Considerations for clinical trial design in PML

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Specific Challenges for clinical trial design in PML

Rare disease

- Lack of reliable natural history data
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Heterogeneous population

- Eligibility criteria
- Endpoint selection
- Selection of interventional approach
- Accounting for complex clinical outcomes

Patient heterogeneity

Inclusion criteria

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- **anti-viral drug**: might be offered to all PML, from first diagnosis
- **immune rescue therapies**: might be reserved for PML refractory to conventional immune-reconstitution approaches

Stratification factor considerations

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Underlying disease

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- MRI measures

Selection of clinically relevant endpoint

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- Ranked outcome (survival + disability)
- Surrogate outcome

Complex clinical course

Adjudicating complex outcomes

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- Adverse drug reaction

Lack of natural history data, lack of established clinically meaningful biomarkers

Consensus on core set of key secondary outcomes

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JCV PCR assay and threshold standards

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- JCV PCR assay and threshold standards
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- Key immunological measures

Patient acceptability

Integrating the patient voice

Limiting travel, decentralized outcomes

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- More trials!

Sample size (statistical efficiency)

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- PML-specific survival is clinically relevant. Is it feasible?
- Composite disability score including death (e.g. mRS) could be driven by death
- How about virological endpoint?
- How might inclusion criteria affect sample size requirements?

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- **Virological response**. E.g., A responder is defined as a CSF JCV DNA ≥0.25 log10 decline over 60 days from baseline
- **Ordinal scale.** E.g., Improvement (≥0.25 log10 *decline* over 60d), stable, and worsening (>log10 *increase* over 60d)

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- **Ordinal scale.** E.g., Improvement (≥0.25 log10 *decline* over 60d), stable, and worsening (>log10 *increase* over 60d)
- **Fold-change over 60 days as a continuous endpoint,** i.e., $\frac{JCV\ on\ day\ 60}{JCV\ at\ baseline}$

Sample size and endpoint

Endpoint	*Survival (at 1y)*		JCV copy number		
			Responder: Improvement vs no improvement	*Ordinal: Worsening vs Stable vs Improvement*	*Continuous decline:*
Effect size*	RR = 0.6		OR = 2.5	OR = 2.5	Fold change ratio = 4
SOC	47%	20%	32% improvement	32% Improvement 19% worsening	2-fold increase from baseline
Intervention	65%	38%	54% improvement	54% improvement 8% worsening	50% of baseline
n per arm**	137	86	86 per arm	80 per arm	32 per arm

Clinical relevance

Feasibility

*Effect size are based on what generally considered moderate-to-large
**1:1 RCT for 80% power and 5% significance.

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- Using JCV copy number reduces n to varying extent, depending on *how* the endpoint is defined (e.g. binary, ordinal, continuous).
  - Large effect size (OR=2.5) is possible if the intervention directly reduces viral load
  - JCV change is a faster endpoint to observe than survival
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- Use of composite disability score with death (e.g., modified RS) may be primarily driven by death, depending on the patient population.

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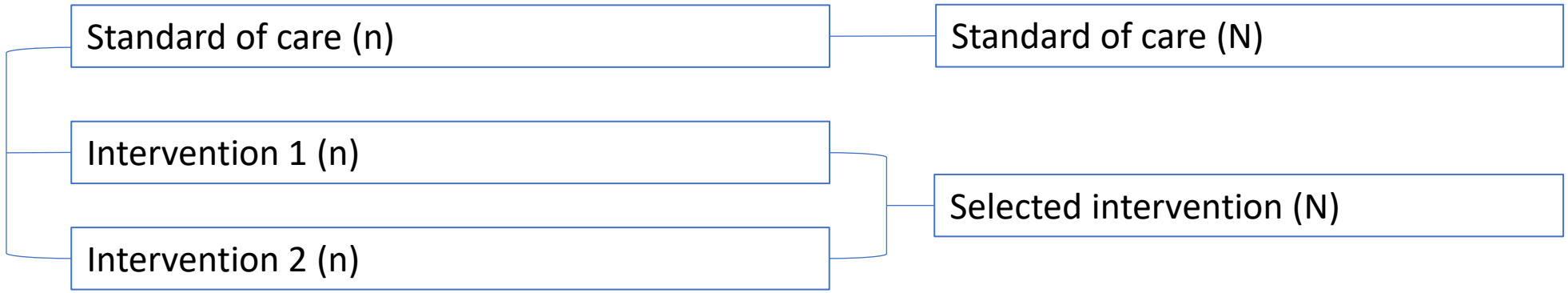
Shared control by multiple interventions and new design concepts: adaptive randomization ratio & more

Design concept I: Seamless phase 2/3

- Total sample size will be larger than a two-armed trial
- Shared control
- Interventions can be different drugs, doses of same drug, or combinations of drugs.



Phase 2:

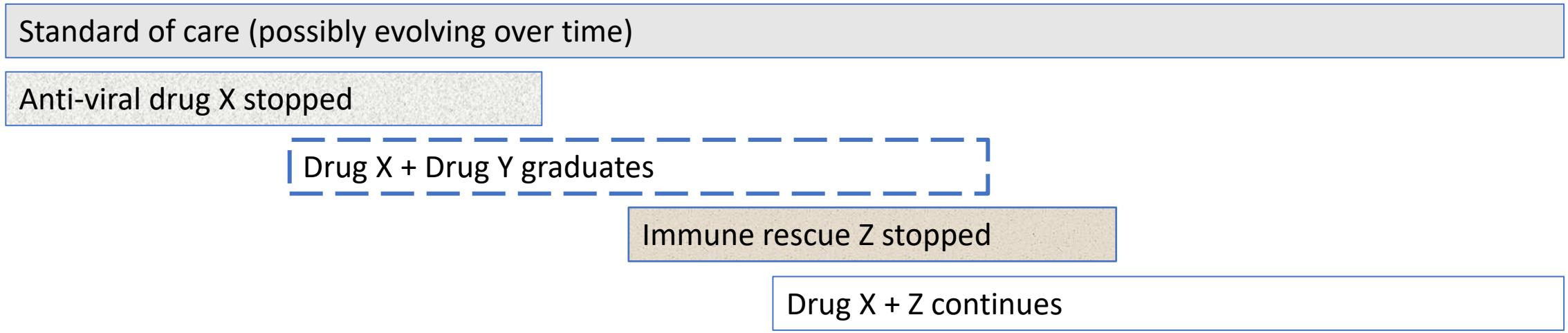
- **Proof-of-concept:** Go/no go based on JCV
- **Efficiency:** "drop-the-loser"; shared SOC
- **Adaptive:** N estimation based on phase 2
- Safety monitoring

Phase 3:

- **Clinical relevance:** Survival endpoint
- **Efficiency:** Uses Phase 2 data
- Safety monitoring

Design concept 2: Platform trial

- Intervention candidates enter in a staggered fashion: take advantage of infrastructure; master protocol; IRB; etc.
- Reduce n by continuous monitoring of efficacy data (e.g. Drug X in scheme below)
- Possibly facilitate head-to-head comparison (Drug X vs Drug X+Y)



Other design concepts that may *not* work

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  - Reduce n substantially
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- **N-of-1 trials** aim to identify optimal personalized best intervention by randomizing different interventions to a patient
  - Not aim to achieve statistical significance at the population level
  - Not applicable unless there is a very quick endpoint that predicts survival

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A multi-center consortium to enroll patients, coordinate regulatory efforts (IRB), and run the trials would be a worthy effort