# Designing Master Protocol Trials for Single-Arm Studies

---

Peter Jacko

Joint work with Günter Heimann (Novartis) and Tom Parke (Berry Consultants)

Lancaster University, UK

# The Strategic Context

# The Pipeline Bottleneck in Rare Diseases

The Bottleneck:

- In rare diseases and pediatric oncology it is often infeasible to run large RCTs due to population constraints

Current Paradigm:

- Heavy reliance on single-arm studies comparing each intervention to historical controls or "expert opinion"

The Efficiency Gap:

- Traditional frequentist methods lack the "real-time" predictive ability needed to optimize patient allocation across a portfolio of available interventions

# The Methodology Project

Beyond the Trial:

- We are not just designing a study; we are designing a decision engine

Methodological Choice:

- Selecting tools that balance regulatory conservatism (frequentist rigor) with operational speed (Bayesian-like intuition)

Project Objective:

- Develop a unified framework for interim monitoring and dynamic allocation in master protocols for intervention portfolios

# Single-Arm Studies

# Single-Arm Studies

Consider a Simple, General Design:

- Any endpoint, although in this talk we illustrate binary endpoint
- Will collect responses from $N$ participants on the same intervention
- Any method for the final analysis and decision rule for declaring study success

Remarks:

- This allows to compute the Type I and Type II errors
- Adaptive (e.g. two-stage) designs can be considered but left out of this talk

# A Case Study

Neurofibromatosis (NF):

- A benign nerve tumour affecting children (rare & pediatric)
- Depending on its location, it can affect child's growth or functions

Imagine Your Child is Diagnosed with NF:

- The clinician says that there is no approved intervention, as all previous confirmatory trials were unsuccessful
- Your child is given supportive care (pain management) and watchful waiting (MRI scans): the rate of the tumour shrinking is $0\% - 5\%$

# A Case Study (Cont.)

Imagine:

- There is a confirmatory single-arm study enrolling (Phase I data showed early signs of actually shrinking these tumours)
- Would you join the trial?

# A Case Study (Cont.)

Imagine #2:

- There are several confirmatory single-arm studies are enrolling
- Which trial would you join, if any?

# Allocation in Master Protocols and Portfolios

# Rare Disease Motivation

Neurofibromatosis (NF):

- The EU-PEARL master protocols defined sample size $N = 40$ for every subtrial (single-arm study), and using equal randomization between all open (eligible) subtrials
- Slow enrolment due to limited population: 1 patient per month
- Evaluation of 4 interventions in parallel would bring their declarations in around 11-14 years

# The Limitation of Fixed Randomization

Equal Fixed Randomization (EFR):

- Used due to simplicity and tradition

The Inefficiency:

- If Intervention A is clearly working and Intervention B is stalling, EFR delays the "Success Declaration" for Intervention A

The Costs:

- Not being adaptive means that a working intervention reaches the next phase or out-of-trial patients later than it could
- Treating interventions in the platform equally means that the "Next Intervention" in the pipeline starts its study later than it could

# Our Engine: Predictive Probability (PrP) of Study Success

Interim Monitoring:

- For any single-arm study with decision rule for declaring study success if observing at least a certain number of responses, $c_N$
- We need to know the probability of crossing the threshold $c_N$ given current data at time $n$
- We define the frequentist predictive distribution for future participants $N - n$ after observing $Y$ responses from $n$ participants

$$G^{PrP}(c_N - Y - 1 | N, n, Y) := \sum_{y=0}^{n} b(y \mid n, \widehat{p}_n(Y)) \texttt{Bin}(N - n, \widehat{p}_n(y))$$

- This serves as our "value metric" for every time $n$ of the study, which can be used to define decision rules at interim analyses to stop early

# Innovation: The "Highest-PrP" Allocation Procedure

**Allocation Decision Logic**

Assign the next available participant to the subtrial with the highest current Predictive Probability of Study Success.

