EUROPEAN MEDICINES AGENCY
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Real-World Data to Optimise Oncology Drug Development and Access

Regulator's perspectives

Cancer Drug Development Forum

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An agency of the European Union

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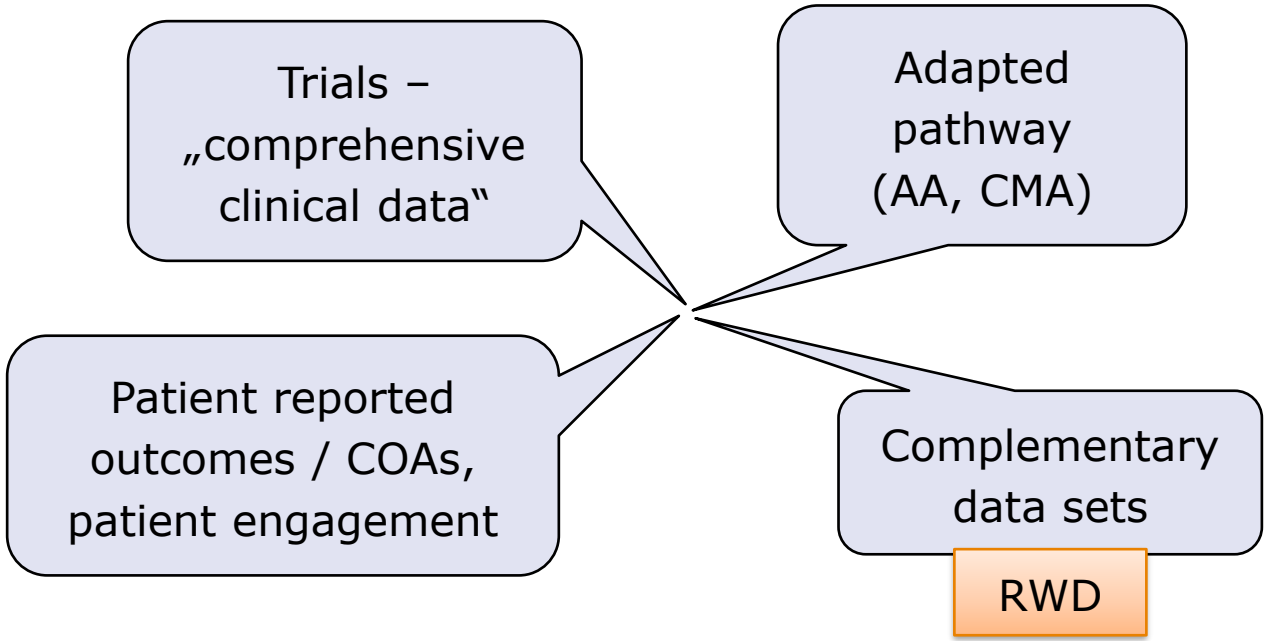
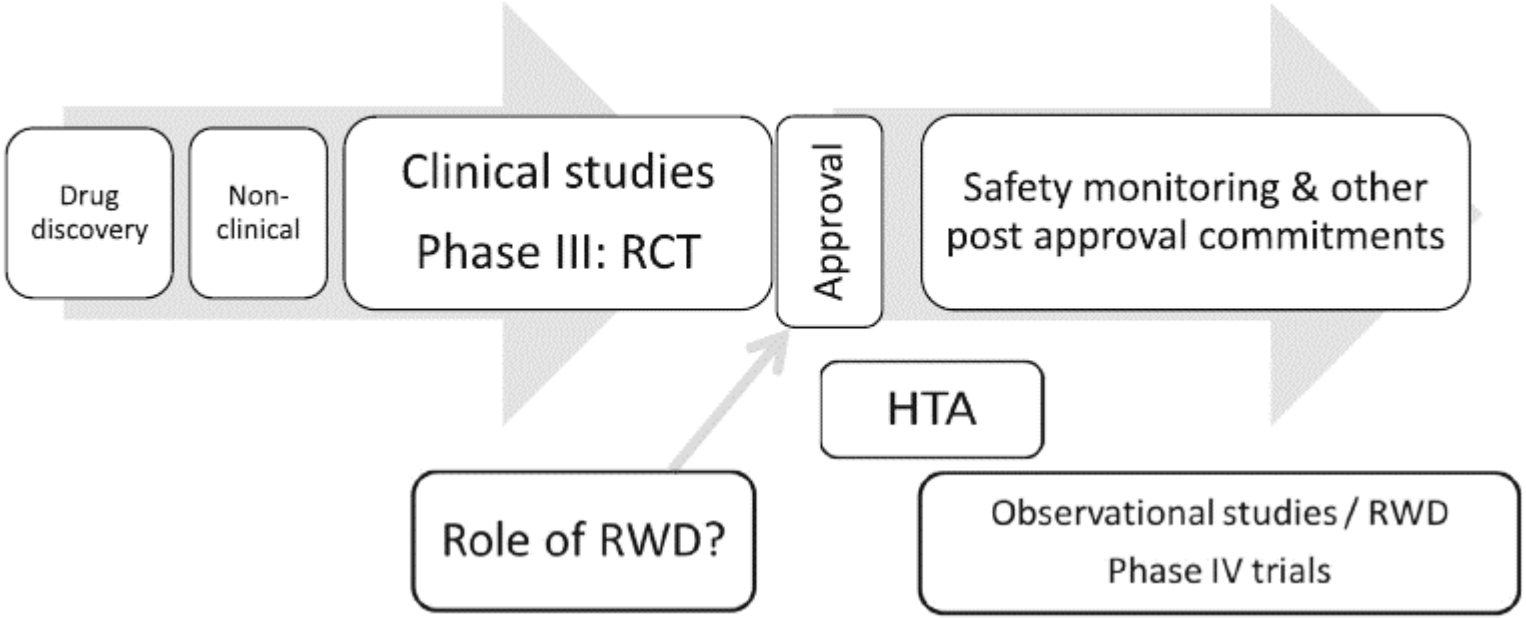
Shared intentions: to advance clinical research & development in oncology, in several domains at the same time



