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Avenues of knowledge generation throughout a medicine's lifespan: methodological issues

Presented by Rob Hemmings

Flow

- Drug development evolves …
- … but is underpinned by the RCT
- Scenarios that challenge the RCT
- Methodological and trial design issues relevant to AP
- Experience from the pilot

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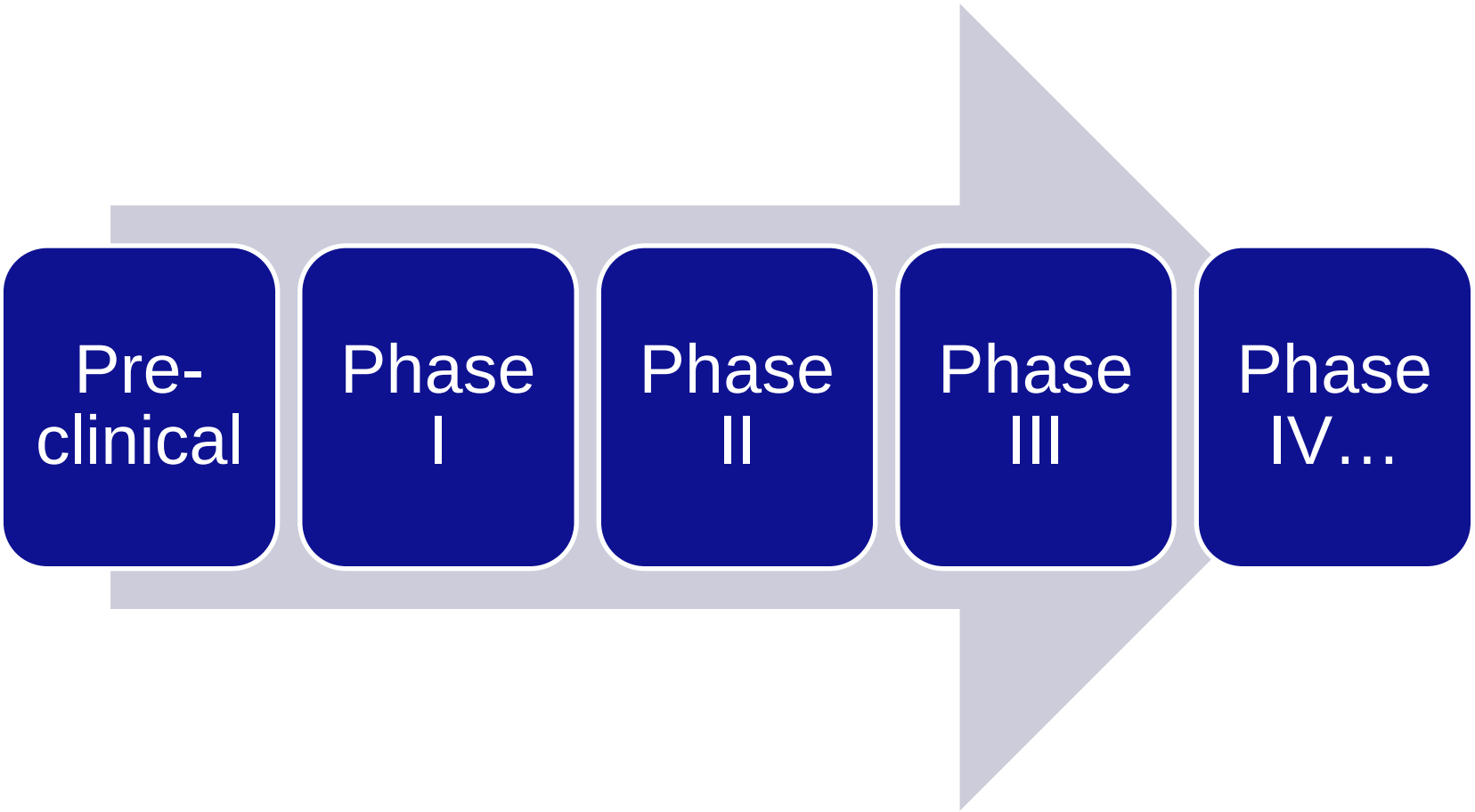
Drug development evolves …
… but is underpinned by the RCT

