Project Optimus and Impact on Randomization

Randomization Working Group

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Agenda

- Background – Project Optimus
- Impacts – to Industry and Randomization
- Randomization Comparison of Project Optimus vs Master Protocols
- Summary / Discussion

Before Project Optimus – Early Phase Oncology

Paradigm / Trial Design:

Determine Maximum Tolerated Dose (MTD)

- Stepwise, increasing doses
- Small number of patients at each dose level
- Short periods of time (dosed)
- Until prespecified rate of severe or life-threatening dose-limiting toxicities (DLTs)
- MTD (or close) then used in subsequent clinical trials

Operational Design for Patient Allocation

- Non-Random (Dose) Cohorts
- Quick / Easy (may be done without an IRT)

Worked well historically with chemo, but.....

Refs (FDA, Guidance for Industry, 2024) (FDA, Project Optimus, 2024)

MTD Does Not Meet Needs for Modern Oncology

MTD aligns with Traditional Chemotherapy

- Higher Doses:
  - Generally, kills more cancer cells
  - Results in higher toxicity and higher efficacy
  - Yields higher clinical benefits
- Many Chemotherapy regimens are administered for limited duration

Modern Oncology Therapies

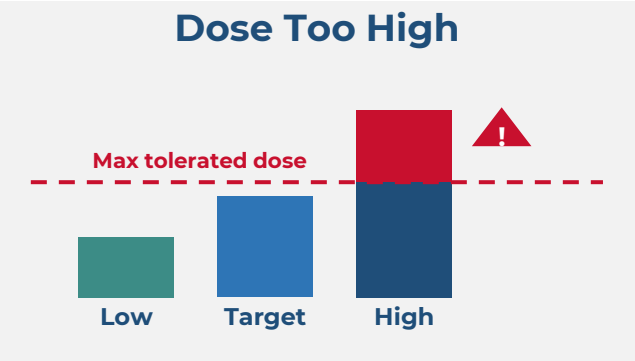
- Behave differently than Chemotherapy
- Higher Doses:
  - Results in higher toxicity
  - But efficacy increases little or not at all
  - Provides little additional benefit
  - Substantially more risk
- Many Modern Therapies reach optimal doses well below MTD
- Modern Therapies are taken for longer durations

Refs (FDA, Guidance for Industry, 2024) (FDA, Project Optimus, 2024)

Problems with this approach for Modern Oncology

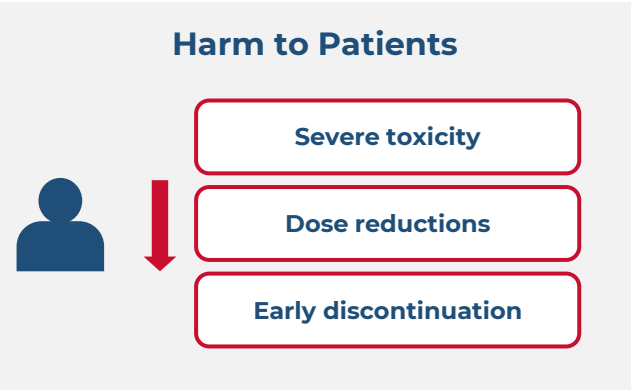
Inadequately Characterized Doses

- Used in later phases / label
- More toxicity without additional efficacy
- Not adequately tolerated



Negative Impact on Patients

- Persistent / severe / intolerable / irreversible toxicities
- Adverse impact on functioning and quality-of-life
- High rate of dose reductions
- Premature discontinuation
- Missed opportunity for continued benefit from the drug
- Difficulty tolerating subsequent treatments
- Limited options for receiving subsequent therapies



"Patients still have high unmet medical needs for effective and tolerable therapies."
FDA, Guidance for Industry, 2024

Refs (FDA, Guidance for Industry, 2024) (FDA, Project Optimus, 2024)

Real World Examples of these Problems

Oncology Drugs with Post-Market Dose Modification
**from Ayon's Short Course ASA Biopharm Workshop 2024*

