figure 1. Typical Features of Different Types of Randomized, Controlled Trials (RCTs).

The figure represents the general differences in the characteristics of traditional "efficacy" RCTs, pragmatic RCTs, and RCTs based in health insurance systems.

Personalised / stratified medicine :

biomarker profiles

new trial designs

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Trial centred on the patient, not on the product:

what is the best treatment option for this patient / group of patients ?

Biomarker stratification ?

Personalised / stratified / precision medicine : biomarker profiling, big data and artificial intelligence

- **Clinical data**
  - observational, retrospective or prospective, cohort integration
- **Omics**
  - Genotype : genomics (germinal, somatic, microbiome)
  - Phenotype : transcriptomic, proteomic, metabolomic profiles
- **Imaging**
- **Multimodal data management (secure data warehouse)**
- **Multimodal data analysis for patient stratification**
  - Hypothesis-driven
  - Data-driven : machine learning

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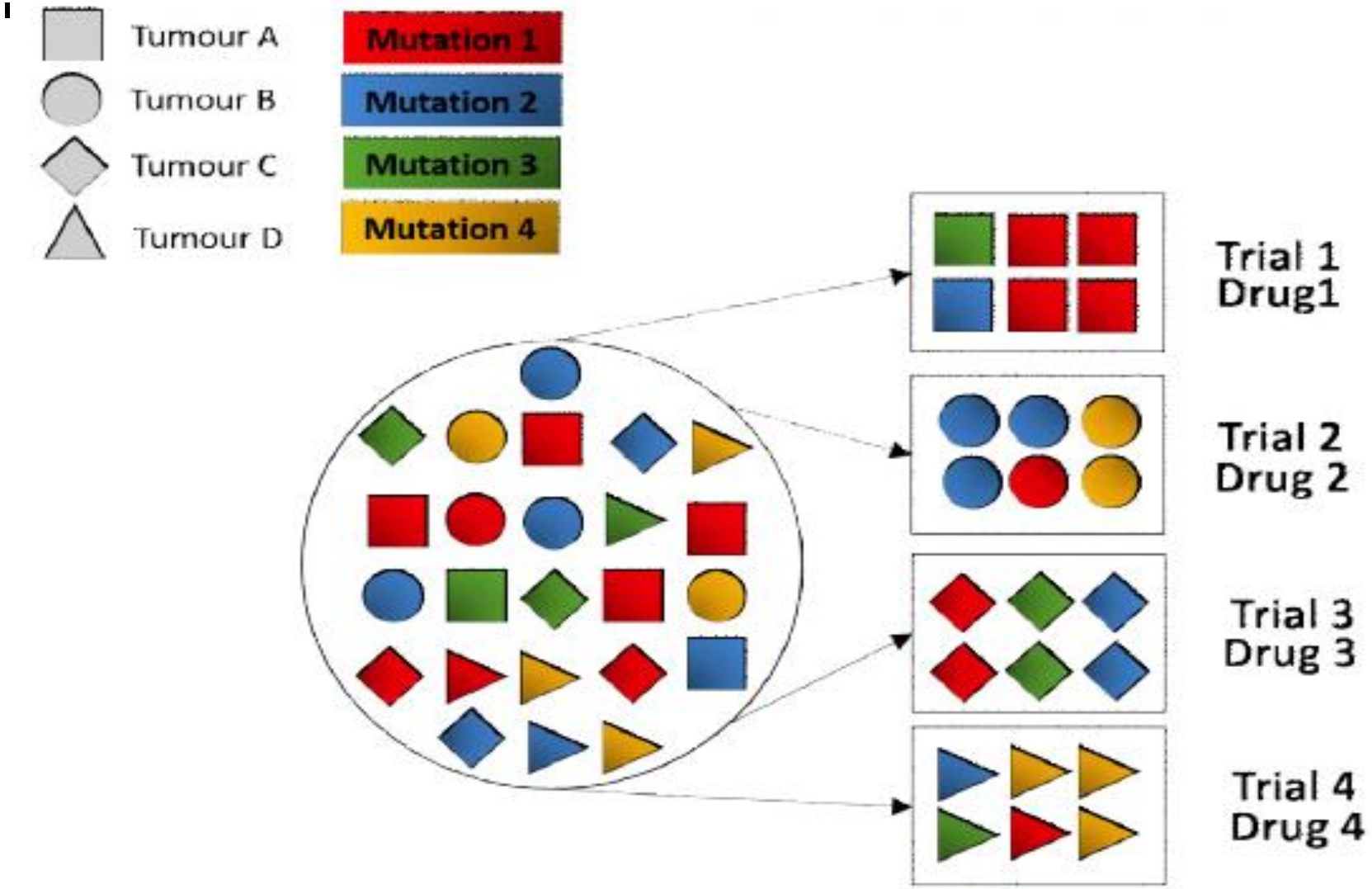
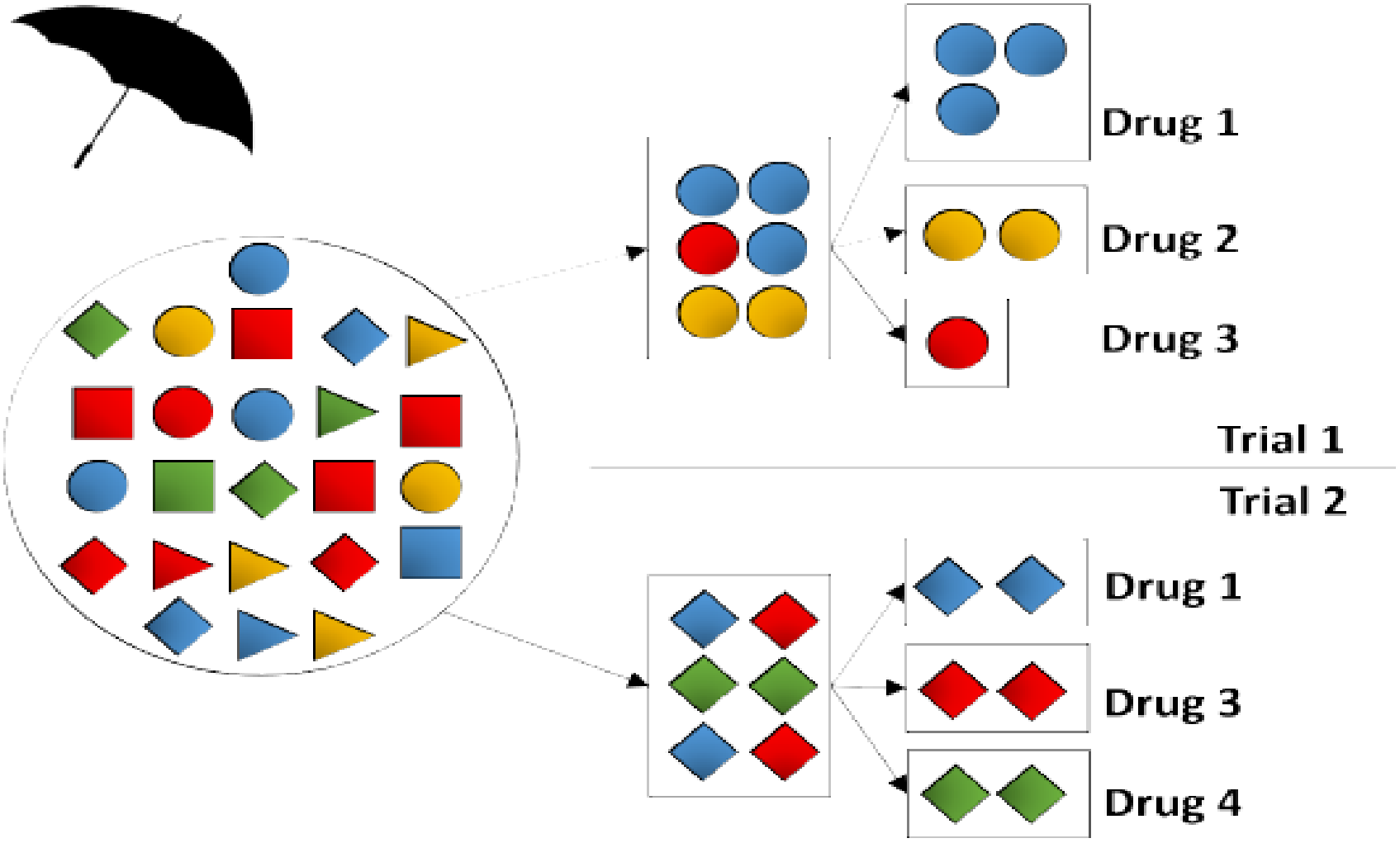
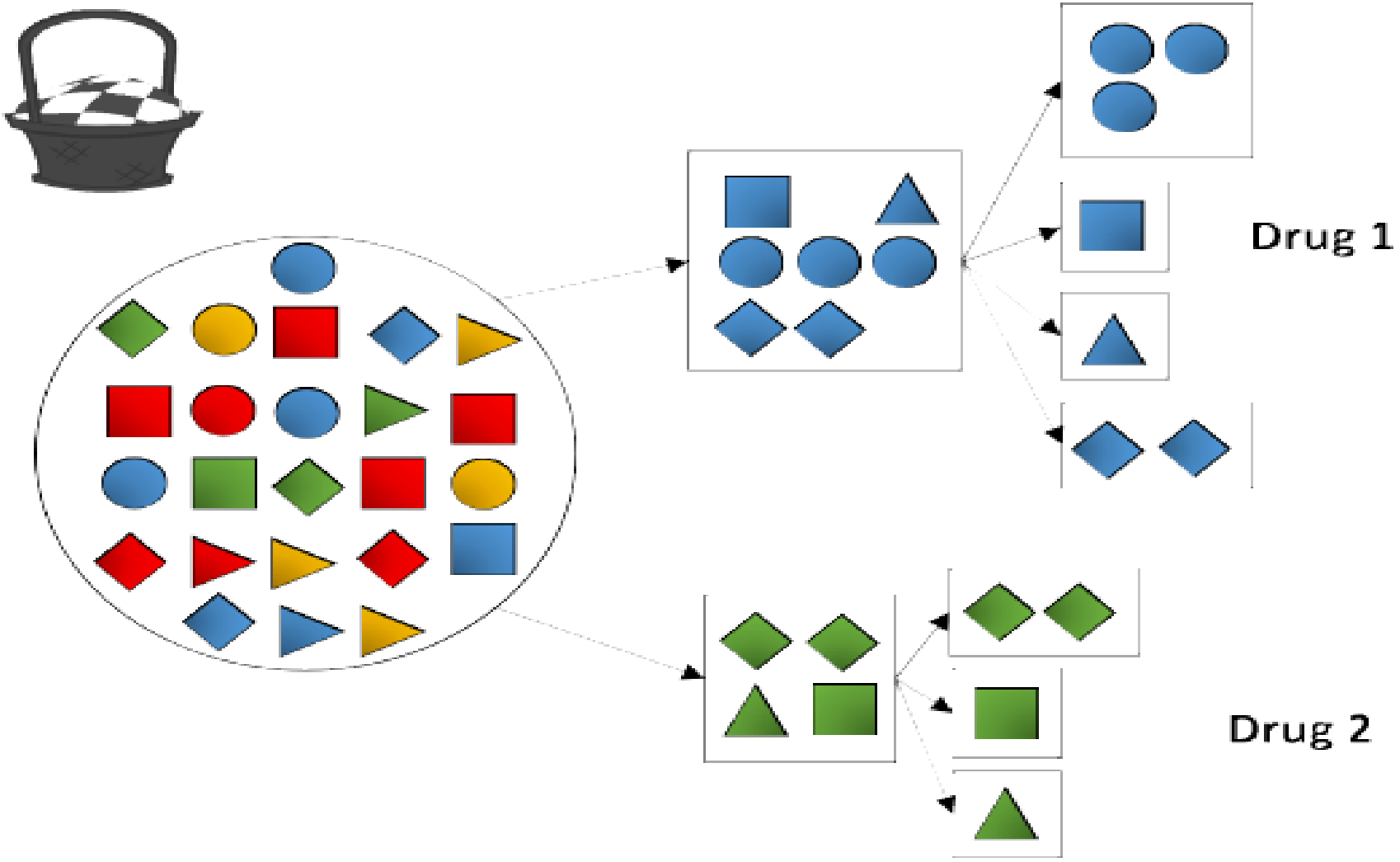
Non-targeted therapy : tumor histology determines treatment



