Beyond Randomization: Statistical Innovation for Rare Disease Trials

Global biopharma company with presence in around 30 countries delivering medications to patients in many more

Unlocking the potential of breakthrough innovations, transforming the everyday life for people living with rare diseases

Focus on rare diseases within hematology, immunology and specialty care

Head office in Stockholm, Sweden with hubs in Switzerland and US. Approximately 1,900 employees across the world

Disclaimer:
Views expressed in this presentation are the author's personal views and not necessarily the views of Sobi

The rare disease landscape

3rd most populous country

+10,000 identified rare diseases

80% genetic origin

400 million

4-8 yrs to diagnosis

5% with approved treatment

50% children

[The landscape for rare diseases in 2024]
[Rare Disease Facts and Statistics | NORD]

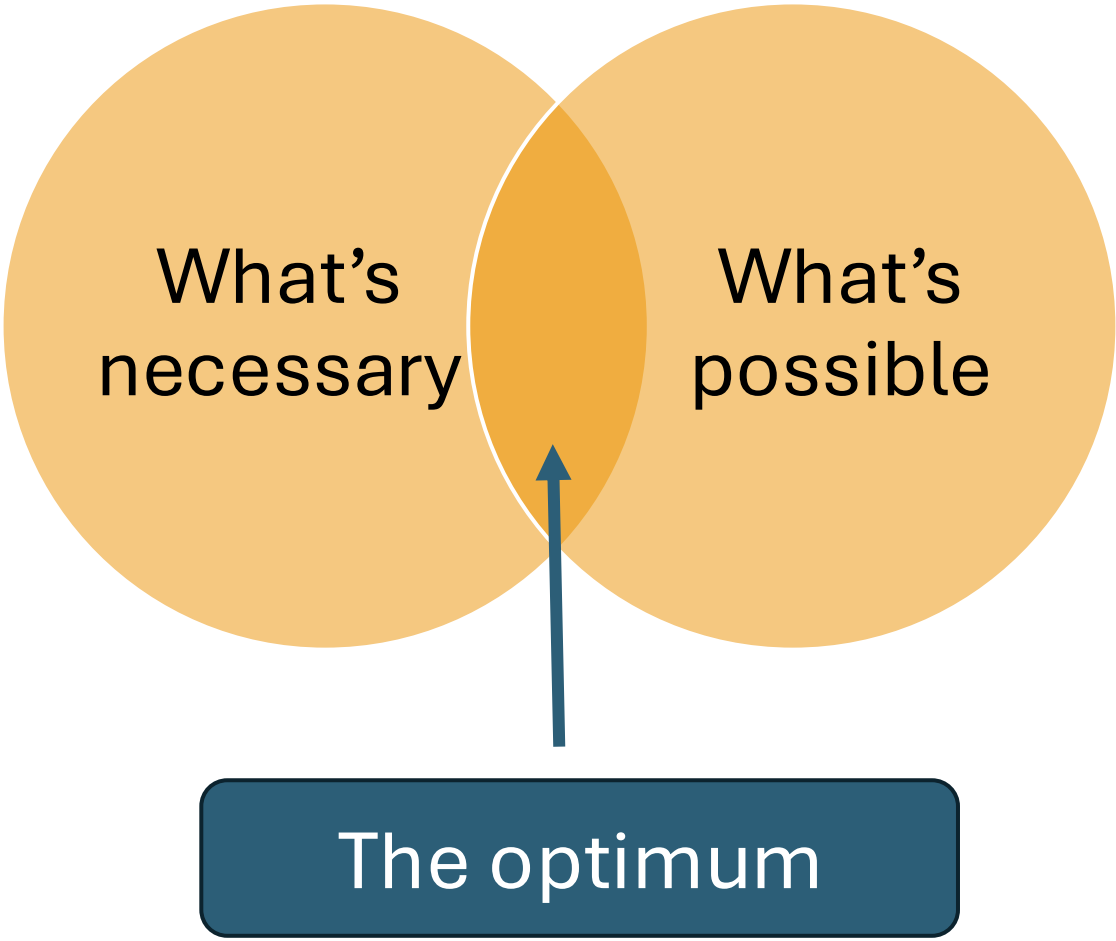
The rare disease landscape presents challenges

Ethical limits	Placebo not always ethical or feasible
Small populations	Enough patients to run a trial? Control group?
Endpoints	No established endpoints, only biomarkers
Sample Size	Low statistical power
Inference gap	How to assess results without randomization?
Safety	How to evaluate safety with a small sample size?
Design challenge	Need alternative statistical framework
Authorities	FDA, EMA and other authorities not always aligned

WHAT TO DO?

