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Supplementary information

Advancing innovative clinical trials to efficiently deliver medicines to patients

In the format provided by the authors

DIA/FDA Conference Summary: Advancing Complex Innovative Clinical Trial Designs to Efficiently Deliver Medicines to Patients

Co-Sponsored by the U.S. Food & Drug Administration (FDA) & the Drug Information Association (DIA)

Tommy Douglas Conference Center | Silver Spring, MD | March 2 - 3, 2020

DIA/FDA Advancing Complex Innovative Clinical Trial Designs to Efficiently Deliver Medicines to Patients

Conference: March 2-3 | Tommy Douglas Conference Center | Silver Spring, MD

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Overview

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Complex Innovative Trial Designs (CID) have the potential to increase the efficiency and lower the cost of drug development which will accelerate patient access to life altering therapies. The 21st Century Cures Act (Cures Act) and the sixth iteration of the Prescription Drug User Fee Act (PDUFA VI) recognize the need for CID and include provisions to advance their use to enhance medical product development. One such provision within PDUFA VI is the launch and implementation of the FDA CID Pilot Meeting Program which aims to foster discussions and education of the use and value of CID within drug development programs.

In an effort to promote CID, this unique conference will provide a platform for extensive scientific exchange among the FDA, other global health authorities including EMA, PMDA, and CFDA, patient advocates, and drug development innovators on CID topics such as master protocols, complex adaptive design, and Bayesian techniques, highlighting also the potential of alternative data sources.

Each session will begin with an introductory presentation by an FDA representative to set the stage followed by presentations and perspectives from a diverse group of expert speakers and panelists. The suitability of each CID topic and the proposed innovations from a US and global regulatory perspective, their usefulness from a patient perspective, and how challenges in the designs can be overcome, will be explored.

This conference is designed for key drug development decision-makers including clinicians, regulatory scientists and reviewers, and other key stakeholders, in addition to statistical specialists. Join us in this unique forum that will catalyze progress in advancing innovation in drug development.

The program is developed in collaboration with BIO, PhRMA and FDA.

Bio Biotechnology Innovation Organization

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Who Should Attend

Professionals involved in:

- Biostatistics, Including Adaptive Design and Bayesian Statistics
- Clinical Research
- Research and Development
- Trial Design
- Clinical Operations
- Therapeutic Area Development, Management, and Operationist
- Rare disease, Oncology, Immunology, Alzheimer's disease
- Medical Affairs
- Medical Science Liaisons
- Medical Writing
- Regulatory Affairs

Schedule At-A-Glance

DAY ONE | MONDAY, MARCH 2		ROOM
7:00AM-5:00PM	Registration	Mezzanine
7:00-8:00AM	Continental Breakfast and Networking	Mezzanine
8:00-8:30AM	**Welcome and Opening Remarks**	Ballroom AB
8:30-9:00AM	**Keynote Address**	Ballroom AB
9:00-10:30AM	**Session 1:** PDUFA VI Pilot Program and Discussion	Ballroom AB
10:30-11:00AM	Refreshment and Networking Break	Mezzanine
11:00AM-2:15PM	**Session 2:** CID - Master Protocols	Ballroom AB
12:20-1:15PM	Luncheon and Networking	Cafeteria
2:15-5:05PM	**Session 3:** Flexible, Efficient Decision-Making: Complex Adaptive Design	Ballroom AB
3:00-3:30PM	Refreshment and Networking Break	Mezzanine
5:05-6:05PM	Networking Reception	Mezzanine

DAY TWO | TUESDAY, MARCH 3		
7:30AM-5:00PM	Registration	Mezzanine
7:00-8:00AM	Continental Breakfast and Networking	Ballroom AB
8:00-8:10AM	**Welcome to Day Two**	Ballroom AB
8:10-8:40AM	**Day 2 Keynote**	Ballroom AB
8:40-11:30AM	**Session 4:** Bayesian Designs: Continuous Learning and Decision-Making	Ballroom AB
9:40-10:10AM	Refreshment and Networking Break	Mezzanine
11:30AM-12:30PM	Luncheon and Networking	Cafeteria
12:30-3:20PM	**Session 5:** Alternative Data Sources and Historical Controls	Ballroom AB
1:50-2:20PM	Refreshment and Networking Break	Mezzanine
3:20-4:50 PM	**Session 6:** Global Regulatory Affairs	Ballroom AB
4:50-5:15PM	Closing Remarks	Ballroom AB

Learning Objectives

At the conclusion of this conference, participants should be able to:

- Explain how complex innovative clinical trial designs (CIDs) contribute to increased efficiency and other enhancements of medical product research in order to ultimately accelerate patient access to innovative therapies
- Describe the purpose, anticipated outcomes, and progress to date of the FDA CID Pilot Program
- Discuss the views of global regulatory authorities (e.g., FDA, EMA, PMDA, and NMPA) on CIDs and their suitability/applicability for clinical research in their respective regions
- Explore aspects and further opportunities for alignment among global regulatory agencies in regard to CID adoption
- Examine several examples of CIDs, including master protocol designs, complex adaptive designs, and designs using Bayesian techniques, and discuss their regulatory suitability, potential challenges, and benefits for patients and medical product developers.

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DAY ONE | MONDAY, MARCH 2 — ROOM

7:00AM-5:00PM — **Registration** — Mezzanine

7:00-8:00AM — **Continental Breakfast and Networking** — Mezzanine

8:00-8:30AM — **Welcome and Opening Remarks** — Ballroom AB

Session Chair and Speakers

Bill Allman, Chief Technology Officer, DIA

Robert A. Beckman, MD, Professor of Oncology, Biostatistics, Bioinformatics, & Biomathematics, Georgetown University Medical Center

Fanni Natanegara, PhD, Principal Research Scientist, Eli Lilly and Company

Richard Moscicki, MD, Executive Vice President, Science and Regulatory Advocacy, Chief Medical Officer, Pharmaceutical Research and Manufacturers of America (PhRMA)

E. Cartier Esham, PhD, Executive Vice President, Emerging Companies Senior Vice President, Science and Regulatory Affairs, Biotechnology Innovation Organization (BIO)

8:30-9:00AM — **Keynote Address** — Ballroom AB

Abby Bronson, MBA, Senior Vice President of Research Strategy, Parent Project Muscular Dystrophy

9:00-10:30AM — **Session 1:** PDUFA VI Pilot Program and Discussion — Ballroom AB

Session Chair

Dionne Price, PhD, Director, Division of Biometrics IV, Office of Biostatistics, OTS, CDER, FDA

Karen Lynn Price, PhD, Senior Research Advisor, Statistical Innovation Center, Eli Lilly and Company

The Complex Innovative Trial Design (CID) Pilot Program was launched in August 2018 with the goal of advancing the use of novel designs when appropriate. The CID Pilot Program will achieve this goal through increased interactions between regulatory staff, industry, and public discussion of case examples for learning and information sharing. In this session, we will discuss the goals and progress of the program and set the stage for subsequent sessions by introducing case examples.

The Complex Innovative Trial Design Pilot Program: Setting the Stage

Dionne Price, PhD, Director, Division of Biometrics IV, Office of Biostatistics, OTS, CDER, FDA

Panelists

William H. Dunn, MD, Director, Division of Neurology Products, OND, CDER, FDA

Danise Subramaniam, PhD, Senior Director, Global Regulatory Affairs, Eli Lilly and Company

May Mo, Executive Director, Biostatistics, Amgen Inc

Abby Bronson, MBA, Senior Vice President, Research Strategy, Parent Project Muscular Dystrophy

10:30-11:00AM — **Refreshment and Networking Break** — Mezzanine

11:00AM-2:15PM — **Session 2:** CID - Master Protocols — Ballroom AB

Session Chair

Zoran Antoijevic, Msc, Head of Biometrics, MedSource

Min (Annie) Lin, MD, PhD, Mathematical Statistician, Division of Biostatistics, CBER, FDA

Rui (Sammi) Tang, PhD, Head of US Biostatistics and Programming Department and Medical Writing, Servier Pharmaceuticals

Master Protocols test multiple therapies in one indication, one therapy for multiple indications, or both. They also allow for discontinuation or addition of treatment arms and the concept known as platform trial. Master Protocols can significantly improve the efficiency of drug development when appropriately

designed and implemented. In this session we will discuss how to manage Master Protocols design and implementation complexities. We will present one case study and then follow up with novel approaches that focus on the confirmatory stage of development.

A Master Protocol for Chronic Pain: a Brief Overview and Lessons Learned
James Travis, PhD, Senior Staff Fellow, OB, OTS, CDER, FDA

Design and Analysis of Treatment Trials of Ebola Virus Disease
Michael Proschan, PhD, Mathematical Statistician, Biostatistical Research Branch, National Institute of Allergy & Infectious Diseases, NIH

Master Protocols and Clinical Trial Innovation
Lisa LaVange, PhD, Professor and Associate Chair Department of Biostatistics; Director of Collaborative Studies Coordinating Center, University of North Carolina at Chapel Hill

Complex Innovative Design for a Basket Trial
Vlad Dragalin, PhD, Vice President, Scientific Fellow, Janssen R&D at Johnson & Johnson

Panelist
Nora Carbine, Georgetown Breast Cancer Advocate

12:20-1:15PM — **Luncheon and Networking** — Cafeteria

2:15-5:05PM — **Session 3:** Flexible, Efficient Decision-Making: Complex Adaptive Design — Ballroom AB

Session Chair
Yi Liu, PhD, Senior Director Biostatistics, Nektar Therapeutics

Cristiana Mayer, DrSc, PhD, Director, Statistics and Decision Sciences, Janssen Research & Development, LLC

Panelist
Gregory Levin, PhD, Deputy Director, DBIII/OB/OTS/CDER/FDA

Novel methods for planning decision-making in Complex Innovative Designs comprise different features of adaptive efficient trials. Efficiency can be viewed from different angles to balance correct decision-making as early as possible for a drug development program with cost effectiveness and quantification of multiple metrics to measure "success" of a trial. An example of a platform trial in the infectious disease area is presented to illustrate a Bayesian approach to utilize longitudinal data for developing a predictive model for the long-term clinical outcome. In confirmatory settings, the use of a basket trial will be used to illustrate the effect of adaptive trials on cost effectiveness and feasibility of drug development in rare diseases and/or subgroups of common diseases like cancer. A third presentation will address an optimal sample size adaptation rule that maximizes return on investment, a metric to balance time to market, trial costs, and probability of success.

Speaker
Cesar Torres, PhD, MS, Mathematical Statistician FDA

Improving Efficiencies in Drug Development Through a Platform Trial
Kyle Wathen, PhD, MS, Senior Directory Advanced Analytics, Gilead Sciences

Efficiency and Type I Error Control of a Generalized Confirmatory Basket Trial Design
Robert A. Beckman, MD, Professor of Oncology and of Biostatistics, Bioinformatics, & Biomathematics, Georgetown University Medical Center

Optimal Sample Size Re-estimation in Adaptive Design based on Return on Investment
Yi Liu, PhD, Senior Director Biostatistics, Nektar Therapeutics

Panelist
Gregory Levin, PhD, Deputy Director, DBIII/OB/OTS/CDER/FDA

Nora Carbine, Georgetown Breast Cancer Advocate

3:00-3:30PM — **Refreshment and Networking Break** — Mezzanine

5:05-6:05PM — **Networking Reception** — Mezzanine

DAY TWO | TUESDAY, MARCH 3 — ROOM

7:00AM-5:00PM — **Registration** — Mezzanine

7:00-8:00AM — **Continental Breakfast and Networking** — Mezzanine

8:00-8:10AM — **Welcome to Day Two** — Ballroom AB

Robert A. Beckman, MD, Professor of Oncology, Biostatistics, Bioinformatics, and Biomathematics, Georgetown University Medical Center

Fanni Natanegara, PhD, Principal Research Scientist, Eli Lilly and Company

8:10-8:40AM — **Day 2 Keynote** — Ballroom AB

Gianna McMillan, PhD, Bioethics Program Administrator, LMU Bioethics Institute

8:40-11:30AM — **Session 4:** Bayesian Designs: Continuous Learning and Decision-Making — Ballroom AB

Session Chair

Fanni Natanegara, PhD, Principal Research Scientist, Eli Lilly and Company

Telba Irony, PhD, Deputy Director, Office of Biostatistics and Epidemiology, CBER, FDA

Through the CID Pilot Program afforded by PDUFA VI, FDA supports the advancement and use of Bayesian clinical trial designs. The Bayesian framework enables continuous learning from various data sources and provides decision-makers with straightforward probabilistic statements. This session will motivate the use of Bayesian approaches in CID by presenting case studies in broad therapeutic areas including rare diseases and highly prevalent chronic disease and discussing success stories, challenges, and opportunities to facilitate drug development.

Speakers

Telba Irony, PhD, Deputy Director, Office of Biostatistics and Epidemiology, CBER, FDA

Roger J. Lewis, MD, PhD, Professor and Chair, Department of Emergency Medicine, Harbor UCLA Medical Center

Complex Bayesian Primary Analyses in Confirmatory Trials

Scott Berry, PhD, President and Senior Statistical Scientist, Berry Consultants LLC

Bayesian Modeling in the CID Pilot Program: Lilly's Pain Master Protocol

Jon David Sparks, PhD, Principal Research Scientist, Eli Lilly and Company

Panelist

Gianna McMillan, PhD, Bioethics Program Administrator, LMU Bioethics Institute

9:40-10:10AM — **Refreshment and Networking Break** — Mezzanine

11:30AM-12:30PM — **Luncheon and Networking** — Cafeteria

12:30-3:20PM — **Session 5:** Alternative Data Sources and Historical Control — Ballroom AB

Session Co-Chairs

Pritibha Singh, MBA, MSc, Novartis

Maria Apostolaros, JD, MS, PharmD, RPh, PhRMA

Laura Lee Johnson, PhD, Director, Division of Biometrics III, Office of Biostatistics, Office of Translational Sciences, CDER, FDA

Karen Lynn Price, PhD, Senior Research Advisor, Statistical Innovation Center, Eli Lilly and Company

The CID program enables the exploration of the innovative use of alternative data sources. This exploration continues to be increasingly important as we encounter the emerging challenges with alternative data sources in methodological approaches to data collection, analysis, and benefit to the patients, regulators, and biopharmaceutical companies. This session will inspire and open you to the possibilities of utilizing alternative data sources, e.g. digital approaches to identify, screen, enroll, collect data on, and provide an intervention to patients.

