Identifying the Future Needs for Big Data in Medicines Regulation

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Disclaimer

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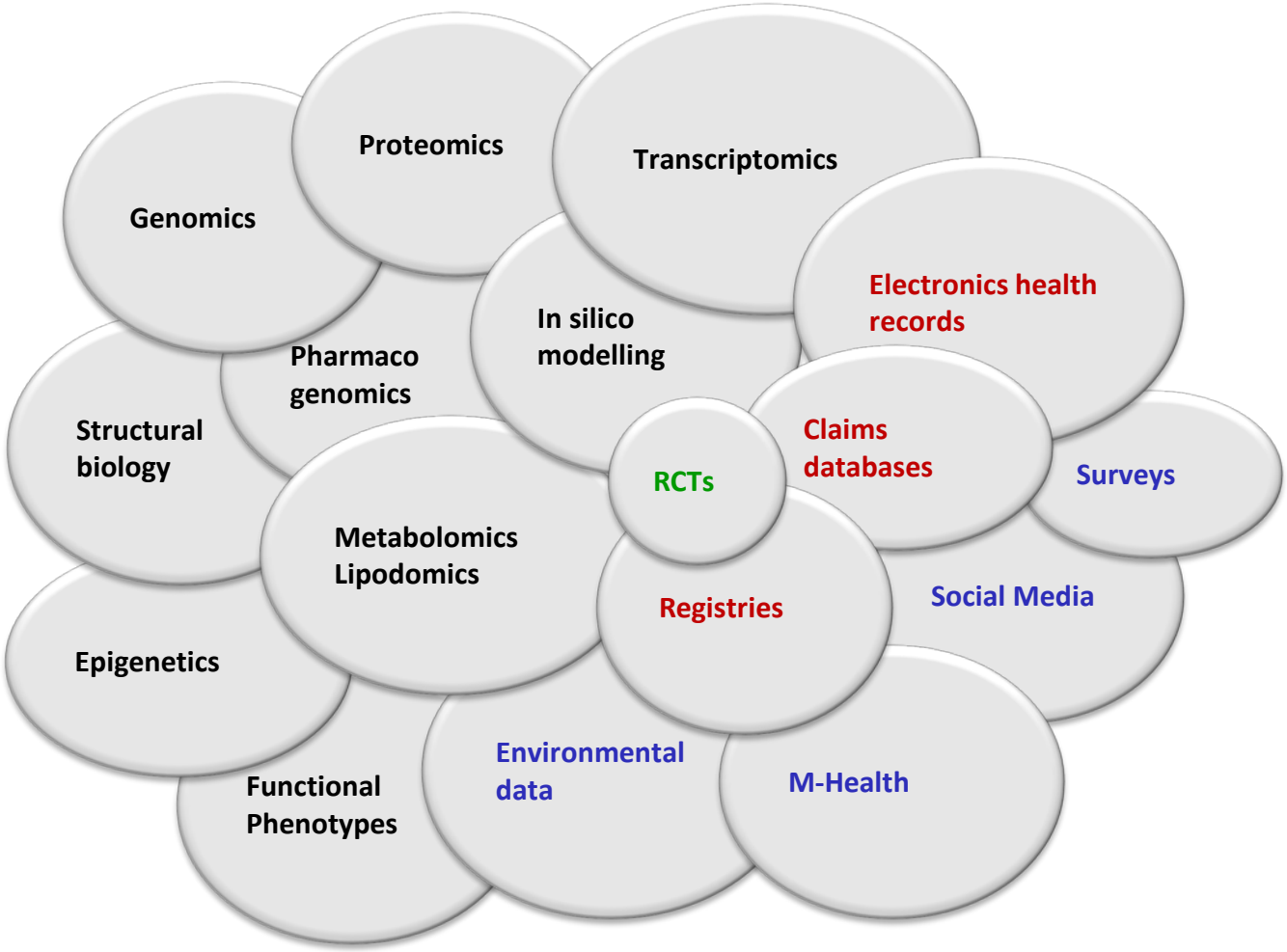
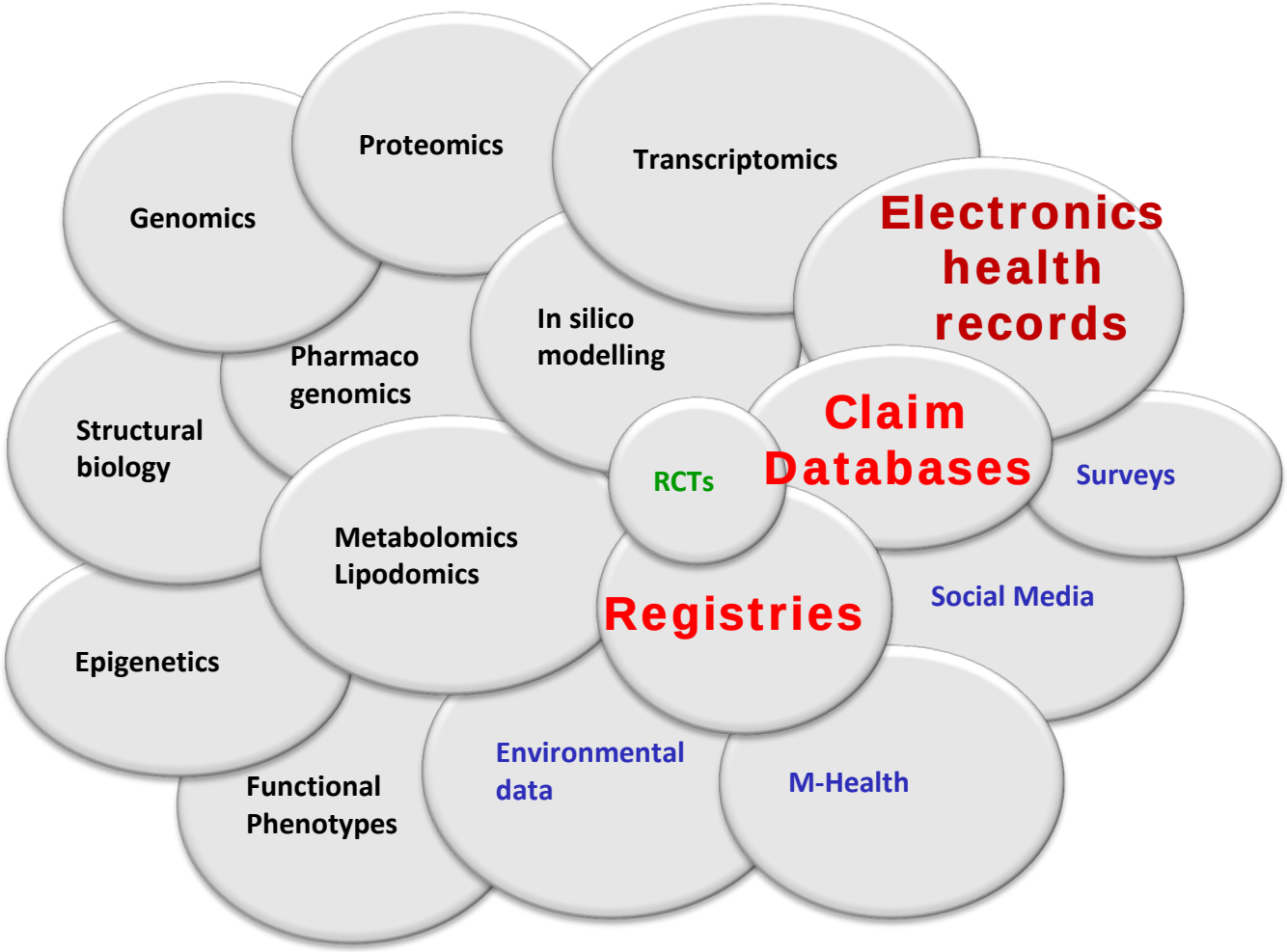
Big Data