Potential clinical trial designs to overcome the problem

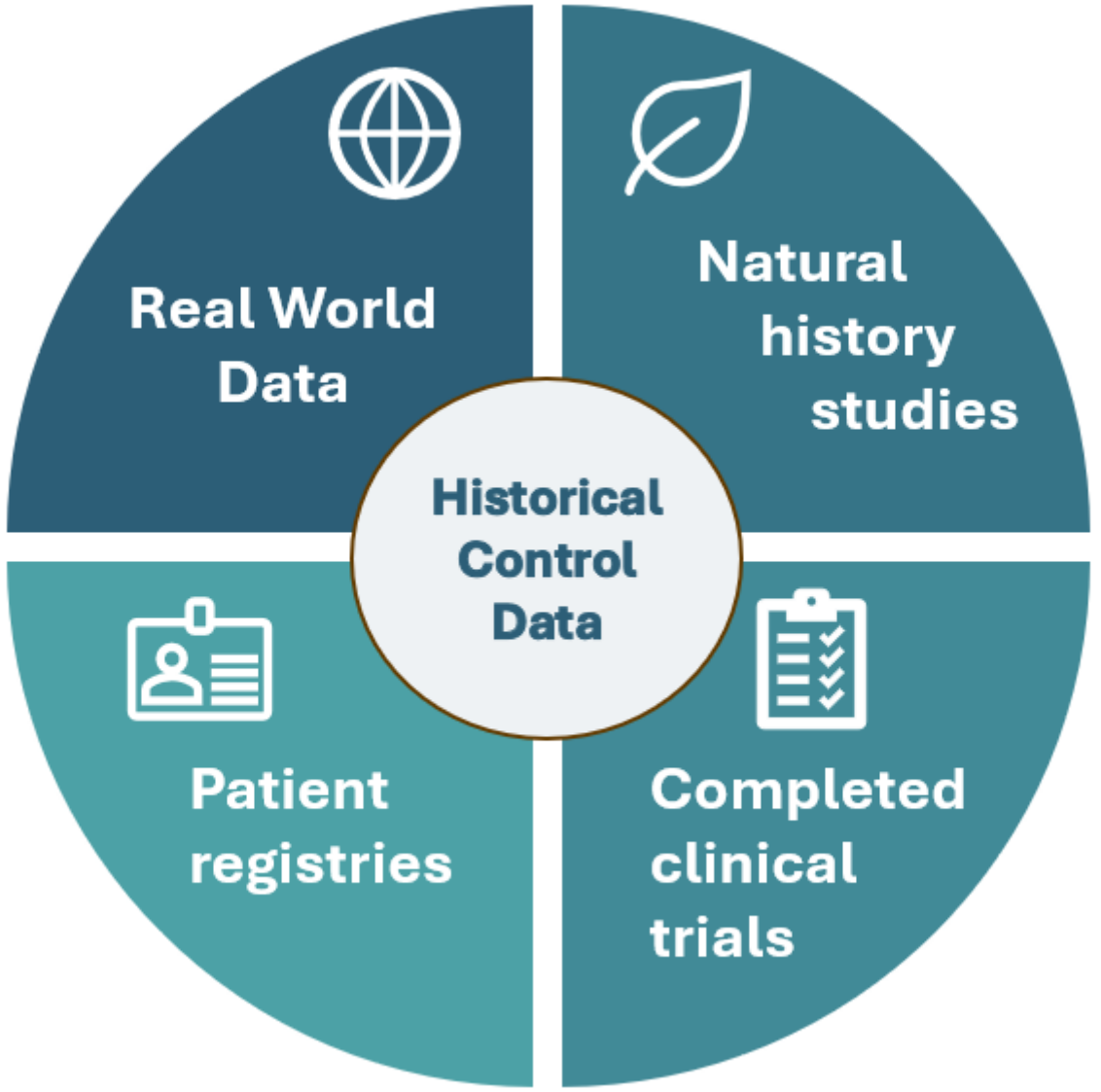
- Single arm trials
- Adaptive designs
- Cross-over trials
- N-of-1 trials
- Basket trials
- Bayesian designs
- External control arms



Historical Controls to maintain scientific validity

Key Principles for selection:

- Comparable populations
- Reliable data source
- Be aware of, and adjust for bias
- Regulatory alignment



Can we trust the data?

