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Adverse Drug Reaction (ADR) screening in clinical trials

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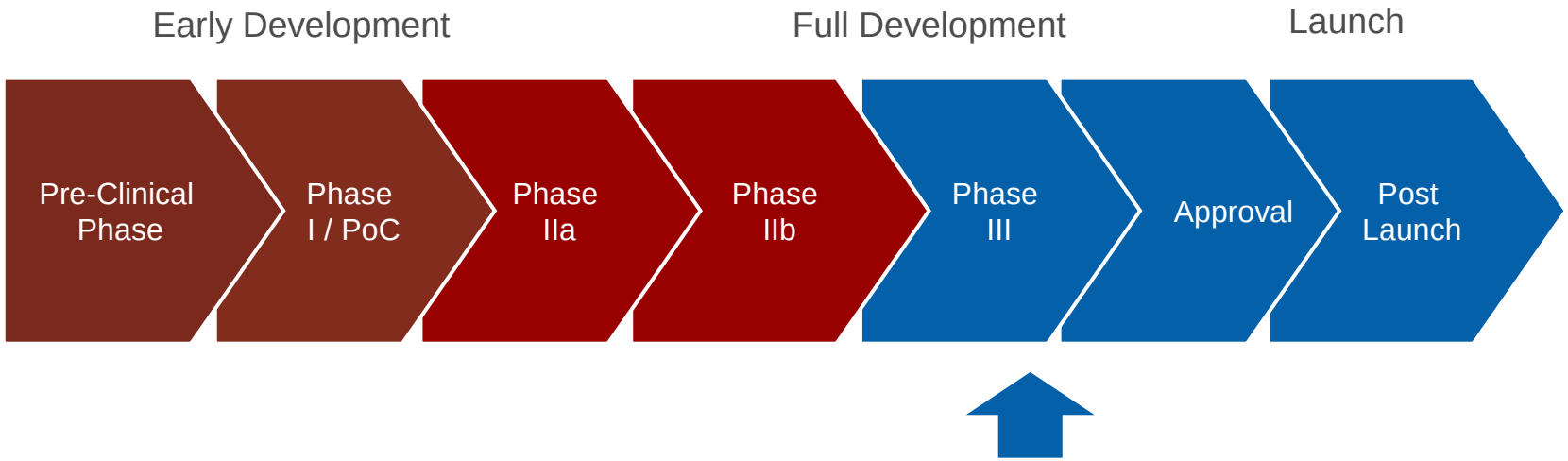
Today's talk at a glance

- How do we screen thousands of Adverse Events (AEs) reported in the case study to identify Adverse Drug Reactions (ADRs)?

- The Bradford Hill criteria to assess causal association between drug and AE (i.e. AE → ADR).

- The Double False Discovery Rate (DFDR) approach (Mehrotra & Adewale (2012)) applied to case study.

Lifecycle stage: Phase III



- Pre-approval, Cardiovascular, Phase III program:
  - 1 large RCT, ~8000 patients
  - ~5 years planned follow-up
  - thousands of **AEs** to screen for ADR candidates

AE → ADR

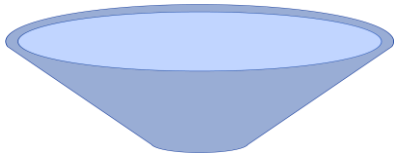
1st dose administered to patient

last dose administered to patient

Treatment period

+ time after last dose

An adverse outcome reported in this period is an **Adverse Event** (AE*)



Bradford Hill Criteria

An **Adverse Drug Reaction (ADR)** is an AE/Serious AE (SAE) with at least reasonable possibility of a causal relationship between a medicinal product and the event ....: (FDA website)

*An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (FDA website)

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AEs coded and summarized

Large Phase III Clinical Trial

Table XX.X.X (Page 1 of~500)

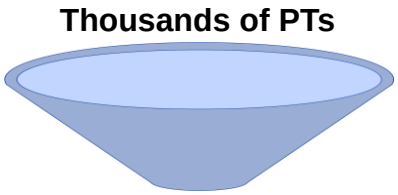
Treatment Emergent Adverse events by treatment