Proteomics
Transcriptomics
Genomics
Electronics health records
In silico modelling
Pharmaco genomics
Structural biology
Claims databases
RCTs
Surveys
Metabolomics Lipodomics
Registries
Social Media
Epigenetics
Environmental data
M-Health
Functional Phenotypes

Big Data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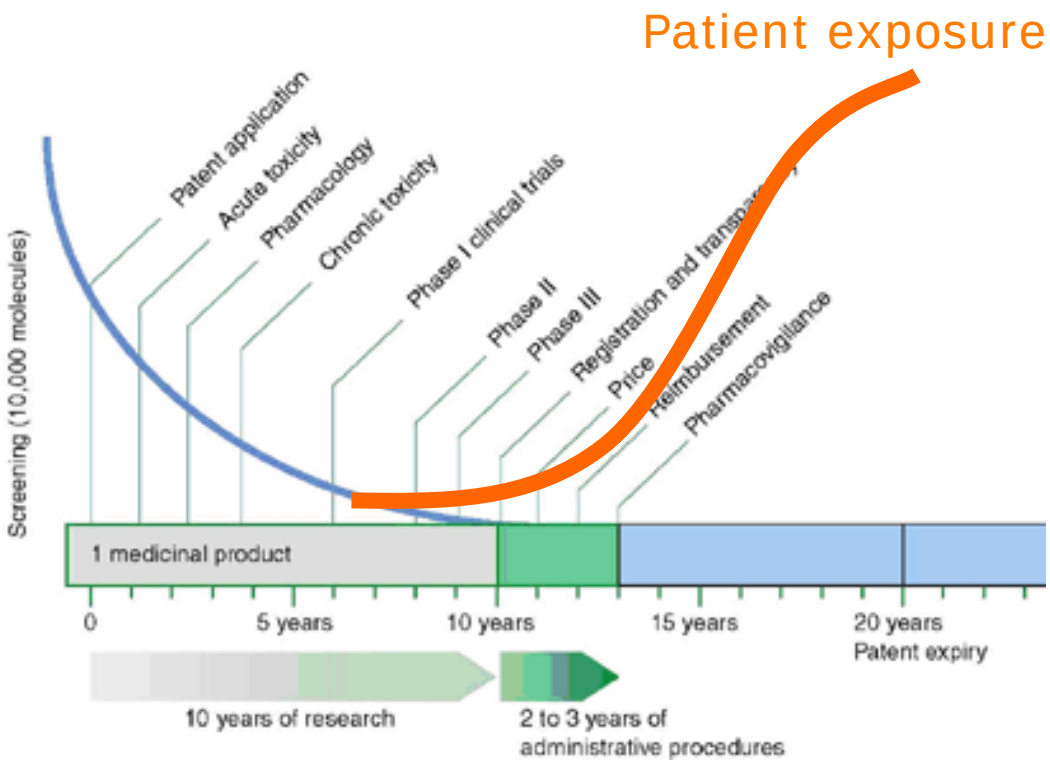
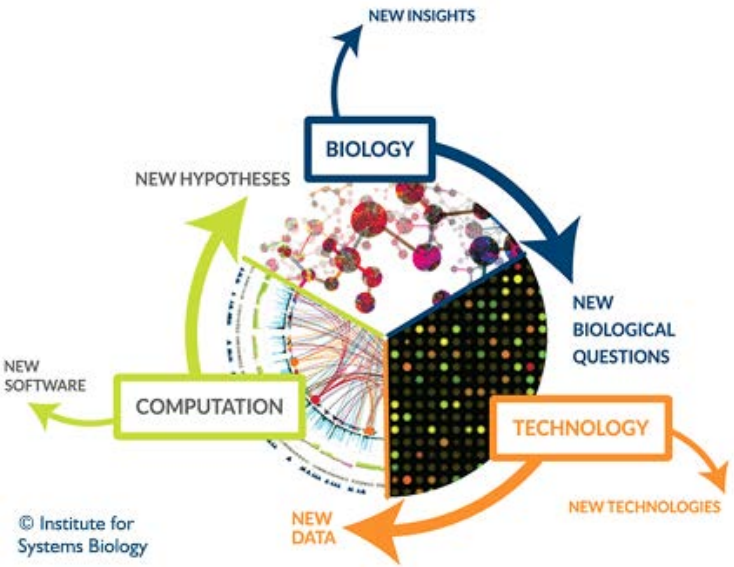
A drug's life cycle



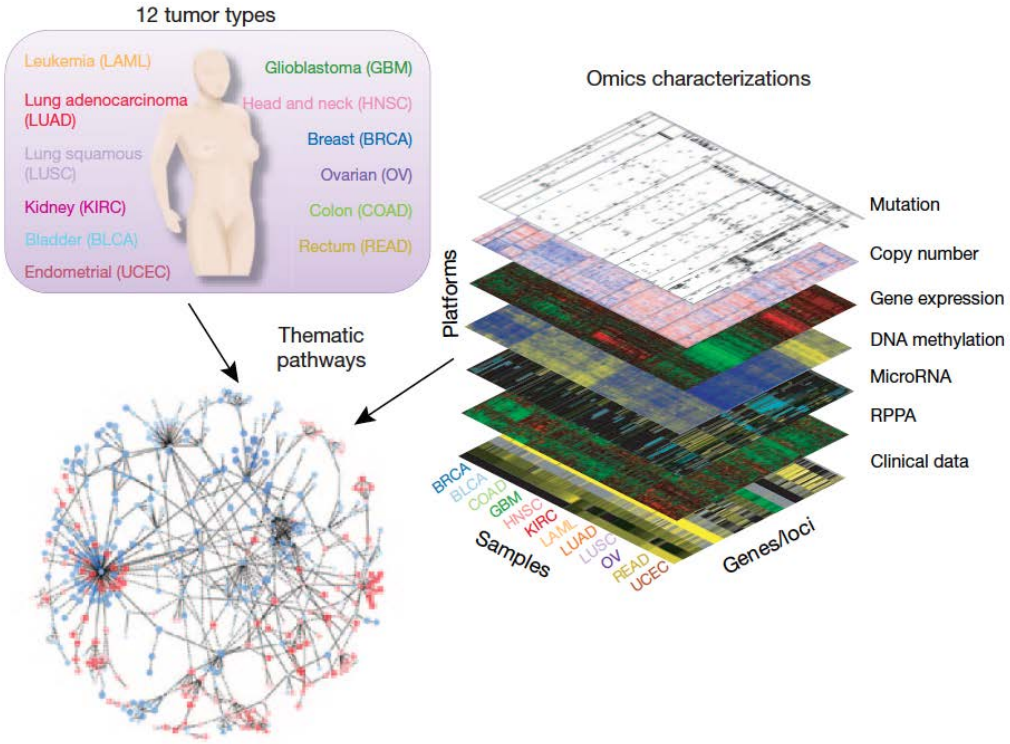
At registration

- Limited patient exposure (strictly defined populations)
- Focus on efficacy
- Rare Adverse Events cannot be detected