Biomarker-stratified subgroups within the same disease condition

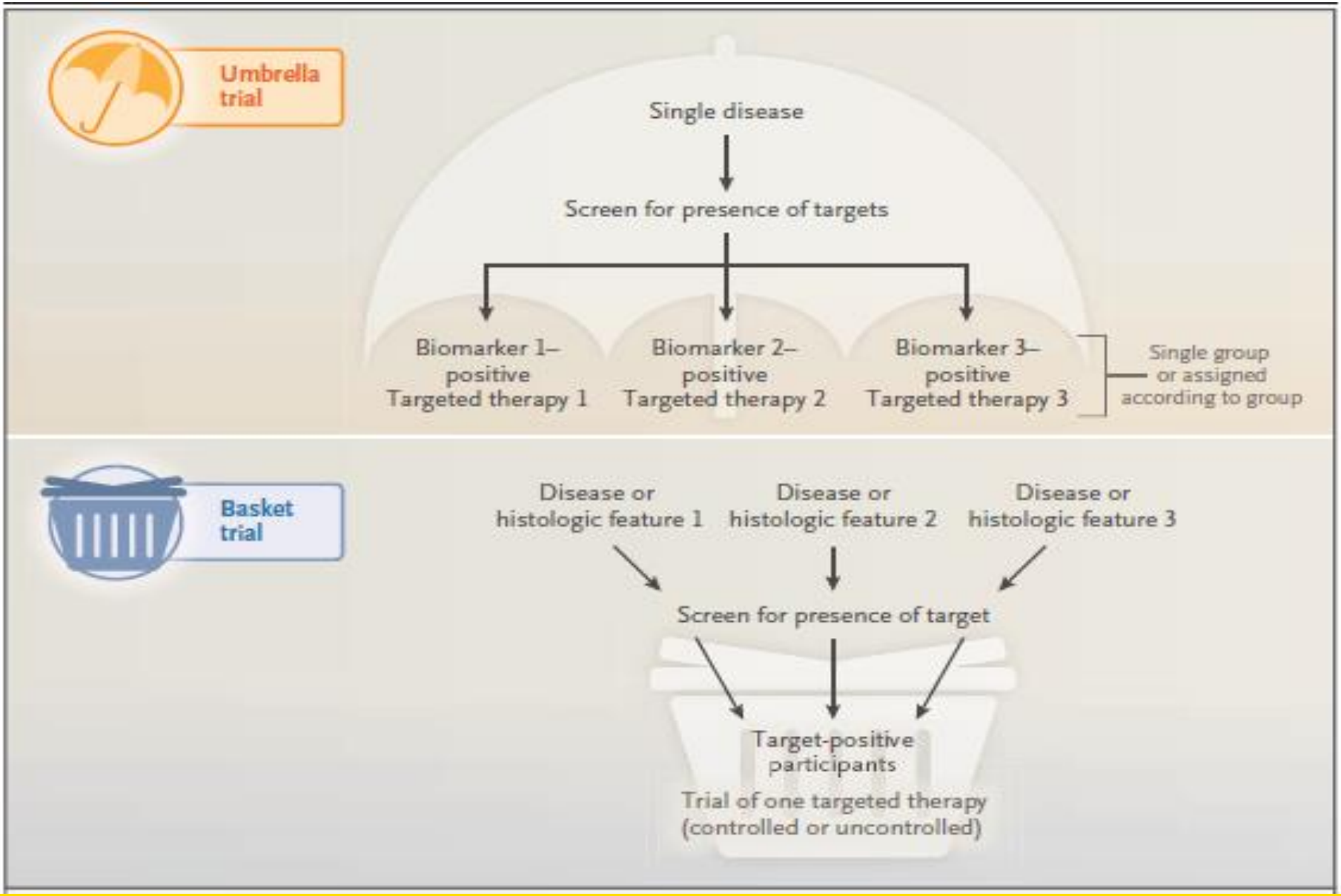


Biomarker-stratified subgroups across multiple disease conditions



Umbrella vs. basket trials

N Engl J Med 2017;377:62-70.
DOI: 10.1056/NEJMra1510062



REVIEW ARTICLE

N Engl J Med 2017;377:62-70.
DOI: 10.1056/NEJMra1510062

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*

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

Table 1. Types of Master Protocols.

