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A Ballad of a Basket Trial: Application in Neurodegenerative Diseases

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SYNAPSE-FTLD Trial

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Targets 5 incurable neurodegenerative diseases – all associated with **challenging and inappropriate behaviour.**

bvFTD
Behavioural variant frontotemporal dementia

PSP
Progressive supranuclear palsy

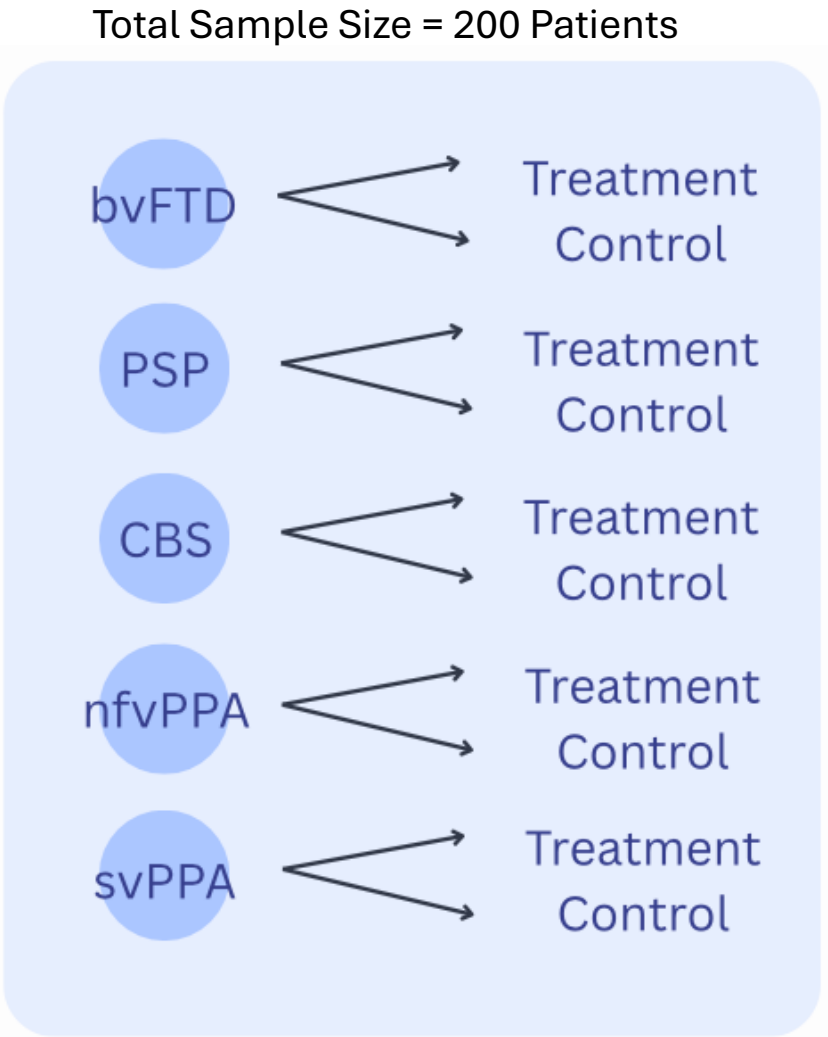
CBS
Corticobasal syndrome

svPPA
Semantic variant primary progressive aphasia

nfvPPA
Non-fluent variant primary progressive aphasia

How it Started

- Single experimental treatment
- Five parallel disease cohorts
- **Random allocation**
- This is a '**basket trial**' design.