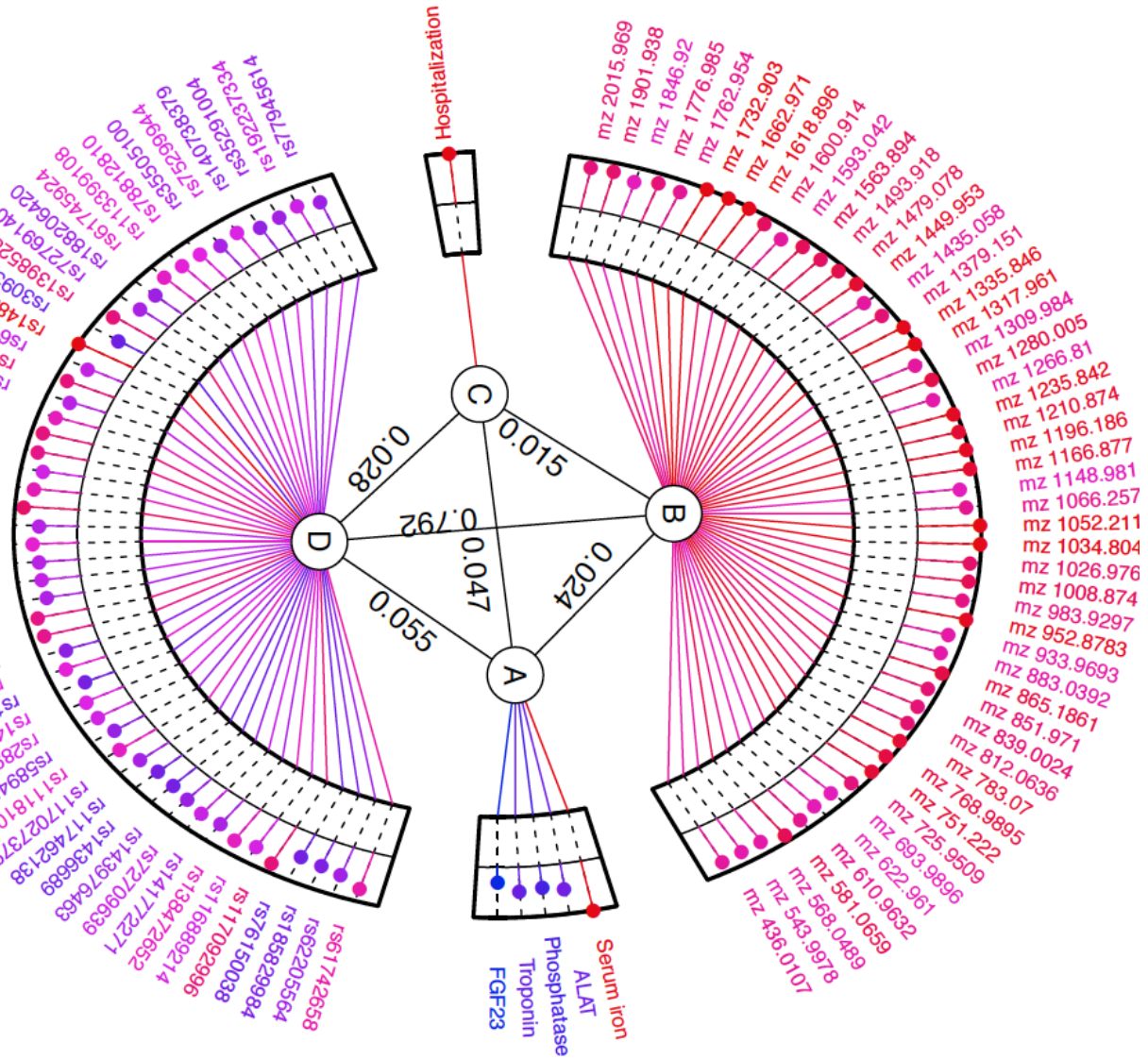
Research and Discovery



The Cancer Genome Atlas Pan-Cancer analysis project



Nat Genet. 2013 Oct;45(10):1113-20



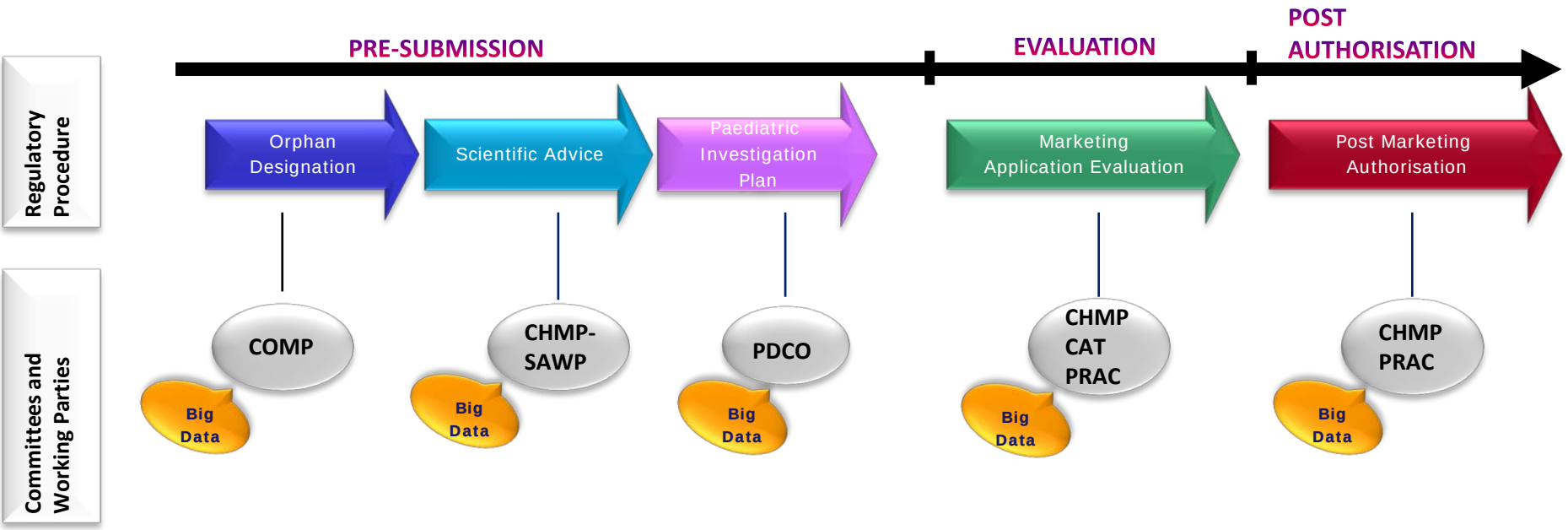
2,245 patients with new onset of worsening heart failure
729,530 SNPs
913 protein/ peptide peaks
144 biomarkers of heart failure

Penalized generalized canonical correlation analysis: Integrating high-dimensional genomic and proteomic markers with routine biomarkers and clinical data to a better understanding of complex diseases. Ouwerkerk et. al.. In preparation

Selection of main committees and parties involved

- The Committee for Medicinal Products for Human Use (CHMP)
- The Pharmacovigilance Risk Assessment Committee (PRAC)
- The Committee for Orphan Medicinal Products (COMP)
- The Paediatric Committee (PDCO)
- The Committee for Advanced Therapies (CAT)
- The Scientific Advice Working Party (SAWP)

