J. Kyle Wathen, PhD
Vice President of Scientific Strategy and Innovation
Cytel

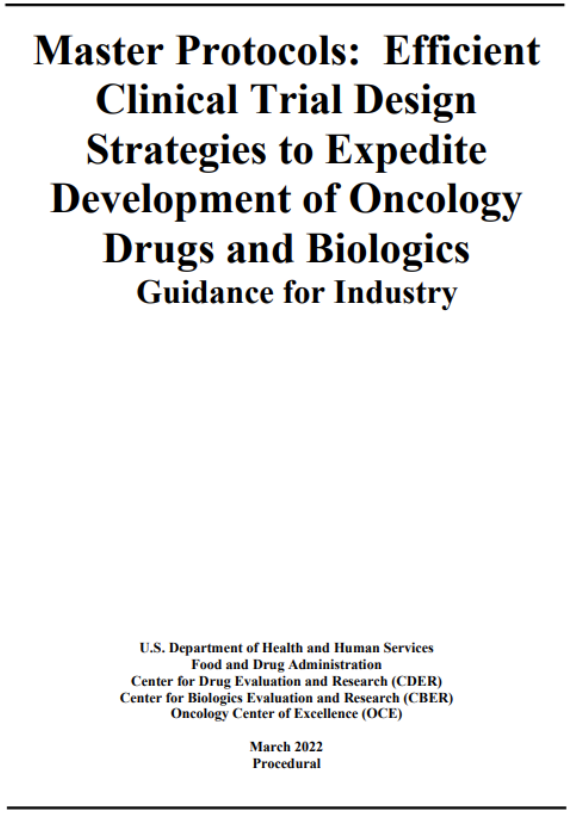
Joint work With Zoetis, Inc Including
Georgiana Fisher, Jezaniah Kira Tena, Marike Visser, Jennifer Forney, Hilde Moyaert, Leen Van Brussel

Outline

- Introduction to platform trial and motivation
- Example walk through of a platform trial
- Design option and trade-off exploration
- Simulation results
- Introduction to OCTOPUS - R package for simulation
- Conclusions

Reference

- Master Protocols: Efficient Clinical trial Design Strategies to Expedite Development of Oncology Drugs and Biologics, Guidance for Industry
  - https://www.fda.gov/media/120721/download



Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

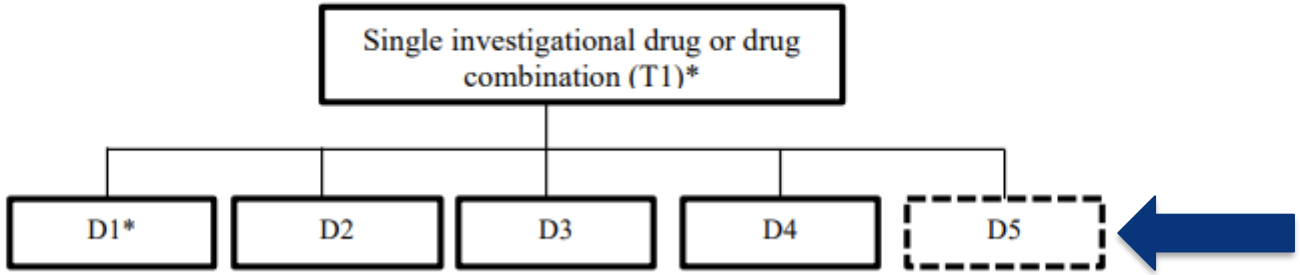
March 2022
Procedural

Reference – Basket Trial

A. Single Investigational Drug or Investigational Drug Combination Across Multiple Cancer Populations

A master protocol designed to test a single investigational drug or drug combination in different populations defined by different cancers, disease stages for a specific cancer, histologies, number of prior therapies, genetic or other biomarkers, or demographic characteristics is commonly referred to as a *basket trial* (shown in Figure 1). A basket trial evaluating an investigational drug combination may include a dose-finding or safety lead-in component to identify safe doses of the combination before proceeding with an activity-estimating component.

Figure 1: Schematic Representation of a Master Protocol With *Basket Trial* Design



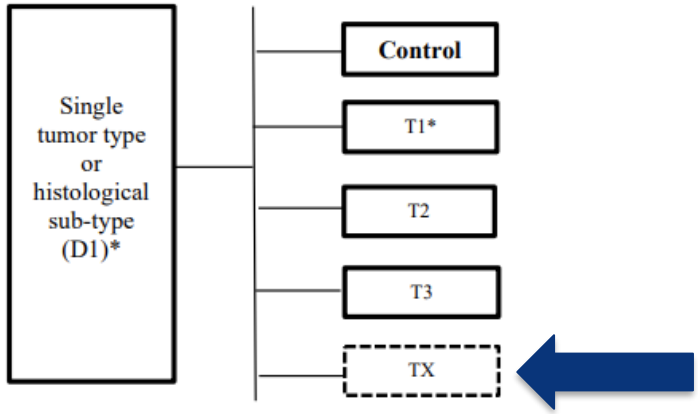
* T = investigational drug; D = protocol-defined subpopulation in multiple disease subtypes; D5 = dashed lines indicate potential amendments to include additional subpopulations.

Reference – Umbrella Trial

B. Investigational Drugs or Investigational Drug Combinations in Single Cancer Type

A master protocol that is designed to evaluate multiple investigational drugs administered as single drugs or as drug combinations in a single disease population is commonly referred to as an *umbrella trial* (shown in Figure 2). Substudies within umbrella trials can include dose-finding or safety lead-in components to identify safe doses of an investigational drug combination before proceeding with an activity-estimating component. As previously stated, sponsors should ensure the RP2D for each investigational drug has been established before evaluation in a master protocol.