From Historical Controls to Borrowing Information: Statistical Integration Frameworks

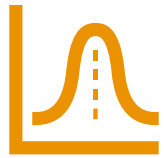
Frequentist

Historical Data

Propensity score matching
Meta-analysis
Threshold crossing
Test-then-pool

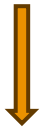
Statistical inference

Bayesian



Historical Data

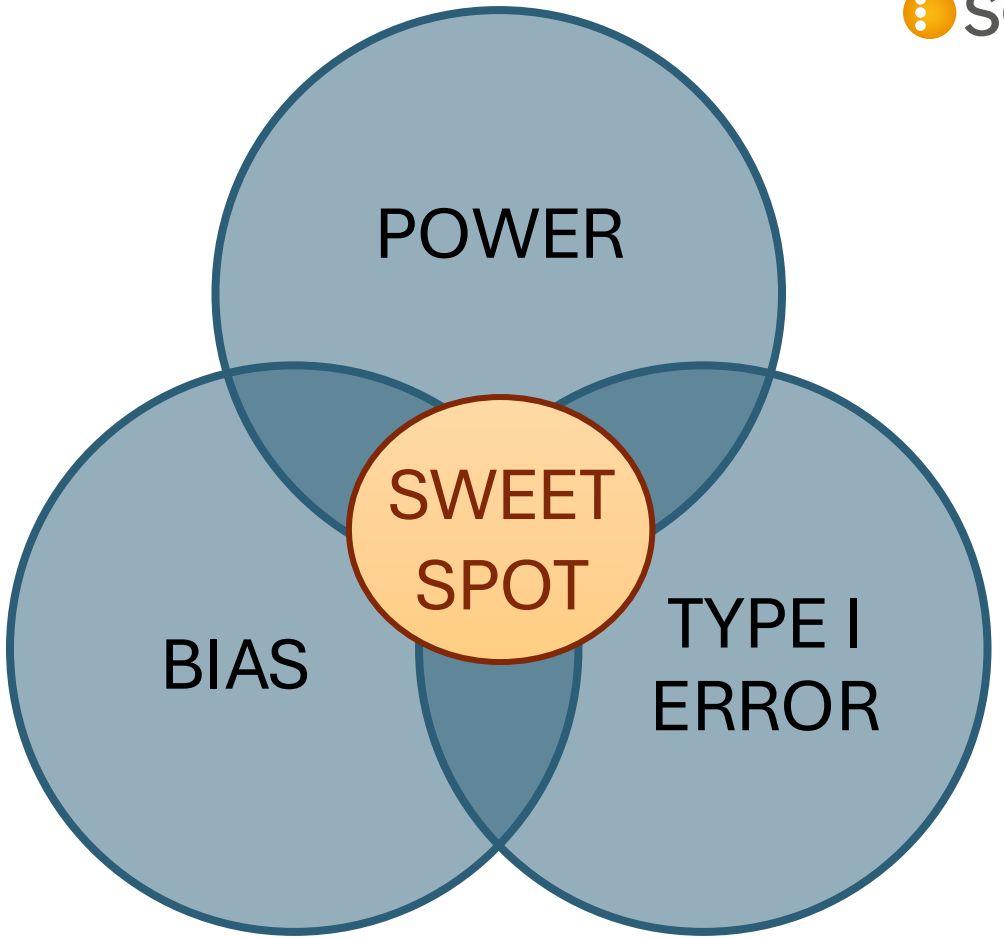
Power prior
Meta-analytic predictive (MAP)
Dynamic Borrowing



Statistical inference

The Sweet Spot

- Simulation
  - Quantifies operating characteristics curve (power, type 1 error, bias, MSE)
  - Identifies the sweet spot – improved precision without inflated error
  - Compare static vs dynamic borrowing methods
  - Document code and reproducibility for regulatory review
- Sensitivity analysis
  - Vary priors, exclude HCs, test missing data assumptions
  - Demonstrate robustness across plausible bias structures