Basket Trials

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Multiple Patient Groups

Tests a single intervention across several related diseases simultaneously

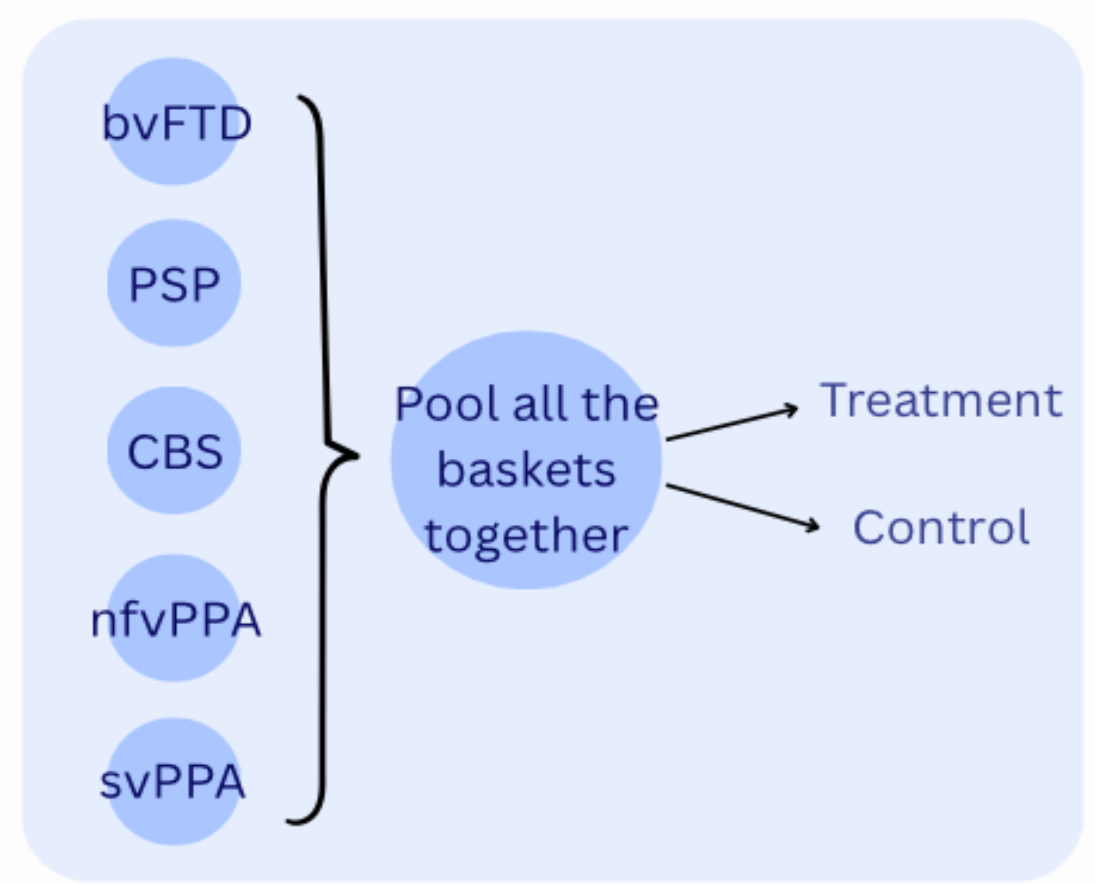
Common Feature

All patients must share a common biological or clinical trait, e.g. genetic marker, symptom

Personalised Medicine

Treatments target specific traits rather than disease types as a whole

Initial Design Idea



Advantage ☑

Larger sample size = more accurate estimations

Disadvantage ⚠

Could miss interesting results in some baskets

An Alternative: Bayesian Information Borrowing

"As all patients share a common trait, they'll respond similarly to treatment"

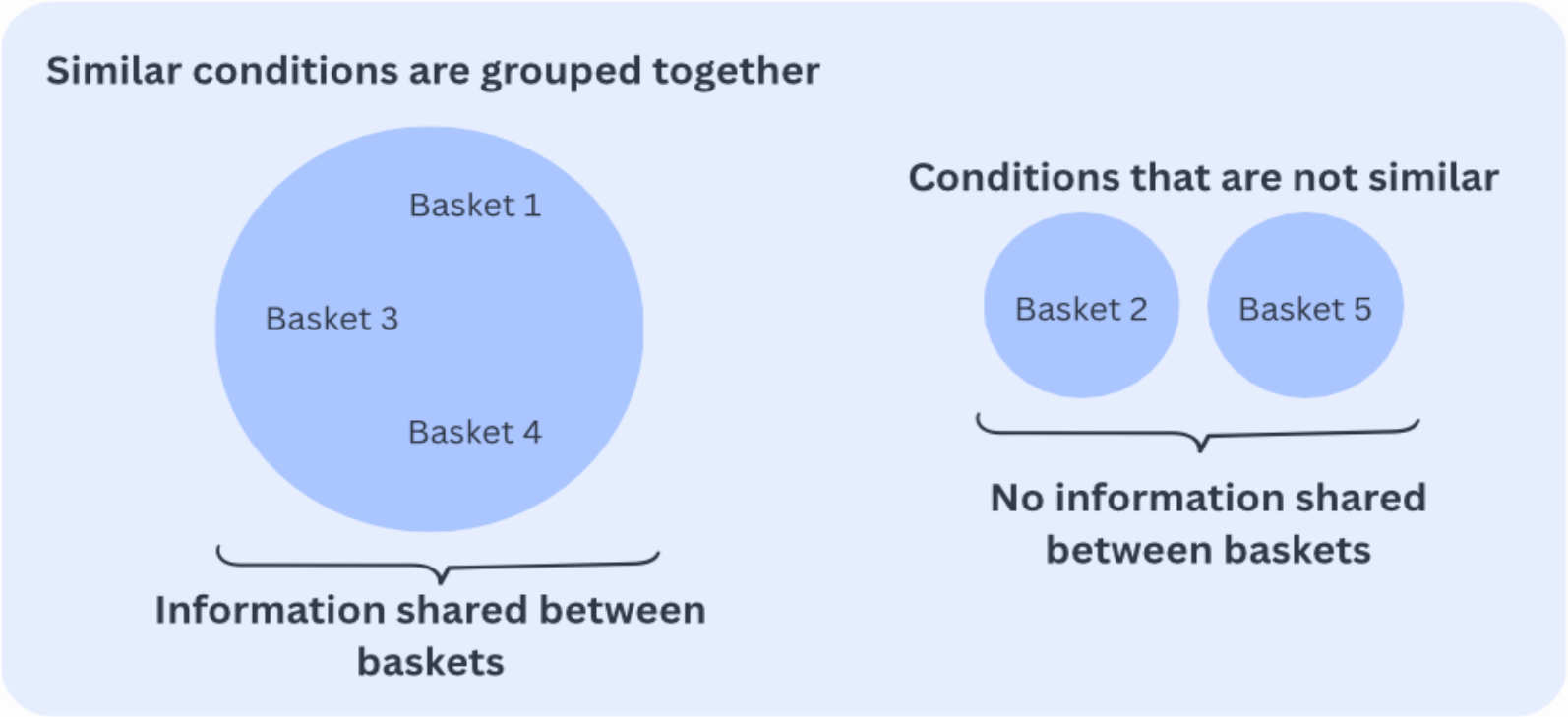
Assumes a degree of **exchangeability** in treatment response