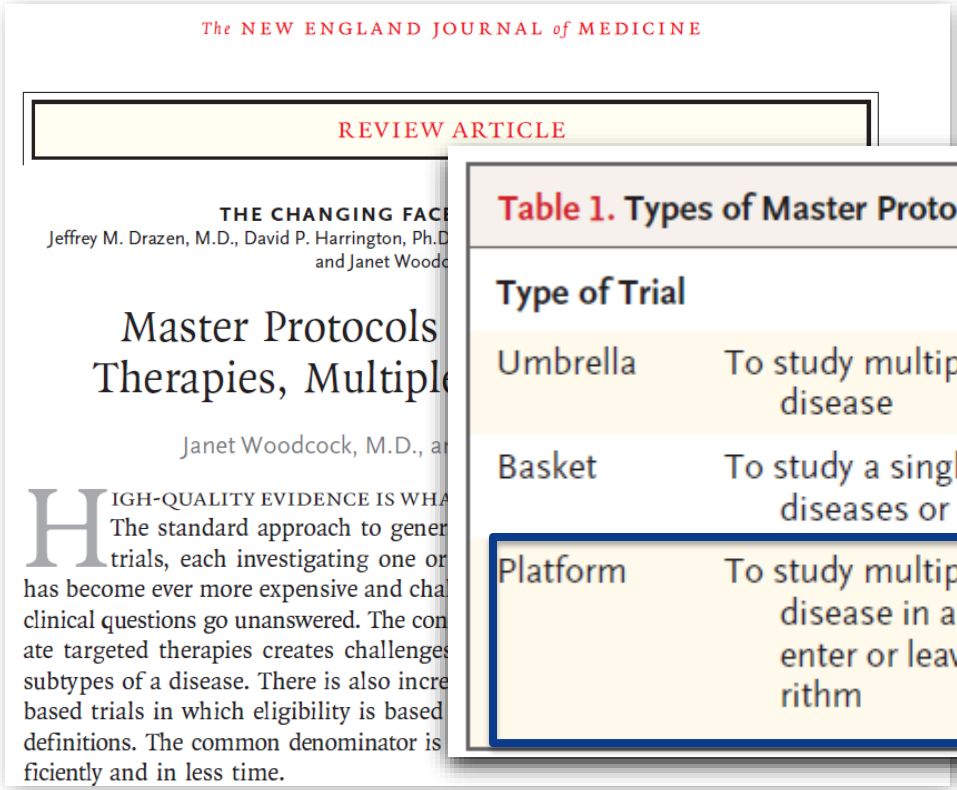
Figure 2: Schematic Representation of a Master Protocol With *Umbrella Trial* Design



* T = investigational drug or investigational drug combination; D = protocol defined subpopulation in single disease subtypes; TX = dashed lines indicate potential amendments to include future treatment arms.

Reference

- Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. N Engl J Med. 2017 Jul 6;377(1):62-70. doi: 10.1056/NEJMra1510062. PMID: 28679092.



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D.
and Janet Woodc

Master Protocols
Therapies, Multipl

Janet Woodcock, M.D., a

HIGH-QUALITY EVIDENCE IS WHA
The standard approach to gener
trials, each investigating one or
has become ever more expensive and cha
clinical questions go unanswered. The con
ate targeted therapies creates challenges
subtypes of a disease. There is also incre
based trials in which eligibility is based
definitions. The common denominator is
ficiently and in less time.

Table 1. Types of Master Protocols.

Type of Trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

What is a Platform Trial?

An experimental infrastructure to evaluate multiple treatments and/or combinations of treatments in heterogeneous patient populations

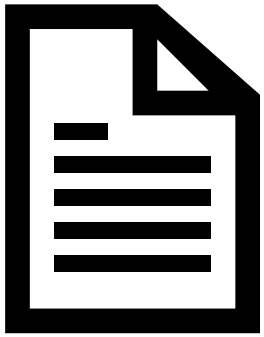
- Not all interventions are included, or even known, at the start of the platform
- Pre-existing infrastructure for clinical operations and trial implementation
- Patient data can be shared to improve analysis

Common Questions - Protocol

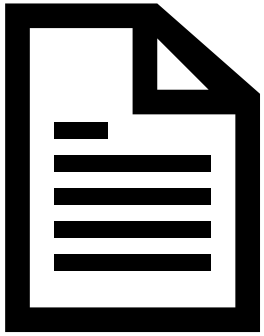
- We already have a protocol designed for one intervention, how is it different?
  - We need to organize it differently. Information about the treatment(s) is moved to the ISA, information about the trial that is independent of the treatment is kept in the master protocol.
- How do we organize a protocol when we don't know exactly what treatments/subtypes are in the platform when we write it?
- How does a platform compare to consecutive studies in terms of recruitment of patients?
- How do we know how well this will work in practice?
  - Simulation