Opportunities for Big Data involvement throughout medicines lifecycle



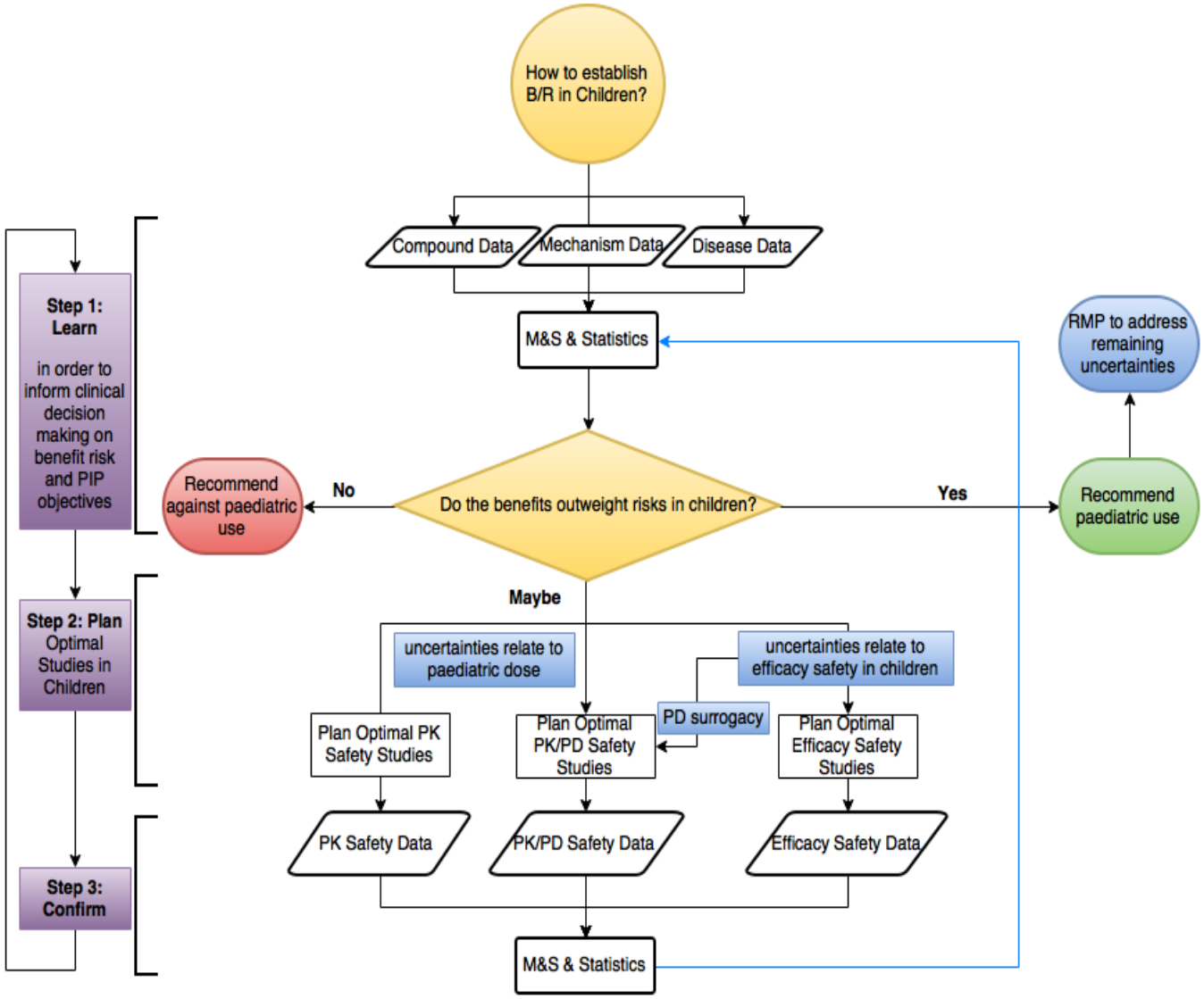
Submission / evaluation Zalmoxis

- SAWP/COMP/CAT/CHMP/PDCO/PRAC
- Indication
- Prevalence
- Existence of other methods of treatment
- Significant benefit of Zalmoxis

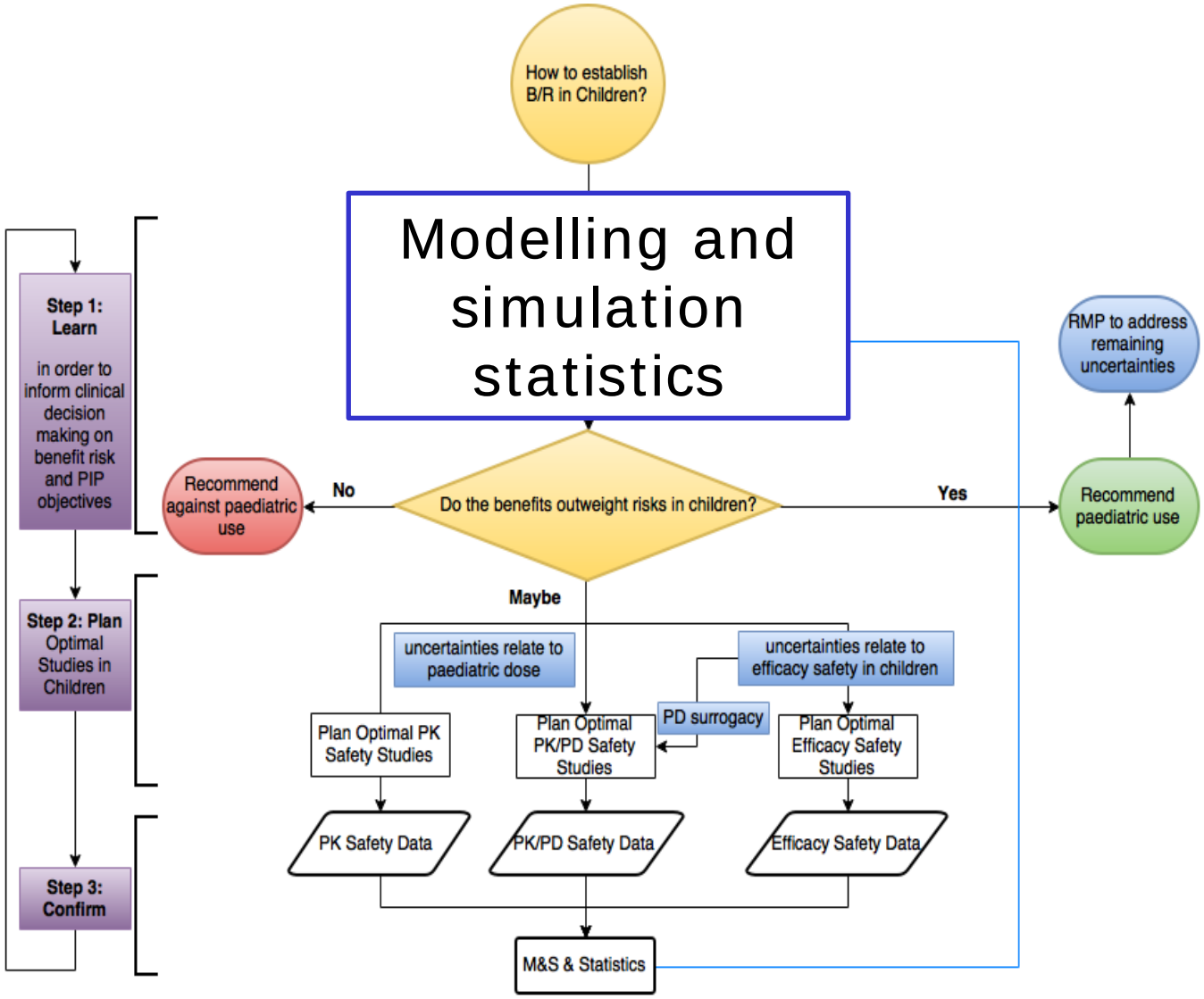
Submission / evaluation Zalmoxis

- Non Interventional PASS
  - Safety and effectiveness in real clinical practice
  - Long-term safety and effectiveness
  - Using the EBMT registry including the patients treated with Zalmoxis

