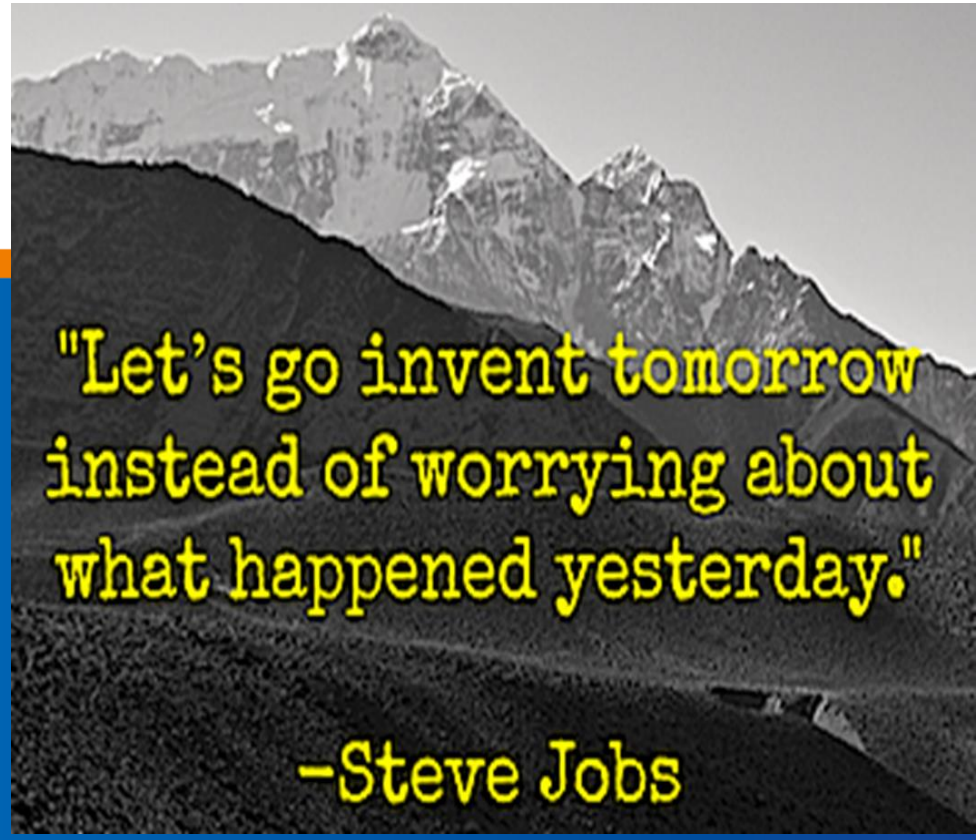
Pharmacovigilance
LOOKING TOWARDS THE FUTURE



Sabine Straus
CBG
18 februari 2021

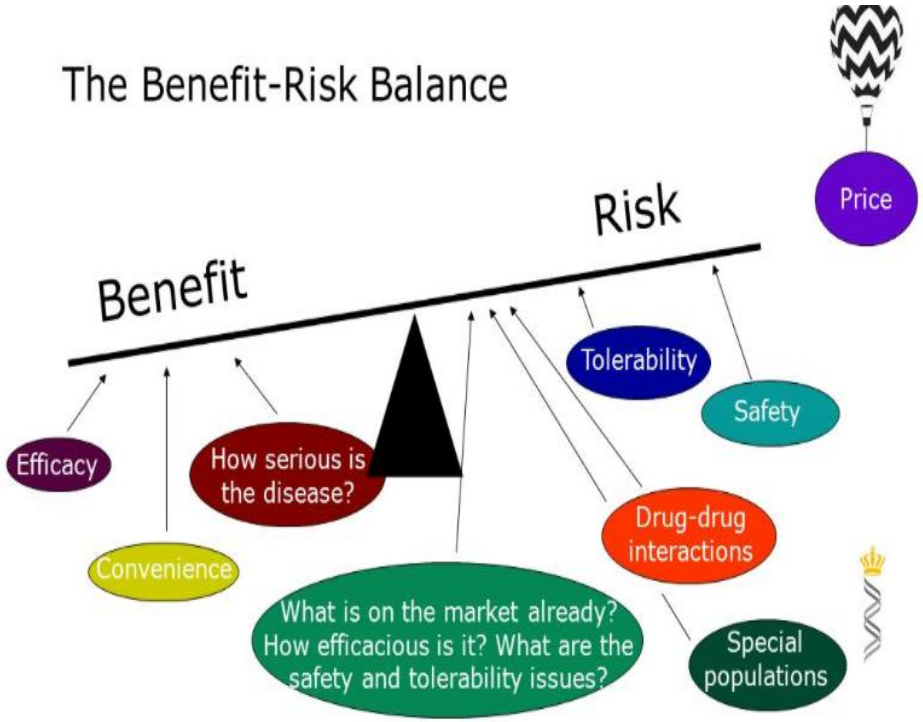
GOOD MEDICINES USED BETTER

Starting point

Pharmaceutical advances over the past 50 years have benefited many people in terms of disease prevention and management. However, probably without exception, most pharmaceutical products can cause adverse consequences of varying severity and frequency.