Protocol Organization

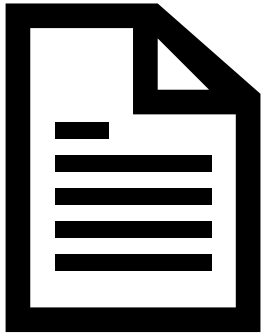
Master Protocol



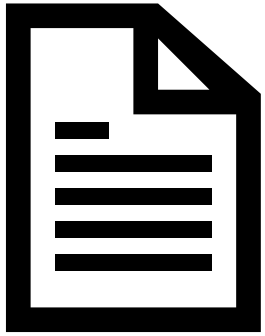
ISA 1



ISA 2



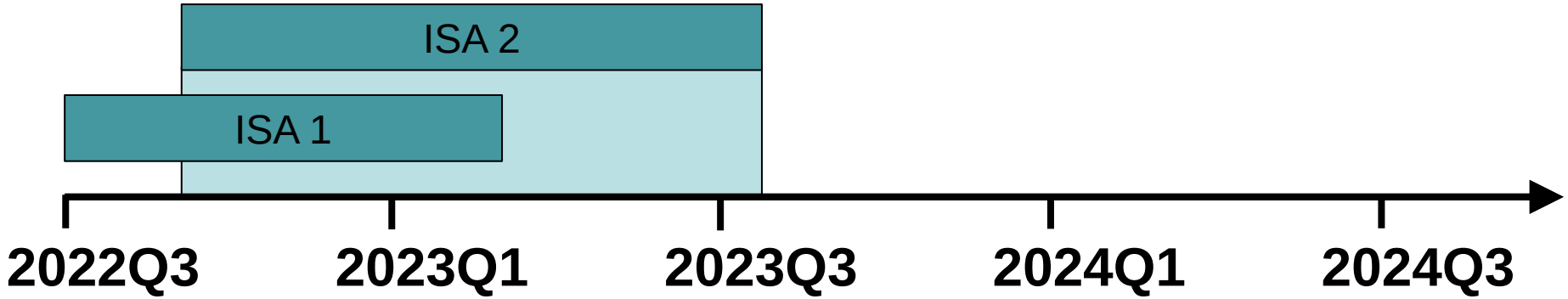
ISA 3



ISA = Intervention Specific Appendix
Contains experimental treatment(s) & matched control

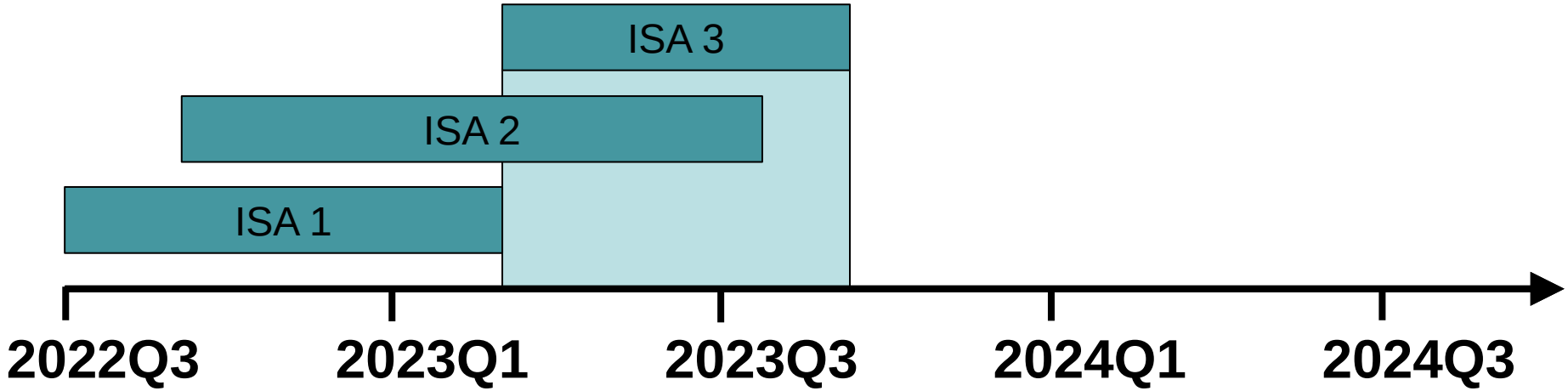
Example Platform – Adding New Treatments

ISAi – Intervention Specific Appendix i, which contains Control vs Experimental i



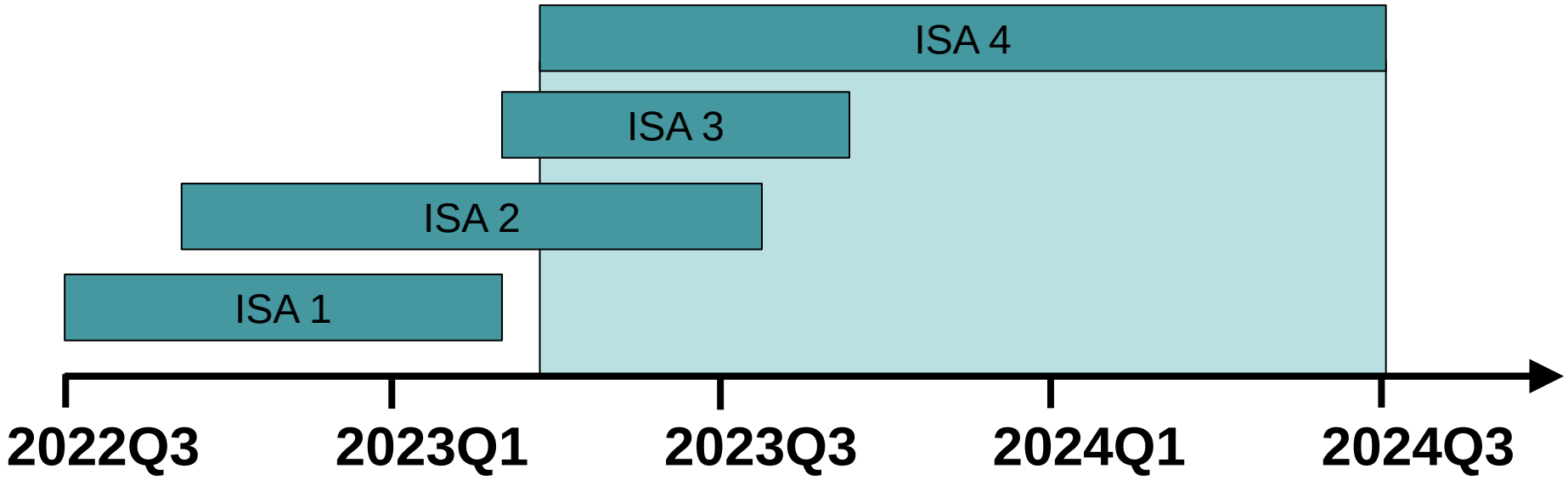
Example Platform – Adding New Treatments

