Adaptive Trial Design and Incorporation of Biomarkers to Maximize Achievable Objectives

In Early Phase Clinical Studies
Exclusive Offer for Attendees!

Stay tuned until after the webinar to receive details on our exclusive offer for webinar attendees!
Polling Question #1
Key Objectives

Over the course of this webinar, we will aim to:

01. Discuss adaptive designs and strategies for incorporation in early phase studies.

02. Discuss the utility of biomarker evaluation and its influence on drug development in early stages.

03. Present relevant examples from previous WCCT programs in which the aforementioned strategies were implemented.

04. Address the relevant statistical issues that arise in this setting, and discuss strategies to ensure that valid statistical inferences can be drawn for each of the objectives.
Adaptive Clinical Trial Design
Adaptive Clinical Trial Design

FDA (2010):

“An adaptive design clinical study is defined as a study that includes a **prospectively planned** opportunity for **modification** of one or more specified aspects of the study design and hypotheses based on analysis of data (usually **interim** data) from subjects in the study.”
Adaptive Clinical Trial Design

Structure of an Adaptive Design

Adaptive Design

- **Scope of Adaptations**
  - Stop trial early
  - Resize the trial
  - Modify endpoints, etc.

- **Assumptions to Check**
  - Event rate
  - Effect size
  - Variability, etc.

- **Decision Rules**
  - Frequentist/Bayesian
  - Blinded/Unblinded
  - Probability-based

- **Valid Inference**
  - Control type 1 error
  - Combine before/after info

- **Trial Integrity**
  - Study governance
  - Objective, blinded assessment

**Note:**
- Objective, blinded assessment
Bayesian Decision Rule

- Historical Data
- Publications
- Expert Knowledge
- Contextual Evidence
- Observed Data

Average of Past & Present info

= Updated Evidence

“Prior” + “Likelihood” = “Posterior”
Adaptive Designs in Early Phase Trials

**Scopes**

- Futility
- Dose Finding
- Adaptive randomization
- Sample-size Re-estimation
- Enrichment
- Seamless Phase 2/3
Futility via Conditional Power

Are we going anywhere?

- At interim, calculate the probability of success, given the data so far. If the probability is low then stop the study.
- Can be accomplished by a frequentist or a Bayesian calculation.
- No type-1 error penalty
- Need to consider: Expected sample size vs. Max sample size
Adaptive Dose Finding

A host of designs:

- Goal is to identify the maximum tolerable dose (MTD)
- Design choices:
  - Escalating Cohort Design:
    - Assign 6 subjects to dose 1
    - If toxicity < 0.2 (≤ 1 DLT in 6 subjects) then assign 6 new subjects to dose 2
    - Otherwise stop, and declare MTD at lower dose
  - “3+3” Design
    - Assign 3 subjects to dose 1
    - If 0 DLT in 3 subjects then assign 6 new subjects to dose 2
    - If 1 DLT in 3 subjects then add 3 new subjects to dose 1
      - $\frac{1}{6} \rightarrow$ go to dose 2
      - 2 or more $\rightarrow$ stop, and declare MTD at lower dose
    - If 2-3 DLT in first 3, then stop, and declare MTD at lower dose
  - 3 + 3 converges on MTD defined with $\Pr\{DLT\} = 20\%$
  - That is changeable (e.g. for a target $\Pr\{DLT\} = 10\%$, one can use a 5+5 Design
Adaptive Dose Finding

Additional Design Choices:

- Up and Down Design
  - Search can go in both directions
- Continual Re-assessment Method (CRM)
  - MTD := a dose associated with Pr[DLT] = \(x\%\)
  - Model-based
Adaptive Dose Escalation

1. Select a mathematical model to describe the relationship between dose and PR [DLT]
2. After each patient, update the model, and estimate the probability of toxicity for each dose level
3. Treat the next patient at the dose who estimate is closest to some pre-specified target, for example, 20%
4. Stop when a maximum sample size is reached
Adaptive Randomization