Cancer drug development forum 2016



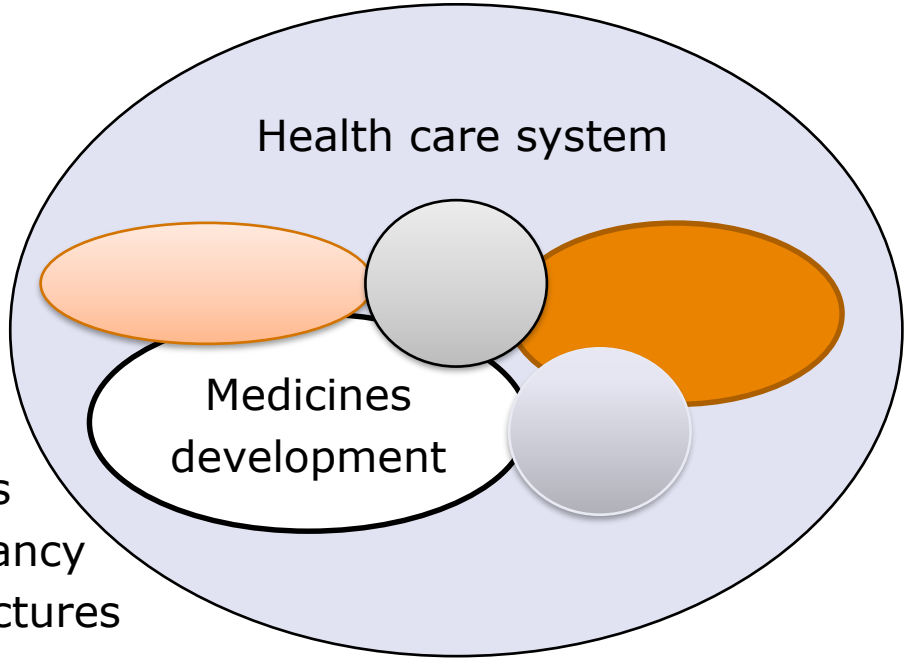
Skovlund E, Leufkens HGM, Smyth J. The Use of Real-World Data in Cancer Drug Development. European Journal of Cancer 2018; 101: 69-76 https://doi.org/10.1016/j.ejca.2018.06.036