ISAi – Intervention Specific Appendix i, which contains Control vs Experimental i



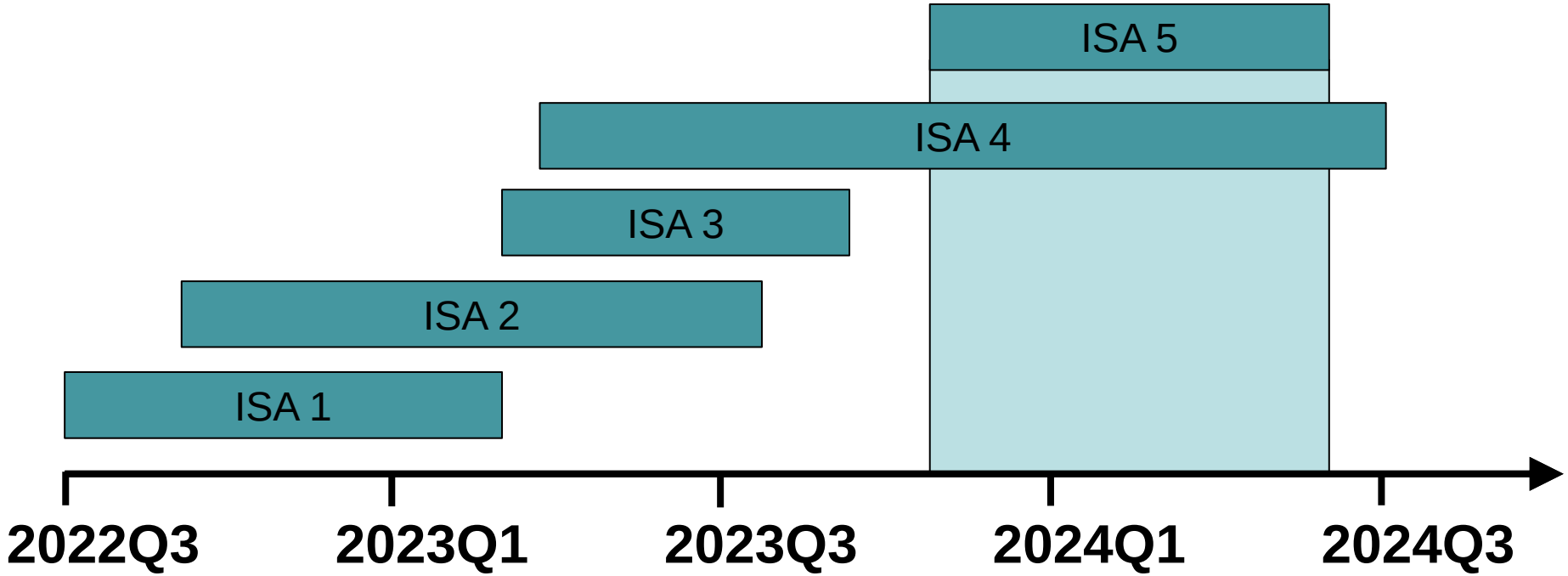
Example Platform – Adding New Treatments

ISAi – Intervention Specific Appendix i, which contains Control vs Experimental i



Sharing Information Between ISAs?

ISAi – Intervention Specific Appendix i, which contains Control vs Experimental i



Information Sharing

- Easier to justify sharing of control patients between ISAs that are in the platform during same time frame
- Harder to justify sharing between ISAs that have no overlap and are separated by a “significant” amount of time.
- Statistical approach
  - Test and pool or only concurrently enrolled
  - Model time trends
  - Discount patients enrolled prior to the start of an ISA
  - Hierarchical model for borrowing
- Why is this important?
  - Borrowing control patients between ISAs allows the randomization in each ISA to favor the new treatment, eg 3:1 or 4:1 so fewer patients receive placebo or control
  - Increase power without increasing sample size

Platform Study – Animals?

- Previous study data to help guide decision making in first ISA
- Set up of study at veterinarian centers can be time consuming
- Consistency of study sites improves data quality and reduces variability
- Understand trade-off of typical approach vs platform study

Design Options to Explore

- Operational platform – ignore previous study data and do not borrow control data across ISAs
- Borrow previous study to build prior for ISA 1
  - Consider varying amounts of borrowing from only the mean with larger variance up to 100%, eg prior effective sample size equal to prior sample size
  - ISA 2, 3, … How much control data to borrow?
    - Borrow all data accrued in platform
    - Borrow only concurrent enrolled data
    - Test and pool with previous ISA
    - Only the most recent patients enrolled in previous ISA
- Understanding options:
  - After the first ISA can the number of animals on control be reduced and maintain the same probability of Go, eg false-positive/power?
  - Keep the same sample size but improve decision making ability?