Type of Trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

- Umbrella and basket trials beyond cancer ?
- Treatment options for complex, mechanism-agnostic, biomarker profiles ?

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Data reuse, data sharing

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Reuse of health data for research purposes

- **Observational (cohorts) or interventional (trials)**

➢ security, data protection, data standards, interoperability

- resue of healthcare data :
  - electronic health records
  - electronic data capture
- reuse of national health databases and registries

Mc Cord et al. Trials (2018) 19:29
DOI 10.1186/s13063-017-2394-5

Trials

REVIEW Open Access

Routinely collected data for randomized trials: promises, barriers, and implications

Kimberly A. Mc Cord[1], Rustam Al-Shahi Salman[2], Shaun Treweek[3], Heidi Gardner[3], Daniel Strech[4], William Whiteley[2], John P. A. Ioannidis[5,6,7,8,9] and Lars G. Hemkens[1*]

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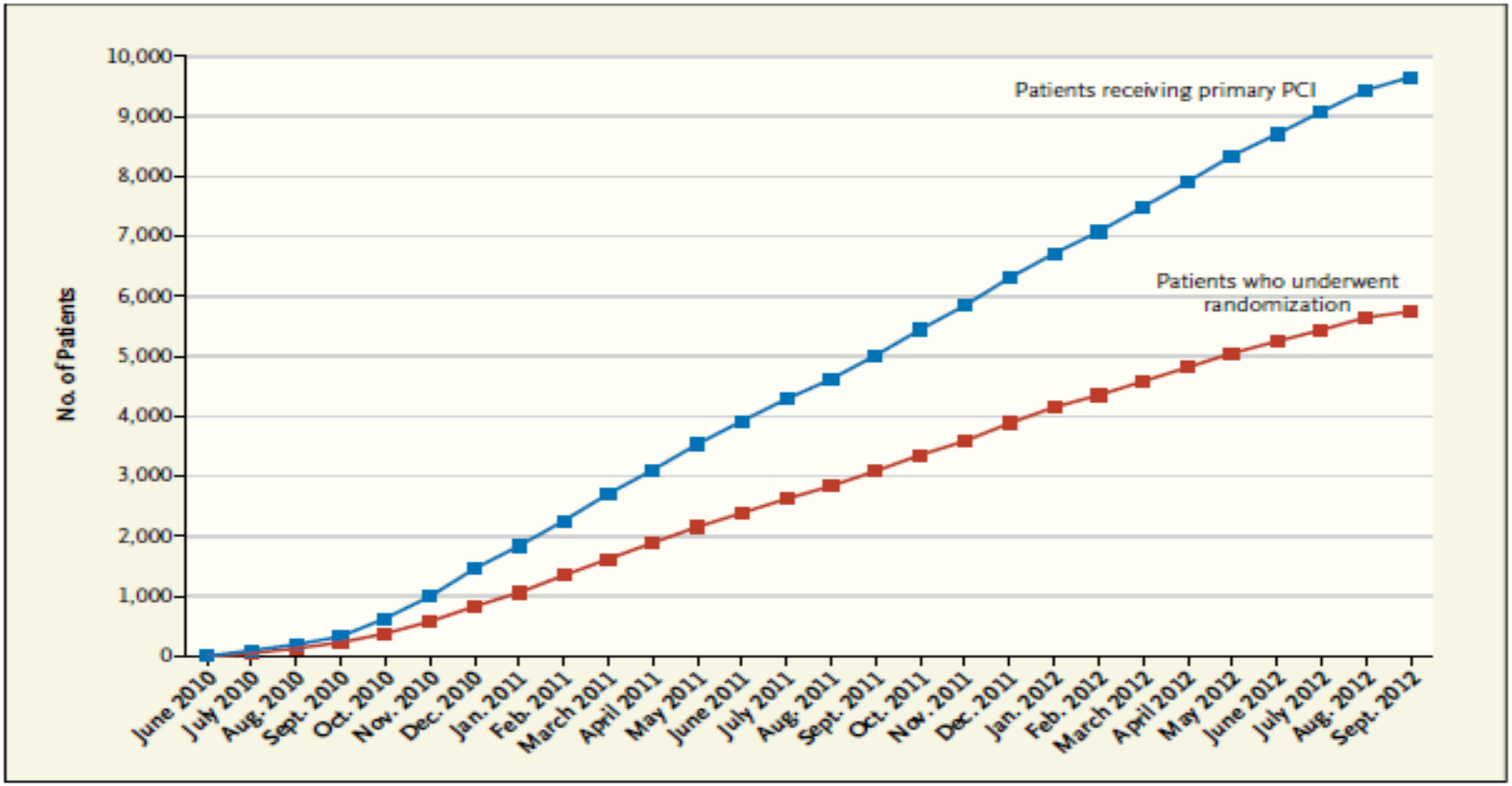
The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