Challenges for regulators

-Provide early access
-Safeguard the public
-Promote public health
-Prevent unnecessary harm
-Stimulate innovation
-Prevent unnecessary hurdles
-Strike the right balance between risk and benefits



Pharmacovigilance 2030 Invited Commentary for the January 2020 "Futures" Edition of *Clinical Pharmacology and Therapeutics*

Peter Arlett[1,*], Sabine Straus[2] and Guido Rasi[1]

A new healthcare system is emerging that encompasses systems approaches to biology and medicine, radically enhanced capabilities for collecting, integrating, storing, analyzing, and communicating data and information, and increasing numbers of networked and activated patients and consumers.

Changing landscape (1)

Technological innovation:

- mean time between changes
- machine learning and algorithms
- AI

ECO models: from siloed to integrated

Transaction models for ICSRs

- digital processing
- from vertical to shared/horizontal
- From scarcity to abundancy: new models needed

Initiatives **like ODHESI** data collection and analyses standardized

Changing landscape (2)

Population focus	Precision (personalised)
medicine	
Monotherapies	Complex (combination)
regimens	
Short/mid time horizons	Decade/life-long horizon
(Randomised controlled) trials	Full spectrum of methods
Pre-licensing knowledge generation	Lifespan/-cycle approach
Silos (insurers, regulators, developers)	Shared approach
Research-practice	Learning health care

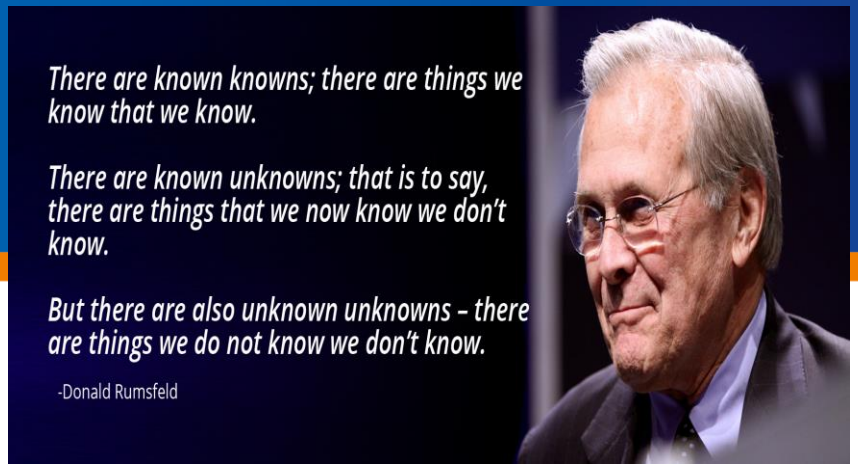
ATMPs as an example

CAR-T cell design and delivery raises the hope of a cure for many more people with malignancies, and heralds an exciting new era in cancer treatment

While researchers, physicians, patients, and investors alike are understandably seduced by such potential, there are still several major hurdles to overcome. For the vast majority of patients with blood cancer, and all with solid cancers, CAR-T cells are not yet proven to be effective, are too toxic, or are not available due to expense or geography.

Charrot S, Hallam S. CAR-T Cells: Future Perspectives. Hemasphere. 2019;3(2):e188. Published 2019 Mar 19. doi:10.1097/HS9.0000000000000188

ATMPs
what we know



Uncertainties at MA:

Single arm pivotal trials, small sample sizes, external controls , limited number of eligible patients

Duration of efficacy , dosing , errors-> FU post MA

Long-term safety/different aspects of safety, e.g insertional oncogenesis , development, growth

Dilemma:

Provide (early) patient access or wait for evidence?

