

**Complex Innovative Designs for Gene Therapy and
Rare Disease Drug Development:
*Efficient Randomized Designs with Intra-Patient
Comparisons - Overview***

Qing Liu, Ph.D.

Quantitative & Regulatory Medical Sciences, LLC

Email: Liu.Qing@QRMedSci.net

LinkedIn: Qing Liu

Oct 22, 2019 BASS XXVI

Charlotte, NC

**Complex Innovative Designs for Gene Therapy and
Rare Disease Drug Development:
*Efficient Randomized Designs with Intra-Patient
Comparisons - Overview***

Jeff Castelli, Ph.D.

Chief Portfolio Officer

Amicus Therapeutics

Fred Holdbrook, Ph.D.

Director of Biostatistics

Amicus Therapeutics

Non-Technical Seminar Series

Complex Innovative Designs for Gene Therapy and Rare Disease Drug Development

- *Regulatory, Trial Design and Application Overview*
- *Virtual Matched Control Analysis to Compare a Single Arm Trial with Natural history Controls*
- *Adaptive Hybrid Designs Incorporating Phase 2 Single Arm Trial and Natural History Control*
- *Adaptive Hybrid Phase 2/3 Design Incorporating Natural History Control*
- *RWE Randomized Enrichment Designs*
- *Randomized Delayed Start Design with Integrated Analysis of Efficacy*
- *Totality of Evidence with Composite Ordinal Categorical Endpoint*

Technical Seminar Series

Randomized Enrichment Design with Real-World Evidence

- *Controlling Placebo Effects in Intra-Patient Comparisons with Concurrent Control through Tipping Point Analysis*

Technical Seminar Series

Randomized Delayed-Start Design with Integrated Analysis of Efficacy

- *Controlling Placebo Effects with Randomized Withdrawal*
- *Doubly-Randomized Delayed Start-Design*
- *Combining Randomized Controlled Trial with Open-Label Extension Study*

Outline

- I. Regulatory Considerations
- II. The General Framework
- III. Intra-Patient Comparisons
- IV. RWE Randomized Enrichment Design
- V. Randomized Delayed-Start Design

Discussion

Part I

Regulatory Considerations

- Substantial Evidence
- Challenges with Rare Diseases
- Complex Innovative Designs
- FDA Gene Therapy Guidance for Rare Diseases
- Enrichment Designs
- Principles of Regulatory Innovations

Substantial Evidence

- **US Food Drug & Cosmetic Act**

*“The term ‘**substantial evidence**’ means evidence consisting of **adequate and well controlled investigations**, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”*

Challenges with Rare Diseases

2.29.2012 is RARE DISEASE DAY. LOU GEHRIG'S HYPOPARATHYROIDISM RECURRENT RESPIRATORY PAPILLOMATOSIS AND 7000 MORE

1 in 10 Americans has a RARE DISEASE.

That's 30,000,000 men, women, and children. A disease is considered "rare" if it affects fewer than 200,000 people in the U.S.

What is it like to have a rare disease?



LACK of KNOWLEDGE
 It can take years to be diagnosed with a rare disease.
 Once you know what you have and research it, you may know more about your disease than your doctor.



LACK of TREATMENT
 ONLY 200 rare diseases have FDA-approved treatment.
 Without FDA approval, insurance coverage is difficult to get, and prohibitive costs may mean that you don't get the treatment you need.



LACK of RESEARCH
 Very few rare diseases are being actively researched.
 Many people form support groups to share information and raise money to fund research on their disease.

Sigh

As you can imagine, it can feel pretty **LONELY** when you have a rare disease.

But it doesn't have to be.

Let the people around you know that you care. Let them know that you see here to **LISTEN** when they need to be heard.
 Because just as in any difficult situation,

ALONE we are **RARE;** **TOGETHER** we are **STRONG.**

by V.E.R.B for B.

Complex Innovative Designs

- **21st Century Cures Act requires the FDA is to issue guidance on**
“the use of **complex adaptive and other novel trial designs**, including how such clinical trials proposed or submitted help to **satisfy the substantial evidence standard** under section 505(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(d))”

FDA Gene Therapy Guidance for Rare Diseases

- **Recognition of *repeated use of patients in the clinical program*, paving the path for internal natural history controls**
- **Descriptions of study design features, including**
 - ✓ Randomized (blind if possible) **parallel group design** with concurrent controls
 - ✓ Single arm trial with **natural history controls from initial observations**
 - ✓ Single arm trial with **external natural history controls**

Enrichment Designs

Definition of Enrichment

“The prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population.”