*These drugs had to reduce their dose and / or revise schedule due to toxicity**

Drug Type	Drug	Initial Dose	Initial Trials	Modified Dose	Subsequent Trial	Reason for Modified Dose
Small-Molecule	Ceritinib (Zykadia)	750mg PO daily fasted	ASCEND-1	450mg PO daily w/ food	ASCEND-8	Reduce gastrointestinal toxic effects
	Dasabtinib (Sprycel)	70mg PO x2 daily	CA180013, CA180005, CA180006, CA180015	100mg PO daily	CA180034	Reduce hematologic toxic effects and fluid retention
	Niraparib (Zejula)	300mg PO daily	NOVA	200mg PO daily	PRIMA	Reduce thrombocytopenia
	Ponatinib (Iclusig)	40mg PO daily	PACE	45mg PO daily, then 15mg PO daily when <=1% BCR-ABL	OPTIC	Reduce vascular occlusive events
Chemotherapy	Cabazitaxel (Jevtana)	25mg/m2 IV every 3 wks	TROPIC	20mg/m2 IV every 3 wks	PROSELICA	Reduce hematogolic toxic effects / infections
Antibody-drug conjugates	Gemuzumab ozogamicin (Mylotarg)	9mg/m2 IV on days 1 & 15	Study 201, 202, 203	3mg/m2 IV on days 1, 4, & 7	Mylofrance-1	Reduce veno-occlusive disease and treatment related mortality

**Contents in Table from Ref (Ayon Mukherjee, 2024, Short Course - Lecture 3: Project Optimus and the framework of Complex Innovative Designs, ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop – page 62)*

FDA Project Optimus

Est. 2021 by FDA Oncology Center of Excellence

Optimal dose

Find the right dose — not the maximum dose

Project Optimus – Four Goals
To reform Dose Selection Paradigm in Oncology

Reform Dose Selection Practices

- Maximize both efficacy and safety (not just MTD)
- Reduce exposure to unnecessarily high doses

Promote Early Phase Dose Optimization

- Determine best dose before Phase III
- Randomized multiple doses & adaptive designs
- Reduce dose-related post-market challenges

Patient-Centric Dosing

- Patient-reported outcomes (PROs)
- Patient level titration

Enhance Collaboration and Education

- FDA encourages sponsors to engage (early)
- FDA educates their optimization expectations

"An emphasis of such strategies will be placed on performing these studies as early as possible in the development program and as efficiently as possible to bring promising new therapies to patients."
FDA, Project Optimus, 2024

References *(FDA, Guidance for Industry, 2024) (FDA, Project Optimus, 2024) (Singh, 2025) (Novotech, 2025)*

FDA Project Optimus – Impact on Industry

Impacts

Sponsors

- **Redesign of Protocols (From EASY to COMPLEX)**
  - Randomization & Adaptive Designs
  - PK/PD modeling, PROs
- **Greater Regulatory Expectations**
  - Robust evidence / Not just MTD
- **Increased Operational Burden**
  - From quick / low-cost Early Phase Trials to.....
  - Longer Timelines, Higher Costs

Small Biotechs / Emerging Sponsors

- Limited resources for complex early-phase designs
- Investor pressure to move rapidly to next phase

Benefits

Sponsors

- Improved success rates / More effective drugs
- Fewer dose modifications in later phases
- Stronger justification for IND & NDA submissions
- Strengthened regulatory & commercial positioning
- Overall, can make early investment worthwhile!

Patients

- More personalized treatment approaches
- Improved safety and tolerability
- Less toxicity
- Faster access to more effective treatments
- Improved quality of life

References *(FDA, Guidance for Industry, 2024) (FDA, Project Optimus, 2024) (Singh, 2025) (Novotech, 2025)*

Impact on Randomization

*As part of the Project Optimus Initiative, FDA released guidance document in 2024**

Highlights of FDA's Guidance that Impact Randomization

Evaluate & Compare

- Various Dose Strengths / Levels
- Various Formulations (e.g., concentration, volume, size, quantity)
- Additional Dose-Level Cohorts (outside of what is initially planned)
- Different Doses across Subgroups (e.g., populations, tumors, indications)
- Alternative Dosing Strategies (e.g., Visit Schedules)

Methods

- Randomization (instead of non-randomized cohorts)
- Adaptive Designs (e.g., open / close doses)
- Backfill (e.g., reopen cohorts, increase sample sizes)
- Stratification (if possible)
- Robust assessment of safety and tolerability