Speakers
Pritibha Singh, MBA, MSc, Novartis

Data in the Wild: Design Lessons from the Apple Heart Study
Manisha Desai, PhD, Professor of Medicine, Biomedical Data Science, Stanford University School of Medicine

Borrowing Information from Historical Data: A Double-edged Sword
Ying Yuan, PhD, Bettyann Asche Murray Distinguished Professor, Deputy Chair, Department of Biostatistics, University of Texas MD Anderson Cancer Center

DIA Advancing Complex Innovative Clinical Trial Designs to Efficiently Deliver Medicines to Patients
Jackson Kempber Burton III, PhD, Scientific Director, Quantitative Medicine

Laura Lee Johnson, PhD, Director, Division of Biometrics III, Office of Biostatistics, Office of Translational Sciences, CDER, FDA

1:50-2:20PM **Refreshment and Networking Break** Mezzanine

3:20-4:50PM **Session 6:** Global Regulatory Affairs Ballroom AB

Session Chair
Cristiana Mayer, DrSc, PhD, Director, Statistics and Decision Sciences, Janssen Research & Development, LLC

Amy Xia, PhD, Vice President, Biostatistics, Design, and Innovation, Amgen Inc.

John Scott, PhD, MA, Director, Division of Biostatistics, OBE, CBER, FDA

This session will consist of two presentations from EMA and PMDA followed by a panel from FDA, EMA, and PMDA to discuss their perspectives on use of complex innovative designs (CID). We will highlight the regulatory principles, current thinking and activities related to utilization and evaluation of innovative designs in various regulatory agencies. Challenges, opportunities and best practices in applying CID will be described. Furthermore, we will discuss key aspects on how to interact with regulatory agencies in different regions on global trials with CID for the purpose of global registration.

European Reflections on Complex Innovative Designs
Frank Petavy, MS, Head of Biostatistics and Methodology Support, Human Medicines Development, European Medicines Agency, European Union

Yuki Ando, PhD, Senior Scientist for Biostatistics, Office of New Drug I, Pharmaceuticals and Medical Devices Agency

Panelist
John Scott, PhD, MA, Director, Division of Biostatistics, OBE, CBER, FDA

4:50-5:15PM **Closing Remarks** Ballroom AB

Dionne Price, PhD, Director, Division of Biometrics IV, Office of Biostatistics, OTS CDER, FDA

Fanni Natanegara, PhD, Principal Research Scientist, Eli Lilly and Company

Robert Beckman, MD, Professor of Oncology, Biostatistics, Bioinformatics, and Biomathematics, Georgetown University Medical Center

Contents

Executive Summary

Complex Innovative Trial Designs (CID) have the potential to increase the efficiency and lower the cost of drug development which could accelerate patient access to life altering therapies. The 21st Century Cures Act (Cures Act) and the sixth iteration of the Prescription Drug User Fee Act (PDUFA VI) recognize the role for CID and include provisions to advance their use to enhance medical product development. One such provision within PDUFA VI is the launch and implementation of the Food and Drug Administration (FDA) CID Pilot Meeting Program which aims to foster discussions and education of the use and value of CID within drug development programs.

In an effort to promote CID, this unique conference provided a platform for extensive scientific exchange among the FDA, other global health authorities including the European Medicines Agency (EMA) and Japan's Pharmaceutical and Medical Devices Agency (PMDA), patient advocates, and drug development innovators on CID approaches such as master protocols, complex adaptive designs, and Bayesian techniques. The potential of alternative data sources was also highlighted.

Each session began with an introductory presentation by an FDA representative to set the stage for exchange, followed by presentations and perspectives from a diverse group of expert speakers and panelists. The talks explored the suitability of each CID approach and the proposed innovations from a US and global regulatory perspectives, their usefulness from a patient perspective, and how challenges in the designs can be overcome.

Meeting Objectives

- Explain how CIDs contribute to increased efficiency and other enhancements of medical product research to ultimately accelerate patient access to innovative therapies.
- Describe the purpose, anticipated outcomes, and progress to date of the FDA CID Pilot Program.
- Discuss the views of global regulatory authorities (e.g., FDA, EMA, and PMDA) on CIDs and their suitability/applicability for clinical research in their respective regions.
- Explore aspects and further opportunities for alignment among global regulatory agencies in regard to CID adoption.
- Examine several examples of CIDs, including master protocol designs, complex adaptive designs, and designs using Bayesian techniques, and discuss their regulatory suitability, potential challenges, and benefits for patients and medical product developers.

Day 1 Keynote Address

Speaker: Abby Bronson, Vice President, Patient Advocacy and External Innovation Edgewise Therapeutics

Many of the features of CID are used in master protocols and collaborative multi-sponsor initiatives; it is often patient organizations that help drive these efforts. One well-known example is the Parent Project Muscular Dystrophy (PPMD), which works with patients and Sponsors to advance the development of treatments for Duchenne muscular dystrophy (DMD) by helping to drive a master protocol.

DMD is an X-linked pediatric neuromuscular disease. Patients are males and typically diagnosed in the range of three to five years old. One of the main functional milestones is loss of ambulation, which typically occurs between the ages of 12 and 14 years. This means most studies for DMD are recruiting males from five to 12 years of age.

Patients with DMD have many experimental therapies to choose from, with currently 36 companies with products in clinical studies. But there are two major hurdles that dissuade parents/caregivers from consenting to enroll patients in clinical studies for products under development. The first is the chance of being treated with placebo. The second is that most studies take five years to complete, after which the patient has likely aged out and will not qualify for further studies.

Beginning a multi-sponsor master protocol program requires a sufficient drug development pipeline, sufficient investment, enough understanding of the disease in terms of natural history and disease progression, and endpoints that can be standardized across substudies. DMD is therefore an ideal fit for a master protocol.

The particular master protocol standardizes many aspects of studies, including:

- Ability to be a phase 2, a phase 3, or a seamless phase 2/3 study;
- Three to one randomization to minimize the possibility of receiving placebo;
- A standard patient experience; and
- A uniform suite of endpoints.

While the master protocol specifies the main enrollment criteria and which endpoints are measured, individual Sponsors can add enrollment criteria, have different sample sizes, decide which of a suite of collected measures will serve as the comparison's primary efficacy endpoint, and prespecify their specific patient population.

Patients are often initially put off by the concept of being randomized to one of multiple treatments within a master protocol because the patient no longer has the choice of which study to participate in. But educational efforts have been effective in explaining the many benefits of master protocols that positively impact patients, including:

- Limiting the chance of being treated with placebo
- Using fewer participants to have the same power to detect a difference
- Shortening the duration of trials by having most of the protocol already written and having the sites ready to begin accepting participants immediately
- Improving the quality of results by utilizing facilities and staff that are proficient with evaluating performance endpoints

In summary, platform trials are innovative and inherently patient centric. The use of shared placebo data and a master protocol may also provide benefits to other stakeholders. Patient communities can help to drive the use of a master protocol for the relevant disease state.

Session 1: PDUFA VI Pilot Program and Discussion

The Complex Innovative Trial Design (CID) Pilot Program was launched in August 2018 with the goal of advancing the use of novel designs when appropriate. The CID Pilot Program will achieve this goal through increased interactions between regulatory staff, industry, and public discussion of case examples for learning and information sharing. This session discussed the goals and progress of the program and set the stage for subsequent sessions by introducing case examples.

The Complex Innovative Trial Design Pilot Program: Setting the Stage

Speaker: Dionne Price, PhD, Director, Division of Biometrics IV, Office of Biostatistics, Office of Translational Sciences (OTS), Center for Drug Evaluation and Research (CDER), FDA

The FDA's CID Pilot Meeting Program is a part of the FDA's commitment under the sixth iteration of the PDUFA VI to facilitate and advance the use of complex adaptive, Bayesian, and other novel clinical trial designs. The program focuses on trial designs for which analytically derived properties of the trial may not be feasible and thus simulations are needed to determine the properties of operating characteristics. The CID Pilot Meeting Program is a joint effort between the CDER and the Center for Biologic Evaluation Research (CBER).

For the Pilot Program, FDA selects up to two submissions per quarter. The CID program requests are evaluated by a multidisciplinary team based on the following criteria:

1. the need for simulations to assess the trial design operating characteristics;
2. the therapeutic need;
3. the study design appropriateness for the pilot program;
4. the level of innovation of the trial design; and
5. the value proposition of the CID.

The CID pilot program has received several submissions and to date has accepted four, which were presented during the conference. These included the following:

- A master protocol, which evaluated multiple interventions across main pain conditions using a Bayesian hierarchical model to leverage placebo and treatment effect information.
- A study in systemic lupus erythematosus, which includes response adaptive randomization, a Bayesian hierarchical model for dose selection, and interim analyses for futility and to inform dose and endpoint selections for future studies.
- A study in DMD, which utilizes a Bayesian adaptive design with several potential adaptations such as stopping the trial for efficacy or safety, modifying the sample size, dropping an arm, pooling doses, changing the randomization ratio, and also the sponsor proposed to explore placebo augmentation with historical controls.
- A study in multiple sclerosis, which has a Bayesian framework with meta-analytic predictive priors to leverage external adult and pediatric studies.

In summary, while the CID pilot program meetings are led by statisticians, the participation of all relevant disciplines is necessary to facilitate an understanding of the complexities and goals of the designs. The program has highlighted the iterative nature of the simulation process and the importance of appropriate simulation plans and reports to facilitate productive feedback and meetings. Ultimately, the goal of CID is to bring safe and effective products to patients.

Key Takeaways from the Discussion Panel

Panelists: Dionne Price, Billy Dunn, May Mo, Abby Bronson, and Danise Subramaniam

- Many of the problems that patient advocates face are addressed by features of CID.
- CID is a multidisciplinary effort that includes statisticians, clinicians, and patients.
- The CID program is intended to support programs that will provide substantial evidence of effectiveness (i.e., the evidence needed to provide primary support for an eventual drug approval).
- The disclosure requirements for the CID program allow the FDA to discuss information about drugs while they are still under investigation.
- CIDs will become an important way to accelerate the pace of drug development for many indications, particularly rare diseases.

Session 2: CID – Master Protocols

Master protocols can be used to test multiple therapies in one indication (umbrella trials), one therapy for multiple indications (basket trials), or both., or allow for the discontinuation or addition of treatment arms in an ongoing study (platform trials). Master protocols can significantly improve the efficiency of drug development when appropriately designed and implemented.

In this session, James Travis (FDA), Mike Proschan (NIH), Lisa LaVange (UNC Chapel Hill), Vladimir Dragalin (Janssen) and Nora Carbine (Georgetown) addressed how to manage master protocol design and implementation complexities coupled with novel approaches focusing on the confirmatory stage of development.

A Master Protocol for Chronic Pain: a Brief Overview and Lessons Learned

James Travis, PhD, Senior Staff Fellow, OB, OTS, CDER, FDA

The CID program initiative was developed to facilitate and advance the use of complex adaptive, Bayesian, and other novel trial designs in drug development. The intent was to focus on confirmatory trials designed to provide substantial evidence of effectiveness, and the CID program has also accepted exploratory trials in some instances. Master protocols are one such category of novel trial designs the CID program was envisioned to promote (U.S. Food & Drug Administration 2021)

Dr. James Travis of the FDA presents one example from the CID pilot program corresponding to a phase 2 master protocol designed to study chronic pain. The design can also be modified for use in a confirmatory study.

Overview of Study Design

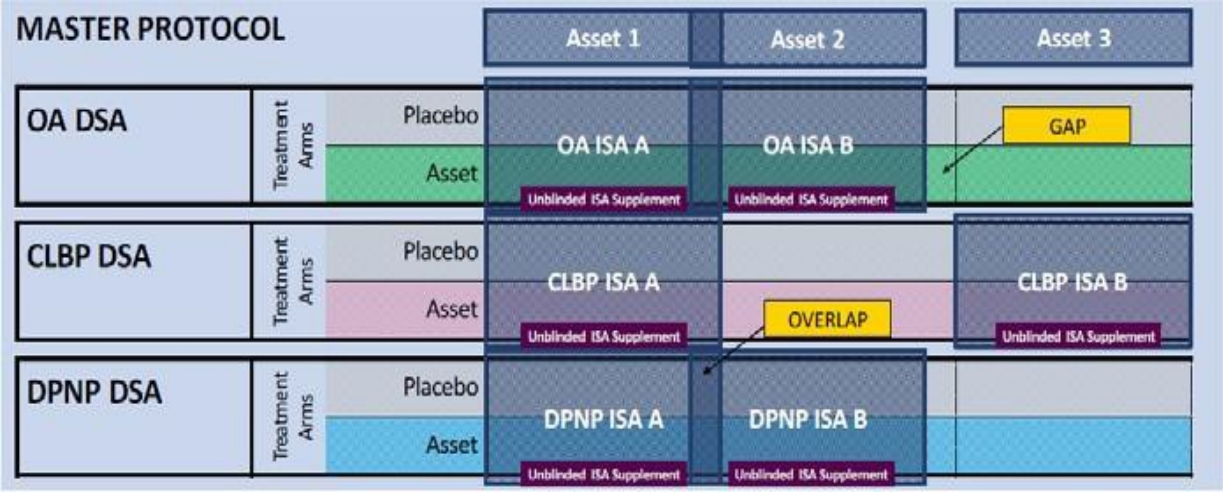
The phase 2 master protocol discussed here as an example, was designed to study multiple indications (e.g., types of chronic pain: osteoarthritis (OA), chronic low back pain (CLBP), and diabetic peripheral neuropathic pain (DPNP)) of interest to the sponsor. In this example, the sponsor also had 3 investigational products (IPs)/assets of interest for some or all types of chronic pain (e.g., Asset 1, Asset 2, and Asset 3). Figure 1 presents an outline for this master protocol.