What can we generate post approval

Tools

Specific and dedicated PAMs/PIPs support benefit-risk assessment

RMP and PhV tools

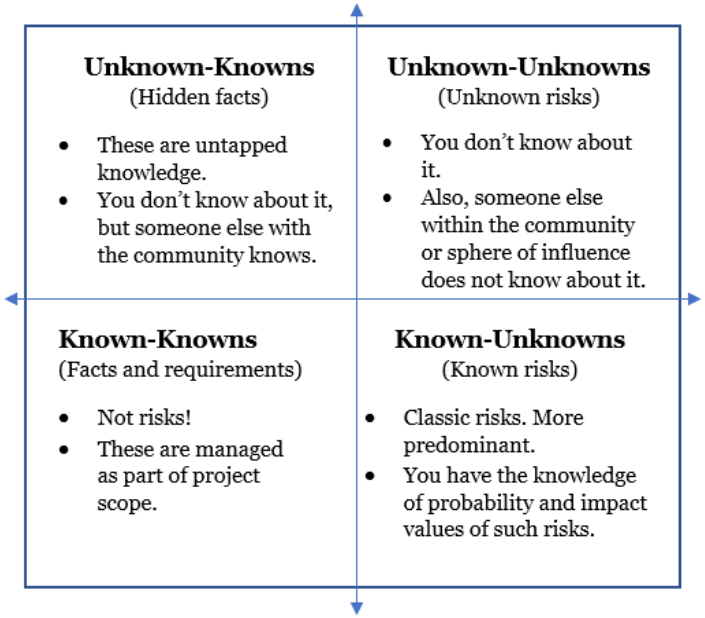


Table 1-1. List of Important Risks and Missing Information

Important Identified Risks	Serious neurologic adverse reactions including cerebral oedema
	Cytokine release syndrome (CRS)
	Cytopenias including aplastic anaemia
	Infections
	Hypogammaglobulinaemia
Important Potential Risks	Secondary malignancy
	Immunogenicity
	Replication-competent retrovirus (RCR)
	Tumor lysis syndrome (TLS)
	Aggravation of graft vs host disease (GvHD)
	Transmission of infectious agents via product
	Decrease in viability of the product due to inappropriate preparation of infusion
Missing Information	Use in pregnancy and lactation
	Use in non-Caucasian patient populations
	New occurrence or exacerbation of an autoimmune disorder
	Long term safety

FDA STATEMENT

Statement by FDA Commissioner Scott Gottlieb, M.D., on new strategies to modernize clinical trials to advance precision medicine, patient protections and more efficient product development

Unfortunately, we've seen a continued reluctance to adopt innovative approaches among sponsors and clinical research organizations. In some cases, the business model adopted by the clinical trial establishment just isn't compatible with the kind of positive but disruptive changes that certain innovations can enable. We appreciate that scientific and technical complexity is a real and ongoing challenge, but industry and academia also need to invest in and leverage these approaches and develop new incentives that reward collaboration and data sharing across the clinical research enterprise.

Data generation pharmacovigilance

RMP

SSS
Important Identified Risks
Important Potential Risks
Missing Information

PHV
RMM

interpretation has varied. For example, the EMA mandates European (EU) risk management plans (RMPs) for all newly authorised products [8]. The EU RMP includes a summary of information about the safety concerns that may impact the benefit–risk profile of the drug and specifies strategies for characterising and managing those risks over time [9]. Other jurisdictions, such as Health Can-

ADRs

Spontaneous reports +
Enhanced data collection

PSURs

PAS (S/PAES)

Challenges and opportunities

Realising the potential of real world data to support decision-making and better public health:

New data sources

New technology

New analytical approaches

Process improvement: greater efficiency and effectiveness through evidenced-based process improvement

Better engagement with the public

Making an impact: change healthcare deliver to benefit public health

STATE OF THE ART

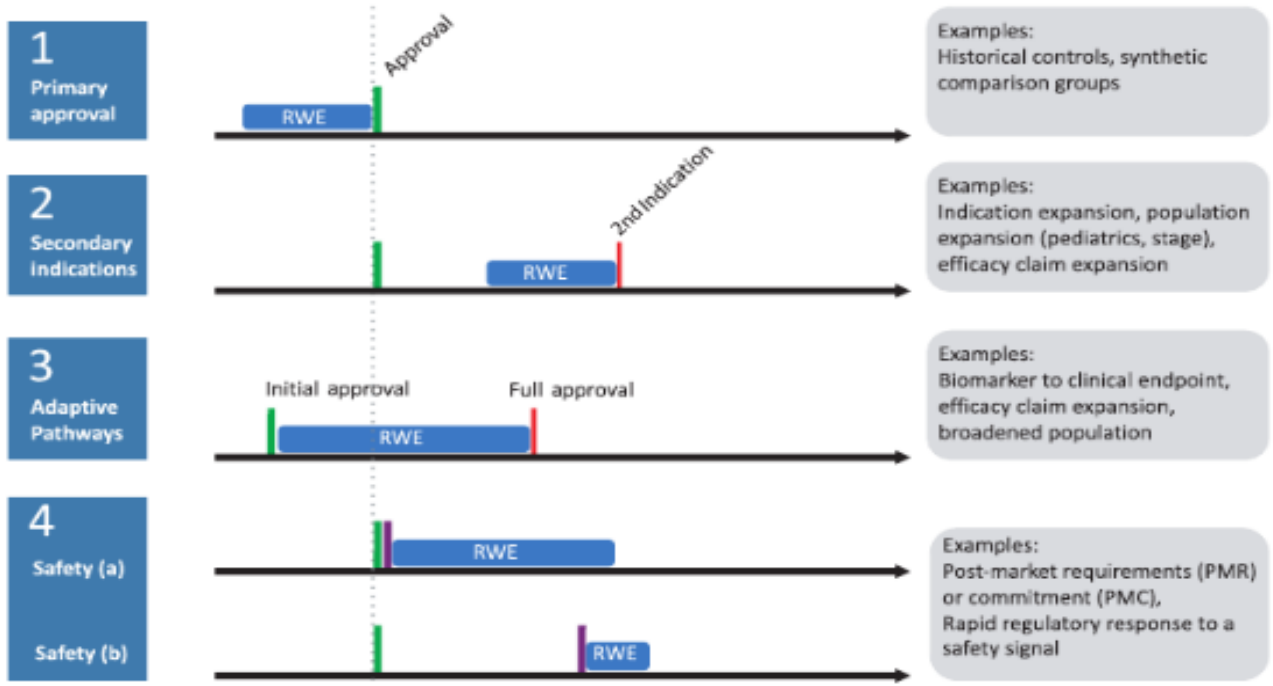


Figure 1 Real-world evidence (RWE) in regulatory decision making: key use cases.

