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SCIENCE MEDICINES HEALTH

Use of Real World Data in Development Programmes

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Industry Stakeholder Platform on Research and Development Support

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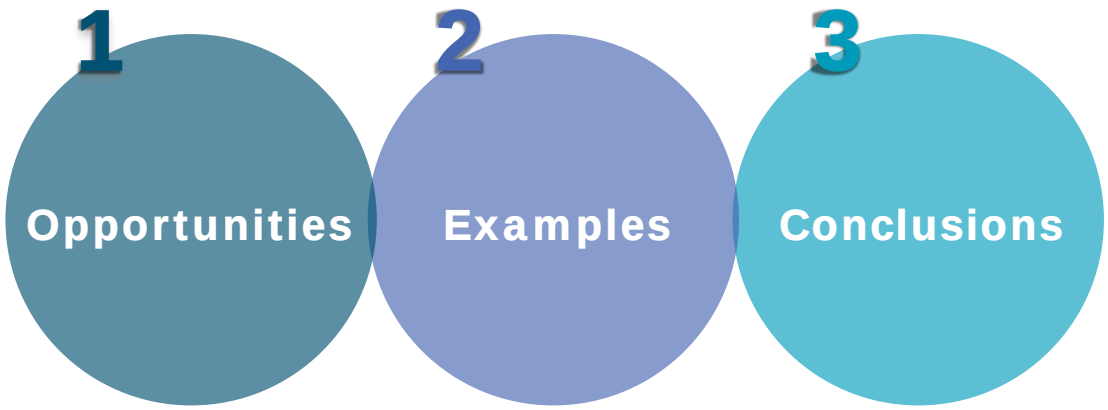
Objectives



Objectives

Opportunities of Real World Data

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Phase 2 → Phase 3 → Authorisation

- Characterisation of natural history of the disease and unmet need
- Understanding current clinical care practices (resource utilisation)
- Drug utilisation
- Identification of the target population
- Understanding potential knowledge gaps
- Validation of surrogate endpoints
- Use of historical controls (rare / orphan diseases)

Opportunities of Real World Data

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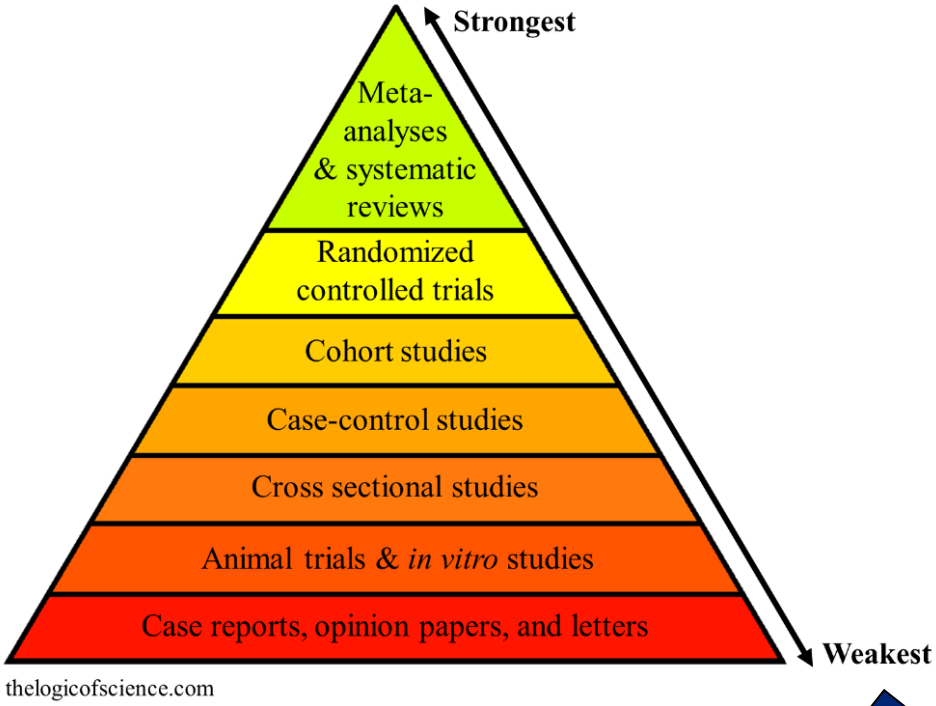
What are the factors affecting acceptability?