Safety Set

Primary System Organ Class Preferred term	Compound XX mg N ~4000 n (%)	Control XXX mg N ~4000 n (%)
Subjects with at least one AE	~3500 (~87.5)	~3500 (~87.5)
Autoimmunity reactions		
- Total	~80 (0.02)	~80 (0.02)
ANKYLOSING SPONDYLITIS	0	1 (0.0025)
AUTOIMMUNE HAEMOLYTIC ANAEMIA	0	
AUTOIMMUNE THYROIDITIS	0	0
BEHCET'S SYNDROME	1 (0.0025)	0
CHRONIC GASTRITIS	1 (0.0025)	1 (0.0025)

Each PT would then be assessed for causality with drug via the Bradford Hill criteria

Bradford Hill Criteria



Context
Case Study
Key message & ?

Howick et al. (2009)

Type of evidence			
Direct Is there an association?	**Experiment** • Experimental data provide strongest causal association evidence	**Strength** • Large associations → more likely causal	**Temporality** • Exposure precedes AE or AE worsens post exposure
Mechanistic How does the drug cause the outcome?	**Biologically plausible** • Biological mode of action can explain association	**Biological gradient** • Dose-response (D-R)	**Specificity** • No other drug(s) could be causally related to AE
Parallel Is this association observed in multiple sources?	**Consistency** • Reproducibility of results, multiple studies or data sources report similar association	**Analogy** • Evidence from another drug within the same class	**Coherence** • Totality of evidence indicates the association makes sense

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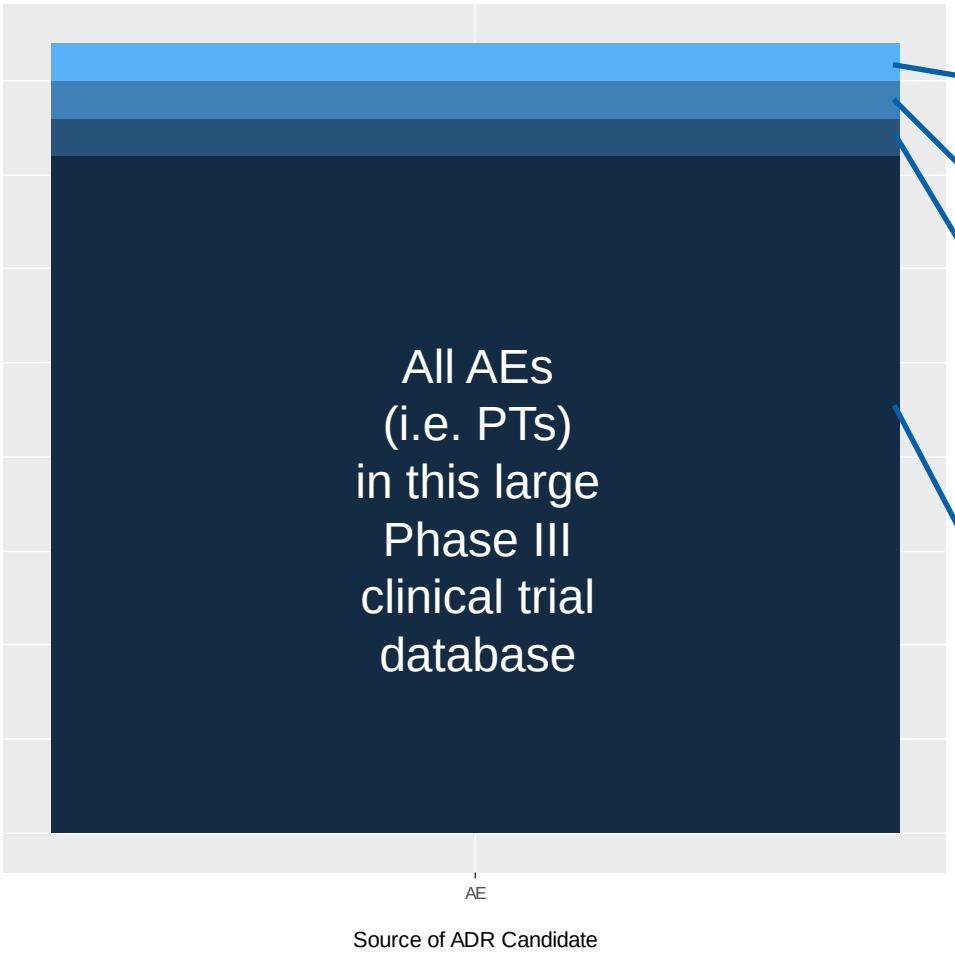
Case study: complex situation