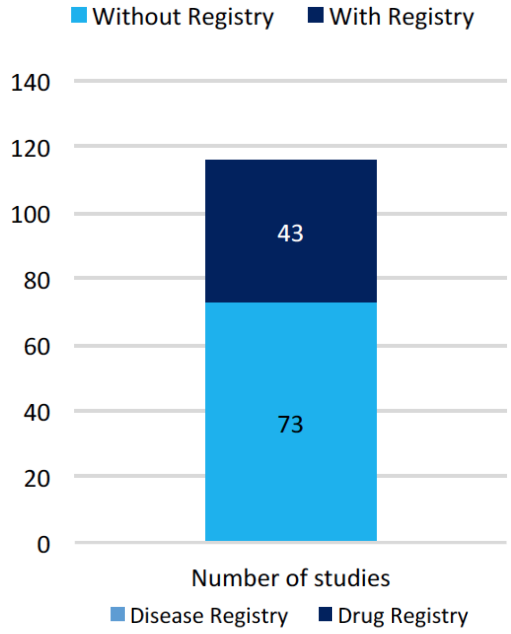
PDCO and extrapolation

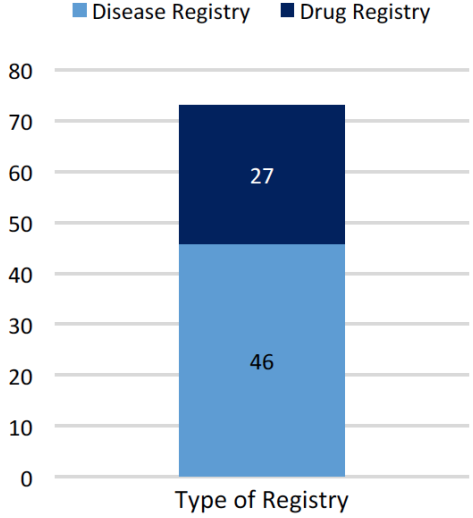


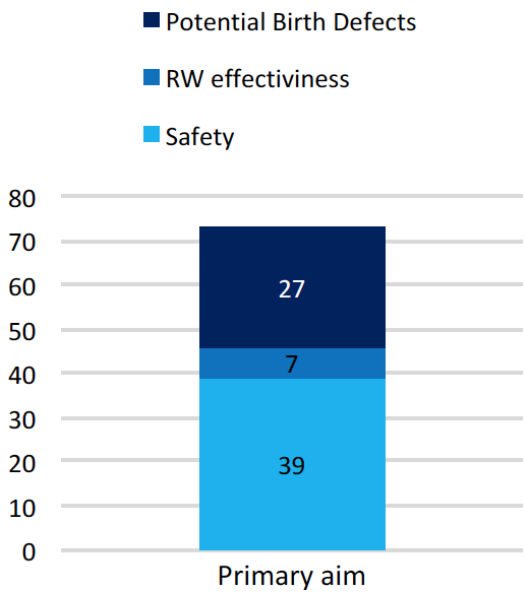
PDCO and extrapolation



Registries supporting new drug applications 01/2007-12/2010



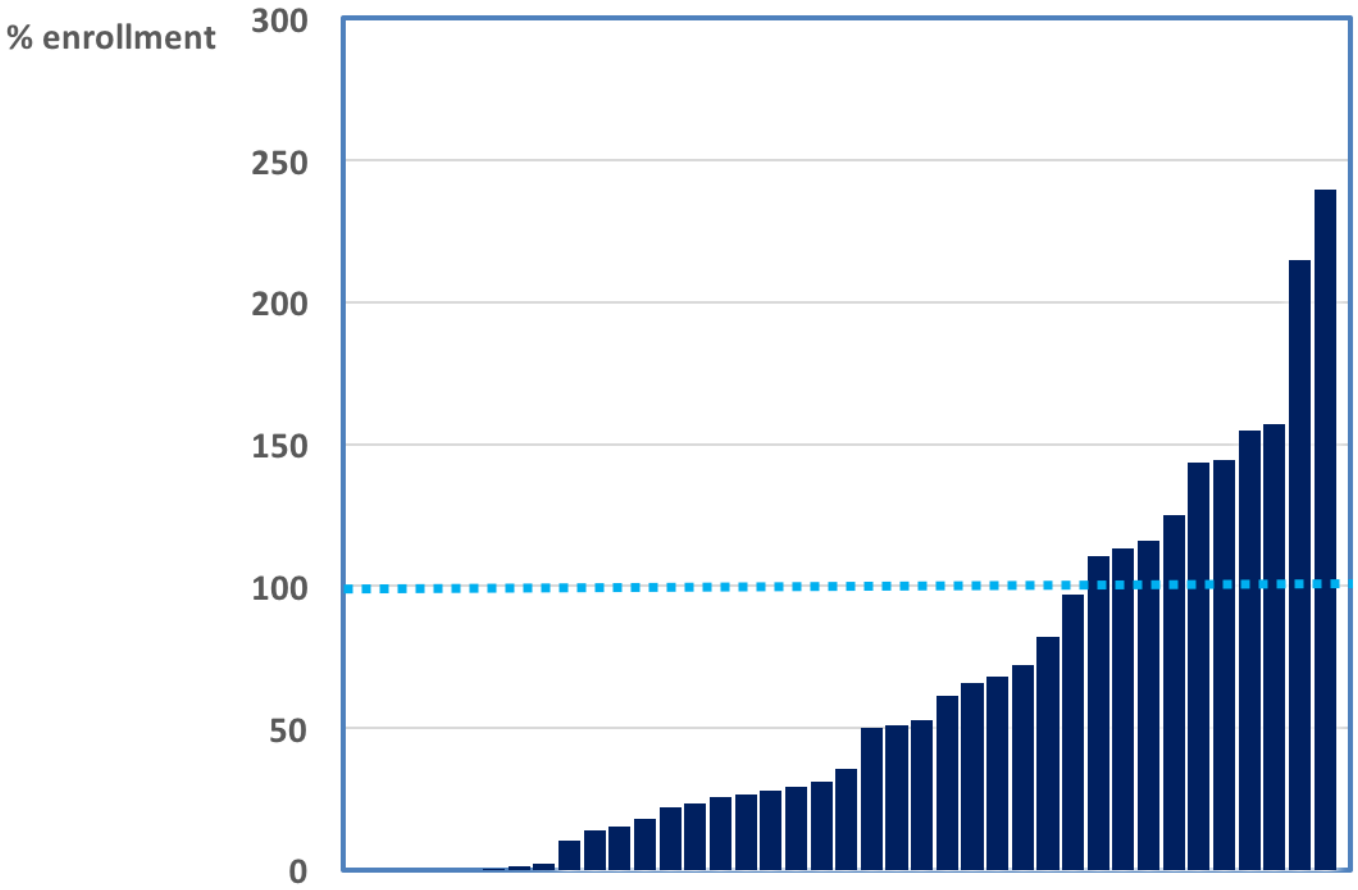




- Registries 1 – 6 per drug
- 9 registry imposed
- Size of safety population 94 - 13,000
- Orphan 15
- Conditional/Ex-ceptional circum-stances 13

