



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# Real world evidence (RWE) – an introduction; how is it relevant for the medicines regulatory system?

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# Why do we need RWE?

**Case study 1:** Patients with unprovoked venous thromboembolism (VTE) after 3–6 months on anticoagulants: recurrence risk of 5–10% per year. Who should/should not receive life-long anticoagulants?

Derivation study to define prediction model: Prospective; 929 patients; approximately 17 years, cost ~€12-15 million

Validation study: secondary analysis of pre-existing (trials) data; ~6 months, cost <€100.000

Could a study like this be based on pre-existing e-HRs (i.e. “RWE”), only faster and cheaper?



## Why do we need RWE?

**Case study 2:** Gene therapy for thalassemia holds promise for once-only administration, initial conditional approval after a few years observation in clinical trial plausible.

Limited information on duration of the effect, safety concern over vector-based gene therapies, i.e. insertional mutagenesis leading to oncogenesis; several years for tumours to develop, risk level is likely to be low → decade-long (or life-long) surveillance of all patients → unrealistic in the interventional research setting

Reliable RWE (from eHRs) would be a key enabler for the development, licensing, reimbursement and safe use



## Why do we need RWE?

**Case study 3:** Oncology: combination therapy offers greatest potential for most patients; a plethora of potential molecules and pathways to target are available.

→ huge “combinatorial complexity”: dose selection, drug combination partners, sequence of treatments, washout periods, changing tumour characteristics, patient-/tumour-related stratification biomarkers → the full potential and optimal use of new agents cannot be characterised before routine use.

RWE is our only hope to come to grips with combinatorial complexity

## A look over the fence - to other industries



E-controls, sensors → real-time analysis →  
keep plane safe in the air **and** inform next-gen product design



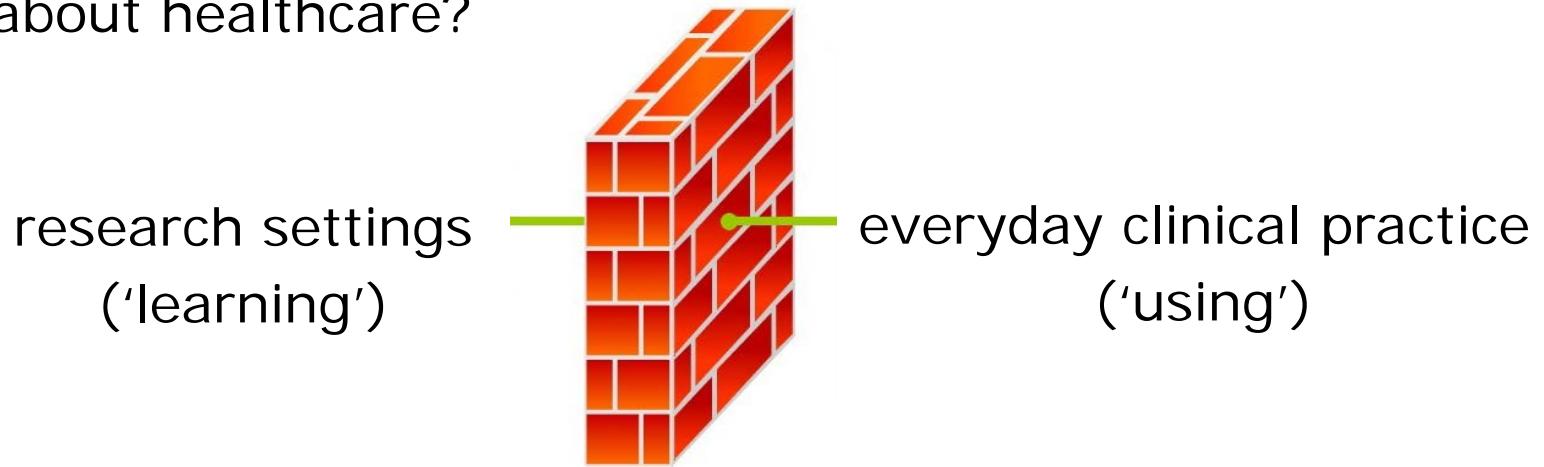
Sensors for real-time monitoring; geocoded maps; soil, weather conditions → raise agricultural productivity **and** inform next-gen product and services design

## Across the fence...

...everyday use ('practice') and R&D are not two separate activities;

future learning and rapid feed-back loops between use and R&D are built into the system from scratch → 'data-driven innovation'.

How about healthcare?





# Going beyond the research-practice divide

Going beyond...

- 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 approach
- Silos (insurers, regulators, developers) → common approach
- Research-practice divide → **learning health care system**



# E-health records: the lynchpin of a learning healthcare system

Are we ready?