Statistical Model

For simplicity, ignore ISA

$X \sim \text{Binary}(\pi_i)$ for i = C (Control) or E (Experimental)

Priors

$\pi_c \sim \text{Beta}(a, b)$; Vary amount of prior data utilized

Non-informative $\pi_c \sim \text{Beta}(0.14, 0.86)$;

Reflect prior response rate of 14%

$\pi_E \sim \text{Beta}(0.14, 0.86)$; Assume prior response rate is same C/E

Decision Criteria

Assuming a Minimal Acceptable Value (MAV) decisions are based on

$p = \Pr(\pi_E - \pi_c > \text{MAV} \mid \text{data}) > P_U$

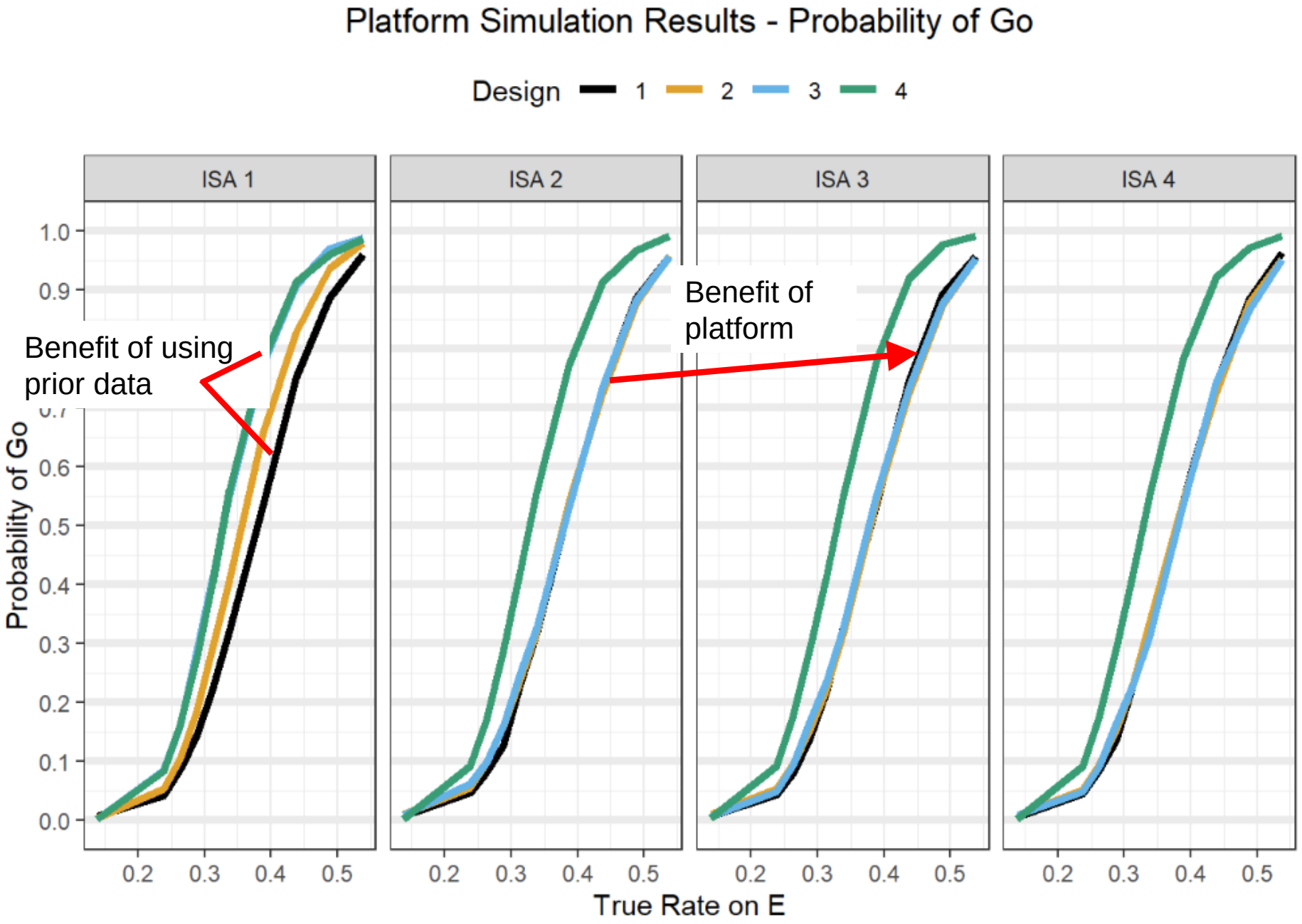
Also tried a more complex model that included a random effect for site and treatment