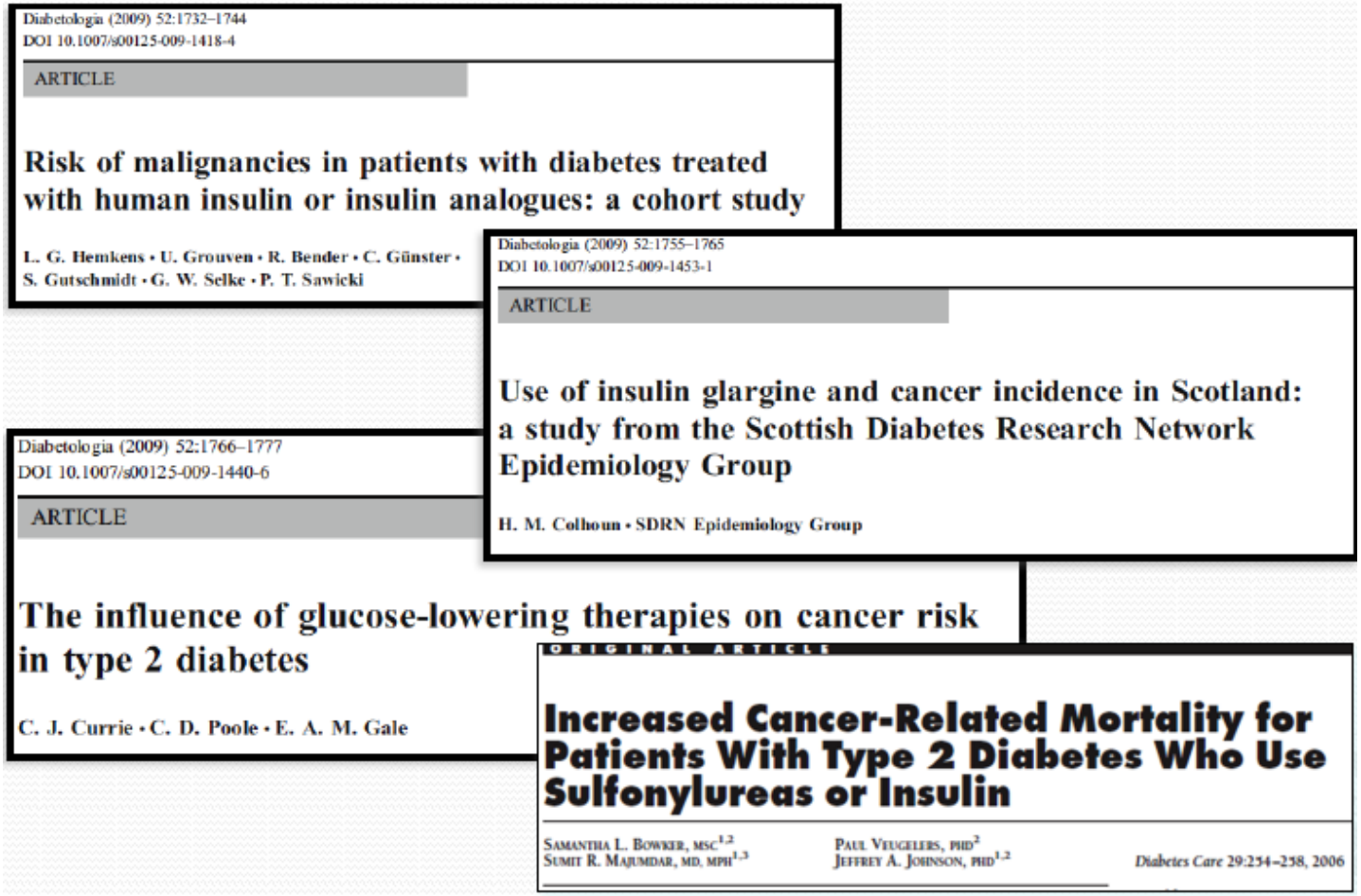
Registries supporting new drug applications. Jonker et. al. in preparation

Enrolment of patients into registries



Drug registries and licensing of drugs: promises, placebo or a real success – an investigation of post-approval registry studies. Jonker et. al. in preparation

Post authorization
Insulin Glargine Controversy



Diabetologia (2009) 52:1732–1744
DOI 10.1007/s00125-009-1418-4

ARTICLE

Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study

L. G. Hemkens · U. Grouven · R. Bender · C. Günster · S. Gutschmidt · G. W. Selke · P. T. Sawicki

Diabetologia (2009) 52:1755–1765
DOI 10.1007/s00125-009-1453-1

ARTICLE

Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group

H. M. Colhoun · SDRN Epidemiology Group

Diabetologia (2009) 52:1766–1777
DOI 10.1007/s00125-009-1440-6

ARTICLE

The influence of glucose-lowering therapies on cancer risk in type 2 diabetes

C. J. Currie · C. D. Poole · E. A. M. Gale

ORIGINAL ARTICLE

Increased Cancer-Related Mortality for Patients With Type 2 Diabetes Who Use Sulfonylureas or Insulin

Samantha L. Bowker, msc[1,2] · Sumit R. Majumdar, md, mph[1,3] · Paul Veugelers, phd[2] · Jeffrey A. Johnson, phd[1,2]

Diabetes Care 29:254–258, 2006

Post authorization Insulin Glargine Controversy

- Assessement CHMP 2009
  - Limitations in the way the studies were conducted, a link between insulin glargine and cancer could not be confirmed or excluded from the results. In addition, the Committee noted that the results of the studies were not consistent.

					Time-related biases			
Study	Short follow-up*	Prevalent insulin users†	Lack of lag period	Residual confounding‡	Immortal time	Time-lag	Time-window	Main limitation§
Colhoun (5)	•			•				Short follow-up
Currie (6)	•		•	•				Short follow-up
Hemkens (7)	•		•	•		•		Time-lag bias
Jonasson (8)	•	•		•				Inclusion of prevalent users

- The CHMP requested further data.

Wu et. al. Diabetes Care 2016

Post authorization
Insulin Glargine Controversy

- 2 cohort studies.
  - 175,000 patients in Northern Europe treated with insulin glargine, human insulin, or combined insulin,
  - Data from 140,000 patients in the United States.
- Case-control study
  - 2 x 750 pts conducted in Canada, France, and the United Kingdom with human insulin and other types of insulin.
- Scientific literature

Post authorization
Insulin Glargine Controversy

EMA concluded (2013):

"Based on the assessment of the population-based studies, the CHMP concluded that overall the data did not indicate an increased risk of cancer with insulin glargine," says the EMA. It notes also that "there is no known mechanism by which insulin glargine would cause cancer and that a cancer risk has not been seen in laboratory studies."