Pre-Qualified ADR candidates
(Tier 1, Crowe et al. (2009))

Designated Medical Events (**DMEs**) – AEs that require special attention regardless of statistical criteria used to prioritize safety reviews (EMA website)

Risk Management Plan (**RMP**) – potential and identified risks for compound (EMA website)

Core Data Sheet (**CDS**) – ADRs for our compound from already approved indications (ICH guideline E2C R2)

How to screen these remaining thousands of AEs (i.e. PTs) for ADRs?

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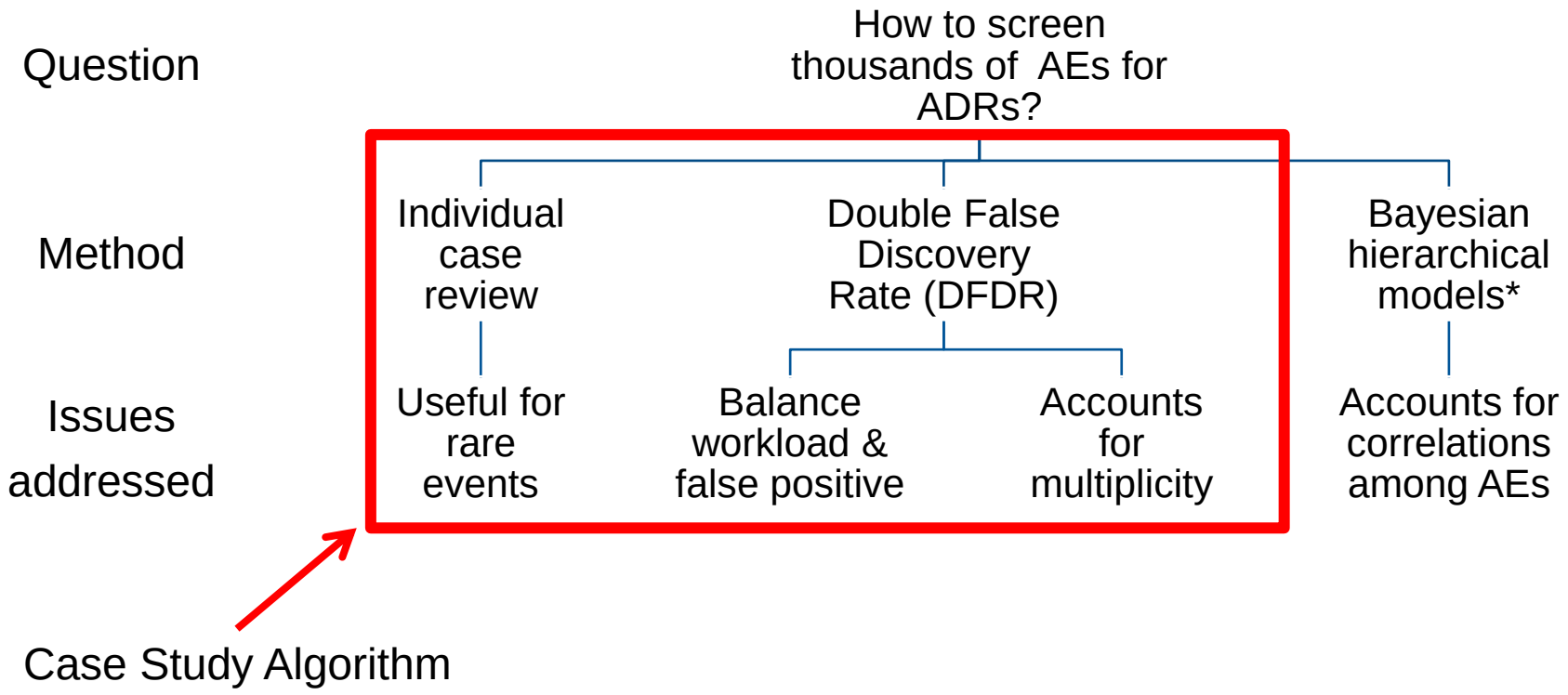
Selection of options



*Berry & Berry (2004)