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 105 NUMBER 4 | APRIL 2019

four key use cases in which RWE could support regulatory decision making

Real World Data

sources are abundant ☺

Registries

Claims data

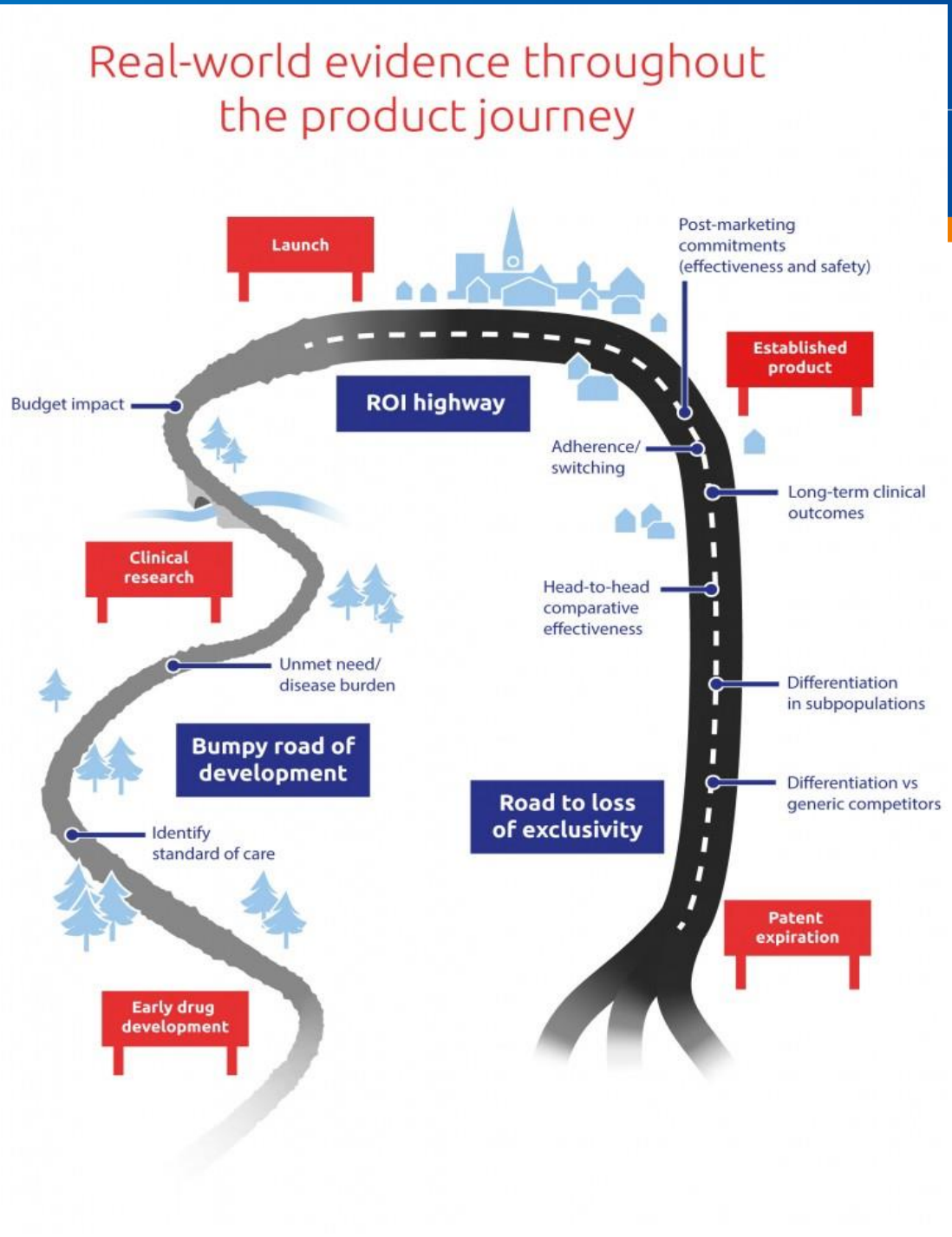
EHR

Pragmatic clinical trials

Active Surveillance Systems

Emerging Technologies

Incorporating the Patient's Voice
RWE can also better represent patients' voices and experiences,
in part through patient-generated data



Ideal situation

Table 1

Characteristics of an Ideal Data Source to Generate Real-World Evidence

- Patient population representative of those with the underlying condition (e.g., demographics, clinical comorbidities)
- Prospectively planned
- Continuously updated with minimal resources
- Longitudinal follow-up
- Rich clinical data: clinician-entered, patient-reported, and patient-generated
- Quality control measures in place
- Integrated within existing data systems

P T. 2018 Aug; 43(8): 464–472

A Comparison of Patient Characteristics and Outcomes in Selected European and U.S. Rheumatoid Arthritis Registries[1]