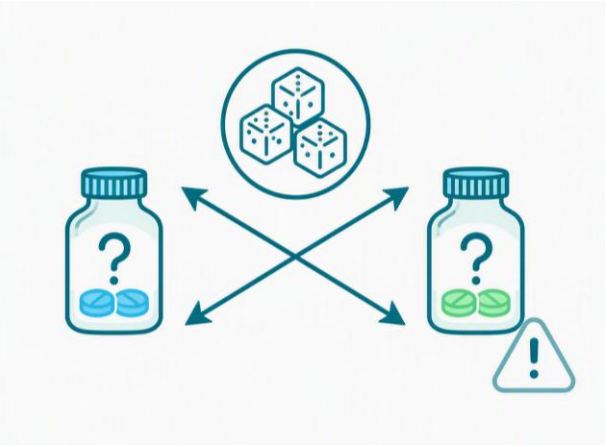
Previous approach had no randomization…..Project Optimus approach requires highly adaptive randomization
Complexities seem similar to that of Master Protocols!

*References *(FDA, Guidance for Industry, 2024) (FDA, Project Optimus, 2024)*

Project Optimus: Randomization Design

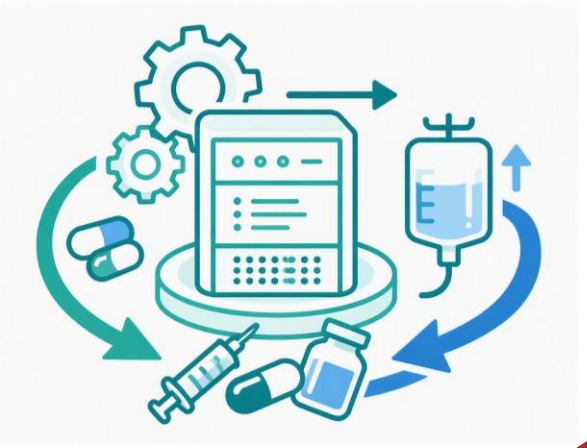
Protocol's randomization design is not fully specified:

- Treatment / Compound Known
- Dose level(s) or regimen(s) included is Unknown



Randomization specified during the trial from:

- From review of dose escalation phase
- From review of expansion / backfill cohort(s)



IRT required to meet the randomization challenges

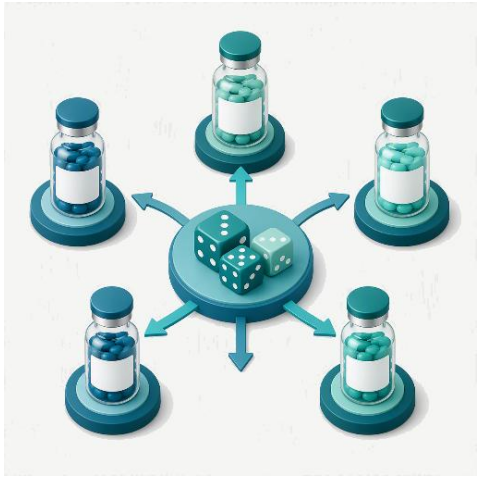
Project Optimus: Randomization Challenges

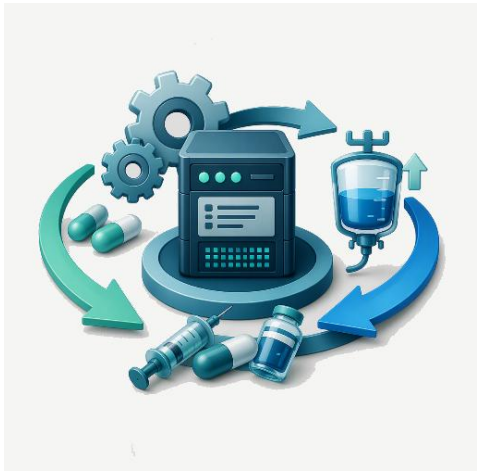
Randomization Evolves as Data Emerges:

- Add / Drop Dose Level(s) / Dose Regimen(s)
- Adjust Allocation Ratio

- Manage Participants eligible for >1 Cohort
- Add Subgroup(s) (Strata / Cohort)

IRT must be able to support the changing needs
Without the time granted from a Protocol Amendment