FDA Draft guidance on Enrichment Dec 2012

Enrichment Designs

- ***Strategies to decrease heterogeneity*** – selecting patients with baseline measurements in a narrow range (decreased inter-patient variability) and excluding patients whose disease or symptoms improve spontaneously or whose measurements are highly variable (decreased intra-patient variability). The decreased variability provided by these strategies increases study power.
- ***Prognostic enrichment strategies*** – choosing patients with greater likelihood of having a disease-related endpoint event or a substantial worsening in condition. E.g. Cardiovascular trial for those at increased risk of MI or stroke.
- ***Predictive enrichment strategies*** – choosing patients more likely to respond to the drug treatment than other patients with the condition being treated- e.g. biomarker or genetic marker selection (oncology); or randomizing responders or non-responders into a subsequent comparison of test agents.

Part II

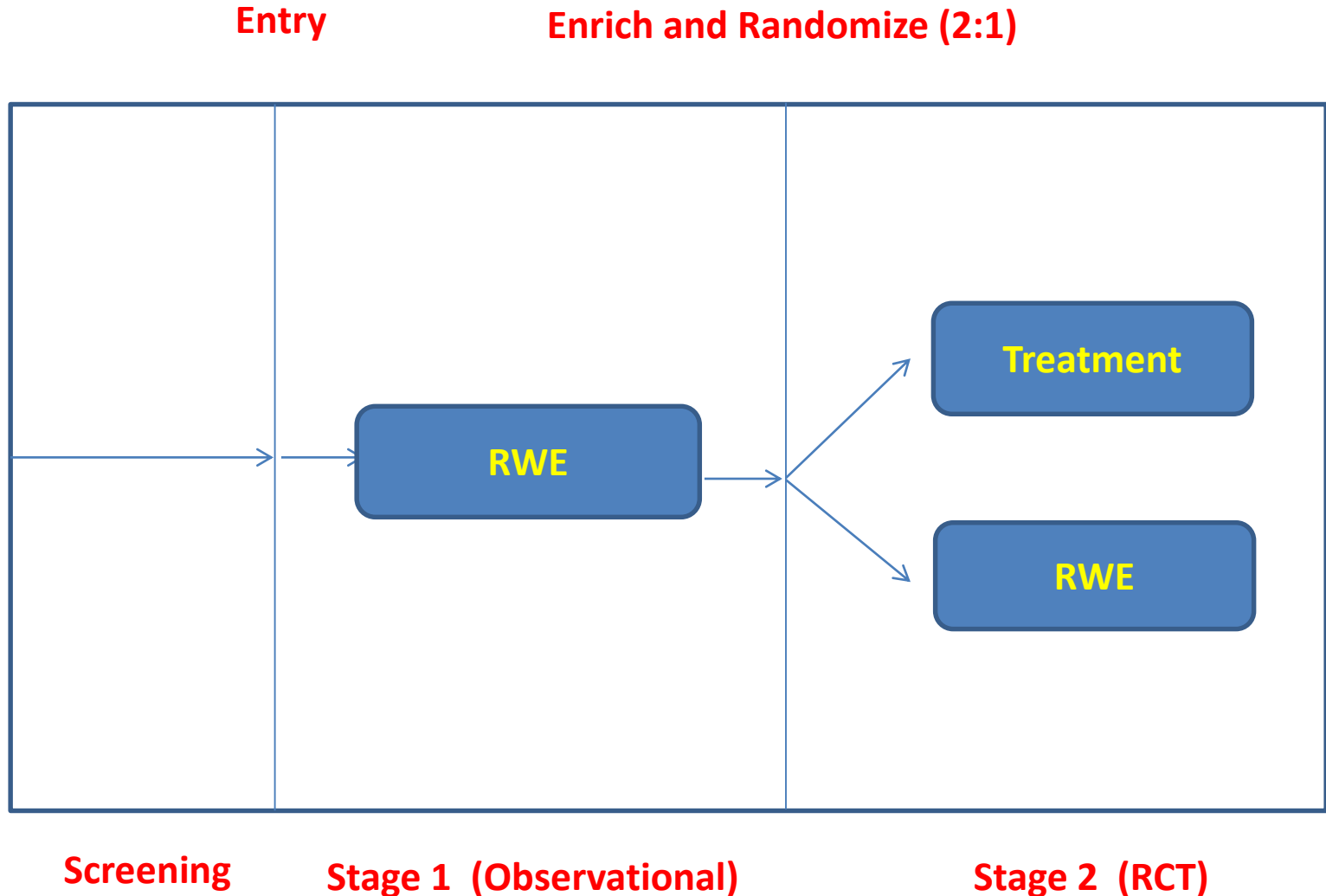
The General Framework

- Objective
- RWE Randomized Enrichment Design
- Randomized Delayed-Start Design

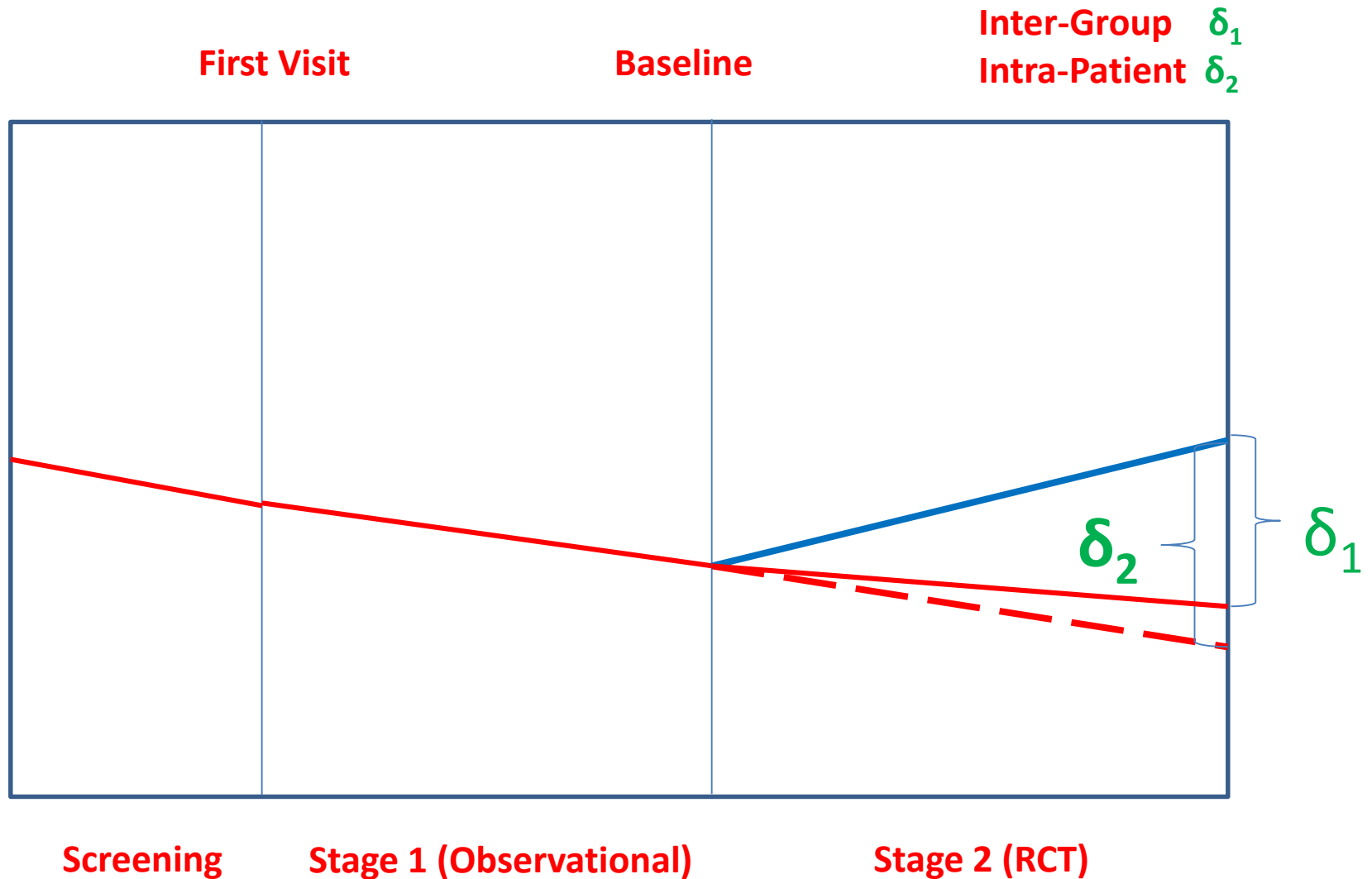
Objective

- ***To Establish Comparative Effectiveness of a Treatment vs a Control***
 - ***Treatment***: new or existing drug or biologics
 - ***Control***: no treatment, existing treatment or standard of care
 - ***Disease***: Oncology or rare diseases

