To Master Protocol or Not To Master Protocol

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Outline

1. Introduction
2. Decision Aids and Scoring – 3 steps
3. Example

Aim: to identify smart opportunities for Master Protocols

Introduction

- In our drug project portfolio:
  - We may have a drug for which we're considering multiple disease indications (so basket trial could be an option)
  - Or we may have several drugs which are targeting the same disease population (so umbrella/platform could be an option)
  - These may follow different but potentially overlapping timelines

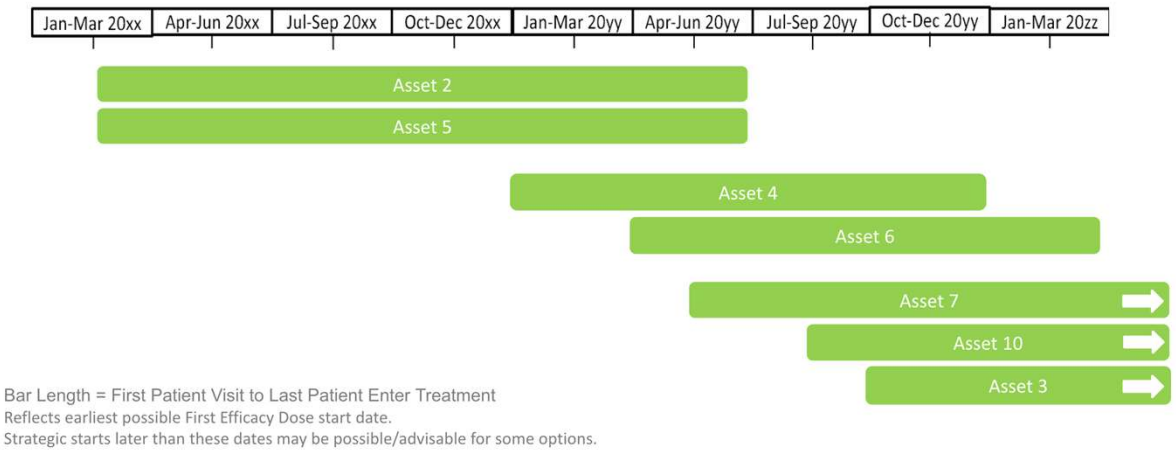


Figure courtesy of Melissa Spann

Step 1: What's Included

Capture info and see what's potentially combinable

Select which trials to continue to next step

Short Name	Asset	Asset ownership	Population	Primary Objective	Study Phase	Rand Comparator	Planned FSI date	Planned LSI date	Planned Primary Analysis
Rose	*Red Drug*	*Me*	*Disease 1*	*Efficacy*	*III*	*Placebo*	*Q1 24*	*Q1 26*	*Q1 27*
…	…	…	…	…	…	…	…	…	…

Short Name	Dosing method & frequency	Treatment duration	Blinded or Open Label	Planned N	Primary Endpoint	Key secondary endpoint(s)	Other complicating features,
Rose	*Oral*	*52 weeks*	*Open*	*300*	*Change @ 1yr*	*Subgroup*	*NA*
…	…	…	…	…	…	…	…

Step 2: Evaluate and Score

Favorable setting for a master protocol. Indicates optimized efficiency and/or low risk as compared to independent trials

Partial efficiency from a master protocol approach as compared to independent trials. Risk and complexity introduced

Least favorable setting for a master protocol. Little to no gain versus independent trials and risk may be introduced

Operational Scorecard

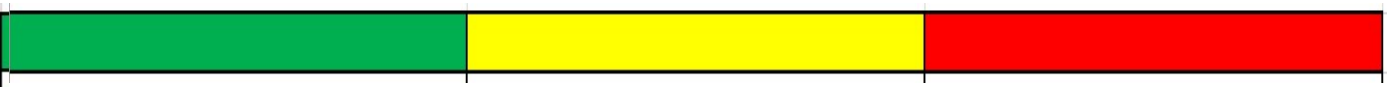
Operational Assessment
Sites
Accrual
Screening
Visit Schedules
Endpoints and assessments
Study Duration and Read-Outs

Descriptions of each category

- Similarity across sub-studies -> combinability -> operational efficiency
  - Can there be compromise to increase combinability?
- Some red/yellow is ok, but do recommend some gains in operational efficiency to proceed

Complexity and Study Integrity Scorecard

Complexity and Study Integrity
Randomization
Blinding
Regulatory Review Issues
Ways of Working
Cross-Team Communication Plans
Read-Out, Reporting, Data Sharing
(Safety) Review Boards and Steering Committees