Strategic Intent:

- Accelerate the graduation of the most promising interventions

Dynamic Pivot:

- As soon as a study reaches its success boundary or hits its $N$, it exits and the "best" remaining intervention takes the lead

Special Situations:

- Interventions with no data get priority
- Ties are resolved using EFR

# Why "Highest-PrP" is Ethical in Rare Diseases

## Rare Diseases

- Every participant is a precious resource
- By shifting participants to the most promising study, we maximize the probability that a trial participant is contributing to an intervention that will actually reach the population
- This benefits the out-of-trial population by shortening the total development timeline

## Randomization Not Strictly Required

- Since all the studies are single-arm, the randomization required in RCTs for statistical validity is not necessary
- Although the procedure can be forced to be randomized if needed

# Results: Speed, Power, and Error Control

# Design Options

## Sample Sizes:

- Exploiting the "saw-toothed" power curve, we identified peaks of smaller sample sizes 17 and 24 to compare with 40 from the protocol

**Table 1:** Unconditional probability of study success declaration for different response rates $\theta_s \in \{0.1, 0.2, 0.3, 0.4\}$ against pairs of sample sizes $N$ and cut-off values $c_N$ of a given single-arm study.

| $N$ | $c_N$ | 0.1 | 0.2 | 0.3 | 0.4 |
|---|---|---|---|---|---|
| 17 | 4 | 0.08264062 | 0.45112380 | 0.79809299 | 0.95357707 |
| 24 | 5 | 0.08507489 | 0.54012267 | 0.88892478 | 0.98655089 |
| 40 | 9 | 0.01549531 | 0.40687287 | 0.88899082 | 0.99393537 |

# Architectural Patterns in Master Protocols and Portfolios

Umbrella Pattern:

- Multiple subtrials for the same disease starting simultaneously

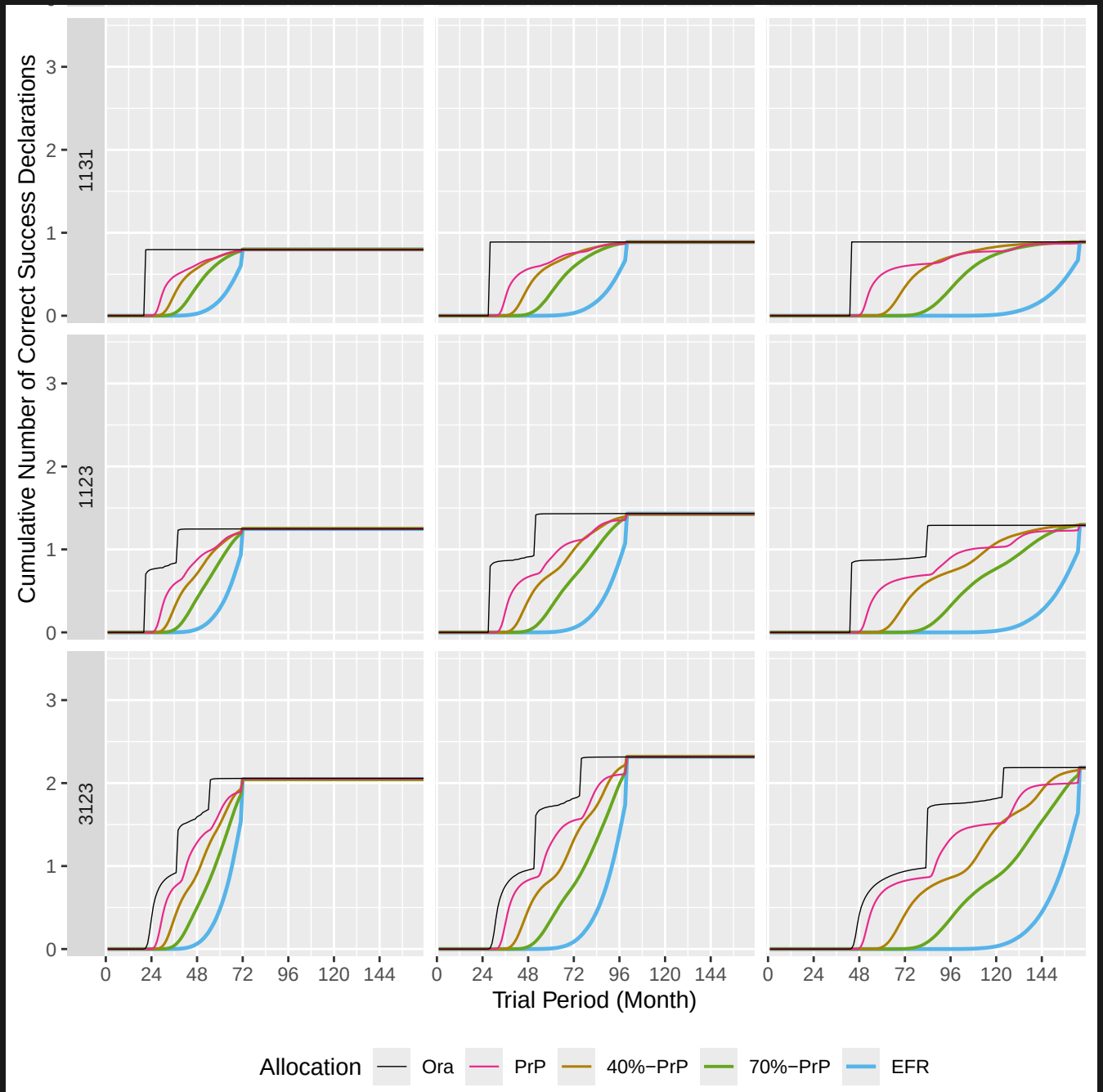
Platform Pattern:

- Subtrials enter and exit dynamically as new interventions are ready, for up to a predefined number of subtrials

Perpetual Pattern:

- A long-term framework where the trial infrastructure is permanent

# Illustration for Umbrella Pattern



# Value for Portfolio Management

# Portfolio-Level Decision Support

Value of Information:

- This framework provides a dashboard for the Portfolio Committee

Go/No-Go Clarity:

- Instead of waiting years for a trial to end, we can state: "There is an 85% probability this study will cross the success threshold within the next 10 patients"

Regulatory Ready:

- Because the foundation is frequentist, the Statistical Analysis Plan is easier to justify to the FDA/EMA than one relying on priors

# Conclusion

Implementation:

- Can be done using an automated Interactive Response Technology system (or an Integrated Data Review Committee) that can handle updates of predictive probability

Technically Robust:

- Fully frequentist approach, easy to interpret

Operationally Fast:

- Highest-PrP allocation delivers the study success vs speed efficiency of the Master Protocol ecosystem

Scientifically Unified:

- A single framework that handles everything from the first patient in a single-arm study to a perpetual platform

Thank you for your attention

Ďakujem za pozornosť

# Joining Roche Group

Early Development Biometrics | Statistical Methodology group

I am joining as a Principal Statistical Methodology Data Scientist in the UK from autumn 2026 (keeping my affiliation with Lancaster University)

2 Senior Statistical Methodology Data Scientist positions are open in Switzerland and Canada: `https://careers.roche.com/global/en/job/ROCHGLOBAL202605113105EXTERNALENGLOBAL/Senior-Statistical-Methodology-Data-Scientist`

# Links

Jacko, Heimann & Parke (2026). *Randomization and Allocation Procedures for Master Protocol Trials of Single-Arm Studies*. Statistical Methods in Medical Research (March 25, 2026 | online first). https://journals.sagepub.com/doi/10.1177/09622802261425426

R code: Designers and simulators of clinical trials based on SIMPLE https://github.com/PeterJacko/simpleR