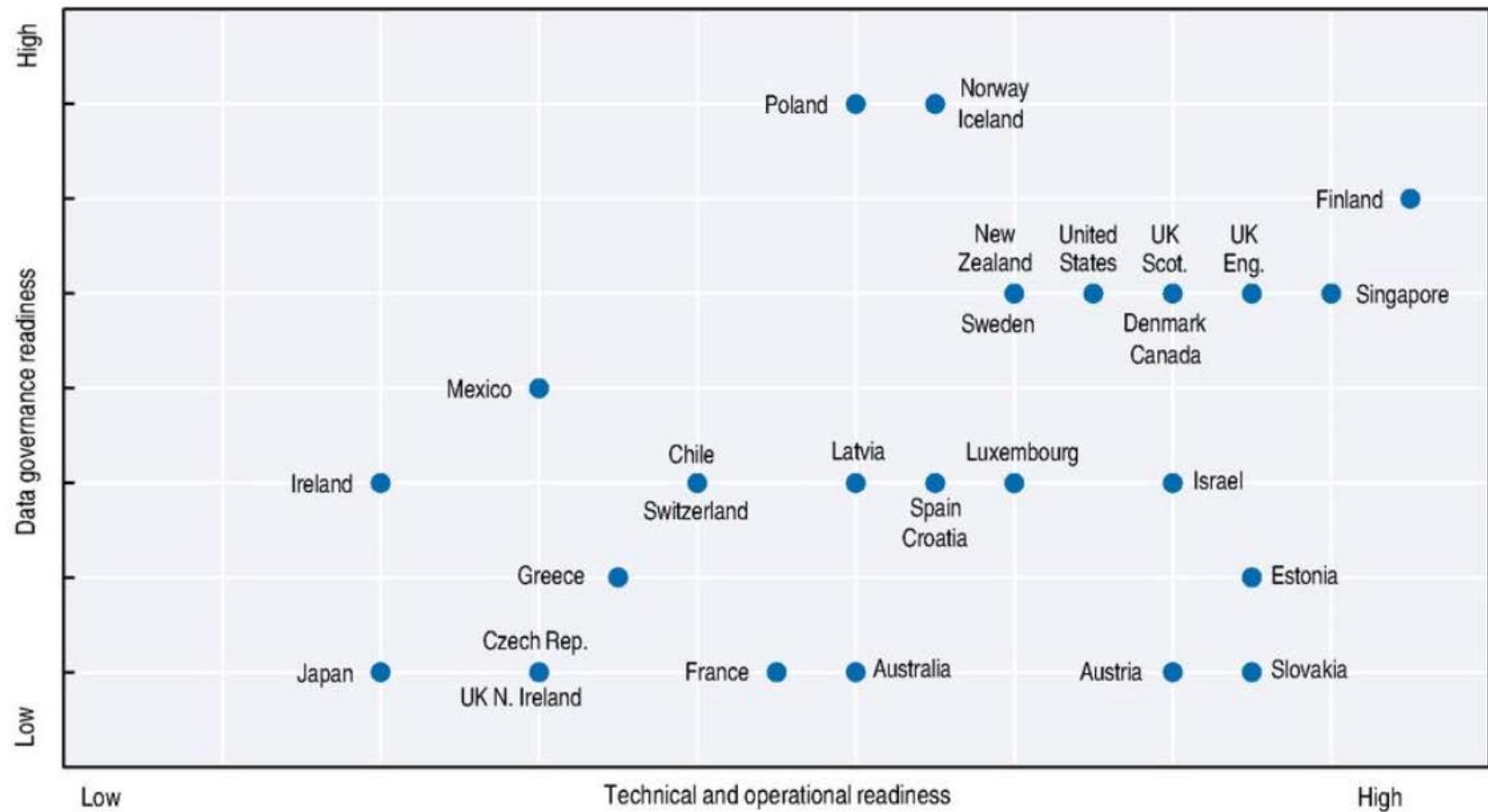
Organisation for Economic Co-operation and Development (OECD) conducts (repeat) surveys of member countries

→ report on the:

“Readiness of electronic health record (eHR) systems to contribute to national health information and research” [OECD website]

Note: **routinely** collected data (“longitudinal record....”), **not** trial data, **not** registries, **not** wearables, ...

# Are we ready?





# Why not learn from learning airplanes, learning harvesters?

Bottlenecks:

- Technology
- Data ownership, politics, ..

"We are different..."

- **Informed consent**
- **Patient data protection**



Support the "datasaveslives"  
petition!



With adequate personal data protection and against *undesirable* use - most patients will support a learning healthcare system



# Can we accelerate the implementation of a RWE-learning/ learning healthcare system?

Giving the *Bandwagon* a big push at the level of..