Drug development evolves…



Drug development evolves…

3Rs

In-silico testing

Adaptive designs

M&S e.g. PBPK

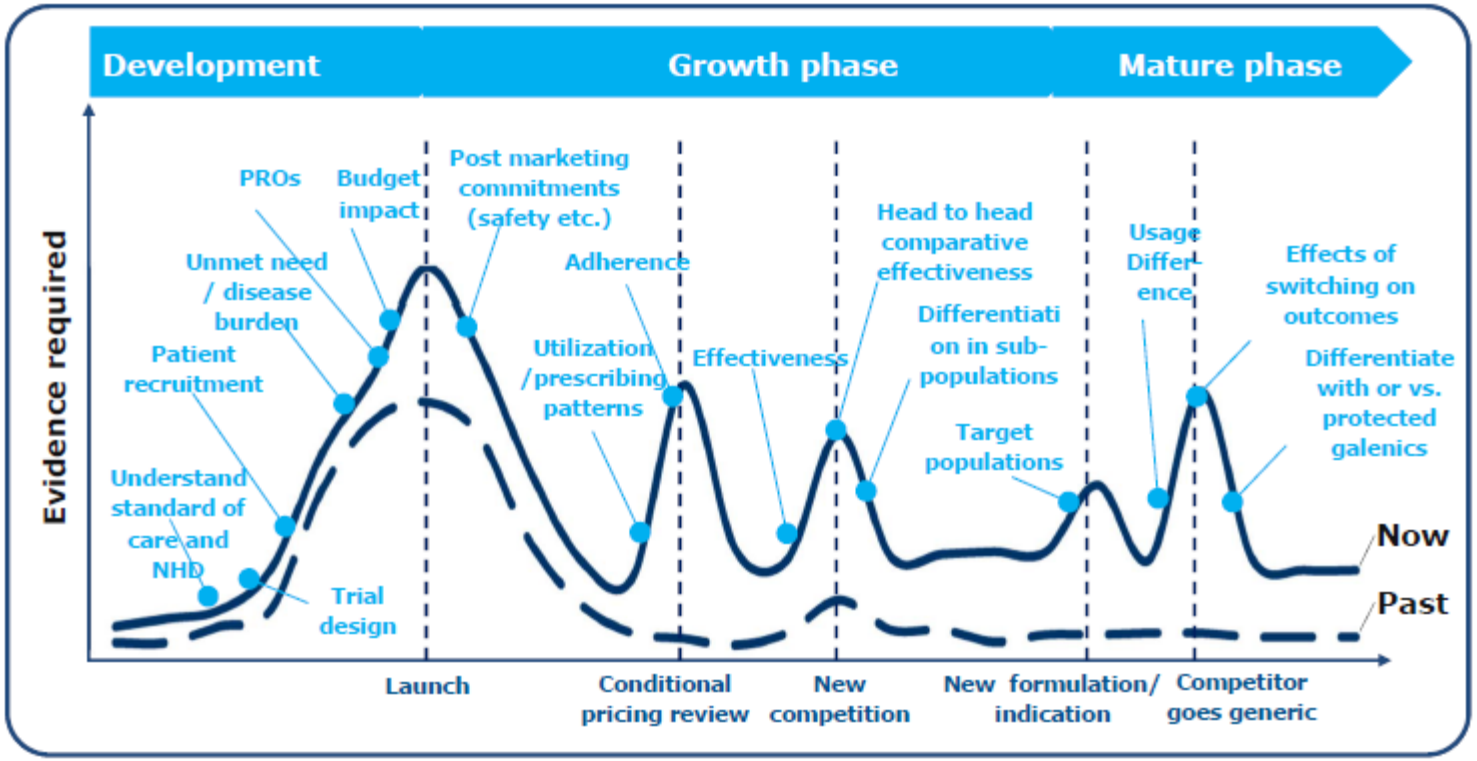
D-E-R e.g. MCP-Mod

Pragmatic

CT simulations

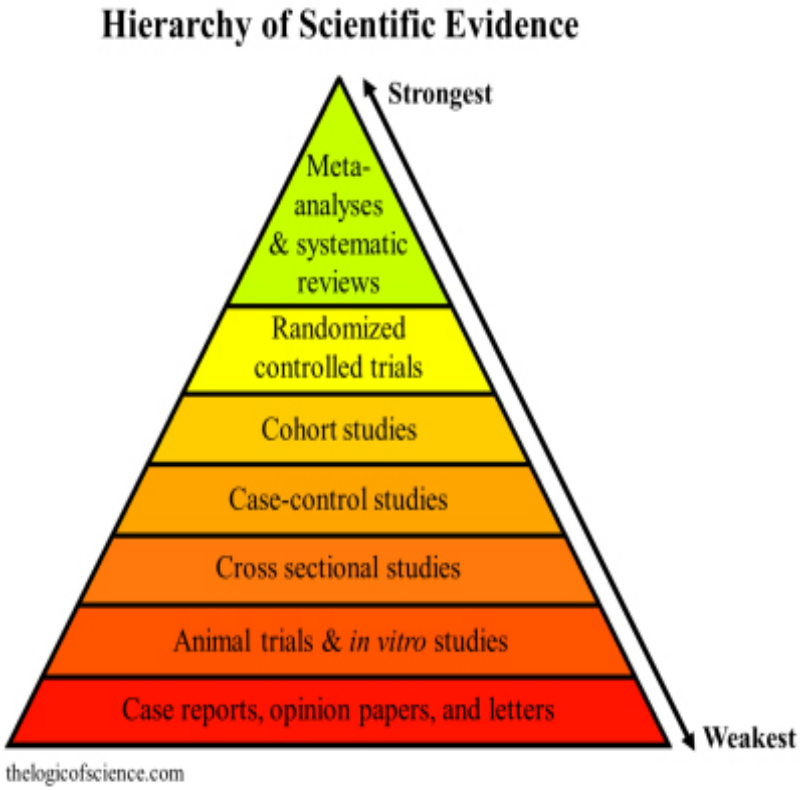
Drug development evolves…

RWE can support access throughout the lifecycle



Source: IMI GetReal

… but is underpinned by the RCT



Evidence for MA:

Mechanistic understanding and plausibility

+

Exploratory, e.g. PD responses, D-E-R

+

(2x) Confirmatory RCT

+

RMP / PASS, PAES.

… but is underpinned by the RCT

R	C	T
the most important design techniques for **avoiding bias** in clinical trials are blinding and randomisation	to allow discrimination of patient outcomes caused by the test treatment from outcomes caused by other factors	to ensure that groups are treated similarly in the course of the study to estimate effects **attributable to treatment**

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Scenarios that challenge the RCT

Scenarios that challenge the RCT

- Self-evident causality (attribution) (**BB 2**)
- (Very) rare diseases, (sometimes). (**BB 4**)
- Extensive follow-up required (**BB 1**)
- Ethical / Feasibility issues
- Unsuitable primary objective

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Selected methodological issues for AP

Selected methodological issues

- Interim analyses
  - Misunderstood?
  - Maintaining the **integrity** of an ongoing trial
  - Impact on **feasibility** to continue the trial (or initiate a new RCT).
  - For Conditional MA, it is required to be “likely that the applicant will be able to provide comprehensive data”

