EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Real-world evidence to contribute to medicine development and access

2021 annual meeting of the members and Coordinating Group of the European network of paediatric research at the EMA (Enpr-EMA)

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Disclaimer

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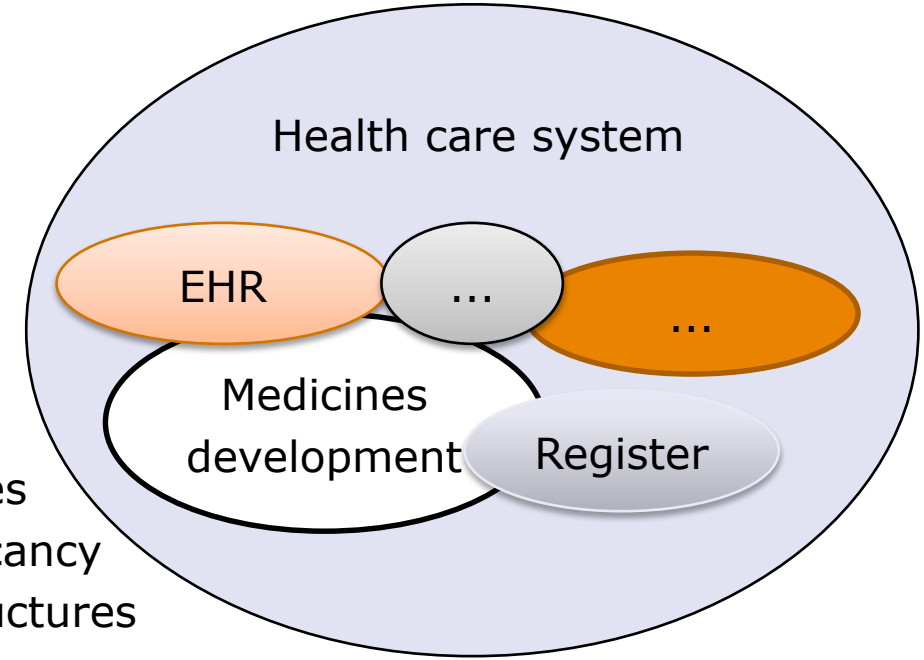
https://www.ema.europa.eu/en/documents/report/european-union-medicines-agencies-network-strategy-2025-protecting-public-health-time-rapid-change_en.pdf

https://www.ema.europa.eu/en/about-us/how-we-work/regulatory-science-2025

Vision for medicines

"To underpin its mission of protecting human health, EMA must catalyse and enable regulatory science and innovation to be translated into patient access to medicines in evolving healthcare systems."

Context: We need a „*learning* health care system“



Agents
Processes
Permancancy
Infrastructures

“science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience.
[… Such systems …] explicitly use technical and social approaches **to learn and improve with every patient who is treated.**”

http://www.learninghealthcareproject.org/section/background/learning-healthcare-system

Plans to generate clinical evidence need to evolve

Drivers

- New trial designs and non-trial data that can make RCTs more robust and generalisable
- Ethical concerns (veritable dilemmas, e.g. high ratio of favourable to unfavourable effects; magnitude of early effects)
- Smaller treatment-eligible populations
- One-time intervention has long-term effects
- Personalised treatment combinations and sequences (“interventional multiplicity”)

Enablers, ***not drivers***

- Availability of patient-level RCT data
- Availability of real-world data (RWD)
- Evolution of capacities for data processing including analysis federation
- Possibilities for large-scale, complex statistical computations
- Availability of legal frameworks such as GDPR and national health system provisions