Figure 1 also illustrates the use of 3 document types involved in the study design of a Master Protocol: the master protocol, disease state addendum(s) (DSA) and intervention specific appendix/appendices (ISA). Definitions for each of these 3 document types are provided in Table 1.

Table 1 Document Types in the Study Design of a Master Protocol

Document Type	Description
Master Protocol	Overarching Master Protocol; 1 per study
Disease State Addendum (DSA)	Document containing all the details that may be relevant for a particular disease; 1 DSA required for each disease type
Intervention Specific Appendix (ISA)	Document containing all the specific details; 1 ISA required for each 'disease type x asset type' study within the Master Protocol (e.g., 'OA x Asset 1' = ISA OA A, Figure 1)

Figure 1 Complex Innovative Design: Master Protocol Outline



OA=osteoarthritis; CLBP=chronic lower back pain; DPNP=diabetic peripheral neuropathic pain; DSA=disease-state addendum; ISA=intervention-specific appendix.

Overall, the study design for each individual ISA of this master protocol is similar to what would be expected for a chronic pain study, including an initial screening period, a washout time and preliminary data entry period, a baseline period, randomization and then a double-blind period followed by post-treatment follow-up. Endpoints used in a master protocol design can be common across disease types or specific to a disease type. In this study, pain intensity and overall improvement are considered common endpoints and physical functioning is considered disease specific, where physical functioning is expected to depend heavily on the disease type being studied. For this disease specific endpoint (e.g., physical functioning), the endpoint measure, change from baseline to endpoint for physical functioning, would be defined in each individual DSA per disease type (chronic pain type).

The endpoints used in this master protocol were proposed to be analyzed using a Bayesian MMRM-model including a treatment variable, baseline pain, region and any additional extra indices to reflect the different ISAs/DSAs.

Innovative Elements of Study Design

Two innovative elements found in this master protocol are: placebo borrowing and treatment borrowing. The concept behind placebo borrowing applies when there are multiple different studies, each collecting placebo information for the same disease (e.g., across ISAs within one DSA). The concept behind treatment borrowing applies when there are multiple different studies, each collecting treatment response information for one investigative product or asset between 2 or more disease types (e.g., within ISAs for one asset between different DSAs). In the chronic pain master protocol, both approaches use Bayesian hierarchical modeling based upon an assumption of exchangeability and choice of selections for the variance parameter specified by 'priors' for the parameter.

Exchangeability Assumption

Bayesian Hierarchical models rely on an assumption of exchangeability, where it is assumed that before seeing the outcome data, any ordering of outcomes is equally likely. With reconsideration for the

structure of the information in the model, borrowing can still occur if the assumption of exchangeability is violated. Such modeling considerations depend on what is known about the data going into the trial. Within the chronic pain trial example, a violation of exchangeability could be anticipated if different types of rescue medication could change between trials. Another violation of exchangeability that could be anticipated is if it is known prior to building a model for borrowing that one treatment is going to be more effective in a particular disease compared to another disease.

Considerations in Study Design

Key considerations when designing a master protocol similar to the one presented include the amount of borrowing, the modeling assumptions, and the assessment of priors.

Lessons Learned and Conclusion

There was a demonstration that borrowing data using Bayesian methods can increase the efficiency of later programs. However, this borrowing comes with a risk of bias when the necessary assumptions are violated, and this risk increases as more weight is placed on the previous data. In master protocols, this risk is reduced by alignment of the study design and conduct.

When borrowing treatment effects across different diseases for the same treatment, there are similar benefits and risks with placebo borrowing, i.e. the more reliance placed on the external data, the greater the gain in efficiency and the greater the risk of bias. The appropriate modelling approach needs to be more carefully considered for treatment effect borrowing than for placebo borrowing. In this context, it may be necessary to consider non-exchangeable methods, for example, methods that weigh data according to relevance, and more discussion and work is needed to further develop these methods.

In summary, there is definite potential scope for the use of master protocol designs and the corresponding methods of Placebo Borrowing and Treatment Borrowing in confirmatory studies. However, additional consideration of some of the lessons learned, including bias-variance tradeoff, issues in borrowing of treatment effect, and method limitations dependent upon modeling assumptions, such as exchangeability and the preservation of the integrity of randomization is needed.

Design and Analysis of Treatment Trials of Ebola Virus Disease

Michael Proschan, PhD, Mathematical Statistician, Biostatistical Research Branch, National Institute of Allergy & Infectious Diseases, NIH

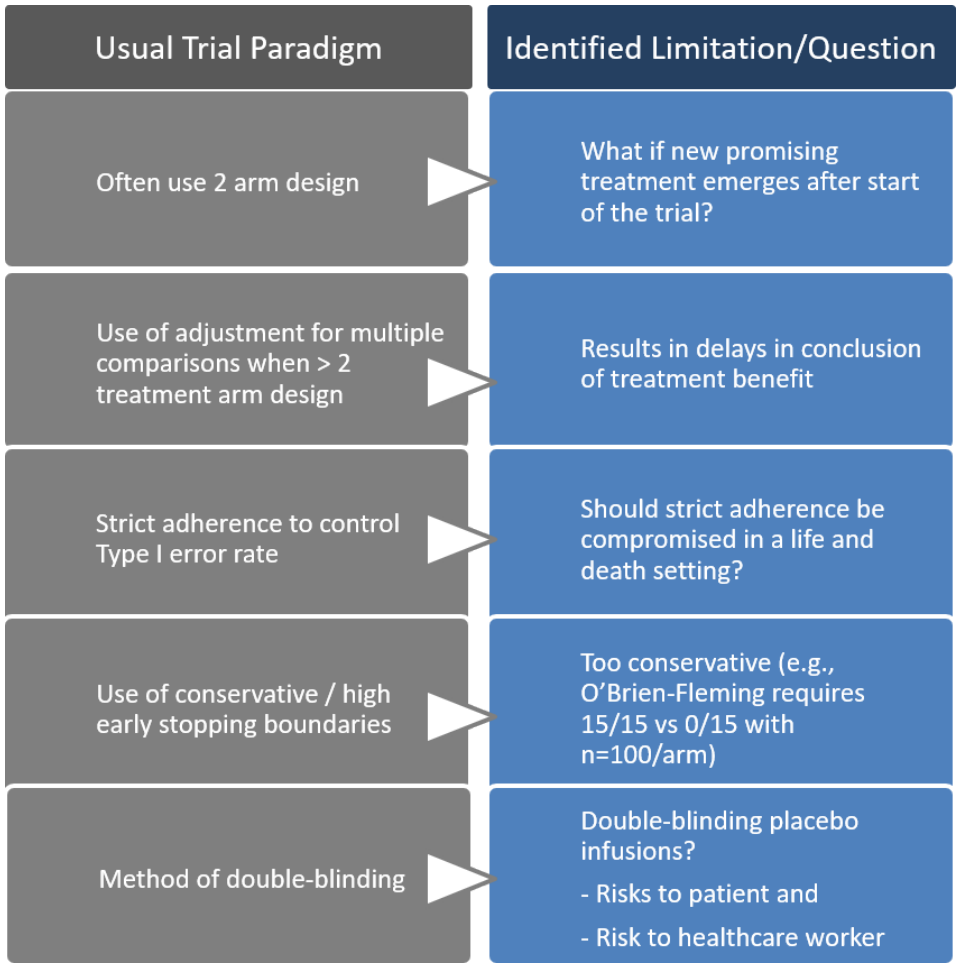
Dr. Michael Proschan of the Biostatistical Research Branch of the National Institute of Allergy and Infectious Diseases within the National Institute of Health (NIH) discusses the design and analysis of treatment trials outside of the usual clinical trial paradigm through the presentation of Ebola Treatment trials including the PREVAIL II trial in Western Africa (2014 to present) and the ongoing Pamoja Tulinde Maisha (PALM) trial in the Democratic Republic of congo (DRC).

Overview of Clinical Need and Inapplicability of the Usual Trial Paradigm

The Ebola virus is one of the deadliest viruses in the world characterized by a 50% mortality rate. Outbreaks such as the outbreak of 2014-2016 in Western Africa (28,000 confirmed cases and 11,000 deaths),and the outbreak of 2018-2020 in the DRC (2,500 cases and 1,700 deaths), with no proven treatments, present the need for the clinical development of lifesaving treatments quickly, and a unique circumstance in which the usual trial paradigm is found impractical in design and level of flexibility. As presented in Figure 2, the life-threatening circumstances of Ebola brought into question characteristics

traditional of a usual trial paradigm, including number of treatment arms, planning of treatment arms, adjustment for multiple comparisons, strict control for Type I error, conservative early stopping boundaries, and methods such as double blinding.

Figure 2 Usual Trial Paradigm Limitations Identified or Questioned in Ebola Treatment Trials



PREVAIL II Trial

The PREVAIL II trial employed a flexible platform trial design to compare ZMAPP + supportive care to supportive care alone for the treatment of Ebola disease, with primary outcome of 28-day mortality at investigative sites in Liberia, Guinea, and Sierra Leone. The flexible design allowed for the addition of promising new treatment arms and use of concurrent controls.

The design and flexibility of the PREVAIL II trial could not use multiplicity adjustments given that the number of treatment arms was to be determined concurrently in the process of the ongoing trial, with the possible addition of new agents. Concurrent adaptations to the trial design, albeit flexible and conducive to the inclusion of newfound promising agents, are problematic for the use of classical statistics, including the calculations of Type I error and determination of a p-value(s), based on a priori estimations/specifications.

In place of classical statistics, where all the possibilities of outcomes would need to be known a priori, the PREVAIL II trial calculated posterior probabilities based on total information (prior information + actual

data). To calculate posterior probabilities, it is necessary to specify prior opinion, preferably in a way that will quickly be overcome by actual data, in order to minimize the magnitude of influence of the prior opinion on results. Within the PREVAIL II trial, prior opinion was specified using a uniform beta-binomial (0,1) prior distribution (i.e., the equivalent of observing two people with disease, one of whom dies) on P (28-day death), the probability of death by 28 days, in each of the treatment arms. Total information (prior information plus actual trial data), was the equivalent of 2+n observations per treatment arm, so that prior data were only 2/2+N (total number of participants), which is less than 2% if n= 100 people per treatment arm.

The classical statistic, P value, was replaced with the posterior probability that the treatment probability of death was less than the controlled probability (i.e., standard of care) of death given the data and the classic corresponding confidence interval was replaced with the credible interval (lower limit/upper limit), such that a posterior probability that PT (probability of death on treatment) minus PC (probability of death on control) is between the lower and upper limit is 95%. In addition, an interim boundary was determined, to stop the trial for early evidence of efficacy if the posterior probability that PT < PC, given the data were at least 99.9%.

The Ebola epidemic during the PREVAIL II trial ended prematurely. At the time of this premature ending, 8/36 patients had died in the ZMapp+supportive care arm, and 13/35 in the supportive care arm. The posterior probability that ZMapp+supportive care was better than supportive care alone was 91% (95% credible interval = -0.34 to +0.06), suggesting evidence for benefit.

Pamoha Tulinde Maisha (PALM) Trial

The PALM trial also employed a flexible design, randomizing patients with Ebola at investigative sites in the DRC to treatment with ZMapp, Remdesivir (a direct, acting antiviral) or Mab114 (an Mab derived from a Congolese survivor), and REGN-EB3 (a triple, monoclonal antibody), added after 15/arm in the other 3 arms. A response adaptive randomization (RAR) design was considered in order to change probabilities to favor arms with lower mortality, but not chosen due to the large potential bias from temporal trends known to be problematic in infection diseases, such as seasonal effects, mutation of virus, and the introduction of vaccines.

The primary outcome of the PALM DRC trial was 28-day mortality, primary analysis was Boschloo's unconditional test (similar to posterior probability, seen in PREVAIL II trial), and a randomization stratified by cycle threshold of the amount of virus in the body (≤22 vs >22).

In Ebola virus disease 97% of the deaths occur within 10 days of randomization. For the purpose of reporting results, the PALM trial used a 10-day surrogate that included all patients who had at least 10 days of follow-up and all deaths up to Day 28, among those with at least 10 days of follow-up. This was done to minimize any bias estimate of the 28-day mortality, in a treatment arm.

Based on data presented in a DSMB Report in August 2019, using approximately 50% total information (681 patients enrolled; 375 with Day 28 outcomes) for the PALM trial, the DSMB made the recommendation to discontinue randomization of ZMapp and Remdesivir, report final results after all patients randomized by August 9th reached 28 days of follow-up, and continue randomization to the Regeneron product (REGN-EB3) and MAb114 in the extension phase of PALM, which will have a cap of 1500 patients.

Lessons Learned

Randomized controlled trials can be successfully executed in an infectious disease setting, like Ebola. Flexible trial designs allow for the addition of promising new agents/treatment arms during an ongoing trial, with comparison to concurrent controls. When using adaptive approaches for the reporting results

in place of classic statistics, such as p-values and corresponding 95% CIs, known to be limited by a priori assumptions and pre-specifications, it is important to note that using the O'Brien-Fleming boundary can be too conservative too early and there is less of a need to strictly control type one error rate in a deadly setting, such as Ebola. Despite the adaptability of Bayesian methods in place of classic frequentist statistics, the general audience still prefers to see results reported as p-values. A 10-day surrogate was a successful solution for minimizing bias estimates of the 28-day mortality and any consequence from lag in DSMB reporting due to fast enrollment.

Master Protocols and Clinical Trial Innovation

Speaker: Lisa LaVange, PhD, Professor and Chair of the Department of Biostatistics, University of North Carolina at Chapel Hill

Master Protocols Overview

The primary impetus behind the conception of master protocols is two-fold; the need for patients to undergo extensive evaluations sequentially to determine if they qualify for clinical trials of exciting new treatments, and the sponsors of those treatments competing for the same patients. With advances in precision medicine making the targeting of drugs possible and growing the understanding of tumor types or patient phenotypes, the eligible patient pool becomes smaller and smaller. As such, collaborations using a master protocol design(s) are of increasing interest to study multiple diseases, multiple patient subgroups (biomarker-defined), and/or multiple therapies under one, over-arching protocol (see Table 2). Patient advocacy groups often serve as the catalyst for creating the necessary collaborations, providing an appealing opportunity to patients to be screened for multiple therapies matched to each patient's biomarker profile under a single protocol (Woodcock and LaVange, 2017).