Jeffrey R. Curtis, MD, MS, MPH,* Archana Jain, MD,*
Johan Askling, MD, PhD,† S. Louis Bridges, Jr., MD, PhD,*
Loreto Carmona, MD, PhD,‡ William Dixon, MRCP, PhD,§
Axel Finckh, MD, MS,¶ Kimme Hyrich, MD, PhD, FRCPC,§
Jeffrey D. Greenberg, MD, MPH,‖ Joel Kremer, MD,**
Joachim Listing, PhD,†† Kaleb Michaud, PhD,‡‡,‖‖
Ted Mikuls, MD, MSPH,‖‖ Nancy Shadick, MD, MPH,***
Daniel H. Solomon, MD, MPH,*** Michael E. Weinblatt, MD,***
Fred Wolfe, MD,‡‡ and Angela Zink, MD, PhD†††,§§

CBGMEB

PRO

clinically rich and generally consistent

Approach more real world setting

CON

not capture longitudinal data or require significant effort and resources to do so.

not necessarily representative of the general clinical use

not include the full spectrum of outcomes, such as patient-reported outcome measures.

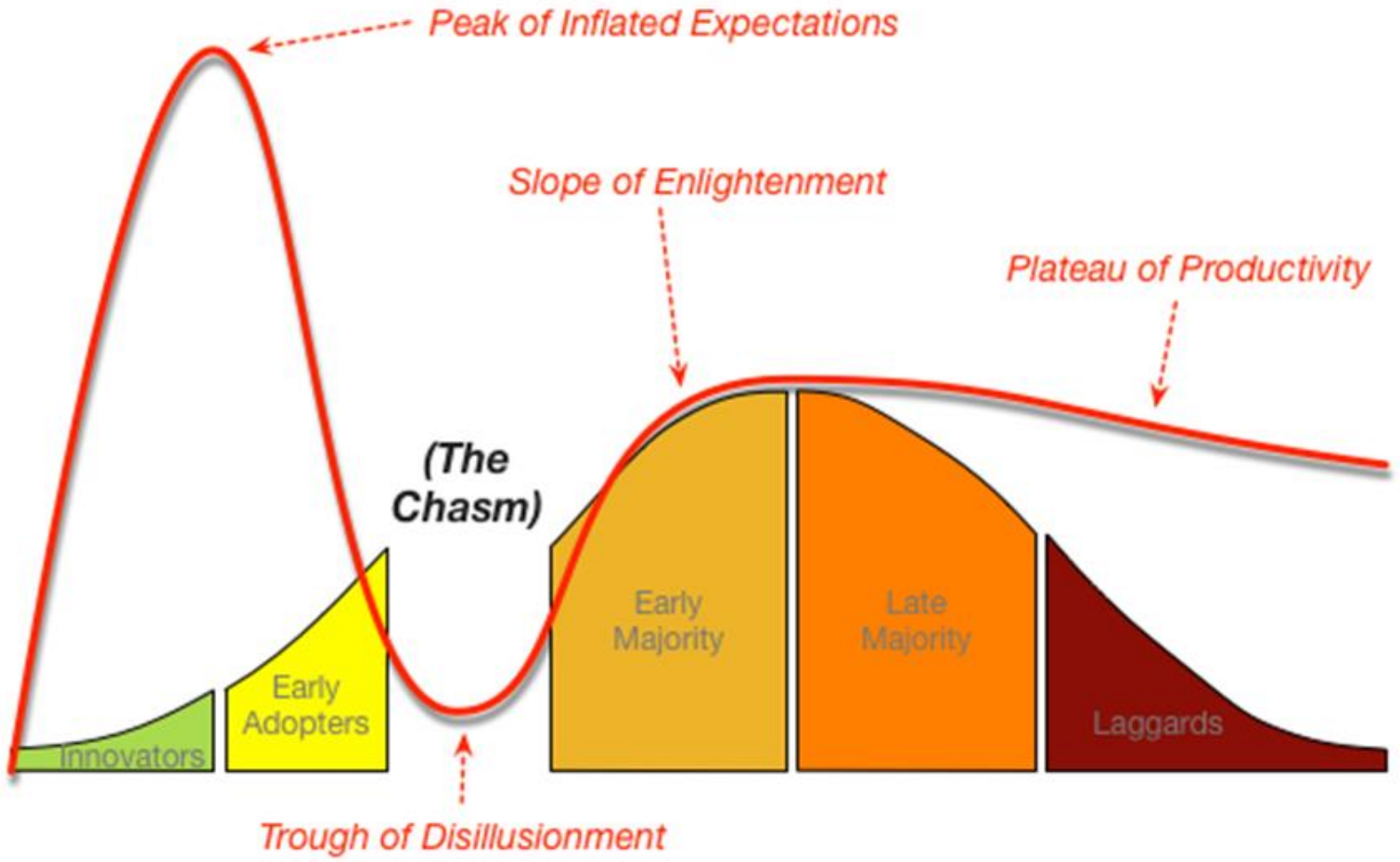
often in parallel to existing data collection systems duplication for greater accuracy