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DFDR multiplicity

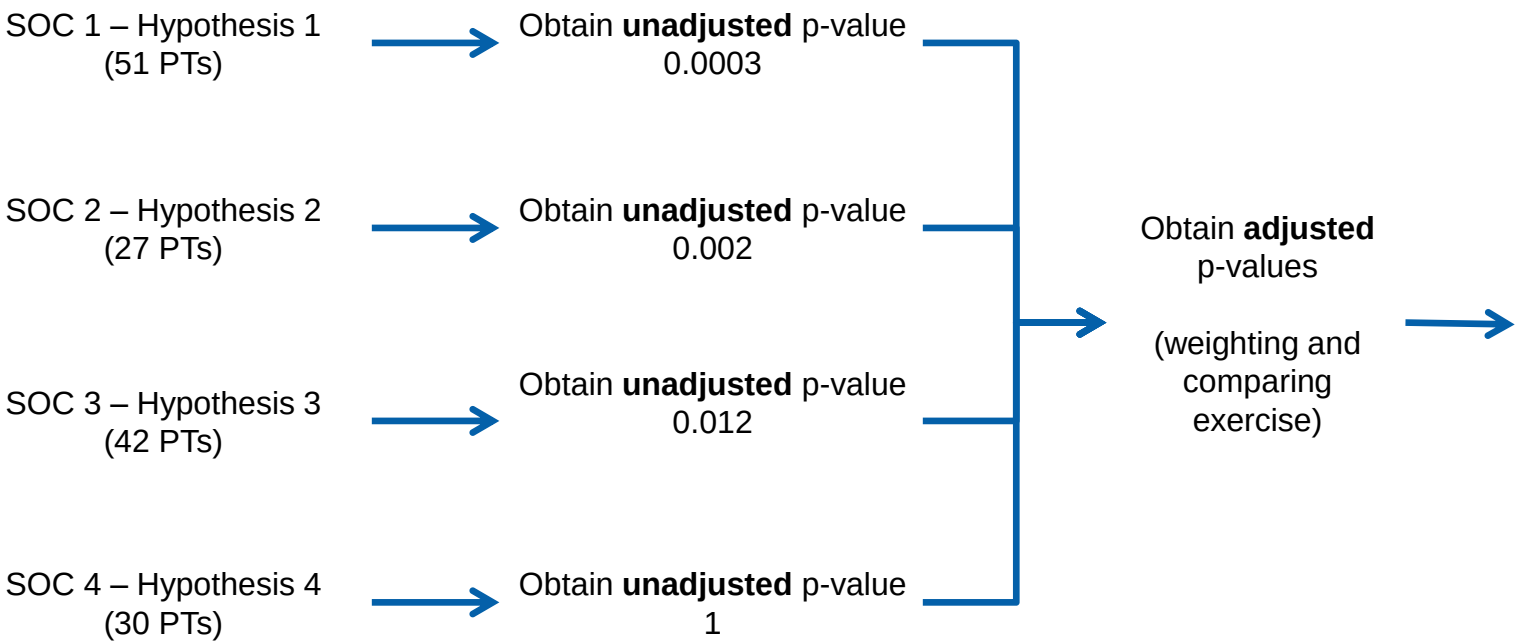
Trial Design

- Efficacy: Superiority/Equivalence/Non-inferiority of Investigational compound vs control
- May have 'a priori' safety concerns (RMP/CDS)

During ADR screening phase

- Large number of AEs → Multiplicity issue (PROTECT Symposium, 2015)
- Potential ADRs not identified at design stage, i.e. same database to generate and confirm multiple safety concerns
- Need to balance increased false positives (e.g. no adjustment i.e. p-value ≤ 0.05) and false negatives (e.g. overly stringent adjustment i.e. Bonferroni)
- Mehrotra and Adewale (2012) proposed the DFDR, which is a two-step process with two adjustments for multiplicity

DFDR: first adjustment (SOC)



Adjusted p-values
SOC 1 = 0.000075
SOC 2 = 0.001
SOC 3 = 0.009
SOC 4 = 1

SOC 1, SOC 2, SOC 3
→ 2nd adjustment

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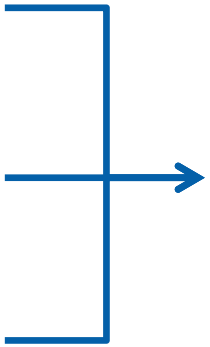
DFDR: second adjustment (PT)