Regulatory and health agencies (e.g., FDA, NIH and EMA) are in active support of programs employing the use of master protocol designs, including the programs I-SPY 2, Lung MAP, PREVAIL II, ADAPT, and DIAN-TU (all actively supported by the FDA) and have made mention of master protocols in recent guidance (FDA 2019; FDA 2020). An FDA Guidance on master protocols for oncology drugs was issued in September 2018 (FDA 2018).

Table 2 Master Protocol Types

Type	Description	Example
Umbrella or Platform Trial	One disease, multiple drugs	NCI Match
Basket Trial	Multiple disease cohorts, one drug	B225 trial of imatinib
Exploratory Trial	Identify best treatment for biomarker-defined patient subgroup	I-SPY II
Confirmatory	Evaluate different targeted therapies relative to control for a single disease in parallel	Lung MAP

Note: most master protocols require regulatory buy-in and need sponsors willing to test drugs in collaboration with others.

Master protocols can realize efficiencies by capitalizing on common biomarker screening platforms, common data elements and procedures, and shared infrastructure. Two foreseeable avenues for innovation include:

- Establish a trial network with infrastructure in place to streamline trial logistics, improve data quality, and facilitate data sharing and new data collection.
- Develop a common protocol that incorporates innovative statistical approaches to study design and data analysis.

Innovative design possibilities for master protocols include:

- Adaptive randomization (response adaptive or covariate adaptive)
- The use of external or historical control data in single-arm studies, or in conjunction with concurrent controls (with 2:1 or higher allocation) to increase power; potential adaptation
- Sharing of control groups, when possible (e.g., within a specific pathway or biomarker-defined subgroup)
- Model-based analysis methods (e.g., hierarchical Bayes) for pooled analysis of multiple diseases, tumor types, markers, or body sites, etc.
- Precision medicine interim analysis to refine target subgroups during the trial, including adaptive enrichment

Lessons Learned

The dynamic nature of master protocols and adaptive platform trials is well-suited for the fast pace of precision medicine drug development. Developing infrastructure and establishing collaboration among multiple sponsors and stakeholders requires more investment in resources initially, but with the potential to produce savings as trials continue. Involvement of patient advocacy groups (e.g., Friends of Cancer Research for Lung MAP) enhances the ability to successfully launch a master protocol in a timely fashion.

Complex Innovative Design for a Basket Trial

Speaker: Vlad Dragalin, PhD, Vice President, Scientific Fellow, Janssen R&D at Johnson & Johnson

In this session, Dr. Vlad Dragalin presents the complex innovative design of a master protocol for a basket trial. In the last few years, there have been some very dramatic changes in the way drugs are approved. For example, many approvals had tumor agnostic labels, in the sense they were not limited to certain tumors but rather for a class of solid, genomic signature-driven tumors.

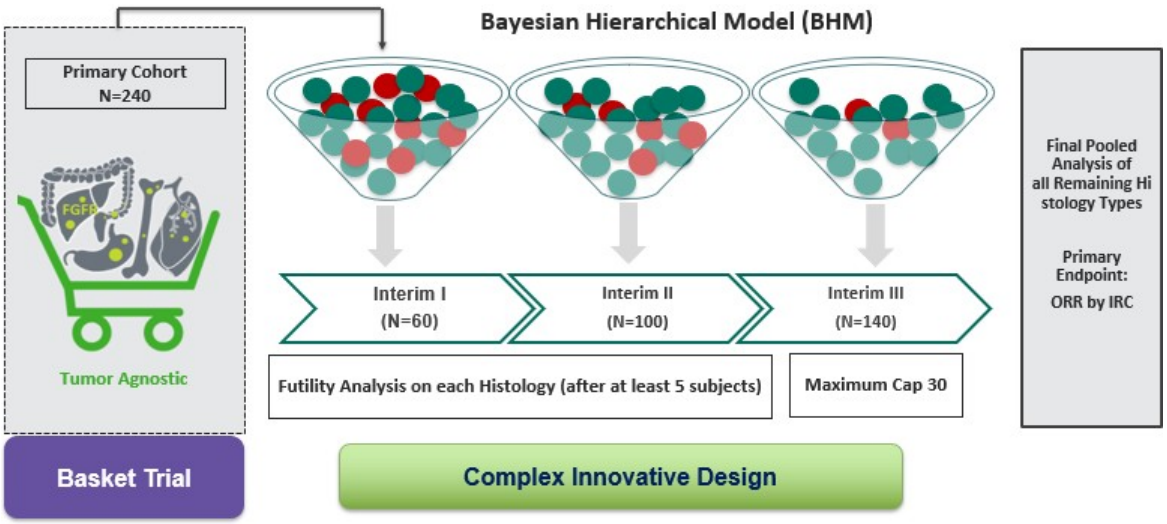
Balversa™ (erdafitinib) received U.S. FDA approval for the treatment of patients with locally advanced or metastatic urothelial carcinoma with certain FGFR genetic alterations in 2019. Consistent clinical activity and efficacy results in different histologies based on previous experience with erdafitinib and preclinical data showing inhibitory and anti-tumor activity in cell lines and tumor xenografts across multiple solid tumor types (e.g., breast, hepatocellular, squamous NSCLC) with FGFR alterations suggests potential for activity of erdafitinib to be consistent across solid tumors. It is of interest to recruit broadly across multiple histologies to validate histology-independent effects, but subgroups that are defined by histology may differ prognostically, and results will inevitably include random highs and random lows in terms of response rates. Therefore, there is a great emphasis on the understanding of tumor biology and the sensitivity of different FGFR alterations (mutations, fusions etc) to treatment. This understanding is arguably a “pivotal” source of evidence in a histology-agnostic development program. However, due to the uniqueness and complexity of FGFR in terms of the broad spectrum and types of alterations observed, compared to other receptor tyrosine kinase targets like EGFR and BRAF, an innovative Bayesian adaptive design is proposed with three planned futility analyses to identify tumor histologies for which the target FGFR mechanism might be confounded by alternative pathways. By screening out those potentially nonresponding histologies, a more homogenous effect is expected among remaining histologies, while exposing fewer patients to ineffective treatment. This would also allow enrollment of more subjects in the remaining histologies, particularly, those with rare solid tumors to provide more informative data about the activity of the erdafitinib to support a histology agnostic indication.

This study is planned to enroll a robust sample size of 240 subjects in the Broad Panel Cohort for primary histology agnostic analysis with capping of each histology at 30 subjects to mitigate the risk that the efficacy could be dominated by a single group.

Details from the proposed design for this study are provided in Figure 3 and included the following:

1. The three interim analyses and the futility criteria are pre-specified via a Bayesian Hierarchical Model that leads to efficient decision making by continuous learning as the data accumulate and allowing 'borrowing' of information across tumor histologies, where the strength of borrowing depends on the homogeneity of the data.
2. The futility analyses will be conducted on the prespecified tumor histologies when the enrollment in a histology is at least 5 subjects. A Data Review Committee (DRC), independent of the study team, has been established to review the interim data and make recommendations on futility.
3. If a few histologies are found futile at interims and stopped for enrolment, the primary analysis will be conducted on the pooled data excluding those histologies that met futility. In this case, a restricted histology-agnostic indication may be considered, excluding those histologies that were futile.
4. The final analysis will use the one-sided exact Binomial Test of ORR on the pooled data of all histologies which didn't meet the futility criteria for the Broad Panel Cohort. The same test will be used for the pooled data in the Core Panel Cohort.
5. The estimate of the primary endpoint ORR and its two-sided 95% confidence interval will be provided. As a supplementary analysis, the posterior probability of ORR > 25% for each individual tumor histology will also be evaluated that will provide further evidence of the contribution of each individual tumor histology that did not meet the futility criteria in the Broad Panel Cohort to the overall result of the final pooled analysis. Sensitivity analyses will be conducted to consider the impact of the tumor histologies that were deemed futile.

Figure 3 Basket trial with complex innovative design



Conclusions in the Utility of a Complex Innovative Design

To conclude, the study is designed to support a histology-agnostic indication (with or without restriction) if the vast majority of histologies are retained in the pooled analysis. The pre-planned adaptation enables the study to expose fewer patients to ineffective treatment in case of heterogeneous response across histologies, and to allow enrollment of more subjects with active or rare tumors. The design maintains statistical rigor that controls the pre-specified false positive error rates to enable the study for registration.

More general, complex innovative designs may be constructed to answer multiple study objectives by testing two or more hypotheses, to reach conclusions as quickly and as efficiently as possible, to address the small sample size per histology by borrowing information across tumor types for improved power, to employ more precise futility stopping, and efficient sample size allocation.

Session 3: Flexible, Efficient Decision Making: Complex Adaptive Design

Novel approaches for flexible and efficient decision-making in drug development may include the use of complex adaptive designs. Efficiency can be viewed from different angles to balance correct decision-making as early as possible for a drug development program with cost effectiveness and quantification of multiple metrics to measure "success" of a trial. An example of a complex adaptive trial design in lupus submitted to the Complex Innovative Trial Design (CID) Pilot Program was presented. An example of a platform trial in the infectious disease area was presented to illustrate a Bayesian approach to utilize longitudinal data for developing a predictive model for the long-term clinical outcome. In confirmatory settings, the use of a basket trial was used to illustrate the effect of adaptive trials on cost effectiveness and feasibility of drug development in rare diseases and/or subgroups of common diseases like cancer. A final presentation proposed an optimal adaptation rule in sample size re-estimation design that maximizes return on investment, a metric to balance time to market, trial costs, and probability of success with the goal to efficiently deliver safe and effective medicines to patients.

Considerations for Complex Innovative Designs: A Case Example

Speaker: Cesar Torres, PhD, Statistical Reviewer, Office of Biostatistics, Division of Biometrics 3, FDA

Dr. Cesar Torres presented innovative elements and design considerations from the initial proposal through the revised proposal for a case example of a complex innovative design for a Phase 2b study in the treatment of systemic lupus erythematosus (SLE) patients randomized to 1 of 4 treatment arms ([placebo, low dose, medium dose, or high dose] + standard of care.

Initially Proposed Innovative Elements

The initial innovative elements included interim analyses (IAs), response adaptive randomization (RAR, a procedure in which the randomization ratio of the ongoing study is modified based on interim study data, typically in a manner that prioritizes treatment arms with more promising interim results) hypothesis test adaptation, and primary endpoint adaptation. Initially 8 IAs were proposed for this study, so that RAR would take place during the 1st through 7th IAs and futility determinations during the 2nd through 8th IAs.

In the RAR procedure, the probability of being randomized to placebo was to remain fixed at 25%. However, after each IA, the randomization probability for each investigational product (IP) dose level could be changed based on observed Week 24 clinical efficacy results. During the futility determinations, futility was to be declared if for each IP treatment arm d, the probability of the response rate difference between IP and placebo being greater than some pre-specified fixed value δ is less than 0.025.

Pre-specified adaptation for hypothesis testing was to be performed at predetermined interim analyses, selecting one of 2 approaches. The first approach pooled data from the different IP treatment arms into 1 group for comparison to placebo and did not use a multiplicity adjustment procedure. The second approach compared the best individual dose to placebo and used a multiplicity adjustment procedure. A separate adaptation was also to be performed such that at some predetermined interim analysis, the primary endpoint could be replaced with one of two other primary endpoints, with all three of these binary endpoints sharing similar components. Due to the similarity of these components, within a given patient it was possible to expect for the response state to be correlated not only across different time points, but also across the three endpoints.

Design Considerations from FDA Perspective

Before the first meeting between the FDA and the sponsor to discuss the CID proposal, the FDA provided comments to guide the sponsor's preparation of the meeting briefing materials, based on the brief description of the proposed CID included in the sponsor's request to be accepted into the FDA's CID program (Table 3).

Table 3 Design Considerations from an FDA Perspective

Design Consideration	Rationale/FDA Perspective
Large number of nuisance parameters to be considered	e.g., the placebo response rate; the patient enrollment rate; the joint distribution across different time points and across the different potential primary efficacy endpoints; and the lag time cutoff to the interim analysis completion
High dimensionality of the CID (given large number of adaptations, potential dose-response relationships, and nuisance parameters)	Possible difficulties for conducting an adequate simulation study that would both comprehensively explore the space of the design and be summarized in an easily interpretable manner.
Interim data being used to adapt the primary efficacy endpoint and/or adapting how patients would be grouped in the primary analysis	Effectively leads to the clinical question being addressed in the primary analysis being dictated, in part, by the interim data.
Patients entering the study toward the beginning of the accrual period may differ from those entering the study toward the end of the accrual period despite fixed inclusion/exclusion criteria.	Use of the RAR procedure could lead to systematic imbalances across the different treatment arms (including placebo) with respect to potentially prognostic baseline characteristics, which could in turn introduce bias in treatment effect estimates and lead to possible ambiguity in the clinical question being addressed.
The meeting requests suggested that the simulation study would only consider dose response relationships that are monotone non-decreasing (i.e., the dose response relationship increases or it stays level with increasing dose—placebo low, medium, or high—but it never goes down).	FDA suggested to the sponsor that to have a comprehensive understanding of the design's operating characteristics, it should consider a variety of shapes for the dose response relationship, such as an "umbrella" shape, where response will be increasing by placebo, low, medium, before dropping off for the high dose.

Changes to Study Design based on FDA Feedback

In response to FDA pre-meeting feedback, the sponsor made some changes to the study design.

1. A few adaptive elements were removed. Specifically, the primary efficacy endpoint will no longer be adapted, and be fixed as SRI-4 response at Week 52. Also, the pre-specified primary analysis will no longer allow for the possibility of pooling the investigational product dose arms into one group to be compared to placebo.
2. Additionally, it was stated that the primary analysis will use a Bayesian hierarchical model. The null hypothesis is that for each dose level of the investigational product, the response rate equal to or at most as high as the placebo response rate.