Breast cancer drug X, external validity

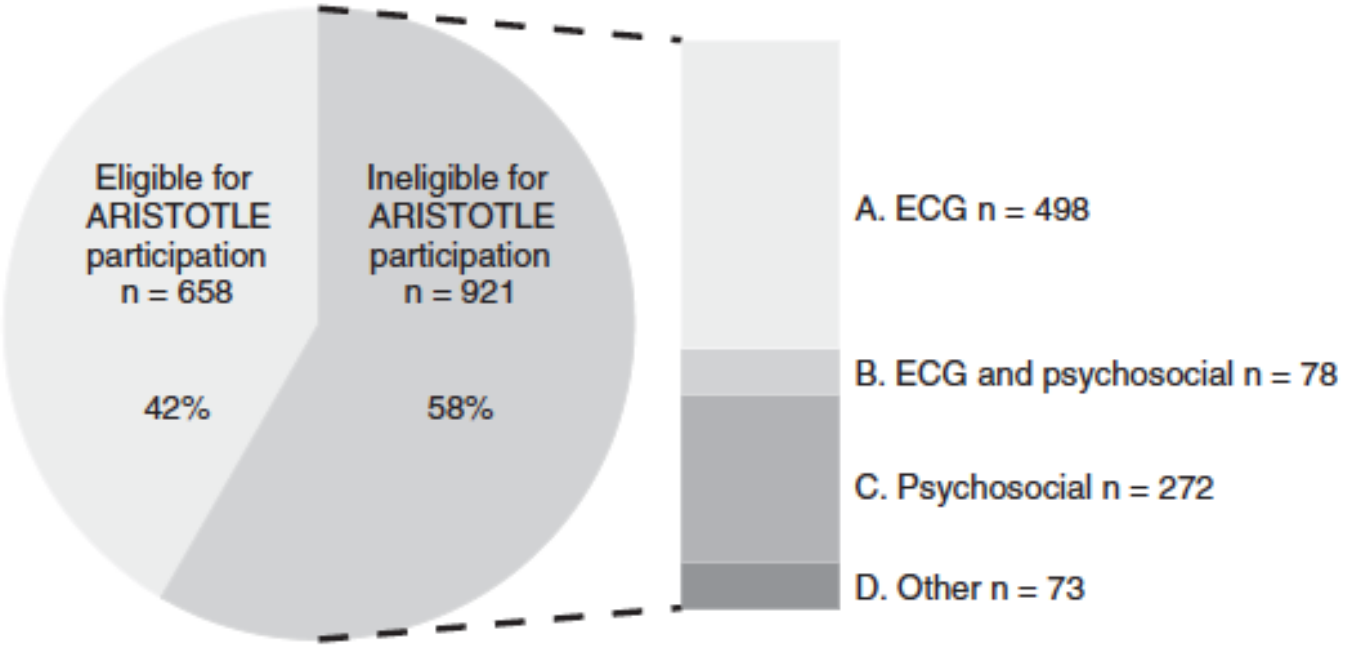
Inclusion criteria

- Age: 20 to 74 years at time of consent
- ECOG performance 0 to 1 (i.e. good performance able to carry out normal activity)

Exclusion criteria

- Cardiac failure, coronary artery disease hypertension
- Patients with serious uncontrolled intercurrent illness, including poorly controlled insulin dependent diabetes mellitus.
- Patients assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol.

External Validity of the ARISTOTLE Trial in Real-Life Afib Patients



A. Did not meet ECG-criteria, B. Did not meet ECG-criteria and had psychosocial problems, C. Had psychosocial problems, D. Other exclusion criteria than above

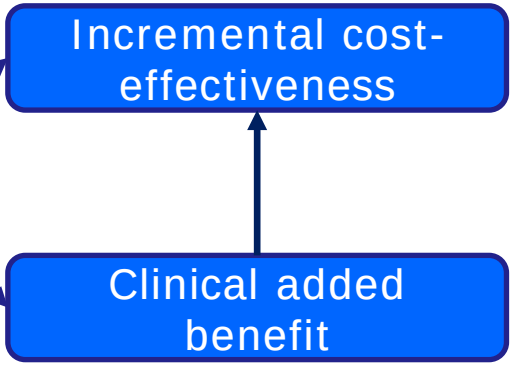
Number and/or proportion of patients with AF suitable for OAC treatment that were eligible/ineligible for ARISTOTLE trial participation (n = 1579). AF, Atrial fibrillation; OAC, oral anticoagulant. Hägg et. al. Cardiovascular Therapeutics 2014

Regulators and HTA

Regulatory decision

HTA decision

OMP	Studies (n)	PA Clin.rel. Effect
30	40	8
	Biomarker EP 36	
	Clinical EP 4	



The efficacy-effectiveness gap: efficacy data do not sufficiently predict real-world effectiveness in the case of orphan drugs for metabolic diseases in the European Union. Schuller et. al. in preparation

Integrating real-life studies in the global therapeutic research framework

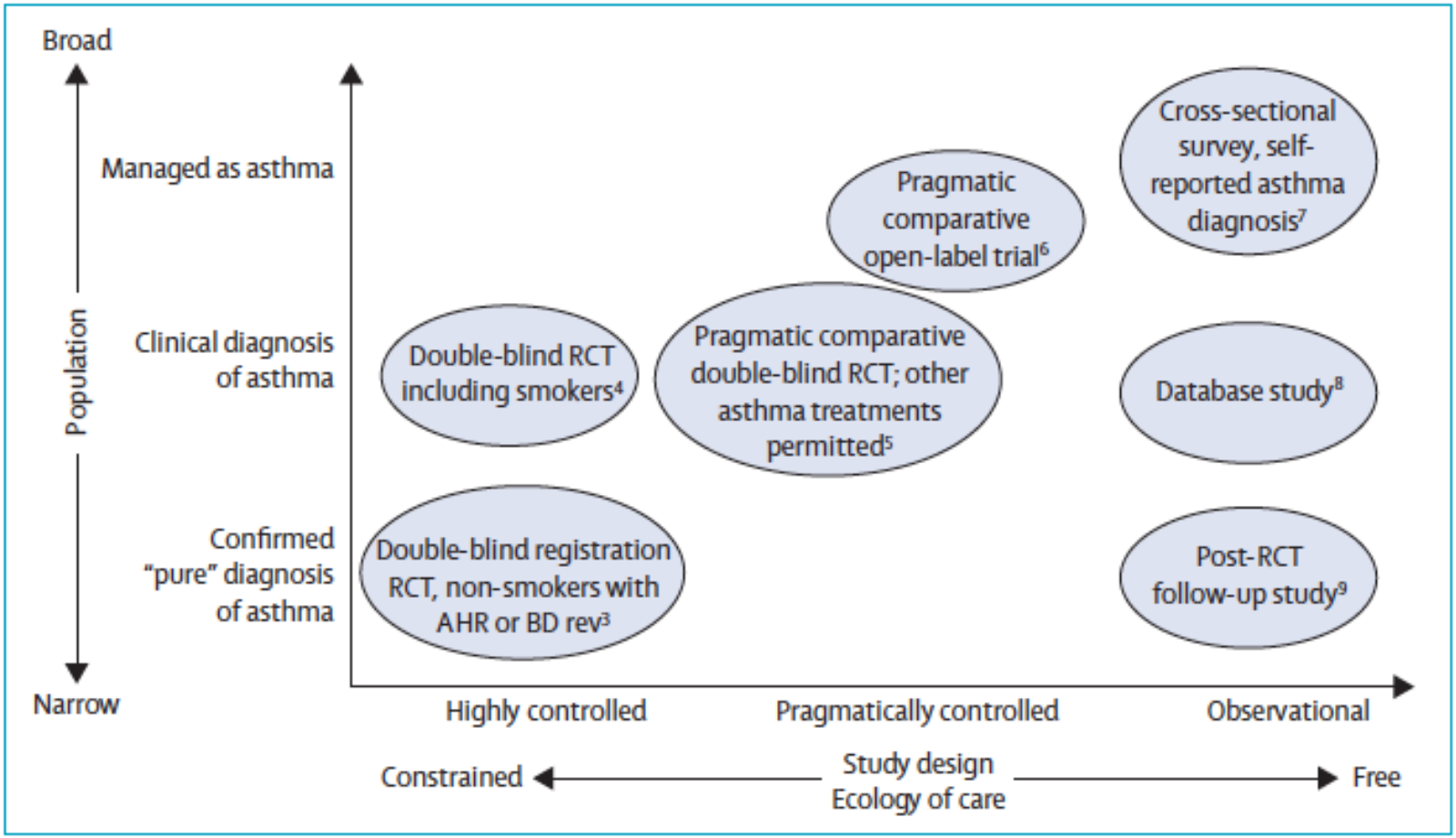
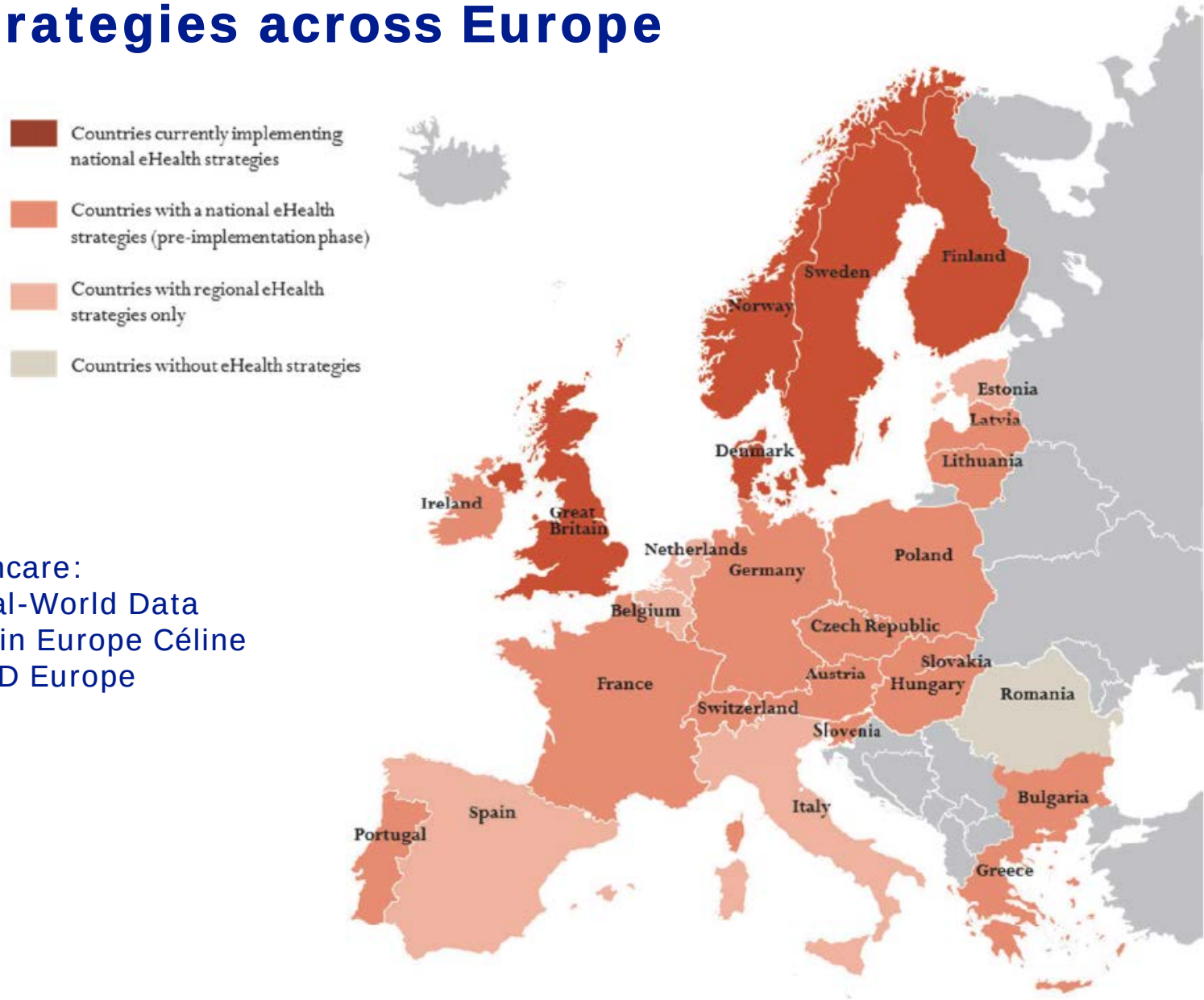