Simulation to Calibrate Borrowing and Control Bias

- Simulation quantifies trade-offs between power and Type I error
- Hierarchical model: stable borrowing, best bias control
- Pooling: aggressive borrowing, higher power but more risk
- Test-then-pool: adaptive, sharp transition near sweet spot
- Sweet spot (0.62–0.70): optimal balance of precision and validity

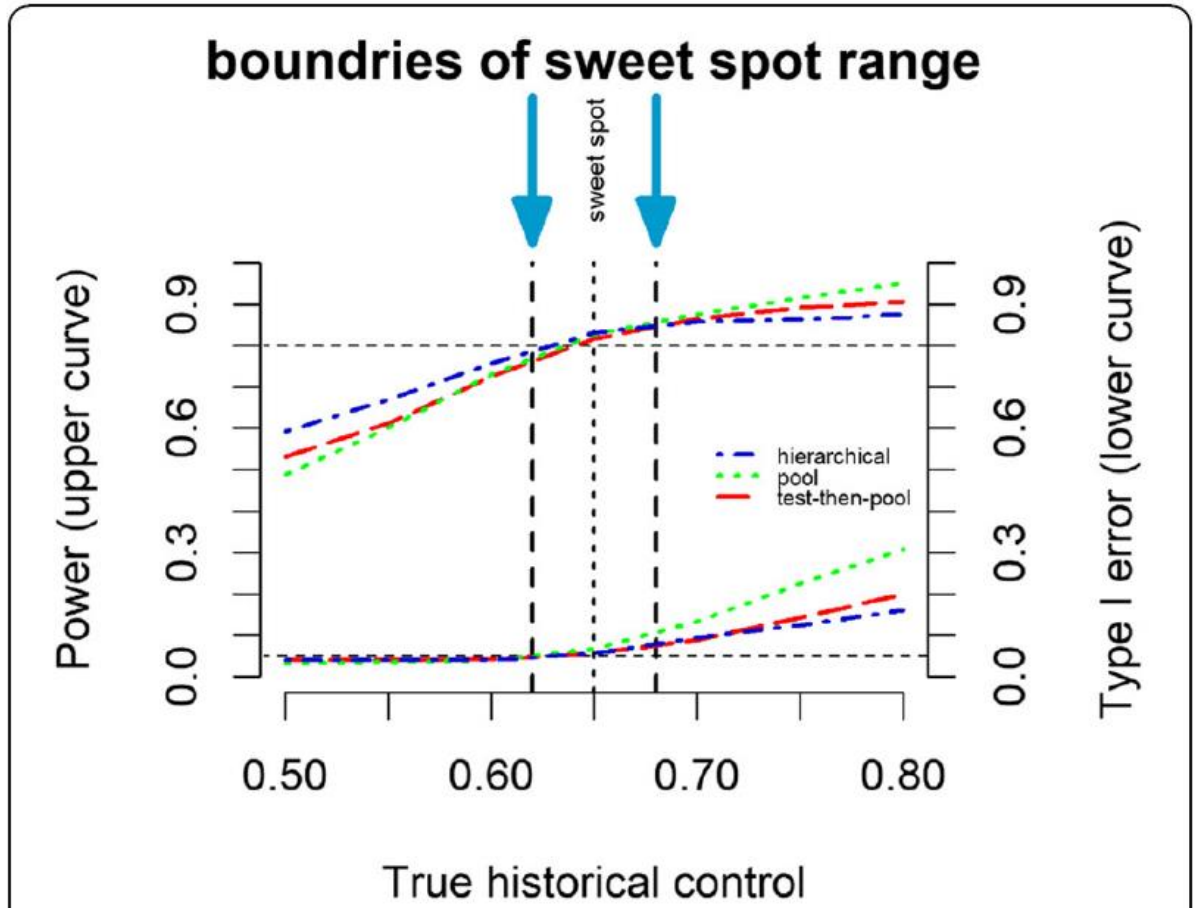


Fig. 3 Visualization of Comparison of the "Sweet Spots" of Methods via Simulation