Upon reviewing the additional details of the study design and the simulation report, the FDA had additional points for the sponsor to consider:

1. First, the simulation report explores only a small subset of the multidimensional space of nuisance parameters. For some operating characteristics being evaluated, only one value was considered for each of a number of nuisance parameters, such as the placebo response rate. The FDA recommended that for each nuisance parameter, the range of plausible values to be explored be justified.
2. The information submitted included comparisons to other designs with inefficient multiplicity control procedures (e.g., Bonferroni corrections). The FDA suggested that the sponsor's conclusion could be strengthened by comparing to more efficient multiplicity control procedures, such as a step-down hierarchical testing procedure.
3. The sponsor concluded that the use of RAR leads to increased power due to more patients being randomized to the more effective doses. However, this conclusion was based on the comparison to a design with a fixed 1:1:1:1 randomization ratio. The FDA suggested that the sponsor's conclusion could be strengthened by comparing the proposed CID to other designs also attempting to allocate patients to more promising treatment arms, such as arm-dropping designs.

Value Added by CID

Evaluating added value of the complex or innovative elements of a study design can contribute to the motivation behind the use of this design and a willingness to accept the added uncertainties that come with the CID. With that in mind, a good practice is to make fair comparisons against competitive alternative designs.

Lessons Learned

Lessons learned from the interactions between the FDA and the sponsor regarding the CID proposal, not specific to the protocol presented herein, included:

1. When incorporating complex or innovative elements into the study design, one should not lose sight of the specific pre-specified question of clinical interest.
2. The use of complex or innovative elements, such as response adaptive randomization and Bayesian hierarchical models, may be acceptable for a registrational study. However, care should be taken to maintain desirable design features, such as adequate type I error control,

appropriate point estimate reliability, and a lack of systematic imbalances between treatment arms.

3. To ensure the feasibility of comprehensive evaluations of the design's operating characteristics, the selection of adaptive elements should be judicious. The full plausible range of nuisance parameters to be evaluated should be justified and should be covered in the simulation study.

Improving Efficiencies in Drug Development Through a Platform Trial

Speaker: Kyle Wathen, PhD, MS, Vice President, Scientific Strategy and Innovation, Cytel

Dr. Kyle Wathen presented an example of a platform study completed at Janssen Pharmaceuticals, including predicting later stage outcomes from data available in earlier stages in the hepatitis disease area, the use of the Bayesian framework in making decisions, the interpretation of simulation results, the improvement of the actual platform, and an R package built over the course of 5 platforms, currently available for public use.

Platform Trials: An Introduction

A platform trial is an experimental infrastructure designed to evaluate multiple treatments and/or combinations of treatments in heterogeneous populations of patients. A platform trial is different from a multiline trial in that not all interventions are included or even known at the start of the platform.

Typically, when setting up a platform, whether internal or external, there would be several compounds in the near future that would be of interest to evaluate. In a platform trial, it is possible to leverage not only information, but resources to conduct the trial. In place of a typical protocol, the platform trial is separated into a master protocol and one or more Intervention Specific Appendices, or ISAs. So as the new compounds become available, the master protocol does not change, and instead, a new appendix is added. Each ISA includes the experimental compound for evaluation, as well as the control, allowing a direct comparison and guarantee of information about control for each ISA. In addition, the borrowing of control data across ISAs reduces the number of patients treated with control over the life of the platform.

The platform trial may allow for early decisions on a compound development much sooner, benefiting sponsors. This acceleration in decision making is very helpful in drug development. From the trial participant's perspective, eliminating the compounds that were inferior sooner minimizes the risk of receiving inferior therapy. Furthermore, graduating effective compounds to the next developmental phase more quickly promotes earlier access to effective therapies for patients.

R Package

The open-source R package ("OCTOPUS") allows the evaluation via simulations of many scenarios to leverage the many similarities from one platform to the next, without the need to reinvent the wheel. The package allows for new code in R source, that allows for new extensions, such as outcomes or analysis to be added easily, and is transparent, developed in a language that which many statisticians are familiar and find easy to read.

The name of the R package developed for use in platform trials is OCTOPUS, which stands for Optimize Clinical Trials on Platforms Using Simulations. A couple key features of OCTOPUS include that it has

random or fixed entry times for the ISA, allowing for a time range, so that variability is modeled within the simulation. Each ISA can have different modeling and decisions.

The information sharing from ISAs to ISA is specified at the ISA-level. So you could have one ISA and completely ignore the others, if applicable. The platform allows the flexibility to add patient new simulators, new analysis, new randomizers, etc., and any number of simulated outcomes. In addition, the R package allows for covariates and the ability to have subgroup-specific decisions.

Efficiency and Type I Error Control of a Generalized Confirmatory Basket Trial Design

Speaker: Robert A. Beckman, MD, Professor of Oncology and of Biostatistics, Bioinformatics, & Biomathematics, Georgetown University Medical Center

Introduction

Basket trials are applicable across many therapeutic areas, including within rare diseases and cancer. There are up to 7,000 different rare diseases and an estimated 30 million sufferers in the U.S. alone; about half of whom are children suffering from progressive debilitating and lethal diseases. In cancer, molecular subtypes create orphan or niche indications in which it's challenging to enroll all the patients with that mutation. This shift to the molecular view of cancer in turn requires a corresponding paradigm shift in the drug development. Additional key concepts of basket trials are presented in Table 4.

Table 4 Key Concepts of a Basket Trial

Design Consideration

• Multiple tumor types, diseases or population groups with one drug and one predictive biomarker or other unifying characteristic.
• Evaluation often based on pooled analysis
  ○ Pooling can be partial in some designs, based on Bayesian hierarchical model. Degree of pooling can be adjusted based on data.
  ○ Indications are considered individually (i.e not pooled) in some designs. In such designs, the basket is more of an operational tactic.
• Premise that molecular subtype or other unifying characteristic is more fundamental than tumor type or other traditional classification
• Single sponsor or consortium
• Opportunity for multiple indications for the sample size of one: dramatic patient and resource savings

Sources: Beckman et al, 2016; Chen et al, 2016.

Common Features of Basket Trials

Basket trials have largely been exploratory and opportunistic in nature. They have mostly been single-arm trials with overall response rate as a primary endpoint. They often use pooled populations for primary analysis to gain broader indications across tumor types. Some confirmatory trials have been performed, but typically involved transformative medicines in patients with great unmet need and exceptionally strong scientific rationale for which single arm trials based on response rates may have been appropriate in the confirmatory setting, despite their limitations.

A New Type of Basket Trial: The Generalized Randomized Confirmatory Basket Trial

Because of pooling, basket trials have the possibility of highly significant increases in efficiency, likely the greatest efficiency increase opportunity of any master protocol or complex innovative design. Basket trials have primarily been employed in exploratory settings, but the majority of the trial participants, and the majority of resources and time expended in development are associated with the confirmatory phase. If basket trials could be generally applied to the confirmatory phase, the increase in development efficiency could be very substantial, dramatically reducing the cost, required number of research subjects and timing of drug development, and thus increasing the accessibility of life altering therapies to patients.

Basket trial designs used to date, often single arm trial based on response rate endpoints, have common issues. Clinical data to support pooling may be limited and the treatment effect may vary between tumor types, pointing to the requirement for significant prior evidence before pooling or borrowing in the confirmatory setting. The basket trial designs that were appropriate for transformational drugs may not be appropriate for the majority of drugs that are effective but not transformational. Not all drugs hoped to be transformational live up to the promise, and sponsors may be biased in believing their drugs are transformational. Response rates may not predict overall survival due to intra-tumoral heterogeneity and tumoral evolution leading to relapses, and are therefore imperfect indicators of clinical benefit. Single arm trials are subject to patient selection bias and other biases enter when comparisons to historical controls are undertaken., Predictive effects of the biomarker on which the basket trial is based will be confounded with any prognostic implications of the marker whenever a single arm design is used.

The pathway design subgroup of the Drug Information Association Innovative Design Scientific Working Group sought to develop a generalizable confirmatory basket design incorporating statistical rigor that would be applicable not only to exceptional cases, but to all effective medicines in any line of therapy (noting that the majority of effective drugs are not exceptional) and following existing accelerated and standard approval pathways to increase potential approvability.

The development of generalizable confirmatory basket designs, by greatly enhancing development efficiency, could lead to increased and accelerated access to effective medicines for patients in niche indications, as well as providing sponsors with cost-effective options for development in niche indications, and providing health authorities with more robust packages for evaluation of benefit and risk.

The general design concept for confirmatory basket trials, which resembles a funnel, is presented in Figure 4, where each of these shapes represents an indication. These indications should be selected carefully, in analogy with a basket of fruit. If you have one moldy fruit in the basket, it might spoil the whole basket, or in a statistical terms, an indication in which the investigational therapy is ineffective might dilute the signal from the active indications. Features of the design are outlined in Table 5.

The design controls Type I error with respect to the pooled basket, against a null hypothesis in which the drugs does not provide benefit in any of the included indications. It maintains high power and, for k indications, can approach a k-fold improvement in efficiency, i.e. a 200-500% efficiency increase.

Figure 1 General Design Concept

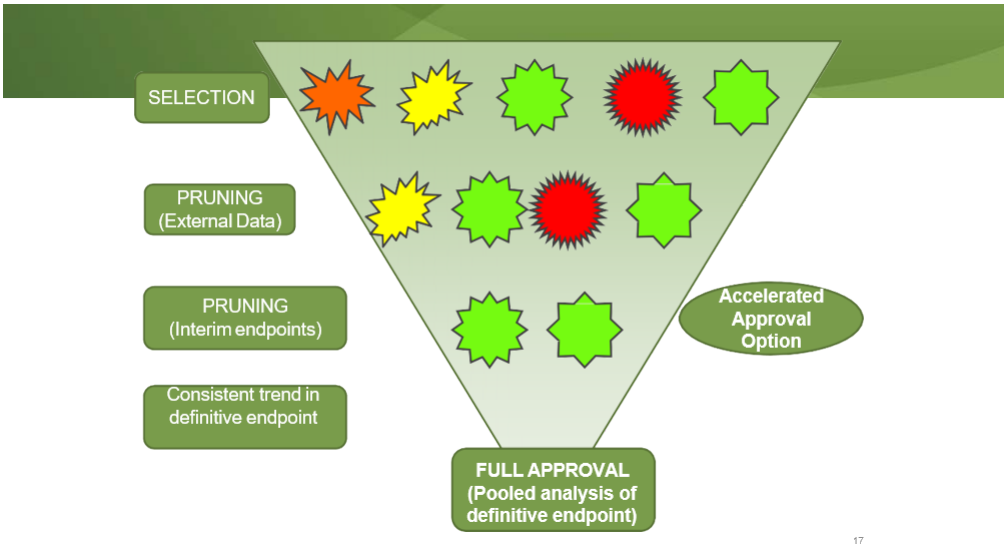


Table 5 Features of the Generalized Confirmatory Basket Trial Design

Design Features
• Indications are further "pruned" if unlikely to succeed based on: 1. External data, maturing definitive endpoint from Phase 2 or other data 2. Internal data on surrogate endpoint or partial information on definitive endpoint • Sample size of remaining indications may be adjusted based on pruning: design may not be suitable for ultra-rare indications • The Type I error threshold will be adjusted to control type I error (false positive rate) in the face of pruning based on internal data that is re-used, where pruning based on external data does not incur a statistical penalty • The study design is compatible with a randomized controlled study stratified by indication cohort. Although not preferred, single arm response rate-based designs may be used • The study is positive if the pooled analysis of the remaining indications is positive for the primary definitive endpoint ○ The remaining indications are eligible for full approval in the event of a positive study ○ Full pooling chosen for simplicity of indication definition in an approval label ○ Some of the remaining indications may not be approved if they do not show a trend for positive risk benefit as determined by definitive endpoint. Criteria for this subgroup analysis should be pre-agreed with health authorities.

Adjusting for Pruning

Type I error control in the design above is affected by pruning, in that the indications that are not pruned at interim may be randomly high due to chance, given that this data is then re-used. However, it is possible to determine the statistical penalty required to compensate for this phenomenon. By working towards a lower nominal type I error rate, which can be calculated, the type I error will be inflated to 0.025 based on the inflation due to the design.

Control of FWER by Indication Subgroups, and an Extension of the Original Confirmatory Basket Trial Design

Some authors have argued that Type I error in a confirmatory basket trial should be controlled by indication subgroup, often referred to as strong control of the family-wise type I error rate (FWER) by indication subgroups. This may be seen as exceeding the rigor of traditional phase 3 studies, in which type I error is formally controlled only for the overall population, not for the many subgroups of relevant prognostic factors which always exist in these populations. Subgroup analyses are done in a more ad hoc fashion. The possible requirement for increased rigor in the context of a confirmatory basket trial may be due to the fact that the definition of the overall population is novel in basket trials, and in fact the indication subgroups are defined by criteria that traditionally define the overall population. The need for control of FWER may depend on if the scientific and medical evidence is sufficient to convincingly justify "redefining the disease" by pooling. In any case, there is a practical need for an extension of the original confirmatory basket design that provides control of the FWER by indication subgroup, in case it is requested in discussions with health authorities.

