Bayesian methods without borrowing in ultrarare diseases

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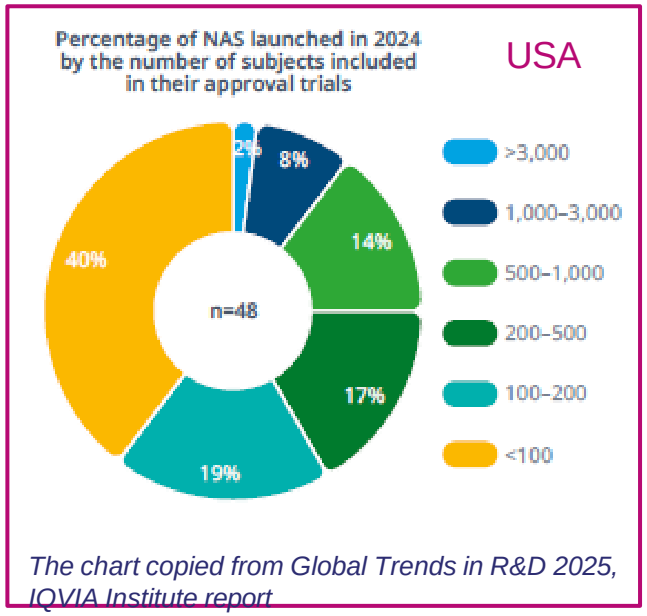
EUROPEAN FEDERATION OF STATISTICIANS IN THE PHARMACEUTICAL INDUSTRY
Representing Statistical Associations in Europe

Rare disease research: EU priority for the last two decades

European Commission: Strengthened European action on rare diseases

- 27 - 36 million people in Europe live with a rare disease
  - 6 000 - 8 000 distinct rare diseases
  - 70% of rare diseases start in childhood

- Important progress but remain a high unmet need
  - More than €3.2 billion invested in collaborative projects (2007 - 2020)
  - 260 orphan medicines authorised by the end of 2024
  - 17 orphan medicines authorized, and 140 products received an orphan designation in 2024
  - Fewer than 5% of rare diseases have at least one approved therapy



The chart copied from Global Trends in R&D 2025, IQVIA Institute report

https://health.ec.europa.eu/rare-diseases-and-european-reference-networks/rare-diseases_en
https://projects.research-and-innovation.ec.europa.eu/en/horizon-magazine/building-blocks-make-rare-disease-treatments-more-common

Challenges of registrational studies in ultrarare diseases

- Small population studies due to limited eligible patient population
- Limited data availability to inform hypothesis
- Conventional powering is not feasible due to limited sample size

63 orphan drug approvals in the EU 2000 – 2010:

22 of 38 randomised controlled trials with sample size <50

- Risk of underpowered study for the primary endpoint and therefore the study may not be funded
  - Emerging biopharmaceutical companies account for over 70% of the research pipeline

Staying ahead: the case for a European Action Plan for Rare Diseases https://www.global-counsel.com/insights/report/staying-ahead-case-european-action-plan-rare-diseases#heading-6
Hilgers RD, König F, Molenberghs G, Senn S. Design and analysis of clinical trials for small rare disease populations J Rare Dis Res Treat. (2016) 1(3): 53-60

IDeAl and IRDiRC: Lessons and recommendations

EU-funded IDeAl (Integrated designs and analysis of small population clinical trials):

- If pharmaceutical companies experience non-transparency in decision rules, the industry will not be able to design the best possible trial programs
- Formulate decision rules in a formal Bayesian decision-theoretic framework
- Adaptive designs have been proposed as a means of gaining efficiency in studying rare diseases

IRDiRC (The International Rare Diseases Research Consortium):

- Do not dichotomise continuous endpoints in the primary analysis
  - Except sensitivity analyses & assessment of clinical relevance
- Use analysis of covariance instead of simple “change from baseline” analyses for reduction of bias and gains in efficiency

Hilgers, RD., Bogdan, M., Burman, CF. et al. Lessons learned from IDeAl -33 recommendations from the IDeAl-net about design and analysis of small population clinical trials. Orphanet J Rare Dis 13, 77 (2018). Day, S., Jonker, A.H., Lau, L.P.L. et al. Recommendations for the design of small population clinical trials. Orphanet J Rare Dis 13, 195 (2018).