Product life stage and the question

- Orphan condition
- Lack of treatment options
- Is a RCT is feasible?
- Natural history of the disease is well understood
- Defined patient population
- Disease context
- Actionable endpoints
- Are datasources available, of high quality and sustainable?
- Understanding of bias and confounders


Strongest
Meta-analyses & systematic reviews
Randomized controlled trials
Cohort studies
Case-control studies
Cross sectional studies
Animal trials & *in vitro* studies
Case reports, opinion papers, and letters
Weakest
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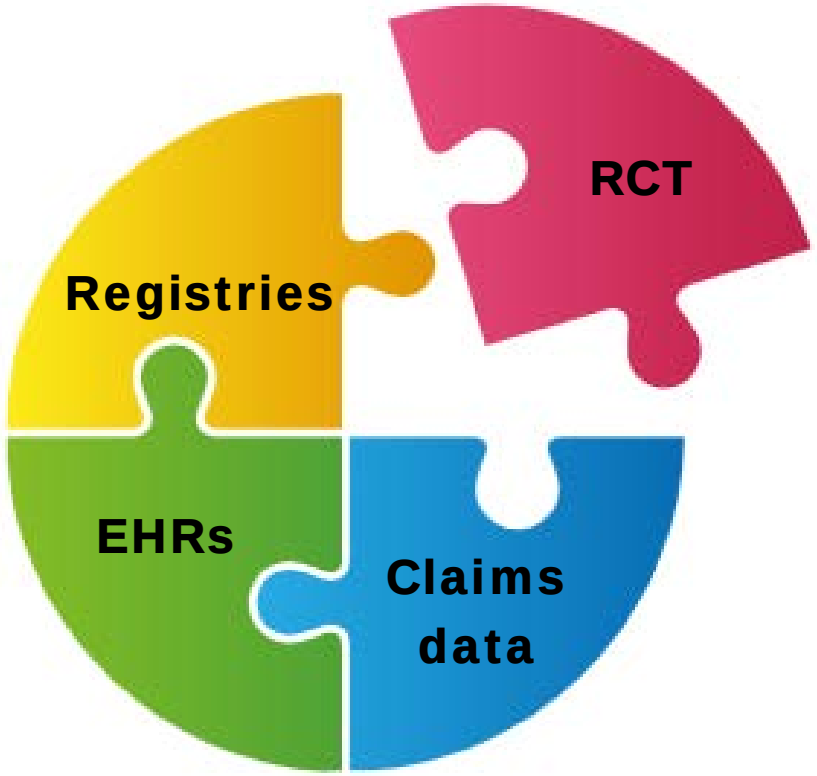
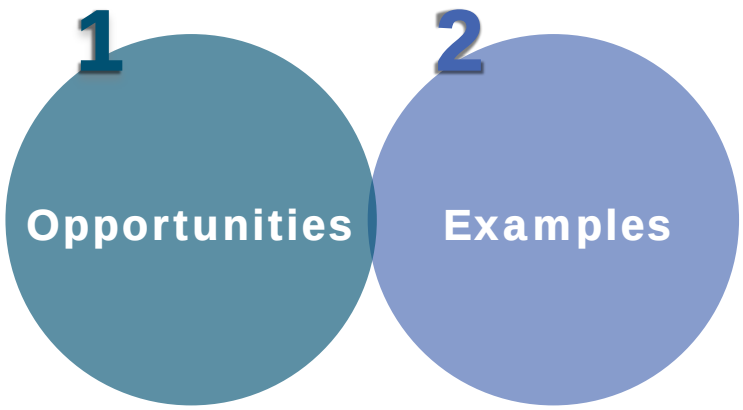

RCT
Registries
EHRs
Claims data

Objectives



Observational evidence in pre authorisation

Experience from Scientific Advice / Adaptive pathways

An **opportunity to reduce uncertainty**

- Capture real clinical practice, adherence, compliance
- Prospective natural history is particularly appealing
- Capture rare, long-term events (safety and/or efficacy) Less costly– important for degenerative and chronic diseases, gene therapy
- *All* subjects could be followed for long term outcomes e.g. ecolizumab
- Personalised medicine: capture more strata/age groups than RCT. Useful to validate biomarkers.