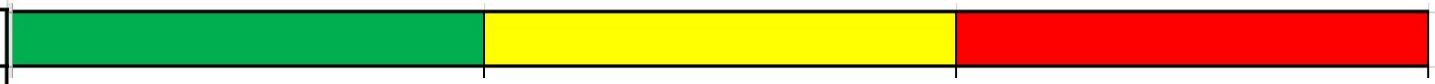


Descriptions of each category

- Again no “show-stoppers”
- Question what is unique to the master protocol approach
- Question what can be managed or mitigated

Scientific and Statistical Scorecard

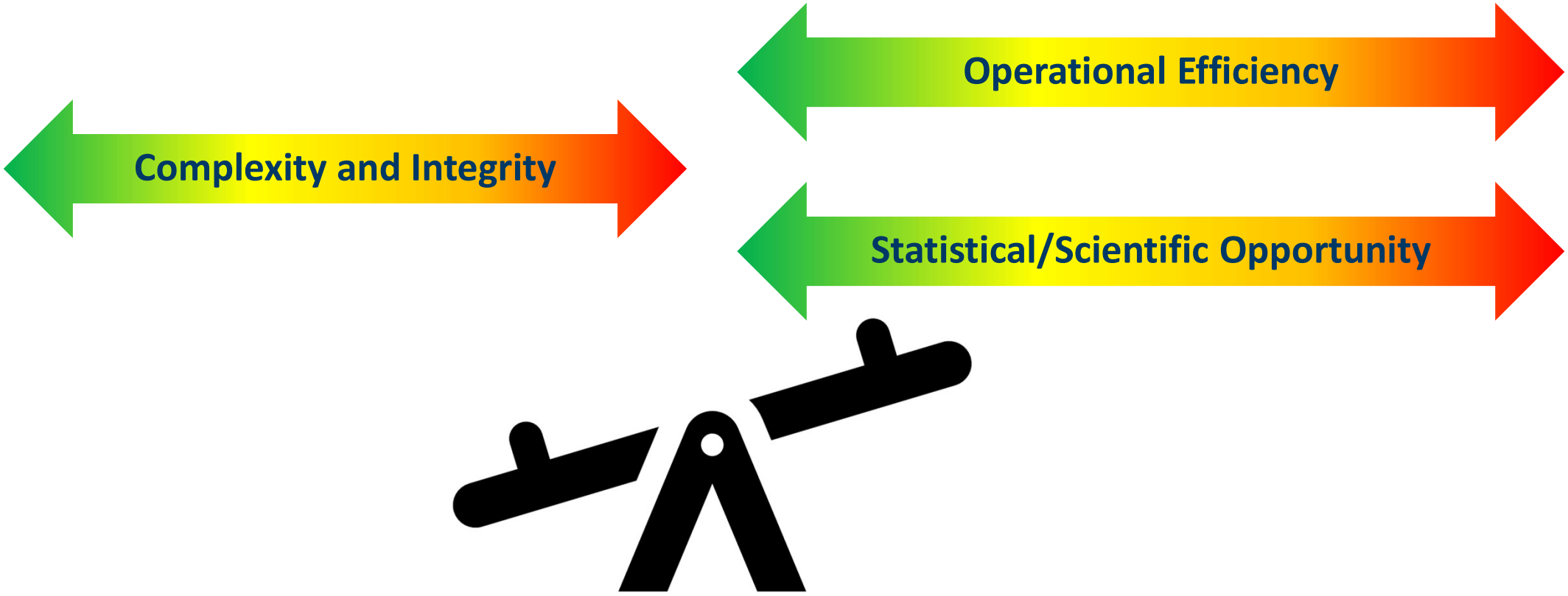
Scientific/Statistical Advantage
Shared Control
Borrowing/Pooling
Scientific Advantages



Descriptions of each category

- No statistical or scientific advantages are required
- However, this domain can add to the benefits of the approach

Step 3: Evaluate and Decide



Example: 3 Trials in Related Diseases
Step 1: What's Included

Asset	Ownership	Population	Phase	Randomized Comparator	Treatment Duration	Primary Endpoint	Planned N
Red Pill	My Company	Disease A	III	None	12 months	Global Scale	Unknown
Red Pill	My Company	Disease B	III	None	12 months	Global Scale	Unknown
Red Pill	My Company	Disease C	III	None	12 months	Global Scale	Unknown