Extended after HG Eichler

RWE is mainly analyses – methodologies promising but…

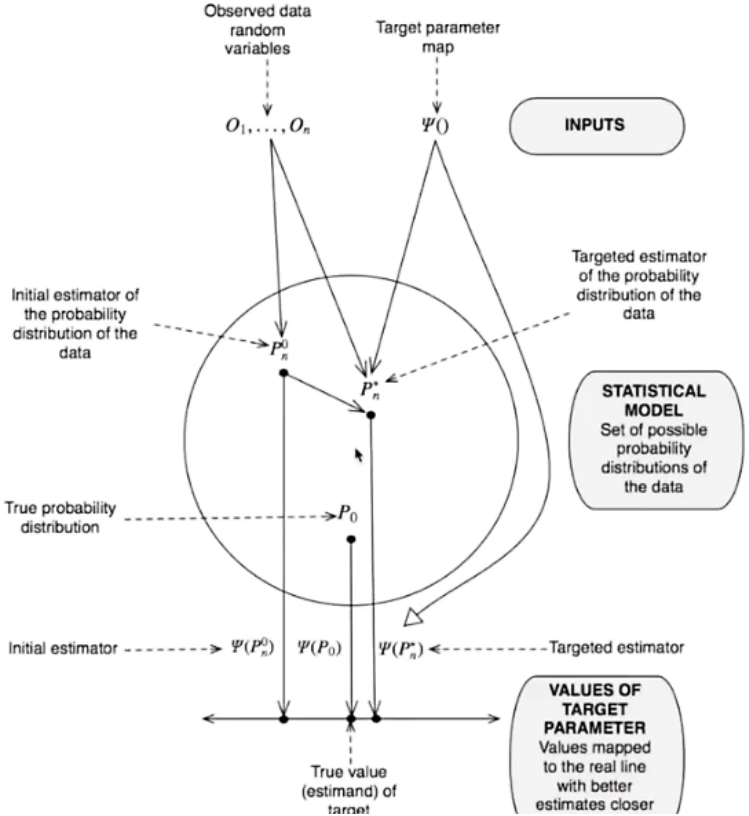
- Important biases (confounding by indication, guaranteed-time bias, ascertainment bias, ...) prevent valid interpretations of most naïve analyses, models are needed
- Unlikely to deliver robust results in all scenarios; not fully validated and accepted
- New data sources without new accepted analysis methods (statistical, epidemiological) and without clear purpose will not move the needle

- To overcome "methodology aversion", need to evaluate a new methodology like new drug: prospectively, well controlled and according to pre-agreed plan
- Call for action: make use of 'methodology qualification procedure' to support acceptance by regulators and other decision-makers

Eichler H-G et al. Are novel, non-randomised analytic methods fit for decision-making? The need for prospective, controlled and transparent validation. Clinical Pharmacology & Therapeutics 2019 https://doi.org/10.1002/cpt.1638

Lab results, medical images, symptoms, genomic data, environmental signals, Pictures, activity data, phenotype data, IVD instrument results, patient demographic information, progress notes, vital signs, medications diagnoses, immunization dates, allergies, etc.

J Gassen 2019-12-07: Analyzing Researcher Degrees of Freedom: A Case Study



M van der Laan 2020-02-05: "Targeted Machine Learning for Causal Inference based on Real World Data" (webinar series)

Values for clinical evidence generation apply to RWE

- Transparency
  - Establishing identifiability of RWE exercise, enhancing public verifiability, sharing accountability, informing future use
- Reproducibility of exercise
  - Understanding RWE exercise should often be open-ended investigation ("investigate how reliably it be shown that ... is ...")
  - Using RWE to be supported by protocols, use of standards, auditing etc.
- Replicability of results
  - Implemented through principles and methods;
    a fundamental expectation for evolving health care systems

Further information

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EMA Regulatory Science to 2025

2. Driving collaborative evidence generation - improving the scientific quality of evaluations
   - Develop the regulatory framework for emerging clinical data generation
     (digital technologies, patient-reported outcomes, complex datasets, modernize GCP)
3. Advancing patient-centred access to medicines in partnership with healthcare systems
   - Reinforce patient relevance in evidence generation
     (capture patient voice, patient involvement, guidelines, HTA collaboration)
   - Promote use of high-quality real-world data (RWD) in decision making
     ("The Agency recognises the benefit of using RWD to generate complementary evidence across the product life cycle and is committed to promote the use of high quality RWD in decision-making.")