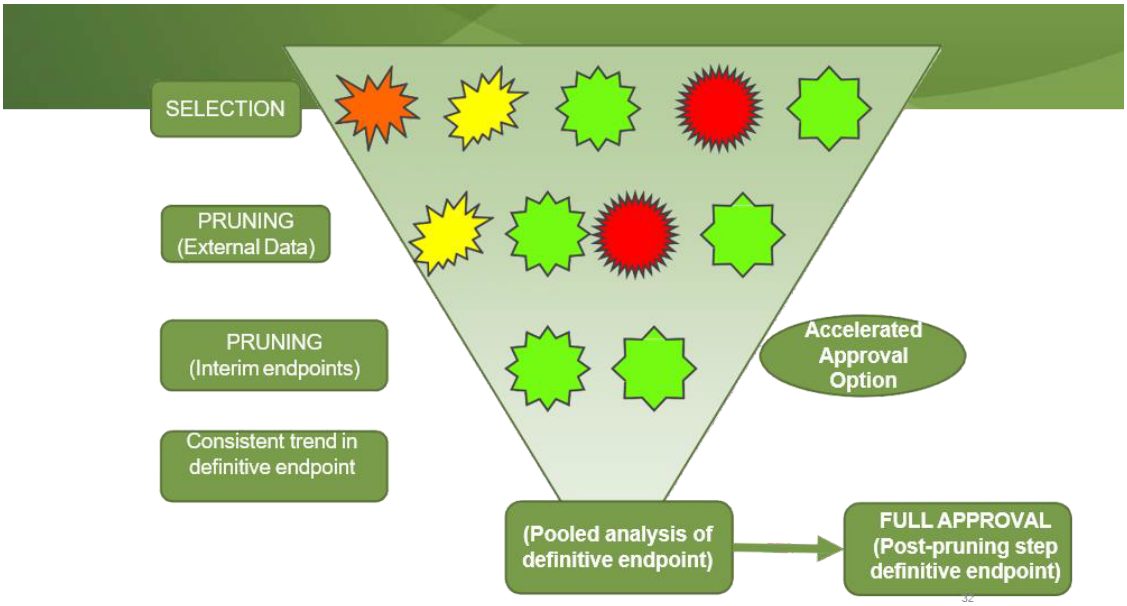
Control of FWER by indication subgroup involves viewing a false positive as any situation in which one or more indications in which the drug is ineffective ("negative indications") is included in an approved pool. For example, one or more strongly positive indications in which the drug is effective can drive an overall pooled positive result and carry along any corresponding negative indications. Simulation of FWER involves a large number of potential cases and the degree to which active indications are active affects the results. A recent study simulated a Bayesian basket trial design using a Bayesian hierarchical model and found FWER of up to 57% (Cunanan et al, 2017).

We characterized the performance of our original design with respect to FWER by indication subgroup, while varying input parameters. However, using the original design we could not control FWER by subgroup at reasonable power levels. Accordingly, we modified the design as shown in Figure 5, to include a post-check of each indication subgroup at low statistical stringency. The FWER is controlled by the cumulative effect of three successive checks: the first by individual indication at the interim analysis ("pruning"), the second on the pool at the final analysis, and the third on each of the individual indication if the pooled analysis is positive.

Simulations were performed on many thousands of scenarios encompassing the challenge of the large number of potential cases. All designs were required to control the FWER by indication subgroup at the level that would have been associated with parallel development of all indications in randomized studies. They were also required to meet rigorous criteria with respect to estimation bias and estimation of the confidence intervals.

Results showed that it was possible to improve efficiency by 40-170% compared to traditional designs while meeting the rigorous requirements stated above including control of FWER by subgroup. This is still a very large improvement in development efficiency (platform trials may give a maximum of 40% increase in efficiency under optimal conditions), although not as large as can be achieved using the original design. It is recommended to discuss with health authorities to see if control of FWER by indication is required, especially given that opinions on this topic may evolve. The original design is preferred if control of FWER by indication subgroup is not required, the new design if this FWER control is required.

Figure 2 Characterization of Performance Constrained by FWER (Strong Control of False Positive Rate)



Conclusions

It is feasible to create a general design concept for a confirmatory basket trial that is suitable for many agents, not only transformational ones as has been observed to date. Such a design can be used whenever a randomized design with time to event data is required, a more rigorous approach. Multiple challenges can be addressed with careful planning and maintaining a 1.4 to 2.7-fold advantage in efficiency. Still larger improvements in efficiency are possible if formal control of false positive rate by subgroups is not required. This is normally not required in Phase 3 studies, but requirements for confirmatory basket trials are an evolving discussion topic.

Benefits to using the confirmatory basket trial design include increased and earlier patient access to targeted therapies for small subgroups, cost-effective methods for sponsors to develop targeted agents in small subgroups, and more robust datasets for health authorities to assess benefit-risk in these small patient groups.

Optimal Sample Size Re-estimation in Adaptive Design based on Return on Investment

Speaker: Yi Liu, PhD, Executive Director Biostatistics, Nektar Therapeutics

In this session, Dr. Yi Liu reviews the most common adaptive design in pivotal trials (i.e. sample size re-estimation design) and proposes the use of financial metrics beyond statistical power for the “right” sample size calculation to more efficiently deliver safe and effective medicines to patients.

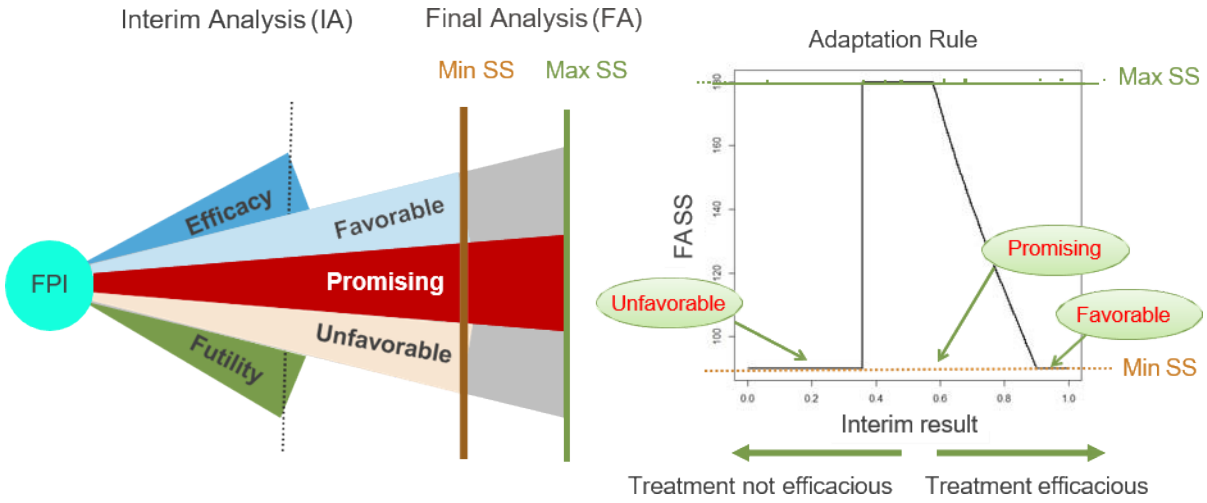
Sample Size Re-estimation Design for Pivotal Clinical Trials

Sample size re-estimation (SSR) designs are most often used for pivotal phase III trials and can be the only adaptive feature or used in combination with other adaptive features. Traditional study size determination is based on an assumed treatment effect, often inaccurate, however, the use of an SSR

design allows the use of the interim estimate of the treatment effect to better determine the "right" study size. Corresponding concerns with the use of an SSR adaptive design include potential Type I error rate inflation, and (statistical or operational bias), in treatment effect estimation.

SSR design is typically planned based on an optimistic treatment effect assumption with a minimum sample size for the final analysis (FA). Then depending on the interim analysis (IA) results, sample size for FA can be increased with a cap at the maximum equivalent to observing the smallest clinically meaningful treatment effect. If interim result shows overwhelming efficacy, i.e. "efficacy zone", the trial can be stopped early for success. On the other hand, if the interim result indicates very little chance of success at final analysis, i.e. "futility zone", the trial can be stopped early for futility. Otherwise, there are three additional scenarios: "favorable zone" - if interim result is favorable although not statistically significant, the trial will remain as planned with the minimum sample size; "promising zone" – if interim result is not favorable but promising, then sample size will be increased to improve the probability of success at the FA; "unfavorable zone" - if interim result is not promising but not futile either, the study will keep the original planned sample size. Therefore, sometimes SSR designs are also called five-zone adaptive designs as shown in Figure 6 (left panel).

Figure 3 SSR Design concept and adaptation rule illustration



Note: SSR design concept (on the left) where interim result is divided into five zones: starting from first patient in (FPI), the trial stops at IA in efficacy or futility zone, minimum planned sample size (Min SS) will be used for FA in favorable or unfavorable zone, sample size will be between minimum and maximum planned sample size (Max SS) in promising zone; An example of sample size adaptation rule where FA sample size (SS) is a function of the interim result (on the right).

Moving beyond Statistical Power in Determining the "Right" Sample Size by Linking Trial Success with Financial Return

When interim result falls into the promising zone, how the "right" sample size for the FA is re-calculated largely determines the performance of the design. Traditionally, sample size is either re-calculated to achieve a certain level of conditional power (e.g, 90%, which is the same as the design level), or updated by assuming the interim observed treatment effect is the truth. Both approaches focus on statistical power, i.e. probability of a positive trial. However, statistical success may not automatically translate into regulatory or commercial success. There are many assessments to be made by the regulatory

agency (e.g., the benefit/risk ratio assessment, the totality of the data), and one of the key assessments of the data is to evaluate the magnitude of treatment effect compared to the current standard of care. In addition, regulatory success does not necessarily translate to the drug being widely used by patients, which is also dependent on the competitive landscape at that time.

Is it possible to link sample size beyond statistical power, for the goal of providing promising drugs into the hands of the patients? To answer this question, cost of clinical trial (decomposed into a fixed cost and the cost per patient times sample size) and revenue of drug sales (that is generated if the drug is approved and accessible in the market) must be co-considered in the context of the 3 components: probability of trial success, market share (measured in patient year as function of treatment effect and market time) and price (measured in dollar amount per patient year as function of treatment effect).

Then the goal is to re-calculate SS based on maximized return on investment (ROI) defined as the difference between revenue and cost. Study timelines are affected by sample size as well, and this can be considered along with their effect on ROI. This provides a simple, yet realistic framework to link the sample size of a pivotal phase III trial to a financial metric, which to some extent can serve as a surrogate for maximal patient benefit. This in turn moves beyond statistical success of trials to focus on optimal resource utilization. It is important to note that sample size adjustment within a given trial may recommend large sample size increases that are optimal for that trial when power is considered, but not optimal for the portfolio if they take too many resources from other programs (Chen and Beckman, 2009a, Cong et al, 2009b, Chen and Beckman, 2014, and Antonijevic 2016).

Summary

Adaptive designs using sample size readjustment are more flexible and typically gain efficiency when there is uncertainty about the true treatment effect at the initial planning phase of pivotal trials. However, blindly increasing sample size to increase a high statistical power may not lead to efficiency on the study level, as well as at the portfolio level. Financial metrics, such as ROI, incorporating both the treatment effect, as well as study timeline, provide additional insights and different perspectives in comparing these different design strategies at the planning stage.

The calculation of ROI is a complicated process that requires cross-functional inputs, discussions, and finalization, and it must be tailored to each specific situation. It is important to look beyond statistical power and use alternative metrics when evaluating adaptive designs.

Day 2 Keynote Address

Speaker: Gianna McMillan, PhD, Bioethics Institute, Program Administrator; Loyola Marymount University

During the Session 4 keynote address, Dr. McMillan shared her experiences as a patient advocate, both personally and with local and national IRBs. Twenty-five years ago, Dr. McMillan's son was diagnosed with medulloblastoma. She was encouraged to enroll her son into a clinical research trial, but she and her husband did not understand clinical research. Their understanding was that they would complete a list of trial procedures and then have a healthy child. The standard of care at that time involved intense radiation that caused significant neurological damage. The trial they participated in used low-dose radiation with concomitant chemotherapy that had not previously been used in children.

One of the chemotherapy drugs was known to have a 40% chance of causing mild hearing loss and a 20% chance of severe hearing loss. After 3 of the 5 planned rounds of chemotherapy, her son had significant hearing loss. Dr. McMillan approached the physician about the hearing loss and was asked "do you want a deaf kid or a dead kid?" This was the event that caused Dr. McMillan to educate herself and become a patient advocate. She and her husband spoke with the research team, and the chemotherapy drug was stopped for her son (the other drug was doubled), and her son remained in the trial.

When they finished the clinical trial, it was an abrupt closure with no exit interview and no follow-up. They never received trial results, and there was no closure to the experience. Her child lived, but he had significant hearing loss and physical and cognitive disabilities. They had been a success story but didn't know it, and it took years of education for Dr. McMillan to discover this on her own. Ten years later, Dr. McMillan was the community member on an IRB at the same institution where her son was treated. She compared the consent form for the latest version of the same protocol with the original to see what had changed. She realized the research team had learned several important points from her child's experience 10 years earlier:

- There is a 20% chance of mild loss in hearing and a 40% chance of significant hearing loss.
- Even with lower dose radiation, the subject needs to be followed with CT scans for secondary cancers.
- There are latent effects of radiation that required neuropsychological evaluations and early school interventions.

Dr. McMillan started a support group for families whose children have brain tumors, which grew into a state-wide non-profit that has supported hundreds of families. She discovered her story was not unique. Most parents with a child in a medical emergency do not understand the context of their child's situation in relation to medical care or research. These parents are asked to participate in a large enterprise where they are at a distinct disadvantage and are not treated as a full partner in the research enterprise. The current consensus, she says, is that when a patient signs an informed consent, they are waiving their rights to the knowledge that was gained from the trial.

Investigators are well qualified and well intentioned, but they can be so focused on their trial goals that they miss why context is important for other parties. Patients have something to offer, and they can be more helpful if they understand why their participation is important. In general, all stakeholders are well intentioned but tend to be siloed because each has their own set of priorities. This is understandable.

The research community is now beginning to understand that all members must work together for a better, stronger, more efficient whole.

> *Patients have something to offer, and they can be more helpful if they understand why their participation is important.*

Compared with 25 years ago, the dispersal of information is much easier with the internet. Additionally, Investigators are encouraged to collaborate, share funding, leverage resources, and enhance efficiency. For an innovative trial design to be effective, all stakeholders must be involved. Patients and caregivers need to know what it is and why it is necessary. Advocates need to know how to explain it to their communities, and they need the tools to do so. There are other options; an innovative trial design is an option, and Investigators need to know it. The subjects and their families and caregivers need to know it. It is the responsibility of the collective research community to educate them.