Case study: ultrarare disease with event count as outcome

- Ultrarare disease with limited patients' pool with feasible enrolment of about 50 patients
- Strong efficacy signal but uncertainly on placebo due to limited data on SOC
- Clinically relevant measure represented by events (count data)
  - The negative binomial model is a model of choice especially when event counts are overdispersed and observation periods vary across participants
  - Responder analysis based on simple change in events frequency to assess clinical relevance
- Group Sequential Design with possibility to declare early efficacy at IA in case of overwhelming efficacy for the primary endpoint confirmed by responder analysis

Negative binomial regressions has been used in many indications:

- non-malignant hematology
- neurology, e.g. multiple sclerosis, epilepsy, migraine
- urology and women health
- pulmonology eg asthma, COPD

Motivation to use Bayesian methods

- Facilitate interpretation for decision-making, including study success criteria and interim futility and efficacy
  - Directly estimate probability of the treatment effect based on observed data and prior
- Group sequential design helps gain efficiency and mitigate for uncertainties of assumptions. Model-based inference increases power while adjusting for baseline imbalances and provides interpretable treatment effect estimates
  - Commonly used frequentists group sequential methods and models rely on asymptotic assumptions which are violated in small population trials and therefore can lead to inaccurate inference and type I error inflation
- Bayesian methods offer an interpretable approach to small population statistical modelling challenges such as non-convergence, model instability, sparse data bias, complete separation etc.
  - Use of weakly informative priors constructed based on clinically plausible values

Bayesian analyses are intuitive and easy to interpret

Primary endpoint analysis

- Negative binomial model output offers an intuitive and clinically meaningful interpretation of treatment effect:
  - Adjusted Risk Ratio (RR), the ratio of event rates between treatment arms adjusted for baseline covariates

Frequentist

- ✓ Point estimate of Risk Ratio
- ✓ 95% Confidence Intervals
- ✓ p value

  If not significant, can not reject the null

  but does not inform the probability of efficacy

Bayesian

- ✓ Whole Posterior Distribution of Risk Ratio
  - ✓ Mean/Median/Mode
  - ✓ 95% Credible Intervals
- ✓ The posterior probability of RR <1, <0.9, <0.8, <0.7, <0.6

Bayesian Design - Operating Characteristic

Scenario		Power	
Treatment Effect Risk Ratio	Difference in % Change	Power Bayesian	Power Frequentist
0.67	-29	74.4	79.3
0.6	-35	90.6	93.4
0.55	-40	97.8	98.6
0.5	-45	99.6	99.8

- Type 1 error evaluated by simulating ~ 250 scenarios under no effect
  - Bayesian design provided similar power while controlled the type I error at one-sided 2.5% by utilizing weakly informative neutral priors
  - Frequentist design inflated type I error up to a one-sided 4.3%

Operating characteristics assessed by simulations (10,000 for each scenario)

Prior helps addressing statistical challenges by regularizing the model

Negative Binomial Regression Model with Weakly Informative Priors

- Neutral prior on treatment effect: centred around no treatment effect
  - Still a wide prior distribution that captures clinically plausible values but not inappropriately diffuse
  - Has negligible influence on posterior which will be dominated by study data
- Plausible prior on shape (variability of counts):
  - Still a wide prior distribution that captures clinically plausible values but not inappropriately diffuse
  - Plausible prior on magnitude of overdispersion

Log (RR) ~ N(0, 2.5)
φ~ Inv_gamma (0.4, 0.3)

- Weakly informative priors regularize the model if extreme values are observed with the small sample sizes
  - Type 1 error control with similar power was confirmed by simulations
  - Supports model convergence and stability was confirmed by simulations
  - Unbiased treatment effect estimates was confirmed by simulations

A non-informative prior was used for response rate in each arm

Conclusions

- Powering of ultrarare disease trials is challenging due to limited sample size
- Bayesian methods directly estimates probability of the treatment effect
- Bayesian methods offer an interpretable approach to small population statistical modelling challenges
- Bayesian methods can be more efficient in small population trials
- In this case study of a small population trial with event count outcome, extensive simulations showed that Bayesian design had adequate power in scenarios of interest while controlling type-1-error across various assumptions