Table 1 OPerational, TechnIcal, and MethodologicAL framework (OPTIMAL) for regulatory use of real-world evidence (RWE)

Objective	Desired criteria for acceptability of RWE	Challenges with use of RWD to generate acceptable RWE	Possible solutions (EU context)
Appropriate use of valid RWE for regulatory purposes (e.g. safety, efficacy, benefit–risk monitoring)	Evidence is: • Derived from data source of demonstrated good quality • Valid (internal and external validity) • Consistent (across countries/ data sources) • Adequate (e.g., precision, adequate range of characteristics of population covered, dose and duration of treatment, length of follow-up)	**Operational** • Feasibility (e.g., data access and cost, availability of relevant data needed, data protection, patients' consent, availability of hospital data source) • Governance (e.g., data-sharing policy, transparency policy towards fundi	**Operational** • Early and repeated consideration of the need for RWD during drug development • Landscaping of potential data sources • Long-term funding for data infrastructures • Published documentation of data source characteristics and policy for collaboration and data sh

Cave Alison, Kurz X, Arlett P
Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe
Clinical Pharmacology & Therapeutics 2019, 106: 36–39. https://doi.org/10.1002/cpt.1426

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; duration of disease-controlling treatment; large early effects)
- One-time intervention has long-term effects
- Smaller treatment-eligible populations
- Personalised treatment combinations and sequences (“interventional multiplicity”)

Enablers

- 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

Analytic methodologies: newly applied to clinical development

A range of methodologies have been proposed or refined, examples:

- borrowing of external control group data
- construction of external control group
- indirect comparisons for relative efficacy or safety
- reweighting of RCT results to reflect real life
- predictive approaches to heterogeneous treatment effects
- extrapolation of inferences to an unstudied population
- predictive approaches to heterogeneous treatment effects
- ...
- replacing RCTs by RWD analyses

After HG Eichler

Analytic methodologies: promising but …

- Unlikely to deliver robust results in all scenarios; not fully validated and accepted
- New data sources without new accepted analysis methods (statistical, epidemiological) and 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

Beyond analytic methodologies: open questions

- Different nature of outcomes in RWE data needs to be understood for clinical reasoning (e.g. relapse is derived as probability based on pre-defined sets of utilised resources)
- Purpose driving RWE approach (e.g., how do costs and value compare to experiment / trial? Whenever an RCT is feasible and necessary, why should it not be conducted?)
- Quality management and good RWE practices (e.g., how could RWE be inspected?)
- Process generating RWE (e.g., documented rationale, control, choices and impact)

- Pitfalls of RWE approaches, notably for oncology (i.e., confounding by indication, handling of intercurrent events and selection bias in complex setting; assessment bias with interim endpoints; guaranteed-time bias)

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
  - Using RWE to be supported by protocols, use of standards, auditing
- Replicability of results
  - Implemented through principles and methods; a fundamental expectation in medicine regulation

Summary

- For this meeting
  - We are curious to hear about experiments and exercises with RWE in oncology
  - We encourage all developers, regulators, HTA, clinicians, patients to comment on RWE approaches
- Product-by-product
  - Seek Scientific advice on exercises to develop and to use RWE in oncology is strongly encouraged
  - Interest in RWE for oncology where this leads to more robust and informative dossiers, in shorter time
- Strategic development
  - Seek Scientific advice qualification procedure for novel methodologies
  - Further develop how RWE supports values of clinical evidence generation

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Thank you for your attention – any questions?

Further information

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