Step 2: Score

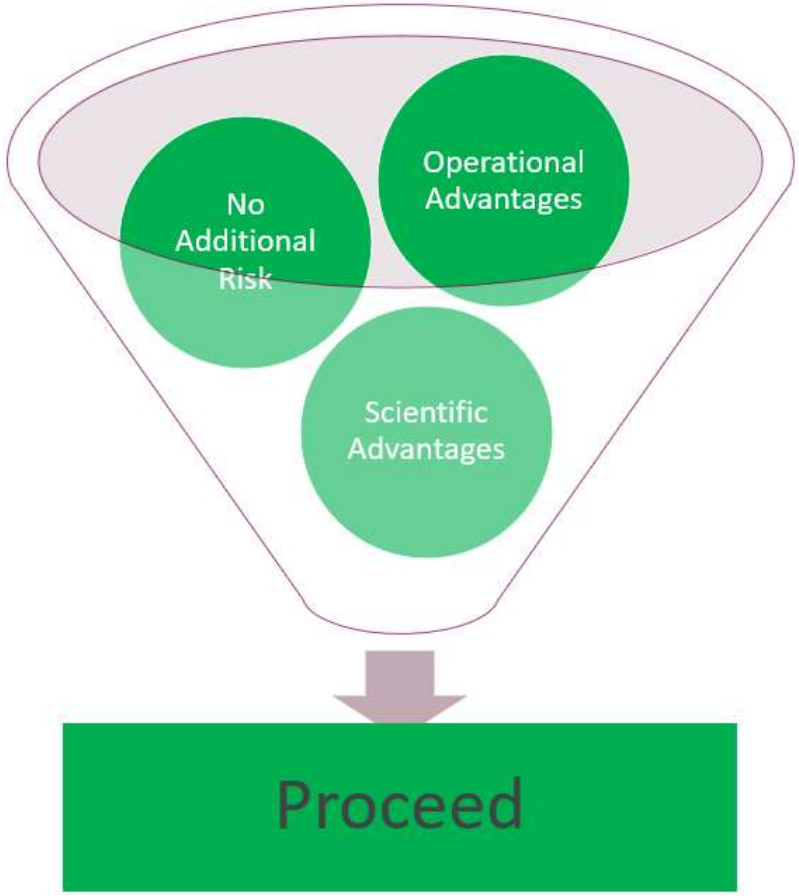
Operational Scorecard	
Sites	Sites may enroll to some but not all sub-studies
Accrual	Reduce sample size depending if can pool/borrow
Screening	Same screening process across sub-studies
Visit Schedules	Same visit schedule across sub-studies
Endpoints and assessments	Some disease-specific secondaries
Study Duration and Read-Outs	FSI and read out expected to the same

Complexity and Study Integrity Scorecard	
Randomization	Not randomized
Blinding	Not required
Regulatory	Single arm phase III
Ways of Working	Internal support and resourcing
Cross-Team Communication	Same compound team across all sub-studies
Read-Out, Reporting, Data Sharing	Same readout and no issues with data sharing
Safety Review Boards, etc.	Established safety committee with oversite of whole master protocol

Step 2: Score – cont.

Scientific/Statistical Advantage Scorecard	
Shared Control	Single arm
Borrowing	May Borrow
Scientific Advantages	Unified data collection support learnings in rare disease

Step 3: Overall Evaluation



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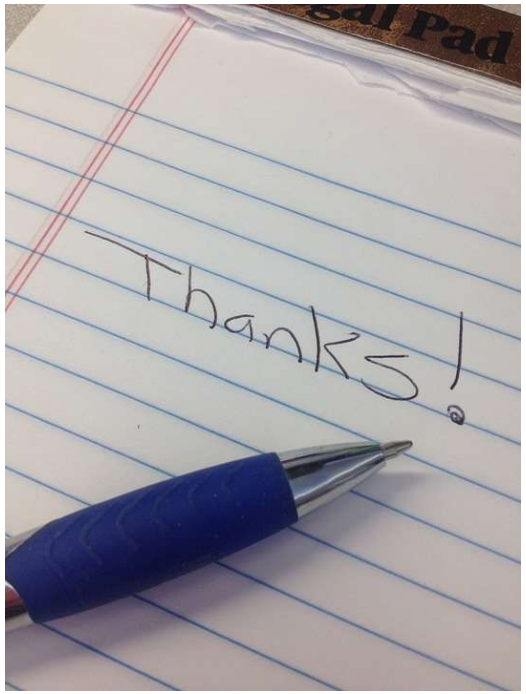

- Manuscript being submitted
- Also see poster by Karin Nelander "Planning a platform phase IIb trial in MASH" to help illustrate some of these concepts