Guiding the Team via Trial Simulation

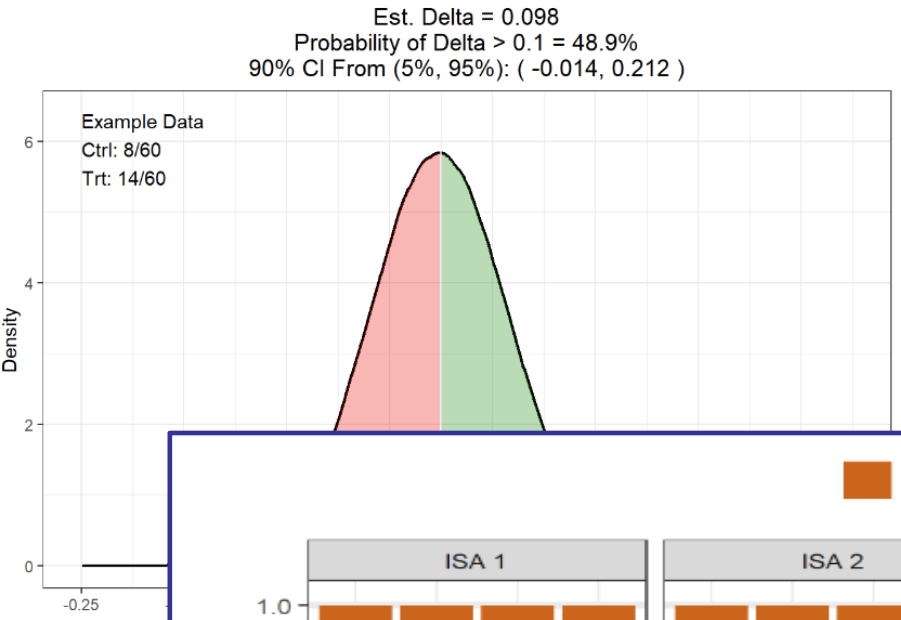
- Assumed 4 ISA – Start every 6 months
- Ramp up of animal recruitment – allows for overlap between ISAs
  - Included sites to add additional variability
- Outcome is measured quickly (eg less than one month)
- Presented no more than 4 design options at a time
  - Platform ISAs make this more complicated
- Simulations included a “standard” approach of consecutive trials, no borrowing to compare to
  - Helpful to start simple and in familiar territory and expand
  - Amount of prior data to include → Borrowing across ISAs → Concurrent borrowing → test and pool → time limited borrowing
- Graphs for Operating Characteristics and example trials