Time lag

CONCLUSION

Because results from RCTs may not be generalizable to clinical practice, biologics registries and cohorts have been set up in various countries to bridge the gap in our knowledge regarding the effectiveness and safety of these agents. The large size of these registries and long duration of follow-up allows analysis of rare events, which generally is not possible with RCTs. Our work highlighting the unique features of several of these cohorts points out their various characteristics that may make them more or less suitable to answer particular research questions. Ongoing work to possibly standardize definitions for outcomes and comorbidities and to harmonize analysis methodologies are likely to result in even greater knowledge from these

RWD


Peak of Inflated Expectations
Slope of Enlightenment
Plateau of Productivity
(The Chasm)
Innovators
Early Adopters
Early Majority
Late Majority
Laggards
Trough of Disillusionment

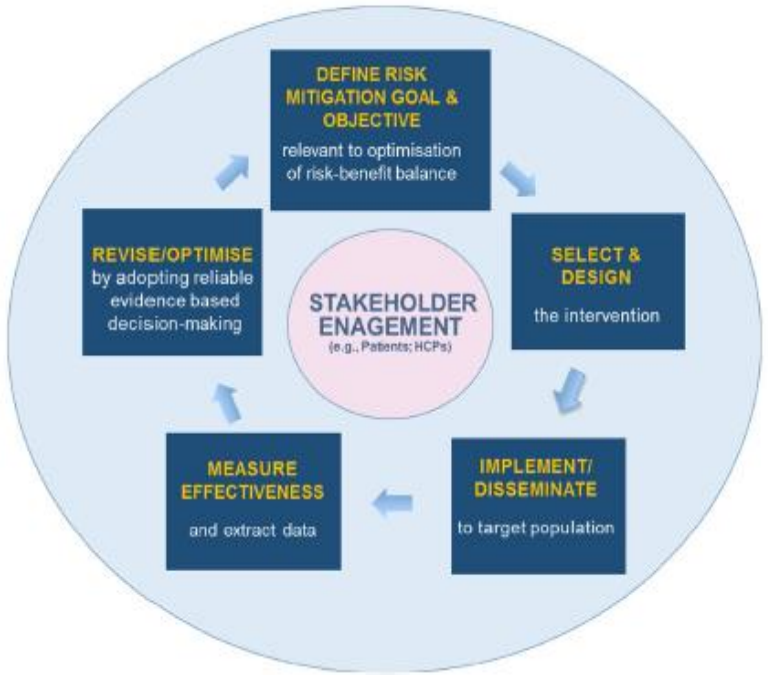


Fig. 1 Cyclical feedback loop for evidence-based design and evaluation of effectiveness of risk minimisation measures. *HCPs* health care professionals

Drug Safety
https://doi.org/10.1007/s40264-020-01033-z

LEADING ARTICLE

Risk Management for the 21st Century: Current Status and Future Needs

Rania Mouchantaf[1,3] · Doris Auth[2] · Yola Moride[3,8] · June Raine[4] · Soon Young Han[5] · Meredith Y. Smith[6,7]

Accepted: 5 December 2020

Some predictions

- ADRs/ signals remain important & require **complementary sources of data/evidence**.
- Collections needs to become smarter
- **Real world data** is an important source grip on growing complexity
- Methodology and Analysis efforts required
- Care: predictive, preventive , personalised and participatory (4 PPPP)
- Binary : pre/post, ICSR/HER, randomisation/observational , safety/efficacy, reactive/active to on market performance
- Transparancy & communication

Incorporating the Patient's Voice
RWE can also better represent patients' voices and experiences,
in part through patient-generated data

Some insights

PhV is much more than than identifying datasources and ICSR collection

The new technologies offer opportunities to better more efficiently and more rapidly process data /ICSRs

Further develop analysis methodologies and causality assessment

Further develop risk minimisation opportunities and possibilities

Risk minimisation is an **iterative, learning activity** which requires multiple complementary data sources, highlighting the need for impact research