- Political/public debate
- Best practice
- Implementation
- Methodology development



## Political/public debate (1)

(All!) OECD Health Ministers 2017 agreed “that governments establish a national health data governance framework to **encourage the availability and use of personal health data** to serve health-related public interest purposes while promoting the protection of privacy, personal health data and data security.” to “encourage common data elements and formats; quality assurance; data interoperability standards; common policies that **minimise barriers** to sharing data for health system management, statistics, research and other health-related purposes that serve the public interest.”



## Political/public debate (2)

- Reinforce the urgency that opportunities for patients are lost; science progresses faster than the “system”, impeding the development and best use of novel treatment options.
- Myth-busting: patient-data protection and secondary data use are **not** a trade-off; both can be achieved at the same time.
- Shift the debate: “Analysing personal health data is a risk to individuals” → “**Not** analysing personal health data is a risk to individuals”.



## Sharing best practice (examples of 'building blocks')

- New Zealand: public consultation in 2015 → national eHR, single longitudinal view accessible to consumers, carers and decision-makers; support precision medicine, ...
- Australia: legislation from an opt-in to an opt-out patient consent model
- 13 countries: offer financial incentives to encourage health care providers to adopt eHRs that conform to natl. standards
- EMA: ENCePP collaboration → Code of Conduct to facilitate cooperation between the private pharmaceutical sector and healthcare systems



## Implementation (examples)

“People Who Say It Cannot Be Done Should Not Interrupt Those Who Are Doing It”.

- Kaiser Permanente: integrated eHR system and applied Big Data analytics → algorithm to predict likelihood of sepsis in new-borns, → reduce unnecessary use of antibiotics; adherence and glycaemic and blood pressure control → improve disease management
- FDA Sentinel initiative: “share answers not data” → successfully address drug safety concerns



# Methodology?

Algorithms and (statistical) methods to extract, analyse, and interpret eHR data are in place and broadly acceptable for a number of research questions.

Achilles' heel: conducting relative effectiveness studies; inherent risk of bias and confounding due to the non-randomised nature of the comparison

Are we making progress?

Can real world data studies (based on eHRs) match the results of an RCT? (predict versus confirm!)



		Real World Data Analysis	Randomized Controlled Trial
Studies of harmful effects (Safety)	(1)	Schneeweiss S, et al. <b>Aprotinin during coronary-artery bypass grafting and risk of death.</b> New Engl J Med 2008;358:771-83.	Fergusson DA, et al. <b>A comparison of aprotinin and lysine analogues in high-risk cardiac surgery.</b> New Engl J Med 2008;358:2319-31.
	(2)	Kim SC, et al. <b>Cardiovascular safety of tocilizumab versus tumor necrosis factor inhibitors in patients with rheumatoid arthritis - a multi-database cohort study.</b> Arthritis Rheumatol 2017*;69(6):1154-64.	Giles JT, et al. <b>Comparative cardiovascular safety of tocilizumab vs etanercept in rheumatoid arthritis: Results of a randomized, parallel-group, multicenter, non-inferiority, phase 4 clinical trial [abstract].</b> Arthritis Rheumatol 2016; 68 (suppl 10).
Studies of beneficial effects (Effectiveness)	(3)	Patorno E, et al. <b>Cardiovascular safety of canagliflozin vs. other antidiabetic agents in routine care.</b> Presented at: 77th Scientific Sessions, American Diabetes Assoc.; June 09-13, 2017; San Diego, USA.	Neal B, et al. <b>Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes.</b> New Engl J Med 2017;377:644-57.
	(4)	Seeger JD, et al. <b>Safety and effectiveness of dabigatran and warfarin in routine care of patients with atrial fibrillation.</b> Thromb Haemostasis 2015;114:1277-89.	Connolly SJ, et al. <b>Dabigatran versus warfarin in patients with atrial fibrillation.</b> N Engl J Med 2009;361:1139-51.
	(5)	Fralick M, et al. <b>Using healthcare claims databases to identify supplemental indications of approved medications.</b> JAMA IM 2018;178:5-63.	Mann JF, et al. <b>Dual inhibition of the renin-angiotensin system in high-risk diabetes and risk for stroke and other outcomes: results of the ONTARGET trial.</b> J Hypertens 2013;31: 414-21.

\* We provide citation to the published manuscript here. Initial results were presented at the 2016 American College of Rheumatology Annual Meeting.



# Conclusions

Science progresses now faster than the “system”, impeding the development and best use of novel treatment options.

Leveraging RWE is a need – and an achievable goal.

Accelerating the use of RWE requires a concerted effort and the necessary upfront investments.

The good news: this is not a zero-sum game, *all* players in the pharmaceutical ecosystem stand to gain.



Thank you  
for listening!

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