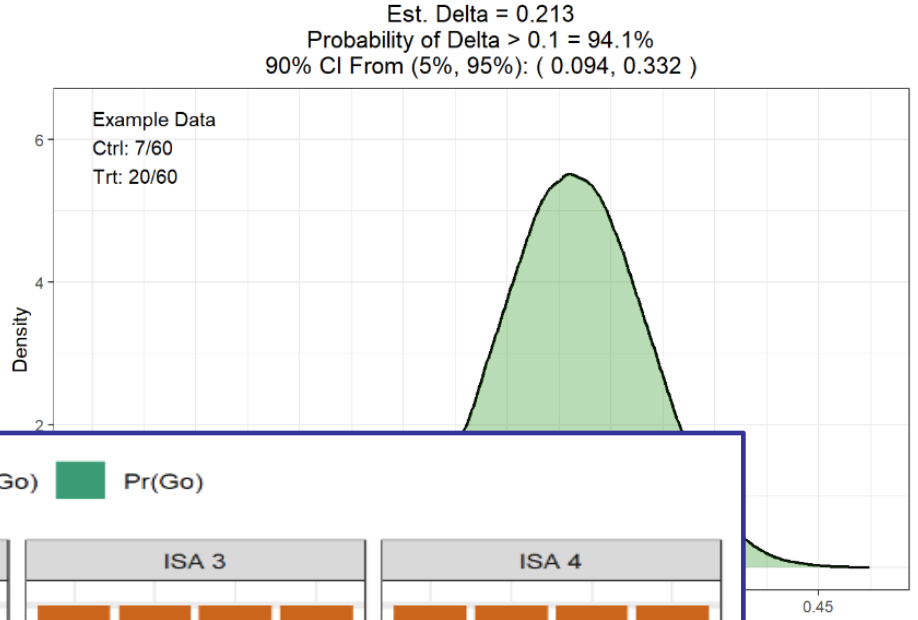
Simulation Results

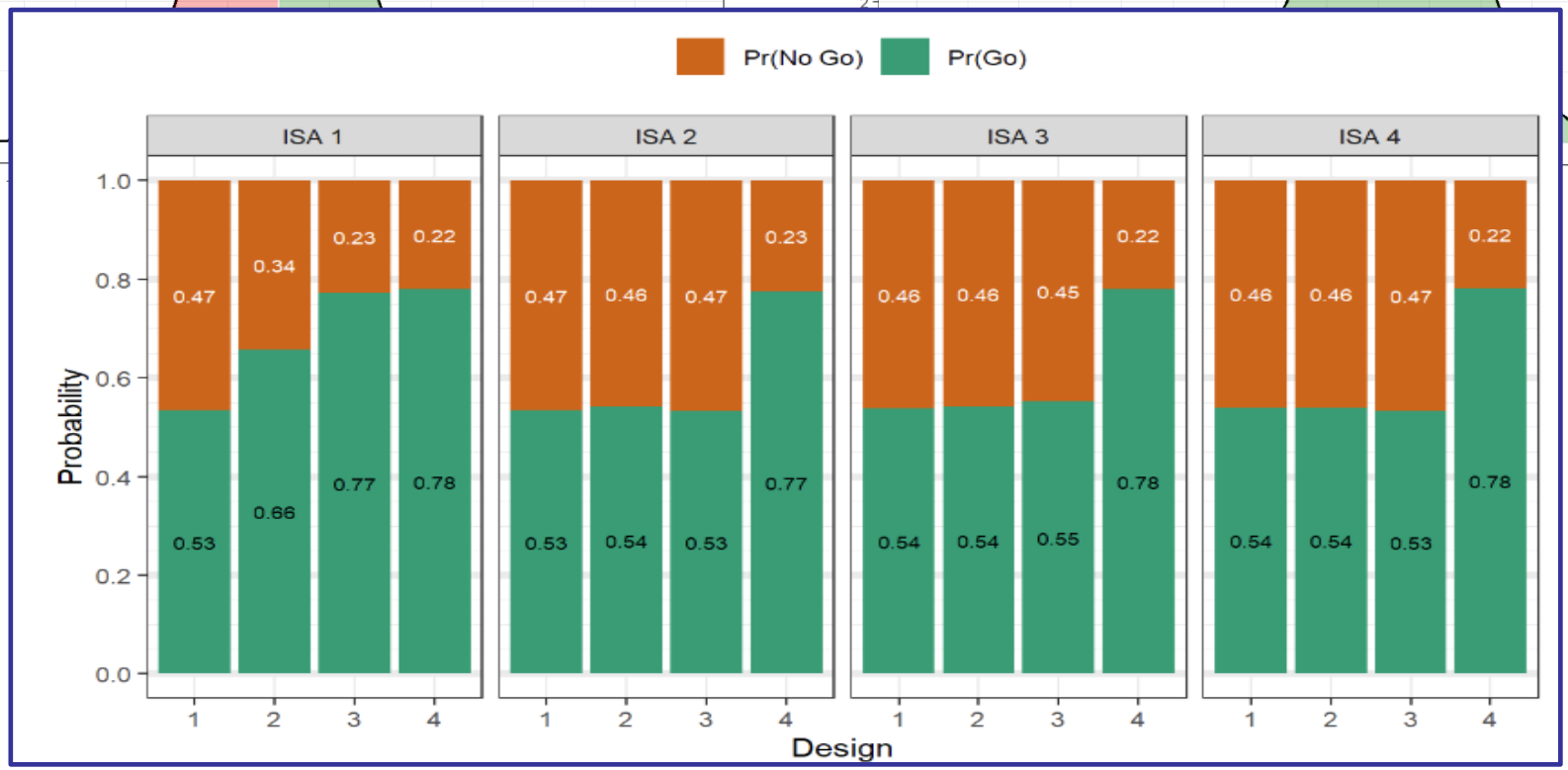
- **Design 1** – Equal randomization, no borrowing
- **Design 2** – ISA 1 prior sample size of 20 (about 30% of prior data), ISA 2-4 use data from platform but not previous study, reduces number of animals on control ISA 2-4
- **Design 3** – ISA 1 prior sample size of ~60 (100% prior data), ISA 2-4 use data from platform but not previous study reduces number of animals on control ISA 2-4
- **Design 4** – All ISAs have prior sample size of ~60 (100% prior data), use data from platform, reduces number of animals on control ISA 2-4
- From an ISA perspective
  - ISA 2-4 Design 2-3 are the same, how much “power” is lost compared to 1 or gained for Design 4?


Platform Simulation Results - Probability of Go
Design 1 2 3 4
ISA 1
ISA 2
ISA 3
ISA 4
Benefit of using prior data
Benefit of platform
Probability of Go
True Rate on E
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.9 1.0
0.2 0.3 0.4 0.5