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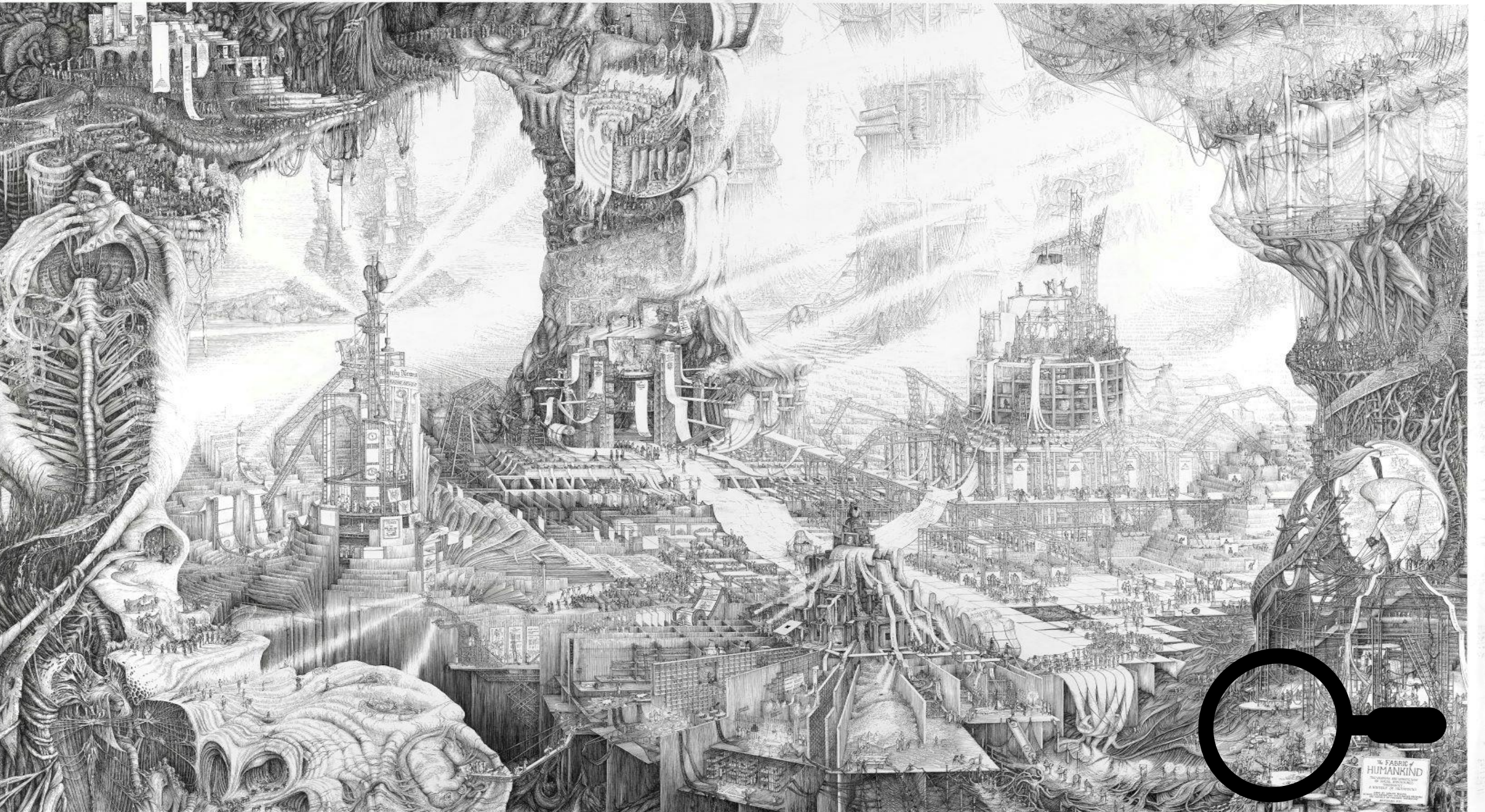
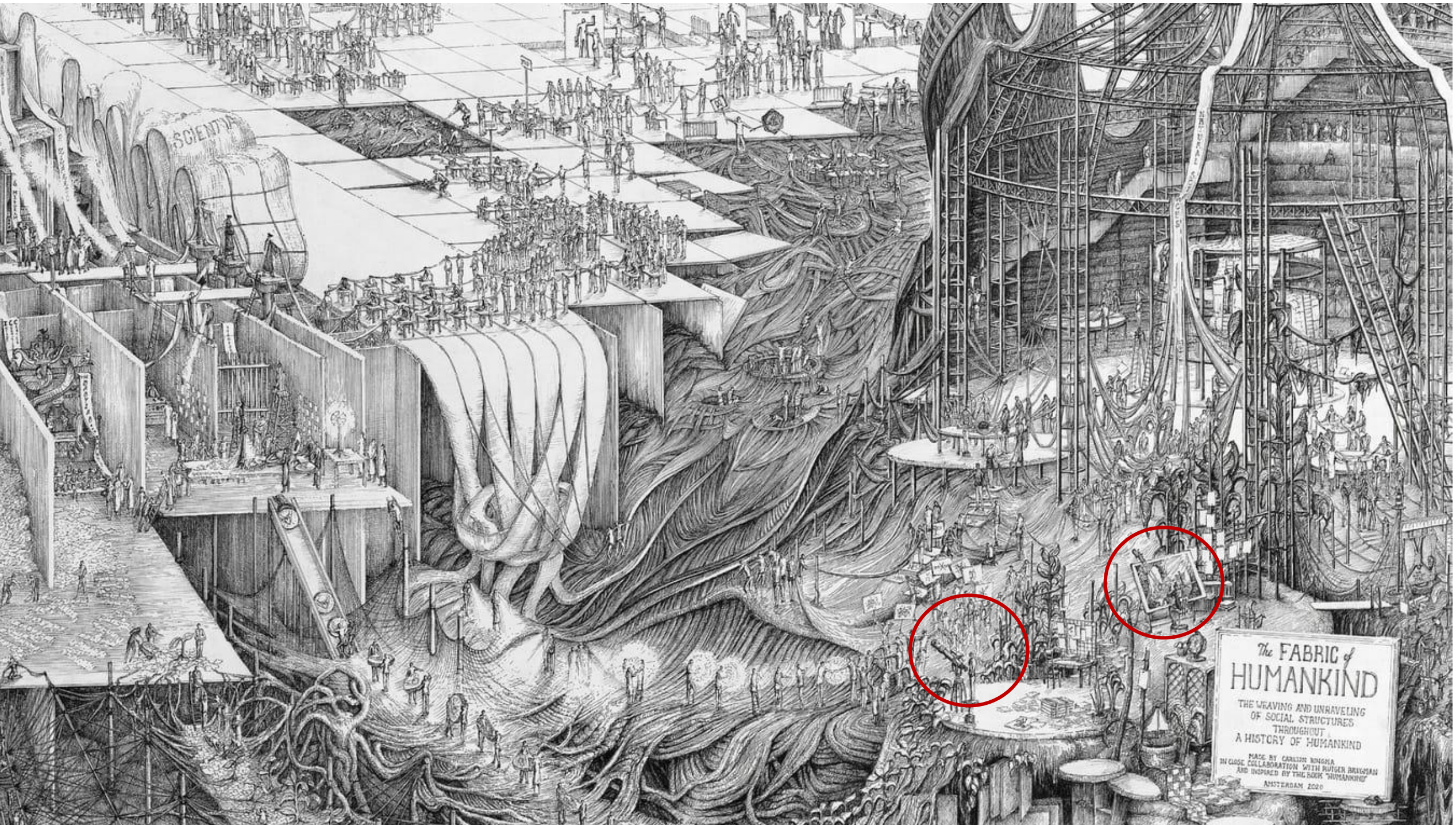
- measure the impact of our work and ensure we make evidence-based process improvements.
- smarter collection and reporting of ICSRs,
- measurement of on-market performance of medicines, learning health care system
- improved engagement of patients and healthcare professionals

