Worldwide Clinical Trials

Infographic

Signal Over Sprawl: Adaptive Randomization to Focus Early Oncology Development

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Many modern oncology compounds possess mechanisms relevant to multiple indications, and the conventional "all-comers" Phase I approach often yields heterogeneous datasets that dilute efficacy signals, complicate indication selection, and conflict with FDA Project Optimus objectives.

This infographic examines the strategic application of Bayesian adaptive randomization to sharpen signal detection and improve capital efficiency in early phase oncology drug development. We discuss how to address the challenges, provide an overview of the importance of strategic portfolio review, and explore how Bayesian Adaptive Randomization (BARD) can improve selection of optimal doses by creating more comparable patient datasets.

Three Key Factors for a Successful Phase I Oncology Trial

From a surface-level view, there are three key factors that, if optimized, can significantly improve outcomes associated with your Phase I oncology clinical trial.

1 Improving Signal Detection

The "Too Many Shots on Goal" Dilemma

1. Modern oncology treatments have mechanisms with potential efficacy in multiple indications.
2. Sponsors often take the "all-comers" approach to Phase I trials, which, unfortunately, creates:
   - Heterogenous Datasets
   - Efficacy Signal Dilution
   - Challenges when Selecting Expansion Indications
   - FDA Project Optimus Complications
3. Investors and partners are increasingly expecting clinical plans to be clearly laid out, capital efficiency, and thorough de-risking milestones to be established.
4. Investors now see too many indications as a risk factor, and, in the crowded market of oncological drug development, may look to other, more focused programs.
5. A more strategic approach narrows down indications from potentially 20+ to ~3-5.
   - This creates a large enough participant pool for rapid enrollment without obscuring the incoming data with excess noise.

2 Rewarding Discipline Over Exploration

Partnering with a knowledgeable CRO who can perform a portfolio evaluation can help narrow the indication pool down to a reasonable number.

A review of each indication highlights:

- Rationale for product use
- Experimental models & translational utility
- EMA & FDA pathway
- Overview for a proof-of-concept (POC) trial
- Estimated timelines for POC completion
- Commercial viability & review of competitive space

Indications de-identified (A → F)
Assessments by independent reviewers
Reconciliations performed
Preliminary rank from most to least favorable (L → R)

Example Portfolio Review for Strategic Decision-Making

For when a molecule has multiple possible indications

Area	A	B	C	D	E	F
Rationale	3	**5**	4	3	4	2
Experimental Models	3	3	4	4	**5**	1
Trial Designs	**5**	2	**5**	3	1	4
Regulatory Pathway	**5**	2	4	4	2	4
Clinical Development Environment	2	**5**	1	4	3	2
Adoption & Access	4	4	3	1	3	3
Total	22/30	21/30	21/30	19/30	18/30	16/30

Numeric rating scale: 1-5 with 5 being highest score.

Based on de-identified, independent review, recommendations for this example would include:

- By totality of effort & stage: A
- By target novelty & program positioning: B
- Indication C is viable, but magnitude of the program & uncertainty make it implausible at the present stage
- Indications D, E, F are not initially attractive

Design Optimization in the Era of Project Optimus

Historic Oncology Perspective: From MTD to Precision Optimization

The Cytotoxic Era
(1940's to 2000)

- "More is Better"
- 3+3 Trial Design

Early oncology focused on highly toxic, nonspecific treatments that used the highest tolerable dose to eliminate cancerous cells, regardless of surrounding healthy tissue.

The Targeted & I/O Era
(2010's)

- Optimal Biologic Dose
- Model-Based Designs

More recently, advances in our technology and scientific understanding of cancer biology have shifted the focus to identifying an optimal dose based on factors beyond toxicity and to using sophisticated model-based trial designs.

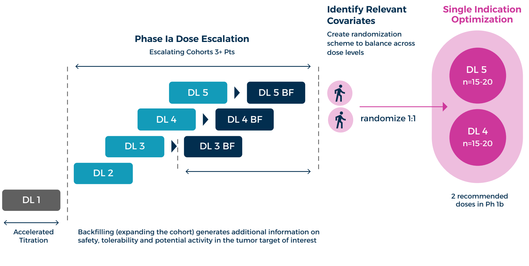
The Modern Era
(2020's)

- Early Optimization
- Adaptive, Bayesian

In the modern era, the sentiment has shifted toward optimizing the dose early in development with more flexible, adaptive methodologies that are easy to operationalize.

3 Conserving Patients While Maximizing Their Data

Bayesian Adaptive Randomization (BARD) | Dose Optimization with Backfill Model



- Using BARD enables an agile, adaptive approach that minimizes the total number of participants in the trial while maximizing usable data from each participant.
- This two-stage methodology initially uses the Bayesian Optimized Interval (BOIN) methodology. Once doses begin to show efficacy, backfilling occurs with the two or three most promising indications from the preliminary data.
- Dose escalation, along with published literature, helps to identify relevant covariates that impact patient response and efficacy.
- Single-indication dose optimization occurs by randomizing patients to two of the most promising dose levels.
- As in a late phase trial, prognostically important covariates are then balanced across the two dose levels using a specified randomization scheme.
- Balancing known variables improves the likelihood of selecting the true optimal dose.

Takeaways

- A thoughtful, de-risked development plan is favored over a catch-all, decide-as-we-go approach.
- It is critical to conduct multi-domain evaluations to determine the optimal indications for your asset.
- It is requisite to use modern trial design methodology to shorten trial duration and better select an optimal dose for future development.

For a deeper dive into Worldwide's portfolio review offerings and an in-depth discussion about implications for oncology, explore more of our content

- Clinical Development at the Crossroads: One Drug, Multiple Indications. Read more
- Biomarkers in Oncology Studies: The Science, the Medicine, and the Impact on Development. Read more

We'd love to connect to discuss your current or upcoming oncology program.

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