Borrow information across baskets to improve power

Advantage ☑
Basket-specific estimates with improved power

Disadvantage ⚠
A more complex design

Information Borrowing



** Similarity is determined by the data*

How much to borrow

More Borrowing = higher power, higher accuracy, more error

When borrowing between baskets which ***have a similar response*** *to treatment*

When borrowing between baskets which ***DON'T have a similar response*** *to treatment*

We had to balance the trade-off through **simulation studies:**

Define Realistic Scenarios → Simulate Trials → Select Borrowing Strength

The Proposed Trial Design

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5 Baskets
bvFTD, PSP, CBS, svPPA

200 Patients
Equal allocation across baskets and treatment arms

3% Type I Error
Per-basket target pre-specified through simulation studies

80% Power
Per-basket power target for detecting a clinically meaningful treatment effect

Bayesian Information Borrowing Model
With calibrated borrowing strength

The First Obstacle

- **40 patients in each basket was going to be hard to achieve.**
- We had realistic recruitment rates for each basket
- Two of the baskets with the lowest recruitment were very similar:
    - **Pool these 2 baskets**, continue with a **4-basket trial.**

The Second Obstacle

- Placebo had higher cost than expected.
- **Reduce the number of patients from 200 → 90.**
- Considered several options:
  - Focus on only **2 baskets** instead of 4.
  - Increase the **treatment effect size.**

Comparing Trial Designs

*Sample size (SS) assumes 5 baskets and **90 patients'** total. SS redistributed such that the total is still 90 based on recruitment rates.*

	True Positive Conclusions, Power (SS)					
	bvFTD (22)	**PSP (36)**	**CBS (12)**	**nfvPPA (7)**	**svPPA (13)**	**Type I Error**
4 Basket Design	62%	66%	61%	62%		22%
2 Basket Design	71%	79%	NA	NA	NA	11%

- 4 basket design isn't viable – **high type I error and low power.**
- 2 basket design still has power less than 80%

Some Very Helpful Information

- **Historical information** on the control arm in each basket.
- Same study centre and **closely aligned** with our trial.
- Reduced sample size by **‘replacing’ control patients in our study.**
- Overcome expensive placebo costs.
- Adjust the design so more patients are allocated to the experimental arm (**2:1 allocation ratio**).

Comparing Trial Designs

	True Positive Conclusions, Power (SS)					
	bvFTD (22)	**PSP (36)**	**CBS (12)**	**nfvPPA (7)**	**svPPA (13)**	**Type I Error**
4 Basket Design (without historic)	62%	66%	61%	62%		22%
3 Basket Design (with historic)	93%	80%		NA	73%	14%

- Incorporating historic information can **increase the power**.
- 3 baskets preferred over 2 → include an additional disease