Updating Treatment Assignments

- Baseline adaptive randomization
  - A large number of stratification variables
  - Balancing treatment arms for all stratification variables is impossible
  - Balance marginally
  - Adaptive minimization

- Response adaptive randomization
  - Based urn models

- Biomarker-adaptive randomization
Polling Question #2
Incorporation of Biomarkers
Utility of Biomarkers

In Early Phase Clinical Trials

- Increase likelihood for success
  - Evaluate the population who can benefit
  - Exclude population with off-target effects
  - Multiple barometers of PD

- Better define mechanism of action
  - More clearly understand disease
  - Identify targets for future development

- Strongly encouraged by regulators
  - Personalized medicine
  - FDA Biomarker Qualification Program
Each biomarker category can have a variety of “Context of Uses” (e.g., a prognostic biomarker can be used for patient stratification of enrichment in clinical trials).

<table>
<thead>
<tr>
<th>Biomarker Categories</th>
<th>Context of Use Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic</td>
<td>Detect a change in the degree or extent of a disease</td>
</tr>
<tr>
<td></td>
<td>Indicate toxicity or assess safety</td>
</tr>
<tr>
<td></td>
<td>Provide evidence of exposure</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Identify individuals on basis of effect from a specific intervention or exposure</td>
</tr>
<tr>
<td>Predictive</td>
<td>Stratify Patients</td>
</tr>
<tr>
<td></td>
<td>Enrichment: inclusion/exclusion data</td>
</tr>
<tr>
<td>Prognostic</td>
<td>Efficacy biomarker/surrogate endpoint</td>
</tr>
<tr>
<td></td>
<td>Show biological response related to an intervention/exposure</td>
</tr>
<tr>
<td>Pharmacodynamic/Response</td>
<td>Indicate the presence or extent of toxicity related to an intervention or exposure</td>
</tr>
<tr>
<td>Safety</td>
<td>Indicate the potential for developing a disease or sensitivity to an exposure</td>
</tr>
<tr>
<td>Susceptibility/Risk</td>
<td></td>
</tr>
</tbody>
</table>

*Source: FDA Biomarker Qualification Program*
Biomarker Categories

- Diagnostic
- Monitoring
- Predictive
- Prognostic
- Pharmacodynamic/Response
- Safety
- Susceptibility/Risk
Biomarker Categories

- Diagnostic
- Monitoring
- Predictive
- Prognostic
- Pharmacodynamic/Response
- Safety
- Susceptibility/Risk

Use in Trial Design

- If the evidence suggests that the benefit of a treatment is limited to the biomarker-positive sub-population, an **enrichment design** strategy with only biomarker-positive patients may be appropriate.

- If there is sufficient reason to suggest that a biomarker can predict that therapy will be more effective in biomarker-positive patients, but the evidence is not compelling enough to rule out clinical efficacy in biomarker-negative patients, a **biomarker-stratified trial design** or an **adaptive enrichment trial design** may be more appropriate.

- In the **biomarker-stratified trial design**, biomarkers are used to guide analysis but not treatment assignment.

- In the **adaptive enrichment trial design**, biomarkers are used to guide the enrollment and not treatment assignment.
Enrichment Design

- **Assess Biomarker**
  - Biomarker Positive
  - Biomarker Negative

- **Randomize**
  - Treatment A
  - Treatment B

- Off study
Biomarker-Stratified Design

Assess Biomarker

Stratify

Randomize

Biomarker Positive

Treatment A

Treatment B

Biomarker Negative

Treatment A

Treatment B
In this Amyotrophic Lateral Sclerosis pilot study, over 10 biomarkers were measured across five different biomarker categories:

- **Diagnostic**
- **Monitoring**
- **Predictive**
- **Prognostic**
- **Pharmacodynamic/Response**
- **Safety**
- **Susceptibility/Risk**

**4 ALS Target biomarkers across 2 modalities (CSF & Plasma)—SOD1, phosphorylated neurofilament heavy chain (pNFH), total tau, and phosphorylated tau**