Michael S. Lauer, M.D., and Ralph B. D'Agostino, Sr., Ph.D.

N ENGL J MED 369;17 NEJM.ORG OCTOBER 24, 2013



Rapid Randomization in the TASTE Trial, with Enrollment of Most Patients Receiving Primary Percutaneous Coronary Intervention (PCI).

Adapted from the Institute of Medicine (www.iom.edu/~/media/Files/Activity%20Files/Quality/VSRT/LST%20Workshop/Presentations/Granger.pdf). The incremental cost of the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial was $300,000, or $50 for each participant who underwent randomization.

CLINICAL TRIAL DATA SHARING

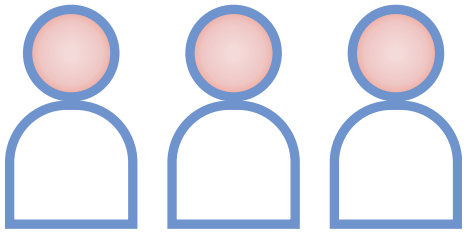
- ✓ data protection, GDPR
- ✓ informed consent
- ✓ anonymized / pseudonymized
- ✓ access (open vs. controlled)
- ✓ standard data format
- ✓ security
- ✓ type of repositories

BMJ Open **Sharing and reuse of individual participant data from clinical trials: principles and recommendations**

Christian Ohmann,[1] Rita Banzi,[2] Steve Canham,[3] Serena Battaglia,[4] Mihaela Matei,[4] Christopher Ariyo,[5] Lauren Becnel,[6] Barbara Bierer,[7] Sarion Bowers,[8] Luca Clivio,[2] Monica Dias,[9] Christiane Druml,[10] Hélène Faure,[11] Martin Fenner,[12] Jose Galvez,[13] Davina Ghersi,[14] Christian Gluud,[15] Trish Groves,[16] Paul Houston,[6] Ghassan Karam,[17] Dipak Kalra,[18] Rachel L Knowles,[19] Karmela Krleža-Jerić,[20] Christine Kubiak,[4] Wolfgang Kuchinke,[21] Rebecca Kush,[22,23] Ari Lukkarinen,[5] Pedro Silverio Marques,[24] Andrew Newbigging,[25,26] Jennifer O'Callaghan,[27] Philippe Ravaud,[28] Irene Schlünder,[29] Daniel Shanahan,[11,30] Helmut Sitter,[31] Dylan Spalding,[32] Catrin Tudur-Smith,[33] Peter van Reusel,[6] Evert-Ben van Veen,[34,35] Gerben Rienk Visser,[36] Julia Wilson,[8] Jacques Demotes-Mainard[4]

development of data sharing plans, tools and services

Ohmann et al., BMJ Open 2017;7:e018647
http://bmjopen.bmj.com/cgi/content/full/bmjopen-2017-018647?ijkey=79SivGTa9igpfbN&keytype=ref



Thank you!

Any questions?

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