Selected methodological issues

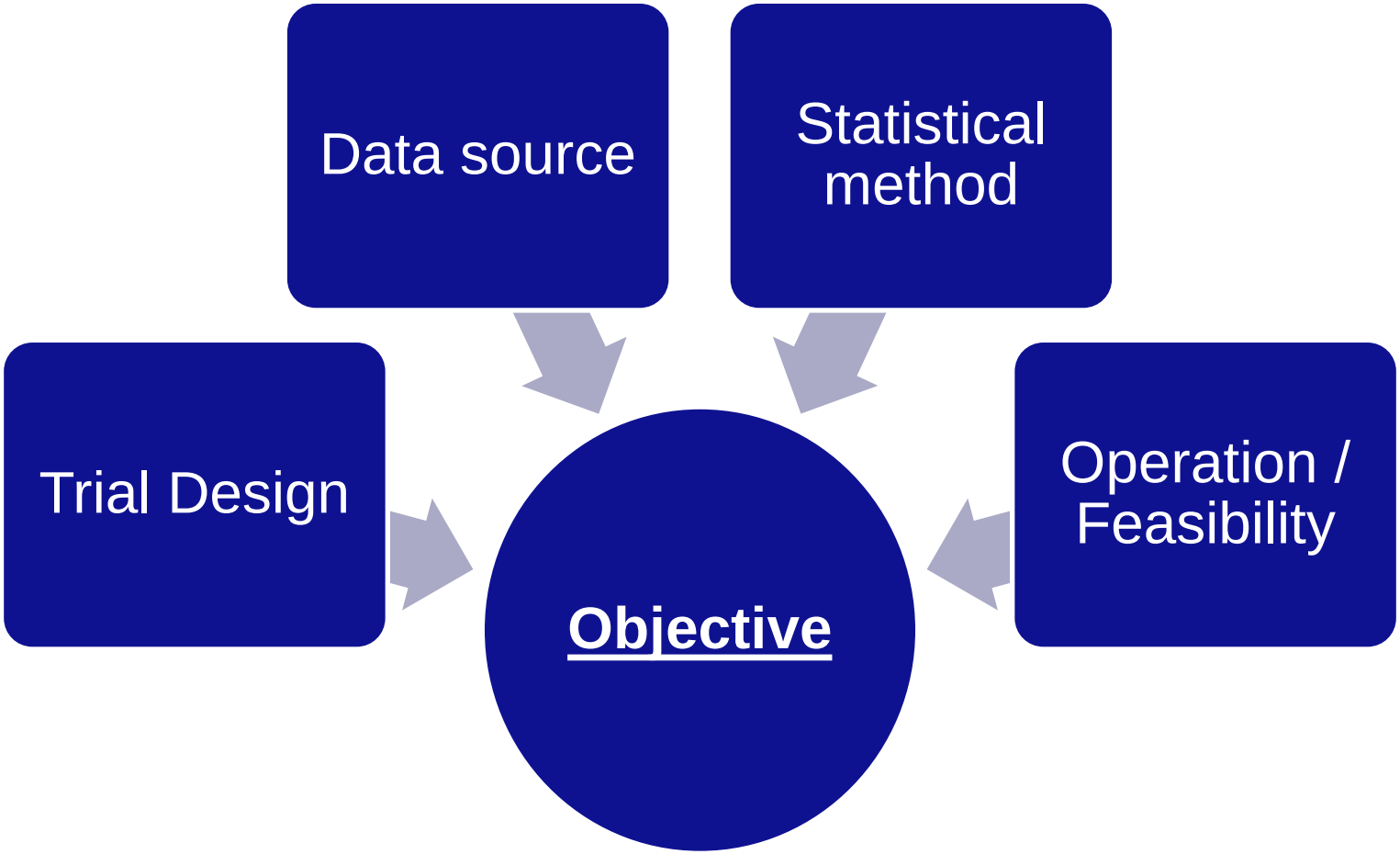
- External control groups / Single-arm trials
  - Justification

  - Discussion points for use of historical control group:
    - comprehensive and representative data
    - trials planned, conducted and reported to the same high standards
    - Contemporary in design and patient management
    - Same ‘estimand’
    - Effect > potential bias