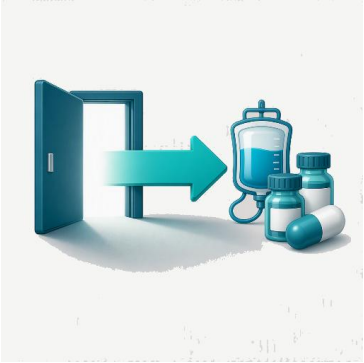


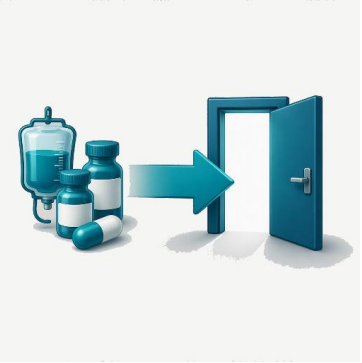
Master Protocols: An Established Model

Master Protocol	Treatment	Disease
Basket	Single Treatment	Multiple Diseases
Umbrella	Multiple Treatments	Single Disease
Platform	Mix	Mix

Treatments can enter and exit over time

- New treatments require Protocol Amendment
- Eligibility (Site-by-Site Roll Out / Participant Level)
- Treatment Allocation Ratio Adjustment





Reliance on IRT from inception to manage ongoing adaptations

Known vs Unknown Adaptations

Aspect	Master Protocols		Project Optimus	
	Know	**Don't Know**	**Know**	**Don't Know**
Add / Drop Treatment	Rand Method	Kit Types Visit Schedules	Kit Types Visit Schedules	New Dose Level New Visit Schedule
Ratio Adjustment	Initial Ratio Planned Ratios	Unplanned / New Ratios	Initial Ratio Planned Ratios	Unplanned / New Ratios
Add Strata	Highly Unlikely New Aspect for Project Optimus		General outline in protocol	Factor(s) / Level(s)

What can be done in IRT given timeline and budget constraints?

Master Protocols: longer timelines / larger budget

Optimus: shorter timelines / smaller budget

Aspect: Add / Drop Treatment(s) / Doses

Master Protocol:

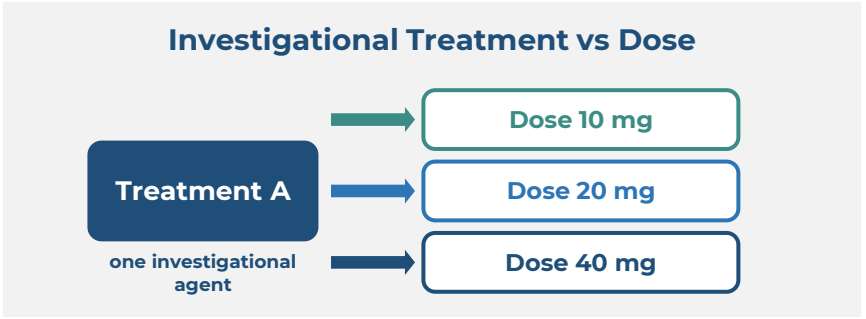
- New Visit Schedule / Kits Dispensation require IRT Amendment
- Protocol expected to amend to allow time for changes

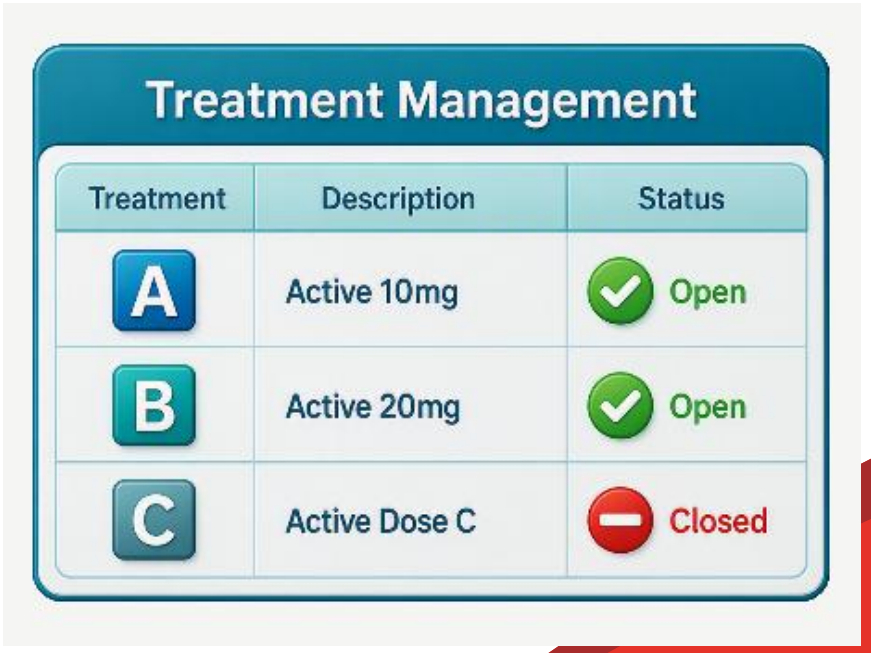
Project Optimus:

- Visit Schedule / Kit Dispensation not impacted
- No protocol amendment for New Treatment

IRT:

- Treatment Management Feature
- Generate list with Placeholder Treatments
- Plan for new lists to be generated / loaded





Aspect: Allocation Ratio Adjustment

Master Protocol:

- Ratios may be pre-specified as 1_c:X_i ratio
  - 1_c for Control; X=N Experimental Arms Open; (1:2:2 for 2 Arms; 1:3:3:3 for 3 Arms)

Project Optimus:

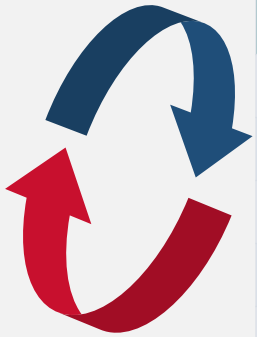
- Ratios generally not expected to change
  - Most defined to assign in even allocation

IRT:

- Switch Lists between alternative ratios
- Switch Lists between other list parameters
  - Block Sizes
  - MTI

1:2:2

RandNo	Trt
1001	A
1002	B
1003	B
1004	C
1005	C

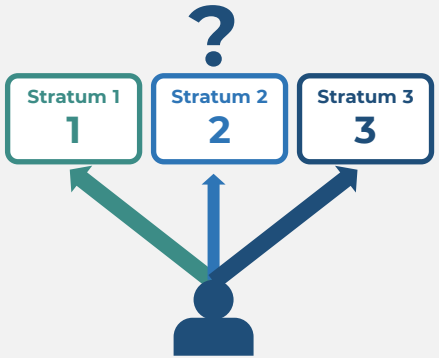


1:3:3

RandNo	Trt
2001	A
2002	B
2003	B
2004	B
2005	C
2006	C
2007	C

Aspect: Add Stratification

This is a new aspect not observed in Master Protocols
In Optimus, strata may be identified from early phase signals



IRT:

- Placeholder Treatment → Placeholder Strata
  - Lists generated with X Strata, defined in Stratum Management

Stratum Management

Stratum	Description
1	Stratum 1
2	Stratum 2
3	Stratum 3

- BARD: Backfill and Adaptive Randomization for Dose Optimization
  - Stage 1: Enrollment or Rand (no Strata)
  - Stage 2: Minimization
    - **Including stratification data from Stage 1**

Stratum Management

Stratum	Description	Count
1	PD-L1: Low	5
2	PD-L1: High	3
3	Stratum 3	0

Master Protocols vs Project Optimus Designs

Aspect	Master Protocols	Project Optimus
Goal	Evaluate multiple therapies/subgroups Efficacy across treatments	Dose optimization (efficacy and safety balance)
Phase Focus	Phase II/III	Phase I/early Phase II
Regulatory Driver	Efficiency and Innovation	Safety and efficacy in dose selection
Design Type	Often adaptive (platform, umbrella, basket)	Adaptive dose-finding
Randomization Use	To assign patients to different treatments and / or subgroups	To assign patients to different dose levels
IRT Use	Essential for managing perpetual randomization adaptations	Newly essential to manage dose level randomization adaptations
Adaptation Goal	Improve trial efficiency and decision making	Identify optimal dose
Adaptation Focus	Treatment arms (specific arms are clearly specified in protocol)	Dose levels / dose variations (some dose levels, dose details are specified in protocol, while others may not; e.g., intermediate doses may be explored)
Decision Speed	Quicker due to pre-specified / streamlined analysis plan	May be slower due to exploratory nature / data driven directions
Add New Treatment	Usually involves a new investigational drug Often requires protocol amendment	Add new dose level Usually does not require protocol amendment
Add New Strata	Requires protocol amendment (also not common)	May not require protocol amendment (e.g., strata may be identified / added based on interim analyses)