Example Trials & Different Visuals





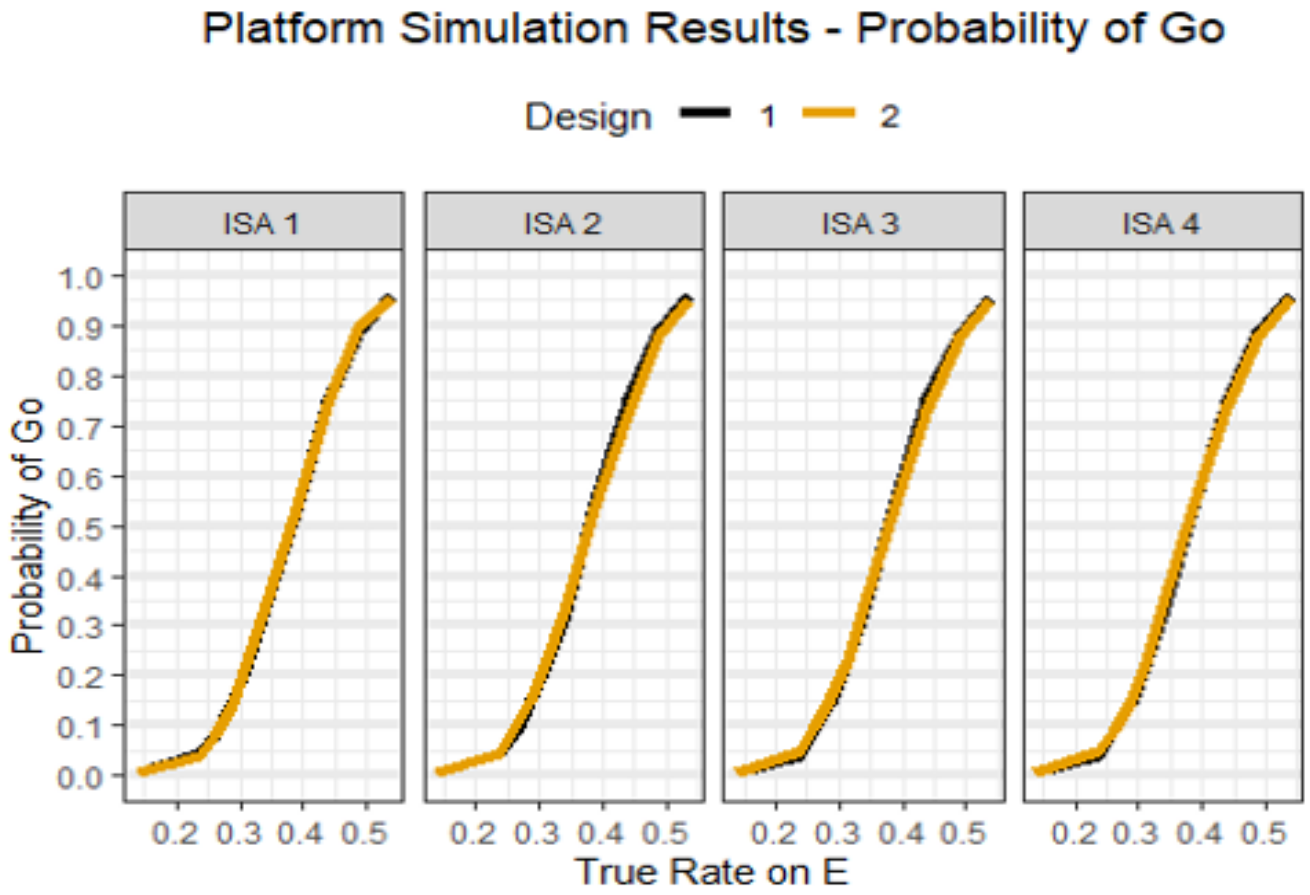


Fine Tune Design – Based on Trade Offs

- As design options are explored, always good to compare to “standard” approach
- Changes from previous study raised concerns that previous data may not be completely applicable
- Design Options
  - Design 1 – No borrowing control data, each ISA has 60 on control/treatment
  - Design 2 – ISA 1 has 60 on control/treatment. Starting at ISA 2, include up to 40 patients from concurrent enrolled or previous ISA, 20 patients on control, 60 on experimental

Simulation Results

Main Question: Can borrowing of control data help reduce sample size while maintaining decision making ability?



Open Source Software - GitHub Page

https://github.com/kwathen/OCTOPUS

OCTOPUS 1.3.0.6 | Get started | Reference | Examples | Changelog

OCTOPUS - Optimize Clinical Trials On Platforms Using Simulation

License

This package is governed by the JRD OCTOPUS License, which is the GNU General Public License V3 with additional terms. The precise license terms are located in LICENSE and GPL.

Introduction

This project is designed to help clinical trial designers simulate a platform trial. This project is intended for simulation purposes only. For the purposes of this project, a platform trial is a clinical trial designed to accommodate multiple treatments or interventions added to the trial either at the beginning of the trial or any time thereafter. Each intervention is added through an Intervention Specific Appendix (ISA). Each ISA typically randomizes between placebo or control and one or more intervention doses (or combinations). If trials for multiple interventions in the same disease area are considered, then a platform trial provides a unified framework for designing and running a single, multiple ISA, platform trial. Potential benefits of a platform trial are shorter, more efficient trials due to a single framework for multiple interventions and borrowing of placebo or control patients across ISAs, thus reducing the overall number of patients treated with placebo/control.

This package is under development. It is functional and has already been used to simulate several trials. As case studies are created, they will be added to the Examples directory of the package to help users create the necessary structures. The tar.gz files in this repository are included as testing versions for beta testers while as new updates and structure are added.

Using your GitHub account, you may want to "Watch" this project for updates. Alternatively, please contact the author to be added to the distribution list.

In order to simulate a platform trial using this package you must specify two structures: 1) Trial Design - this structure specifies details such as the number of ISAs, number of patients for each ISA/treatment, analysis method(s) and trial monitoring scheme, 2) Simulation Design - this structure specifies how to simulate all aspects of the trial such as patient outcomes, patient accrual rates and when ISAs enter the platform. Each of the structures will be details in the sections below.

To help increase flexibility and allow for new additions to be added by the users, S3 class and generic methods are implemented. Many

Links

Browse source code at https://github.com/kwathen/OCTOPUS/

License

Full license

file LICENSE

Developers

J. Kyle Wathen

Author, maintainer

Dev status

coverage 56%

build passing

R Package + Project Specific Files

OCTOPUS Package

Core components
Built on generic functions
Tested
Generalized functions from projects
Community driven development in future versions

Project Specific

Define trial design element
Define simulation design element
Define any project specific functions

Key Advantages – Tested code, reuse general parts, speed up development, learn across projects, project details remain in the project specific files, extendable, generic concepts can be moved from projects to package

Allowed for easy exploration of designs including client provided Winbugs model for analysis and customization to fine the need of client

Conclusions

- Team went through many rounds of simulations, discussion, trade-off considerations to arrive at final design
- Made sure the animal data used in simulation matched what is expected in the trial
- Trying various visualization and explanations helped to explain the complexities and guide the team to find the design that is most likely to answer the important questions
- Many more options to consider in a platform than in a single study
- Careful considerations of the design options to be compared is very important
- Great to see innovation of clinical trial design applied to animal studies

Thank you!

J. Kyle Wathen
Kyle.Wathen@Cytel.com

Questions?