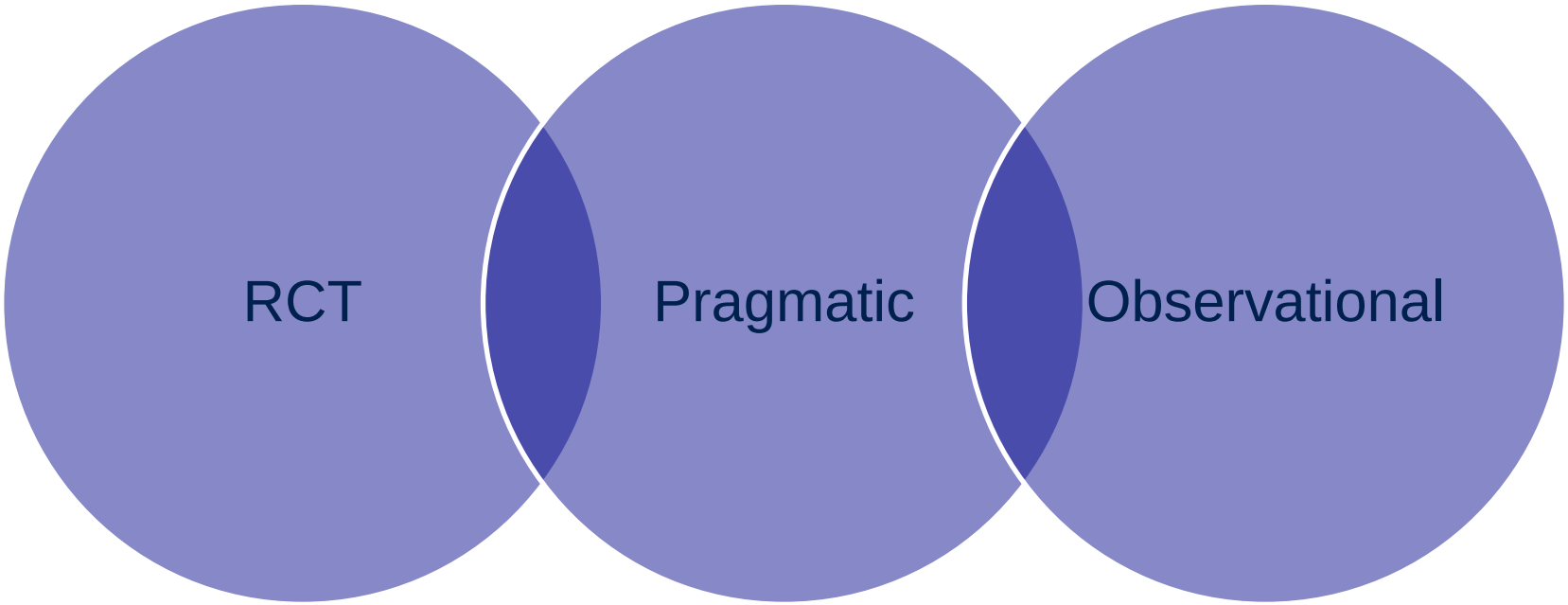
Selected methodological issues

- External control groups / Single-arm trials
  - Matching
    - How?
    - How many?
    - How to confirm absence of important bias?
  - More generally this applies to integration of CT data with data from external sources
    - Weighting?
    - Network meta-analysis

Post-authorisation studies: framework



Trial Designs



Operational challenges

Source: GetReal & www.spirit-statement.org

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Experience from the pilot

Post-authorisation studies: framework

Key Questions

- Does the proposal address **regulatory** requirements?
- Can we align with requirements of other stakeholders?
- Will the study deliver?
- Data source, design and methodology likely to produce estimates of interest without important bias?
- Endpoints and results ‘actionable’ for decision making, including ‘exit strategy’?

Remarks

- RWD currently in use for regulatory decision making, including approvals.
- Potential for increased use exists. Ethical and scientific mandate to investigate what is possible.
- Studies must deliver actionable results, underpinned by sound methodology.
- Dialogue is not trivial. Needs competence, capacity and experience.

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Thank you for your attention