*References *(FDA, Master Protocols, 2026) (FDA, Guidance for Industry, 2024) (FDA, Project Optimus, 2024)*

Project Optimus Aspects in Protocols:

Design elements based on FDA's Guidance / Recommendations, such as the following:

- Multiple Stages: (Stage 1 – Dose Finding, Stage 2 Optimize)
- Randomization across identified optimal doses
- Backfill cohorts for promising doses
- Sample size adjusted for a dose based on analysis
- Protocol specifies planned doses, and Specifies that additional / intermediate doses may explored
- Variations of doses may be compared (e.g., dose level, schedule, formulation)
- Stratification may be introduced if identified in analyses
- Indications may be introduced as identified

Practical Takeaways

Project Optimus fundamentally reshapes early-phase trials

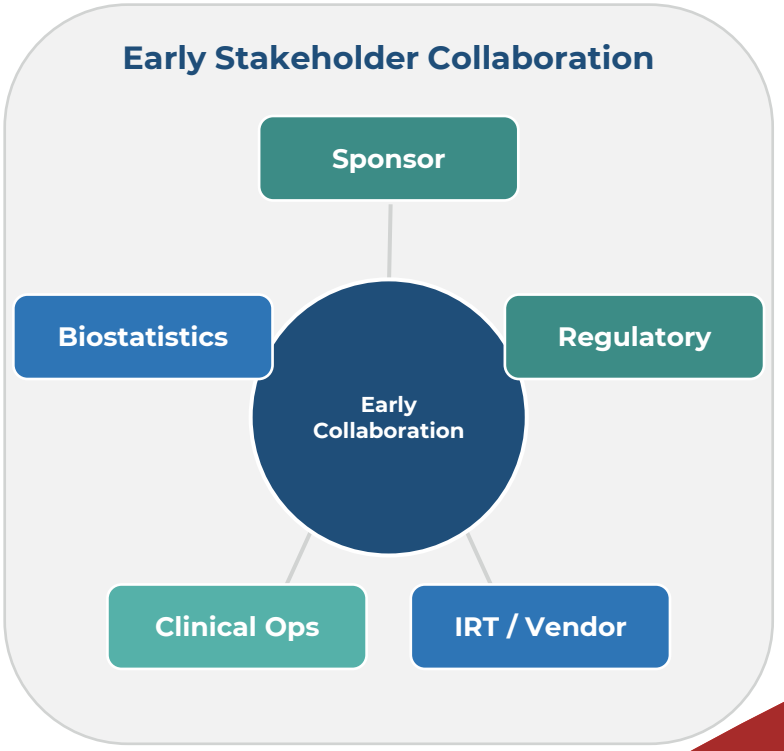
- **Randomization complexity is now unavoidable**

Project Optimus Trials benefit from Master Protocol experience

Plan explicitly for known vs unknown adaptations

- What can be done in timeline / budget?
- What can be done within details in a Protocol Amendment?
- **Early collaboration is essential**

IRT once not required, now is a **strategic asset** in early Phase Trials



Discussion

May take time for industry to adapt

- Pre-Optimus trials did not have randomization
- Post-Optimus trials expect randomization w/ adaptive designs
- Inherently, more time and costs to implement; more effort to manage randomization

Recent Survey of among oncology statisticians - DahShu IDSWG

- Top challenge when designing a dose optimization study with multiple randomized dose cohorts:
  - "Time required for implementation of randomization"
- Recommendation for statisticians:
  - Familiarize cross-functional team on Project Optimus and efficient Randomization Designs
  - Engage early with FDA

What do you see as challenges for randomization implementation of Project Optimus Trials?

*References *(Ananthakrishnan et al, 2026 - DahShu Innovative Designs Scientific Working Group)*

References

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