faster access to life-saving treatments for patients around the world and for these treatments to be used more effectively and safely


THE FABRIC OF
HUMANKIND


The FABRIC of
HUMANKIND
THE WEAVING AND UNRAVELING
OF SOCIAL STRUCTURES
THROUGHOUT
A HISTORY OF HUMANKIND
MADE BY CARLIJN KINGMA
IN CLOSE COLLABORATION WITH RUTGER BREGMAN
AND INSPIRED BY THE BOOK "HUMANKIND"
AMSTERDAM 2020

CBG MEB

MEDICINES EVALUATION BOARD

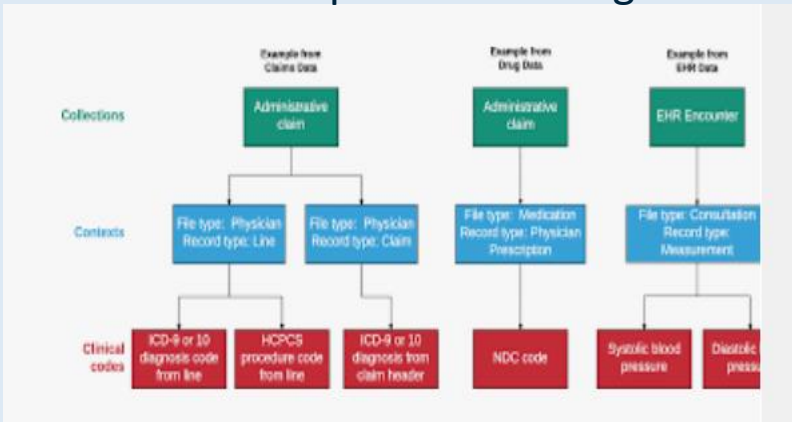
Administrative claims data

- **PRO:**
  - the ease of data collection and abstraction
  - data are universally created
  - capture longitudinal data
  - accepted coding standards
  - data consistency.
  - integrated with existing data platforms.
  - not collected with the goal of supporting research

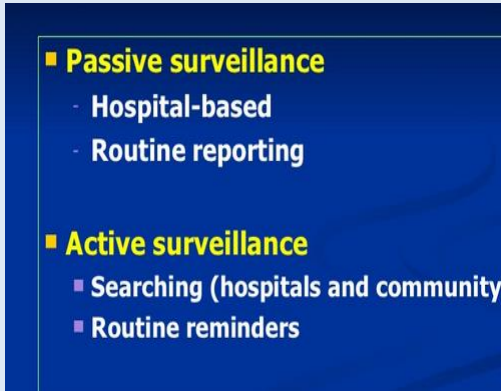
CON

- Not many details
- Use not ascertained
- Comorbidities not easily identified
- Inaccurate
- Not collected with the goal of supporting research
- Time lag

are even more ubiquitous than registries



- PRO
- RCT focused, risks underestimated and benefits overestimated.
- enrollment of larger study populations more representative of people with a given condition,
- fewer restrictions on concomitant therapies or on patients with other comorbid diseases.
- cheaper
- obtain data on a larger number of clinical outcomes.
- **CON**
- infrastructure to facilitate enrollment.
- related to the data source, loss to follow-up and/or incomplete d


Passive surveillance
Hospital-based
Routine reporting
Active surveillance
Searching (hospitals and community
Routine reminders

- Rapid technological innovation: health-related mobile applications, wearable technologies
- fitness trackers, and sync-able technologies such as digital weight scales and portable electrocardiographic sensors
- **PRO**
- patient-generated data andpatient-reported outcomes
- recruiting patients virtually
- detailed and longitudinal information from outside health care
- **CON**
- absence of representative populations.
- not be adapted into health care data platforms