Figure 2: **An illustration of how the conceptual framework could be applied to a specific condition (asthma)[3-9]**

Roche et al. Lancet Respir Med. 2013

eHealth strategies across Europe



Health and Healthcare: Assessing the Real-World Data Policy Landscape in Europe Céline Miani et. al. RAND Europe

Source: Adapted from Stroetmann et al. (2011).

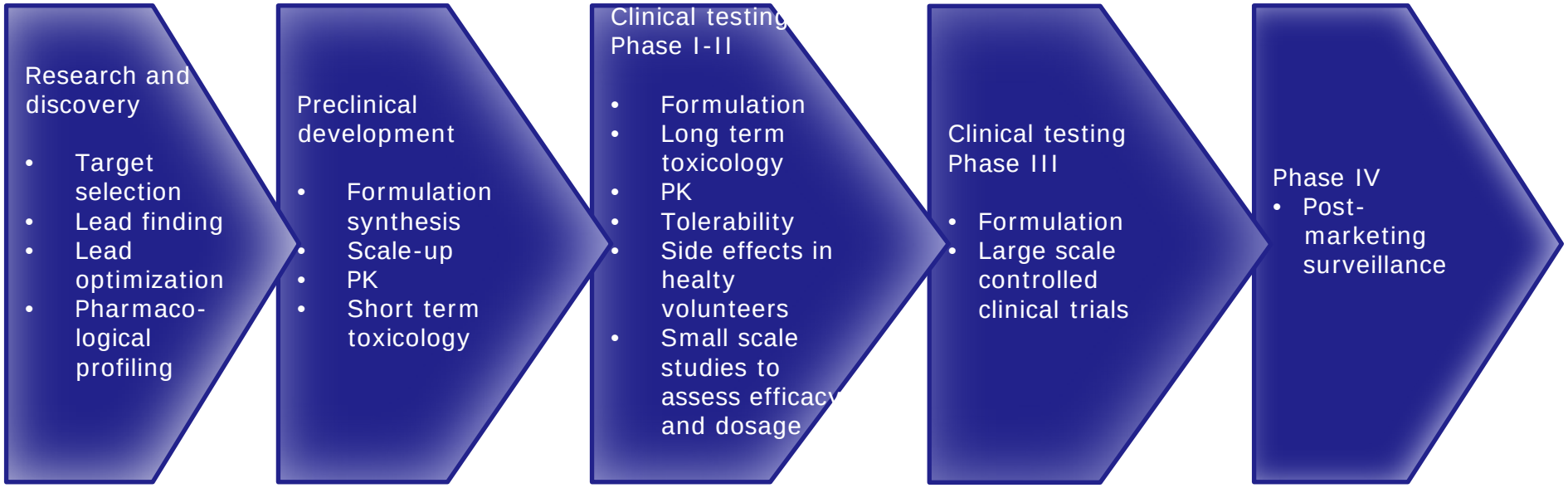
RWD; barriers restricting its full exploitation in medicines regulation

- The absence of common standards
- Governance issues
- Privacy concerns
- Methodological barriers
  - Patients are not randomised to treatment
  - Patients who receive treatment may differ from those who do not
  - Channelling bias or confounding by indication
- FAI **“R”**

Thank you for your attention !

My thanks also to Alison Cave, Jordi Llinares, Spiros Vamvakas, Efthymios Manolis, Koen Norga, Violeta Stoyanova, Peter Mol, Menno van Elst, Carla Jonker.

Stages in the medicine's life cycle where Big Data may get involved



Risk factors of disease

Natural history of the disease

Treatment pathways

Design of clinical trials

Contribute to Risk Management Plan

Effectiveness of risk minimization measures

Provide framework for safety signals

PA safety and effectiveness measures

Drug utilization studies

Value story of drug