**4 efficacy biomarkers/surrogate endpoints—ALS Functional Rating Scale (ALSFRS-R), Force Vital Capacity (FVC), Time Up and Go (TUG), and Hand-Held Dynamometry (HHD)**

**Several safety biomarkers including QT measurement and hematology parameters**
Multiparameter Technologies

Maximizing Potential for Biomarker Discover in Early Phase Trials

Proteomics
- Single-cell proteomics (FACS, CyTOF)

Metabolomics
- Metabolism-related small molecules

Multiplexed immunoassays
- Cytokines
- Chemokines
- Growth factors

Microbiome
- 18S rRNA sequencing

Genetics
- Whole genome sequencing
- mRNA expression
- Single-cell sequencing
A Phase I, Open-label, Ascending Dose Study to Determine the Safety and Reactogenicity of a Wild Type Seasonal A/California/H1N1 2009 Influenza Challenge Virus in Healthy Volunteers, Following a Single Intranasal Administration.

**Study Population:** Normal Healthy Volunteers

**Main Inclusion Criteria:** Absent or low levels of detectable pre-existing antibodies to influenza virus subtypes, the minimum being subjects who have undetectable or low levels of antibody to the potential challenge strain, as determined by a hemagglutination-inhibition (HAI) titer of \(\leq 10\) prior to challenge. Subjects not to have received any influenza vaccine for the previous 2 years.

**Subjects Enrolled:** 36 subjects

**Study Objective:** Determine the dose with the optimal safety profile and infectivity rate of the viral challenge strain for use in subsequent challenge intervention studies to test potential influenza vaccines and/or therapeutics. Additionally, the study aimed to determine immunological responses over the study period, including humoral and cellular immune responses to challenge virus.
Influenza Challenge Model

At WCCT

Virus Strain

- Clinical isolate from 3-year-old during the 2009 flu season
- cGMP manufactured in SPF eggs
- Extensive adventitious virus testing
- Pre-clinical safety established in ferrets

For more information, please refer to handout entitled “WCCT Global Influenza Challenge Model”

Symptoms and Virus Shedding

Atomizer used for nasal virus dosing

Virus inoculation
Influenza Challenge Model
Quantifying Cellular Immune Responses

CyTOF: 40+ parameter single-cell proteomic analysis

N=36 Volunteers

Peripheral Blood Samples

Day: -1 1 2 3 4 5 6 7 8 29 60

Inoculation with A/California/H1N1 2009 influenza virus
CyTOF

40+ Parameter Single-Cell Proteomic Analysis
CyTOF: Simultaneous Quantification of Multiple Immune Cell Subsets

**MONOCYTES**
- cMC
- intMC
- ncMC
- pDC
- mDC

**LYMPHOCYTES**
- B cells
  - B cells Naïve
  - B cells NCSM
  - B cells CSM
  - B cells plasma
- T cells CD4+
  - T cells CD4+ Naïve
  - T cells CD4+ CM
  - T cells CD4+ Effector
  - T cells CD4+ EM
- T cells CD8+
  - T cells CD8+ Naïve
  - T cells CD8+ CM
  - T cells CD8+ Effector
  - T cells CD8+ EM
- NK cells
  - NK cells CD56-
CyTOF: Simultaneous Quantification of Multiple Immune Cell Subsets

**VIRUS**

Study day: -1 1 2 3 4 5 6 7 8 29 60

**NONE**

Study day: -1 1 2 3 4 5 6 7 8 29 60

**MONOCYTES**

- cmC
- intMC
- ncMC
- pDC
- mDC

**LYMPHOCYTES**

- B cells
- B cells Naïve
- B cells NCSM
- B cells CSM
- B cells plasma
- T cells CD4+
- T cells CD4+ Naïve
- T cells CD4+ CM
- T cells CD4+ Effector
- T cells CD4+ EM
- T cells CD 8+
- T cells CD 8+ Naïve
- T cells CD 8+ CM
- T cells CD 8+ Effector
- T cells CD 8+ EM
- NK cells
- NK cells CD56−
CyTOF

Computationally-driven Cell Clustering with SCAFFoLD
CyTOF
Computationally-driven Cell Clustering with SCAFFoLD