Session 4: Bayesian Designs: Continuous Learning and Decision-Making

Through the CID Pilot Program afforded by PDUFA VI, the FDA supports the advancement and use of Bayesian clinical trial designs. The Bayesian framework enables continuous learning from various data sources and provides decision-makers with straightforward probabilistic statements. This session promoted the use of Bayesian approaches in CID by presenting case studies in broad therapeutic areas, including rare diseases and highly prevalent chronic disease and discussed success stories, challenges, and opportunities to facilitate drug development.

The Value of Bayesian Approaches in the Regulatory Setting: Lessons Learned and Opportunities

Speaker: Telba Irony, Ph.D. Deputy Director, Office of Biostatistics and Epidemiology, CBER – FDA

A Bayesian approach is a mathematical method to synthesize and express prior information for a clinical study. Obtaining comprehensive and appropriate prior information may be difficult, but it is increasingly being done including for trials for rare diseases. Good examples are phase 2 studies being used to inform phase 3 studies, and adult prior information being extrapolated to a pediatric population. The FDA Center of Biologics Evaluation and Research (CBER), in collaboration with the National Organization of Rare Disorders (NORD), is conducting a pilot natural history study to be used as prior information for a rare disease clinical trial with the intent to reduce the number of patients randomized to the control group.

The challenge with using prior information is determining what is suitable prior information and the degree of exchangeability of the prior studies with the current study. Some of the factors to consider when determining the use of prior information and adaptive designs:

- Regulators should agree in advance with the choice of the prior.
- Selection bias must be avoided. Examples include when unfavorable prior information is omitted for the treatment group or favorable prior information is omitted for the control group.
- Subjective priors should be avoided; they need to be obtained from valid data sources.
- Control for false positive rate ("type I error") should be relaxed to use prior distribution.
    - The strength of new evidence necessary to make a decision may be determined by factors such as: rarity of the disease (availability of participants for the trial), medical need, patient tolerance for risk and perspective on benefit, and the severity and chronicity of the disease.
- Hierarchical models can be used to dynamically discount the prior information depending on the degree of similarity among the prior studies and current study.
- The current study sample size will increase as borrowing decreases.
- Adaptive designs provide flexibility and can be advantageous for example by reducing or increasing the size of the clinical study as needed based on predictive distributions. This can prevent unnecessary enrollment, enable faster decision regarding the efficacy and safety of the investigational product, and potentially increase the probability of trial success.
- Simulations to estimate and control error probabilities should be conducted at the design stage with a comprehensive number of scenarios. Simulation design requires clinical input and significant effort from biostatisticians. Resources spent designing a Bayesian adaptive trial and conducting simulations are made up for by increases in efficiency and the probability of success.

Case Study in Bayesian Learning in a Clinical Trial: The Chilled Platelets Study (CHIPS)

Speaker: Roger J. Lewis, MD, PhD, Harbor-UCLA Medical Center and Berry Consultants, LLC

The U.S. Department of Defense (DOD) funded a trial to address the critical need to deploy platelets in combat situations and overseas. With a 21-day period of storage, the DOD believed it would be feasible to collect platelets domestically and ship overseas (Krachey et al, 2018). This contrasts with the room temperature safe storage duration of five to seven days recommended to avoid bacterial contamination. It was hypothesized if platelets could be stored at refrigerator temperature the maximum duration of safe storage would likely increase while maintaining hemostatic efficacy.

CHIPS Study: a phase 3 multicenter randomized double-blind adaptive non-inferiority storage duration ranging study in adult and pediatric patients undergoing cardiac surgery. The study will enroll up to 1,000 patients with interim analyses at every 200 patients (NCT04834414).

An adaptive trial design allows a maximum storage duration of 21 days in the cold storage group. The control group receives platelets stored at room temperature up to 5 days, and the primary outcome is a well validated 5-point bleeding score. The objective of the trial is to demonstrate platelets stored in the cold are non-inferior to room temperature or warm-stored platelets in adult and pediatric patients undergoing complex cardiac surgery. If cold storage is deemed noninferior, then the secondary objective is to determine the maximum duration of storage that maintains hemostatic non-inferiority (1 point margin) and an acceptable safety profile. A large amount of biological knowledge went into the development of the model and non-inferiority margin.

Patients are initially randomized 2:1 to cold-stored platelets that are stored up to 14 days and warm-stored platelets. At each interim analysis, a decision is made on whether to increase the maximum duration of cold storage, according to three rules:

1. The current duration of cold-stored platelets must have at least a 50% posterior probability of non-inferiority.
2. The maximum duration of cold storage expansion must have at least a 50% posterior probability of non-inferiority.
3. The expansion cannot be more than seven days.

A simulation determines whether for each duration of cold storage the probability of non-inferiority meets the pre-specified posterior probability threshold of 0.9875. If it meets that threshold, they are declared non-inferior up to that duration of storage. This method of adaptively increasing the duration of cold storage balances the competing needs of progressing rapidly through durations that are acceptable but not increasing so quickly that it becomes a safety hazard. The majority of simulations (about 98%) were in the range of 26 to 28 days as the upper limit, which exceeds the 21 days the DOD thought was necessary to collect platelets domestically and ship abroad.

Complex Bayesian Analyses in Confirmatory Trials

Speaker: Scott Berry, PhD President and Senior Statistical Scientist Berry Consultants LLC

In his introductory remarks, Dr. Berry pointed out that the different elements of either traditional or adaptive designs may be performed using Bayesian methods or more traditional ("frequentist")

methods. An adaptive design may use either Bayesian or frequentist approaches to determine how participants are randomized, to govern how data are collected, and to determine when to stop the trial, and for the final analysis. It is also possible to have trials in which some of these elements use Bayesian methods and others use frequentist methods. Dr. Berry then went on to highlight the use of Bayesian methods in several complex trials.

AWARD 11

AWARD11 was a phase 2/3 trial of the drug Trulicity (dulalgutide) in type II diabetes, with data collected according to a Bayesian design, and with Bayesian posterior probabilities generated for efficacy and safety analyses (Skrivanek et al, 2014, NCT00734474). The phase 2 part of the trial included 9 arms: seven doses of Trulicity, a placebo arm, and an active comparator. Once 50 patients were enrolled, interim analyses were performed every two weeks, and randomization probabilities to the seven active doses were updated to favor doses that performed better based on four endpoints: HbA1c, weight loss, blood pressure, and heart rate.

When the trial had enrolled between 200 and 400 participants, if the predictive probability of achieving non-inferiority relative to the active comparator was large enough, the trial switched to a phase 3 trial and restricted the testing to one or two doses selected by an algorithm. At 200 participants, the algorithm picked the 1.5 mg and 0.75 mg doses.

In the final analysis, both doses were superior to the active comparator for HbA1c control. The speed of the trial meant the drug came to market faster, benefitted patients sooner, and allowed more time to sell the drug under patent. This adaptive trial design tested seven doses with the same resources that three doses would have used. Had the trial been run in a more traditional manner, the 1.5 mg dose may never have been tested.

DIAN-TU

Individuals with a known mutation have a 100% chance of getting Alzheimer's Disease.

DIAN-TU is a platform trial testing multiple drugs for the treatment of dominantly inherited early onset. The trial randomized participants to Solanezumab, Solanezumab placebo, Gantenerumab, or Gantenerumab placebo in a 3:1:3:1 ratio The final analysis compares each active drug with the pooled placebos. The trial was a fixed design, with a final analysis occurring when the last patient enrolled reached four years of treatment (Bateman et al, 2017, NCT01760005) .

The Bayesian primary analysis model evaluates the rate of decline of patients with respect to their years from disease onset. Within each subject, it had two random effects: a random effect for age of onset and a random effect for relative cognitive performance. Relative to a more traditional mixed effects model with repeated measures, this trial has significantly greater power to detect efficacy. The analysis model itself creates a scenario that the power and type I error can only be calculated through simulations, making the analysis "complex" despite the design being straightforward.

ROAR

ROAR is a phase 2 basket trial of Dabrafenib + Trametinib in the treatment of rare BRAF V600E mutations across multiple tumor types, with anaplastic thyroid cancer the most common. The primary analysis used a Bayesian hierarchical cluster model. The model borrows within each modeled cluster based on treatment effect relative to an objective response rate. The primary analysis used a Bayesian posterior probability of superiority to the objective control in each tumor type, borrowing data from all other subgroups (NCT02034110).

Bayesian Modeling in the CID Pilot Program: Lilly's Pain Master Protocol

Speaker: Dr. Jon David Sparks, Principal Research Scientist at Eli Lilly and Company

Some drugs are given better chances than others to succeed. This may be because there is more hope for a particular mechanism of action or there are more resources at the time to study multiple indications. With limited resources, a team is often tasked with picking the most promising indication for an asset with very little preliminary information, and if the initial proof of concept trial fails, the development program may be terminated. The trial design considered below was meant to address some of those difficulties.

Eli Lilly's pain master protocol was selected for the FDA CID pilot program and was designed to borrow placebo information within a pain type and borrow treatment effect information between pain types. The goals were to evaluate a large number of assets in multiple pain types with fewer resources than would normally be required. The resulting trial is both a basket trial and a platform trial (NCT04456686, NCT04874636, NCT04707157, NCT04529096, NCT04627038, NCT04476108).

The master protocol specifies the broad entry criteria and standardizes efficacy endpoints and data collection. Under the master protocol are intervention-specific appendices (ISAs) that contain necessary stipulations particular to each molecule. The combination of the master protocol and the ISAs mean the trial can be standardized to allow data to be borrowed across interventions, and allow the necessary flexibility for individual assets and pain types. Standardization and flexibility are illustrated in many ways, including:

- Primary endpoint (pain numerical rating scale collected daily)
    - ISA can specify sample size, primary efficacy analysis model, and amount and type of borrowing.
- 2:1 ratio of randomization to active vs placebo so that all participants have a 33% chance of receiving placebo
    - ISAs can specify multiple active treatment arms if needed.
- Double-blind treatment period of 8 weeks for active and placebo arms
    - ISA can vary the duration of active treatment.
- Common visit and data collection schedule
    - ISA can add visits and additional analyses.
- Entry criteria
    - ISA can add inclusion/exclusion criteria.

In summary, the pain master protocol allows for direct comparisons between assets within and between pain types, standardizes data collection, and reduces sample size in both active and placebo arms by borrowing information.

Session 5: Alternative Data Sources and Historical Control

The CID program encourages exploring the innovative use of alternative data sources. This exploration continues to be increasingly important as emerging challenges with methodological approaches to collection and analysis of data from alternative sources arise, and benefit to patients, regulators, and biopharmaceutical companies also becomes evident. This session explored the possibilities of utilizing alternative data sources.

Simulation Discussions When Using Data from Alternative Sources: A CID Pilot Program Example

Laura Lee Johnson, Ph.D., Office of Biostatistics, CDER, FDA

Dystance 51 was a phase 2/3 randomized multicenter, double-blind, placebo-controlled study with an open-label extension in ambulatory male patients with Duchenne Muscular Dystrophy (DMD) mutations that are amenable to Exon 51 skipping therapy (NCT03907072). Efficacy assessments included the North Star Ambulatory Assessment (N-S-A-A). The trial planned to include historical control data via Bayesian meta-analytic methods to limit the number of patients enrolled in the placebo arm.

Potential issues included but were not limited to the following:

- assessments at different time periods,
- differences in training of assessors in scoring the N-S-A-A assessment,
- improvement in the quality of assessments over time, and
- declines in the quality of assessments over time.

For review purposes, the FDA needs a simulation plan and a detailed simulation report. Documents should include a high level of detail. Parameters need to vary in simulations and have a range with appropriate increments that are justified. FDA will need simulation code, results, and the overall conclusions (i.e., how was it planned, what happened in the analysis, and what was learned from it).

A multidisciplinary, collaborative effort is required. It is not a process where a single parameter can be adjusted at a time while everything else remains stable. Trials are a complex system that requires an innovative and sophisticated approach.

Data in the Wild: Design Lessons from the Apple Heart Study

Speaker: Manisha Desai, PhD, Professor of Medicine, Biomedical Data Science, Stanford University School of Medicine

The healthcare landscape is rapidly undergoing a digital transformation that impacts the diagnosis, treatment, and monitoring of patients, including through the use of wearable devices. The Apple Heart Study is a prospective, single-arm, open-label study with broad inclusion criteria to evaluate the Apple watch wearable's ability to detect atrial fibrillation (NCT03335800). The Apple watch has an optical sensor that detects pulse waveform that can passively measure heart rate and the detection of a pulse irregularity might indicate atrial fibrillation. In the trial, if an irregularity was detected, the sampling frequency increased, and if there were five irregularities within a given interval, the user was notified to connect with a telehealth doctor, who adjudicated the data and, if deemed appropriate, sent the participant a gold standard e-patch to monitor their heart rate for seven days.

The study enrolled 419,297 participants, and the notification for irregularities occurred for 2,161 (0.5%) participants. Of those, only 44% initiated a visit with their telehealth provider. Of the participants that contacted their telehealth provider, 70% were given an e-patch, and 70% of those returned it for analysis.

Unique challenges presented in the study included:

- A deduplication algorithm required to avoid double counting participants as multiple IDs were generated for a single participant e.g. if the app was deleted then a participant reinstalls the app and re-enrolls in the study with a new participant ID.
- Data capture and integration across multiple discrete data streams from vendors not accustomed to participating in a medical research study.
- Windows around timestamp data were required to accurately associate results from the watch and the e-patch to appropriately adjudicate results.
- The need to account for the unpredictability of participant app usage e.g. participants not wearing the watch for extended periods, changing the time on the watch, and sharing the watch with family and friends.

As the Apple Heart Study shows us, wearable devices and mobile technology have great potential for the research setting and require unique considerations for the noisier data from the wild that arise from a less standardized protocol and participants that do unexpected things.

Borrowing Information from Historical Data: A Double-edged Sword

Speaker: Ying Yuan, PhD, Bettyann Asche Murray Distinguished Professor, Deputy Chair, Department of Biostatistics, University of Texas MD Anderson Cancer Center

The randomized controlled trial (RCT) is considered the gold standard, with participants typically randomized in a 1:1 ratio to the control and treatment arms. However, a RCT is often difficult or not appropriate e.g. in an ultra-rare disease there may be insufficient patients to randomize between treatment and control. This motivated the idea to borrow information from historical data and apply a 2:1 randomization ratio for treatment: control to reduce the number of patients allocated to the control arm.