Comparing Trial Designs

	True Positive Conclusions, Power (SS)					
	bvFTD (22)	**PSP (36)**	**CBS (12)**	**nfvPPA (7)**	**svPPA (13)**	**Type I Error**
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- Incorporating historic information can **increase the power**.
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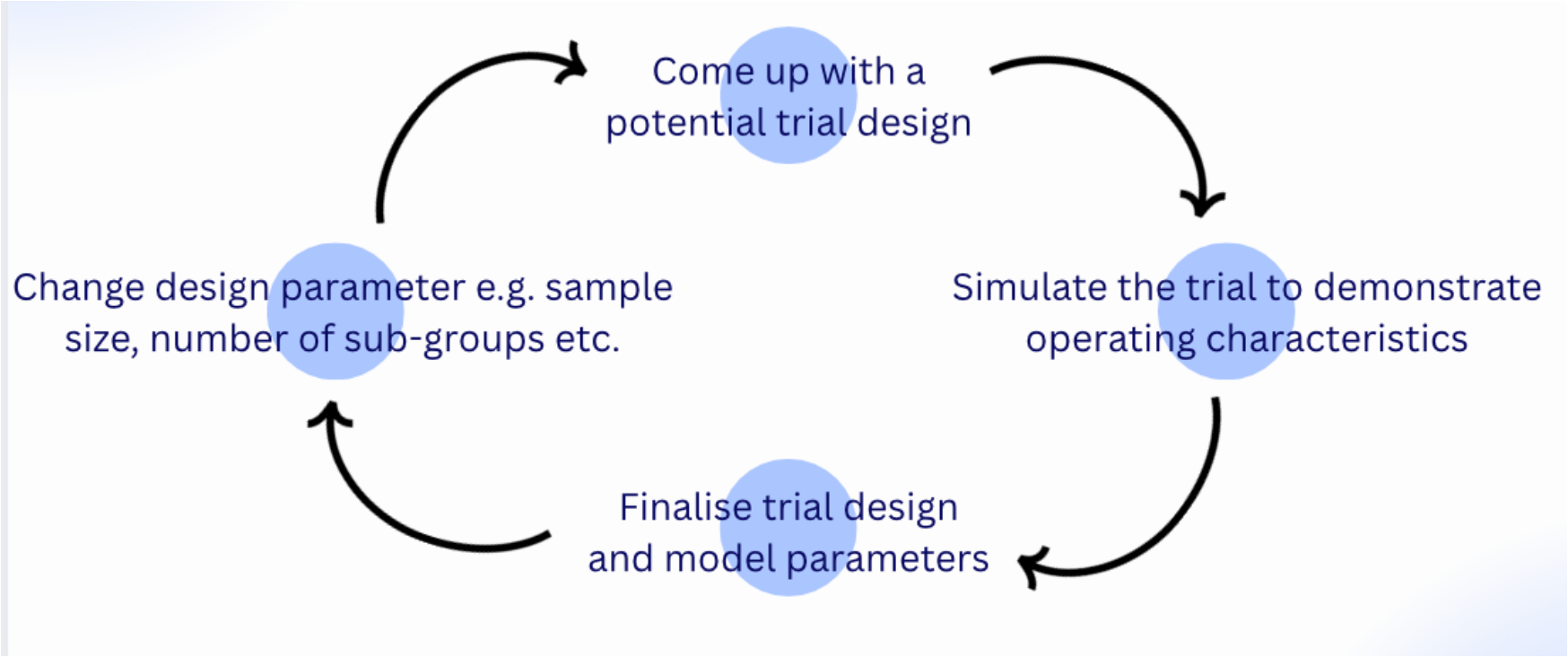
And that's where we are today



Concluding Remarks

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- My first experience working on a trial from the design stage
- **Tweaks** to the trial design are inevitable (and should be expected!)
- **Communicate basket trial designs, potential benefits & limitations**
- Need to consider misalignment between current and historical data

References

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The EXNEX Model

$$
\begin{aligned}
y_{ik} &\sim N(\mu_{T_i k}, \sigma_k^2), & \delta_k &\sim \text{Bernoulli}(\pi_k), \\
\mu_{T_i k} &= \beta_k + T_i \theta_k, & M_{1k} &\sim N(m_\theta, \eta_\theta^2), \qquad \text{(EX)} \\
\sigma_k^2 &\sim \text{Inverse-Gamma}(0.001, 0.001), & m_\theta &\sim N(0, 10^2), \\
\beta_k &\sim N(0, 100^2), & \eta_\theta &\sim \text{Half-Normal}(0, \zeta^2), \\
\theta_k &= \delta_k M_{1k} + (1 - \delta_k) M_{2k}, & M_{2k} &\sim N(0, 10^2). \qquad \text{(NEX)}
\end{aligned}
$$

- π_k (prior mixture weight) set to 0.5.
- ζ controls the amount of information borrowed in the EX component.

The EXppNEX Model

- Robust power prior on the control arm term β_{k}.

$$\beta_k = \gamma_k B_{1k} + (1-\gamma_k) B_{2k},$$
$$\gamma_k \sim \text{Bernoulli}(\pi_{\gamma k}),$$
$$B_{1k} \sim N(\bar{y}_{kh}, \bar{\sigma}^2_{kh}/(\alpha_0 * n_{kh}))$$
$$B_{2k} \sim N(m_\beta, \sigma^2_\beta),$$

Historic data

Basket	n_{kh}	y_{kh}	$\bar{\sigma}_{kh}$
bvFTD	68	3.04	11.57
PSP	173	1.75	8.15
CBS	53	1.87	10.50