CD19

MAXMIN 0
Median expression
MIN 0 MAX
CyTOF

Computationally-driven Cell Clustering with SCAFFoLD

CD8

Median expression

MIN 0 MAX
CyTOF

Computationally-driven Cell Clustering with SCAFFoLD

- CD8+ T cells
- CD4+ T cells
- NK cells
- Basophils
- Granulocytes
- ncMCs
- cMCs
- mDCs
- pDCs
- B cells

Fold vs. Baseline (log2)

CD14+CD16+
Monocyte–like cells
Monocyte Responses During Influenza Challenge

Virus shedding status:

CD14+ Mono

CD14+CD16+ Mono

CD16+ Mono

Fold vs. Baseline (log2)

Day
Monocyte Responses During Influenza Challenge

CD14+CD16+ Monocytes are an early biomarker for total symptoms, peak virus titer, and development of T cell responses during influenza.

**Symptoms**

- Total symptoms (arbitrary units) vs. CD14+CD16+ Mono (Day 6)/baseline (log2) with correlation coefficient $r = 0.37$, $p = 0.03$.

**Virus titer**

- Peak virus titer (log10) vs. CD16+CD14+ Mono (Day 5)/baseline with correlation coefficient $r = 0.72$, $p < 0.0001$.

**Activated T cells**

- Day 8 CD8+CD38+ T cells vs. CD14+CD16+ Mono (Day 5)/baseline with correlation coefficient $r = 0.79$, $p < 0.0001$. 

**R code example** (not provided in the image):

```R
# Load necessary libraries
library(ggplot2)

# Create data frame
data <- data.frame(Symptoms = c(1, 2, 3, 4, 5), Virus_titer = c(0.5, 1.2, 2.3, 3.4, 4.5), Activated_T_cells = c(-0.2, 0.4, 1.6, 2.8, 3.9))

# Plot data
ggplot(data, aes(x = Symptoms, y = Virus_titer)) + geom_point() + geom_smooth(method = "lm")
```
Mapping Disease Course

Applying Multivariate Analysis of Biomarkers

[Graphs showing the fold change in various cell types (Bcells, Tcells, intMCs, PlasmaBcells, CD38+Ki67+CD8+Tcells, Basophils) over time (Day -1 to 29).]
Mapping Disease Course

Applying Multivariate Analysis of Biomarkers
Mapping Disease Course

Applying Multivariate Analysis of Biomarkers
Mapping Disease Course

Applying Multivariate Analysis of Biomarkers

- Bcells
- Tcells
- intMCs
- Plasma Bcells
- CD38+ki67+CD8+Tcells
- Basophils
Multi-variate Predictors of Disease

Recent Literature

- A Four-Biomarker Blood Signature Discriminates Systemic Inflammation Due to Viral Infection Versus Other Etiologies - *Scientific Reports* 2017
- Transcriptomic signatures differentiate survival from fatal outcomes in humans infected with Ebola virus – *Genome Biology* 2017
- Integrated, Multi-cohort Analysis Identifies Conserved Transcriptional Signatures across Multiple Respiratory Viruses – *Immunity* 2015
- An immune clock of human pregnancy – *Science Immunology* 2017
- Lipidomic Profiling of Influenza Infection Identifies Mediators that Induce and Resolve Inflammation – *Cell* 2013
Statistical Considerations
Challenges with Statistical Analysis

- Controlling false positive results
  - More advanced in hypothesis testing area
  - Less understood in estimation and selection type problems

- Validation of biomarkers
  - Easier for prognostic markers
  - Difficult for predictive markers in small trials
  - Need multiple studies to test surrogacy

- Pattern recognition and dimensionality
  - Computer-aided methods
  - Multivariate analysis
Polling Question #3
Exclusive Offer for Attendees!

WCCT is offering up to 4 hours of consulting time with our experts on your study design or clinical development plan. This will include:

- 1hr. Discovery Call
- 2hrs. For research, planning, and design
- 1hr. Review and presentation