Create new family of hypotheses n=120 hypotheses

51 PTs (SOC 1)

27 PTs (SOC 2)

42 PTs (SOC 3)



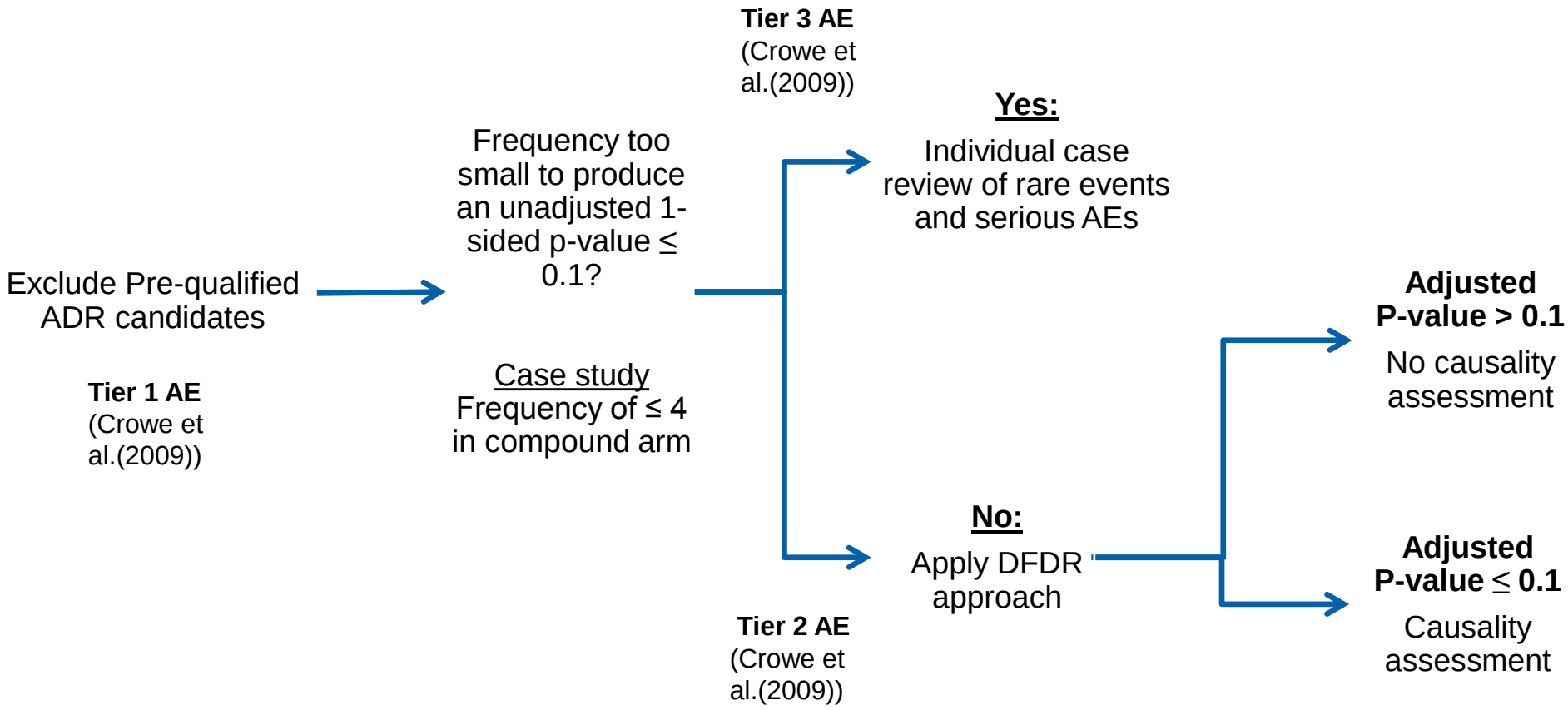
Obtain **unadjusted** p-value for each of the 120 hypotheses