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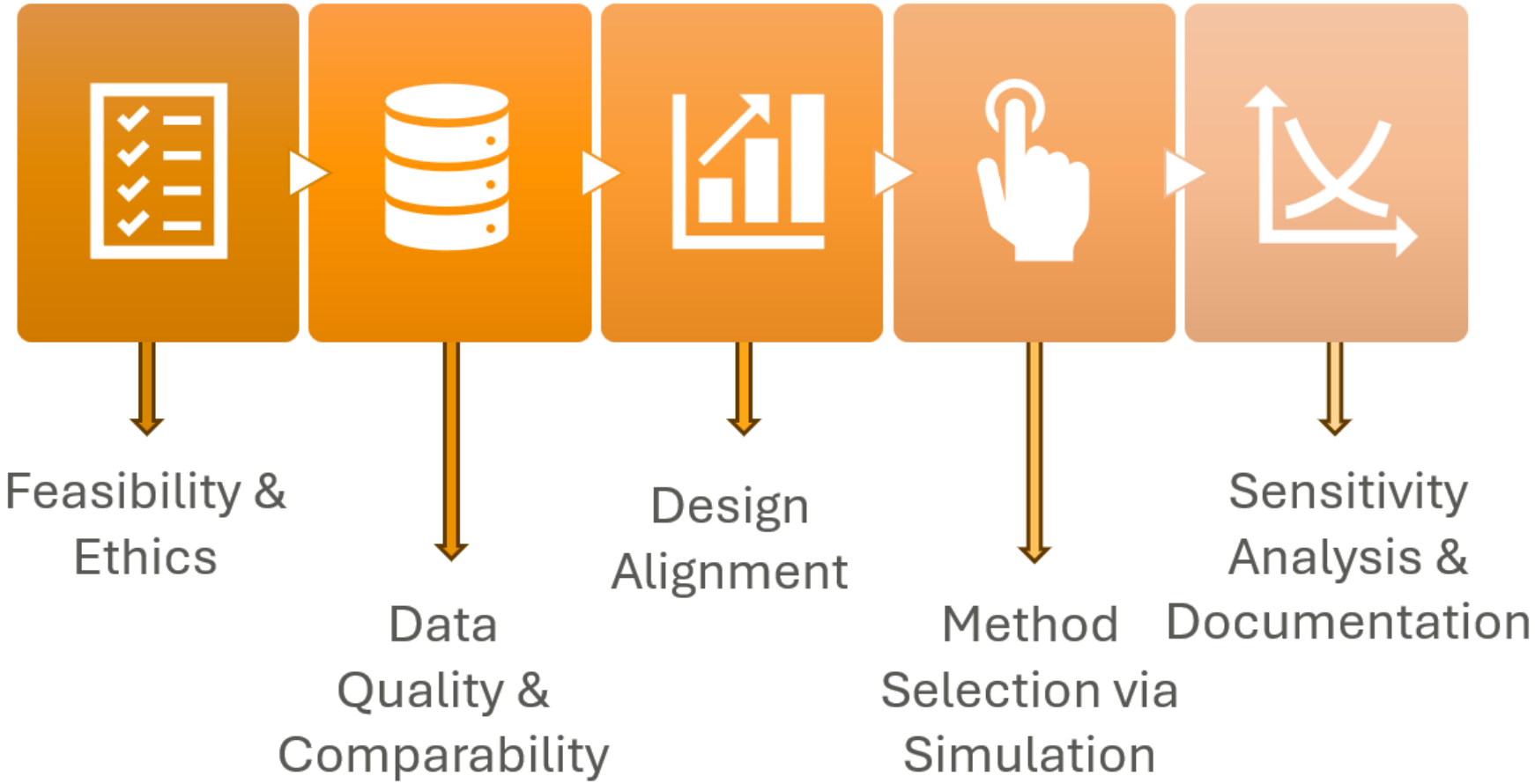
Ghadessi M et al. Orphanet J Rare Dis. 2020; 15:69, https://doi.org/10.1186/s13023-020-1332-x, © The Authors 2020 (CC BY 4.0).

Decision framework for using historical controls



Key Takeaways

Historical controls strengthen evidence when randomization isn’t feasible.

Dynamic Bayesian borrowing offers flexibility and effective bias control.

Simulation is the cornerstone for design validation and regulatory defensibility.

Sensitivity analysis ensures robustness and credibility of results.

Collaboration and standardization drive acceptance and long-term impact.

References

- **Key Scientific Reference**
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Thank you

Together, we advance rare disease innovation

Questions or reflections?