The challenge in borrowing historical data is that historical data may not be similar or congruent with the control data; they may have different target populations, eligibility criteria, or treatment procedures. To maximize the benefits of borrowing historical data and to reduce the risk of a biased outcome requires dynamic information borrowing where historical data that are similar or congruent with the control is borrowed and incongruent data is excluded. The prior distribution is a statistical distribution that represents prior knowledge or belief about the treatment effect before seeing the study data, and then the knowledge about the treatment effect is updated posteriorly (i.e., after the study is complete).

Three notable approaches for borrowing historical data include Power Prior, Commensurate Prior, and Elastic Prior (Table 6).

Table 6 Approaches for Borrowing Historical Data

Approach	Definition
Power Prior	The power prior discounts historical data depending on the congruency between the control and historical data, to control how much information is borrowed (Ibrahim and Chen, 2000).
Commensurate Prior	The commensurate prior also depends on the congruency between control and historical data, but rather than discounting the data, it shrinks the treatment effect of the current control arm towards the historical data. The commensurate prior can be viewed as a special form of Bayesian hierarchical model (Hobbs et al, 2011).
Elastic Prior	The elastic prior specifies a clinically meaningful difference and uses that cut-off to force borrowing information for data that are in range and exclude data outside the range (Jiang et al, 2021).

These approaches improve power; however, borrowing information means the false positive rate (type-1 error) cannot be controlled at exactly 5% because that would require 100% assurance that the data sets are the same. Instead, the goal is to improve power while controlling type-1 error to a reasonable value rather than strictly controlling it at 5%.

Development of a Clinical Trial Simulation Tool for Duchenne Muscular Dystrophy Using Multiple Alternate Data Sources

Speaker: Jackson Kempber Burton III, PhD Scientific Director, Quantitative Medicine Critical Path Institute

The Duchenne Regulatory Science Consortium (D-RSC), a nonprofit collaboration aimed at accelerating novel therapies for Duchenne muscular dystrophy (DMD), developed a clinical trial simulation tool to optimize design of DMD trials. DMD is rare, and the progression rates are very nonlinear and highly heterogeneous. This complicates determining appropriate trial endpoints and trial development.

The D-RSC is credited for the following accomplishments and advancements in determining appropriate trial endpoints and trial design:

- Collaboration within the members of the consortia to aggregate data, who provide data despite the competitive nature of the disease area; data thus come from clinical trials as well as a natural history study.
- Careful data curation and cleaning by data mangers to ensure the data are usable. Note: many trials use the same subset of patients because not all patients are eligible for all trials.
- Development of a CDISC Therapeutic Area User Guide to standardize terminology and ease the integration of data (CDISC 2017).
- Development of a model that supports a clinical trials simulator to predict trajectories from baseline features of a given patient population; by adjusting variables on a sliding scale, trial planners can observe the expected outcome for a given set of parameters.
- Continued building of new models to make better use of outcome measures and biomarkers.

In addition to the above advancements, one possible use for the clinical trial simulation tool developed by the D-RSC is borrowing historical information, where users can simulate a virtual patient population that matches the inclusion/exclusion criteria and other patient features in the protocol to simulate a control group. The features of the patient population can be changed in the simulation to see how various factors might impact the trial design. These drug development tools can be agnostic to a particular therapeutic program. There are formal FDA and EMA regulatory review pathways that can result in official acceptance by the agencies for public use by any sponsor.

Cooperation within the pre-competitive space of the D-RSC offers utility that is not always possible within the individual efforts of organizations, and early engagement with regulators is a critical step towards making these collaborative tools available and actionable.

Discussion Panel Key Takeaways

- Data are only useful if they are good quality. Ensuring the quality of the data requires significant effort from a dedicated team and collaboration with subject matter experts.
- Helping participants understand how their data will inform science could encourage better compliance and reduce noise in the data.
- Understanding potential sources of non-random biases in measurements is key to determining sample sizes.
- The main concerns with sharing data openly include the resources it takes to transfer data, using improperly vetted data that show misleading results, and ethical and privacy concerns.
- A mid-study revisit or exit interview would be an ideal time to discuss using the participant's data for research beyond that study because then the participant is more knowledgeable.

Session 6: Global Regulatory Affairs

This session consisted of presentations from the EMA and PMDA followed by a panel from the FDA, EMA, and PMDA to discuss their perspectives on use of CIDs to highlight the regulatory principles, current thinking, and activities related to utilization and evaluation of innovative designs in various regulatory agencies. Challenges, opportunities, and best practices in applying CID were described. This session included a discussion of key aspects of how to interact with regulatory agencies in different regions on global trials with CID for the purpose of global registration. Co-chairs for this session were Kristen Myer of Johnson & Johnson, Amy Xia of Amgen and John Scott of CBER (FDA).

European reflections on complex innovative designs

Frank Petavy, MS, Head of Biostatistics and Methodology Support, Human Medicines Development, European Medicines Agency, European Union

This presentation summarized the experience of CID trials submitted to EMA including the increased frequency and heterogeneity of type of innovation used in the design . The EMA is working on writing a guidance on master protocols. Mr. Petavy confirmed the interest of EMA in innovative clinical trial proposals. The main channel for introducing innovative proposals is the Scientific Advice Working Party. These proposals have been seen most prevalent in oncology, but with the rest being seen across different therapeutic areas. About half of adaptive designs proposed to the EMA have been sample size re-estimations, and more seamless phase II/III designs have also become more common.

The clinical trial protocol is the key document to demonstrate that the treatment effect will be estimated in unbiased way, with appropriate corrections applied to the testing strategy and control of the false positive error. Studies with adaptive designs for confirmatory studies in particular require:

- Ensuring there are not too many design modifications, which would be indicative of too many unknowns in the effect of the medicine.
- Adequate description of strategies for controlling the false positive rate (type I error).
- Accounting for possible bias in estimating the treatment effect.
- Planning interim analyses to ensure sufficient information is available to see a consistent treatment effect.

Europe has a legal mandate to publish study results within a year of a study completion, but with platform trials with continually ongoing and/or starting substudies, clarity on the legal requirements to publish results without compromising the integrity of ongoing substudies in the platform trial is still under discussion.

Guidance for master protocols is beginning, but currently only a manuscript exists. Borrowing data is complicated in a system like the EU that has a very heterogeneous populations with many countries. It is increasingly important to develop partnerships between regulatory authorities, pharmaceutical companies, and public registries. The main channel for introducing innovative proposals is currently through the Scientific Advice Working Party.

Recent activities related to innovative designs in PMDA

Yuki Ando, PhD, Senior Scientist for Biostatistics, Office of New Drug I, Pharmaceuticals and Medical Devices Agency

This presentation summarized the status of submission and acceptance of CID trials in Japan and the PMDA's overall experience. In Japan, applicants submit a new drug application to the PMDA, which reports the results of their review to the Ministry of Health, Labor, and Welfare. Previously the PMDA reviewed a study report and requested additional analyses if needed. However, the PMDA has begun their own internal analyses since electronic submissions began in 2016. Electronic submissions of all patient-level data that are important for the evaluation were mandated in April 2020.

The PMDA did not issue guidance documents for adaptive designs, Bayesian approaches. However, PMDA is actively participating in writing the ICH guidelines E20 on adaptive trials and will utilize that document as the cornerstone for guidance on innovative clinical trial designs subgroup analyses, or accounting for multiplicity.

The PMDA has had some experience reviewing adaptive designs, primarily in oncology. Sample size re-estimation and seamless phase 2/3 trials have been most common. The PMDA confirmed their increased acceptance of adaptive and/or innovative designs in a clinical program based on evidence presented by the sponsor in demonstrating:

- Necessity and potential efficiency of CID vs standard fixed designs (eg shorter duration to establish a new beneficial and safe therapeutic, more information, faster market entry)
- Methodological statistical validity (type 1 error control, minimization of treatment effect estimation bias)
- Protection of study integrity

The PMDA is also considering the use of its patient registry as a source of alternative data, which has been investigated by a type of consortium called the Clinical Innovation Network. The registry data would be of particular use for rare diseases.

The PMDA currently has eight biostatisticians working for the new drug review offices. The PMDA has only had a few consultation meetings regarding master protocols, and they feel they need more experience.

Joint Discussion Panel Key Takeaways

- Although the three agencies (FDA, EMA, and PMDA) have differing levels of experience and engagement with CID studies, they tend to have similar priorities and aligned statistical approaches in the ICH working groups.
- Alignment among the three agencies is important because so many Sponsors very often design global trials used for submission to different Health Authorities around the globe. The global nature of drug development programs means that lack of regulator alignment will affect a sponsor's willingness and ability to pursue innovative trial designs in support of global registration. Progress in advancing CIDs will be difficult without more frequent and substantive regulator-to-regulator discussions on this issue.

- For Sponsors, it would be ideal to have an increasingly consistent feedback from the different Agencies to ensure a more efficient design of the development program for a new therapeutic intervention.
- Simultaneous talks with the three agencies could be facilitated by CID clusters that are perhaps specific to individual therapeutic areas.
- There is a need for the three major agencies to lend their experience to smaller agencies across the world. There currently are collaborations among individual authorities, and the training available at the agencies is often available for others. Adopting ICH guidelines would be the ideal place for smaller agencies to begin their involvement.
- The same overall conclusions as in other sessions were obtained in terms of the motivation and rationale to utilize CID: the use of innovation should help designing patient-centric clinical trials with the purpose of bringing better and safe medicines to the patients in needs with shorter development timelines.

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Appendix 1: Master Protocol Reference

National Clinical Trial Number	Study Title	Link
NCT04834414	CHIlled Platelet Study “CHIPS” (CHIPS)	CHIlled Platelet Study "CHIPS" - Full Text View - ClinicalTrials.gov
NCT01760005	DIAN-TU: Dominantly Inherited Alzheimer Network Trial: An Opportunity to Prevent Dementia. A Study of Potential Disease Modifying Treatments in Individuals at Risk for or With a Type of Early Onset Alzheimer's Disease Caused by a Genetic Mutation. Master Protocol DIAN-TU001 (DIAN-TU)	Dominantly Inherited Alzheimer Network Trial: An Opportunity to Prevent Dementia. A Study of Potential Disease Modifying Treatments in Individuals at Risk for or With a Type of Early Onset Alzheimer's Disease Caused by a Genetic Mutation. - Full Text View - ClinicalTrials.gov Dominantly Inherited Alzheimer Network Trial: An Opportunity to Prevent Dementia. A Study of Potential Disease Modifying Treatments in Individuals at Risk for or With a Type of Early Onset Alzheimer's Disease Caused by a Genetic Mutation. Master Protocol DIAN-TU001 - Full Text View - ClinicalTrials.gov
NCT00734474	Trulicity:	A Study of LY2189265 Compared to Sitagliptin in Participants With Type 2 Diabetes Mellitus on Metformin https://clinicaltrials.gov/ct2/show/NCT00734474?term=NCT00734474&draw=2&rank=1
NCT02034110	ROAR: Efficacy and Safety of the Combination Therapy of Dabrafenib and Trametinib in Subjects with BRAF V600E-Mutated Rare Cancers	Efficacy and Safety of the Combination Therapy of Dabrafenib and Trametinib in Subjects With BRAF V600E- Mutated Rare Cancers - Full Text View - ClinicalTrials.gov
NCT04456686	Chronic Pain Master Protocol (CPMP): A Study of LY3016859 in Participants with Osteoarthritis	Chronic Pain Master Protocol (CPMP): A Study of LY3016859 in Participants With Osteoarthritis - Full Text View - ClinicalTrials.gov
NCT04874636	Chronic Pain Master Protocol (CPMP): A Study of LY3556050 in Participants With Chronic Low Back Pain	Chronic Pain Master Protocol (CPMP): A Study of LY3556050 in Participants With Chronic Low Back Pain - Full Text View - ClinicalTrials.gov
NCT04707157	Chronic Pain Master Protocol (CPMP): A Study of LY3556050 in Participants With Diabetic Peripheral Neuropathic Pain	Chronic Pain Master Protocol (CPMP): A Study of LY3556050 in Participants With Diabetic Peripheral Neuropathic Pain - Full Text View - ClinicalTrials.gov
NCT04529096	Chronic Pain Master Protocol (CPMP): A Study of LY3016859 in Participants With Chronic Low Back Pain	Chronic Pain Master Protocol (CPMP): A Study of LY3016859 in Participants With Chronic Low Back Pain - Full Text View - ClinicalTrials.gov
NCT04627038	Chronic Pain Master Protocol (CPMP): A Study of LY3556050 in Participants With Osteoarthritis	Chronic Pain Master Protocol (CPMP): A Study of LY3556050 in Participants With Osteoarthritis - Full Text View - ClinicalTrials.gov

National Clinical Trial Number	Study Title	Link
NCT04476108	Chronic Pain Master Protocol (CPMP): A Study of LY3016859 in Participants With Diabetic Peripheral Neuropathic Pain	Chronic Pain Master Protocol (CPMP): A Study of LY3016859 in Participants With Diabetic Peripheral Neuropathic Pain - Full Text View - ClinicalTrials.gov
NCT03907072	Efficacy and Safety Study of WVE-210201 (Suvodirsen) With Open-label Extension in Ambulatory Patients With Duchenne Muscular Dystrophy (DYSTANCE 51)	Efficacy and Safety Study of WVE-210201 (Suvodirsen) With Open-label Extension in Ambulatory Patients With Duchenne Muscular Dystrophy - Full Text View - ClinicalTrials.gov
NCT03335800	Apple Heart Study: Assessment of Wristwatch-Based Photoplethysmography to Identify Cardiac Arrhythmias	Apple Heart Study: Assessment of Wristwatch-Based Photoplethysmography to Identify Cardiac Arrhythmias - Full Text View - ClinicalTrials.gov