Obtain **adjusted** p-values

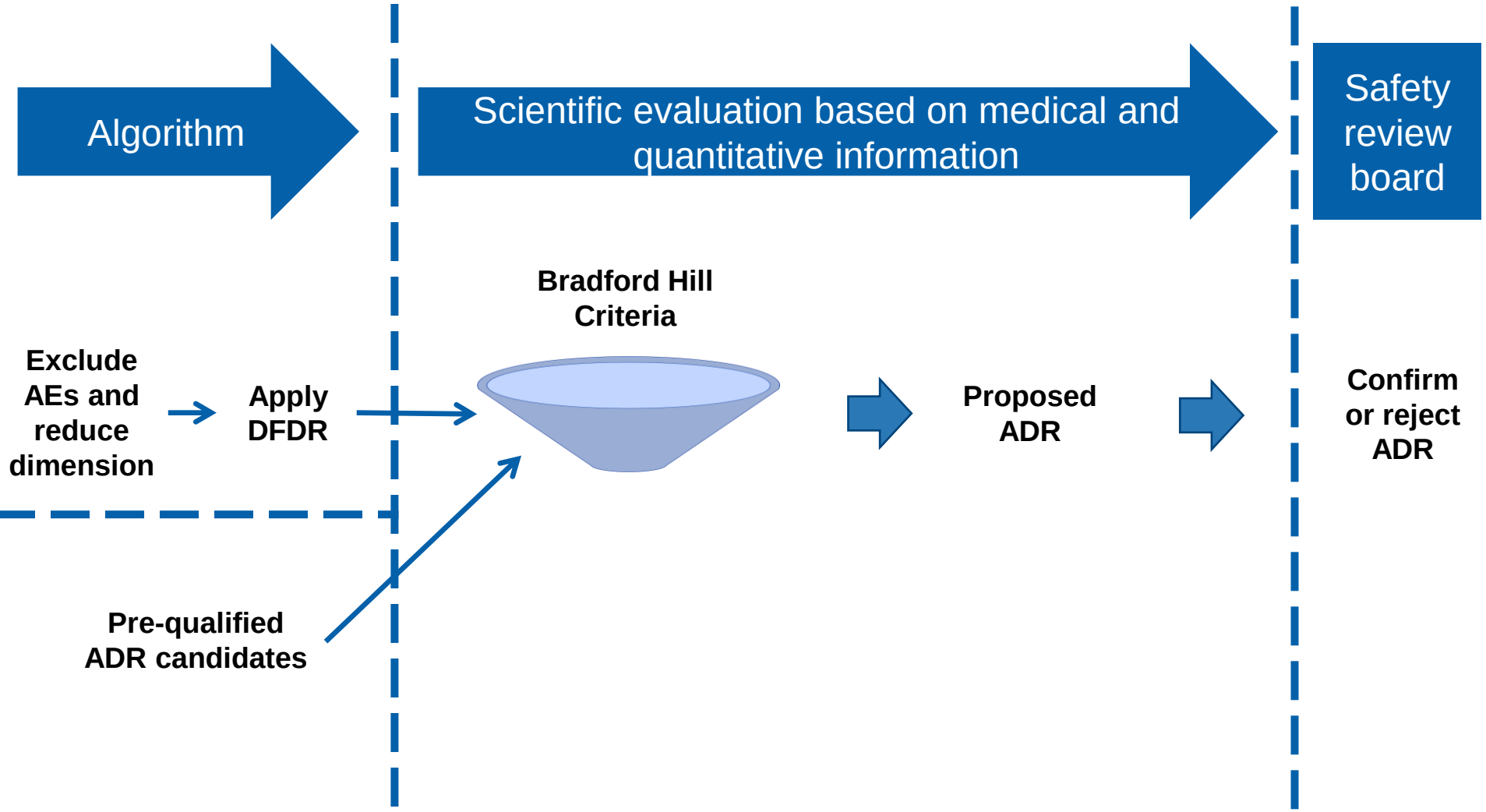
(weighting and comparing exercise)

Flag PTs → scientific evaluation alpha=0.1

Case Study ADR screening strategy (Algorithm)



Summary of ADR process



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Key message

- DFDR is an elegant method to screen thousands of AEs to flag likely ADR candidates.

- DFDR balances workload and false positive signals, accounts for multiplicity, and needs to be combined with a method to evaluate rare events.

- The flagged potential ADR candidates proceed to scientific evaluation based on medical and quantitative information to assess causality.

Questions …

Thank you

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References

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