Not all endpoints are suitable

Consider effort *vs.* need

Registries to supplement RCTs: an AP oncology scenario

Benefit / Risk balance in RCT interim analysis (IA)	MA route at IA	Uncertainties at MAA	Vehicle to address	Timeline of in-market RWD
Compelling	**Full MAA at IA**	In-market safety surveillance (per any marketed product)	RMP (+registry?)	PhV reporting
Efficacy demonstrated, additional safety required	**CMA at IA**	Safety database not adequate or additional safety concerns	Global registry: Early Access Program with protocol and database	X months of data collection to convert to full MAA
Promising efficacy, safety data acceptable	**CMA at IA**	Additional OS data	Global registry: In-market collection of RWD within registry	Y months of data collection to convert to full MAA
Inconclusive	**Await final analysis**	Unknown	Global registry (?)	TBD

Zalmoxis (2016) adjunctive treatment in hematopoietic cell transplantation

MAA: single arm, phase I/II study; Endpoint: immune reconstitution defined as CD3+ cells >100 per µL + A Ph III trial ongoing

CHMP asked to perform a comparison of the treated patients (from both studies) with results from suitable historical controls

EBMT registry used to compile an appropriate control group selected on same criteria as the control arm of the ongoing phase III trial and a specific set of matching parameters:

- patient age (plus or minus 3 years)
- diagnosis (AML, ALL and sAML)
- disease status at HSCT (CR1, CR2, CR3 or relapse)
- time from diagnosis to HSCT (plus or minus 3 months)

The planned ratio of MM-TK patients to control patients was one to four.

Several sensitivity analysis were conducted

Post-authorisation: a non-interventional safety and efficacy study will investigate effectiveness in real clinical practice by collecting data about the disease status and outcome of all patients treated with Zalmoxis using the EBMT registry

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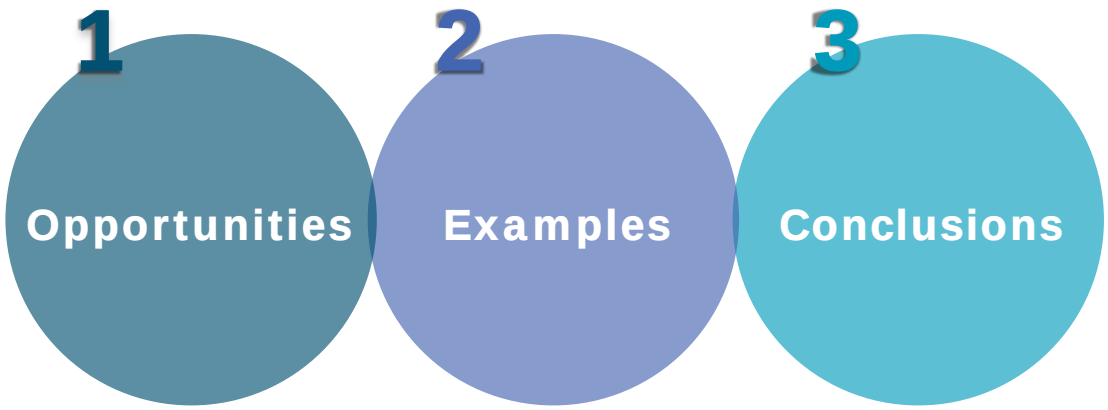

Conclusions: Learnings on regulatory acceptability of RWE in product development

Generally more acceptable for:

- If an RCT is not feasible (time, ethics, rarity)
- Hard endpoints (to offset bias)
- Conditions with known and predictable progression (note: prospective natural history)
- Well thought proposals and trust in their reliability and feasibility

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Thank you

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#AdaptivePathways

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