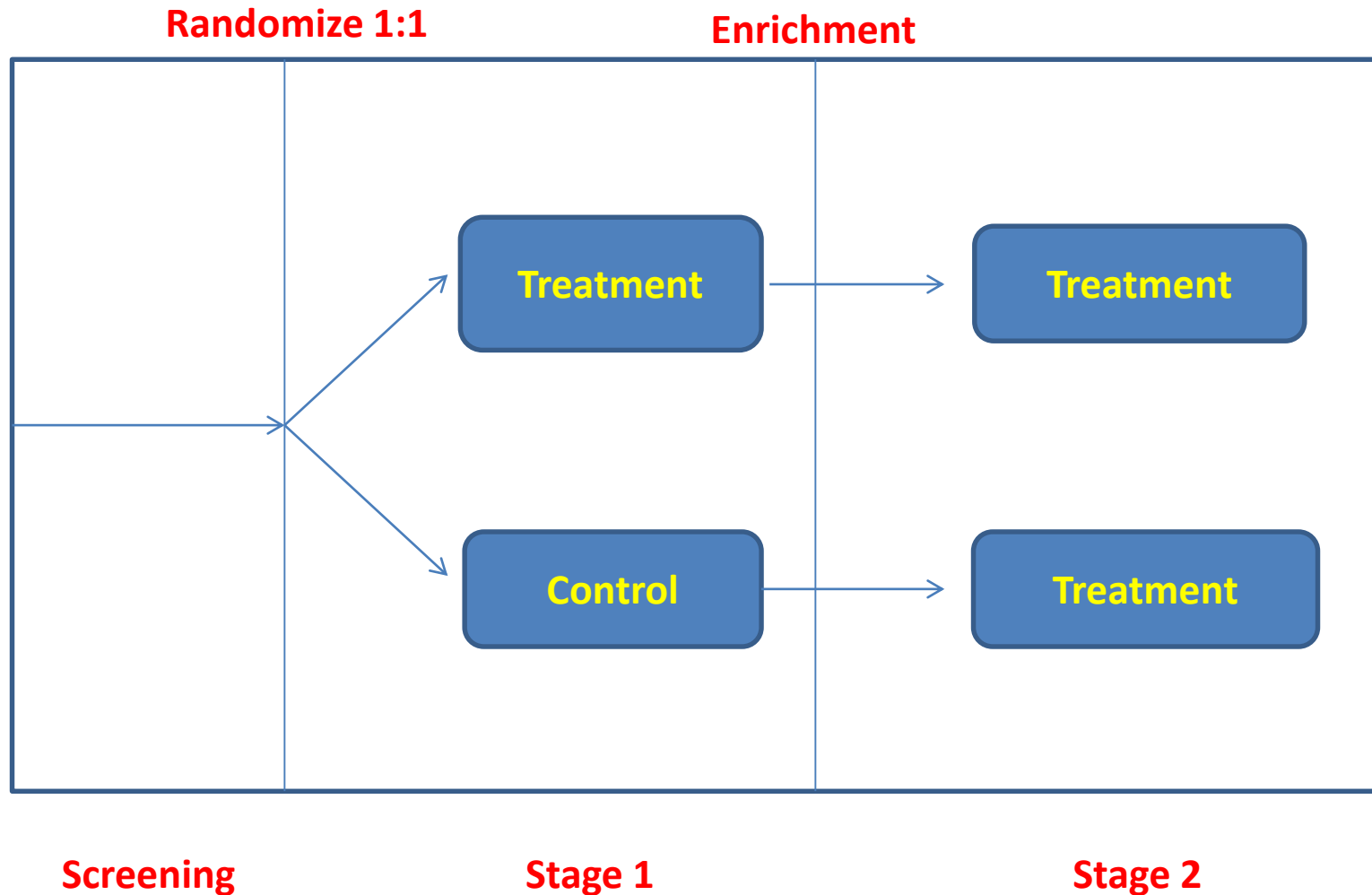
RWE Randomized Enrichment Design (RWE RE-Design)



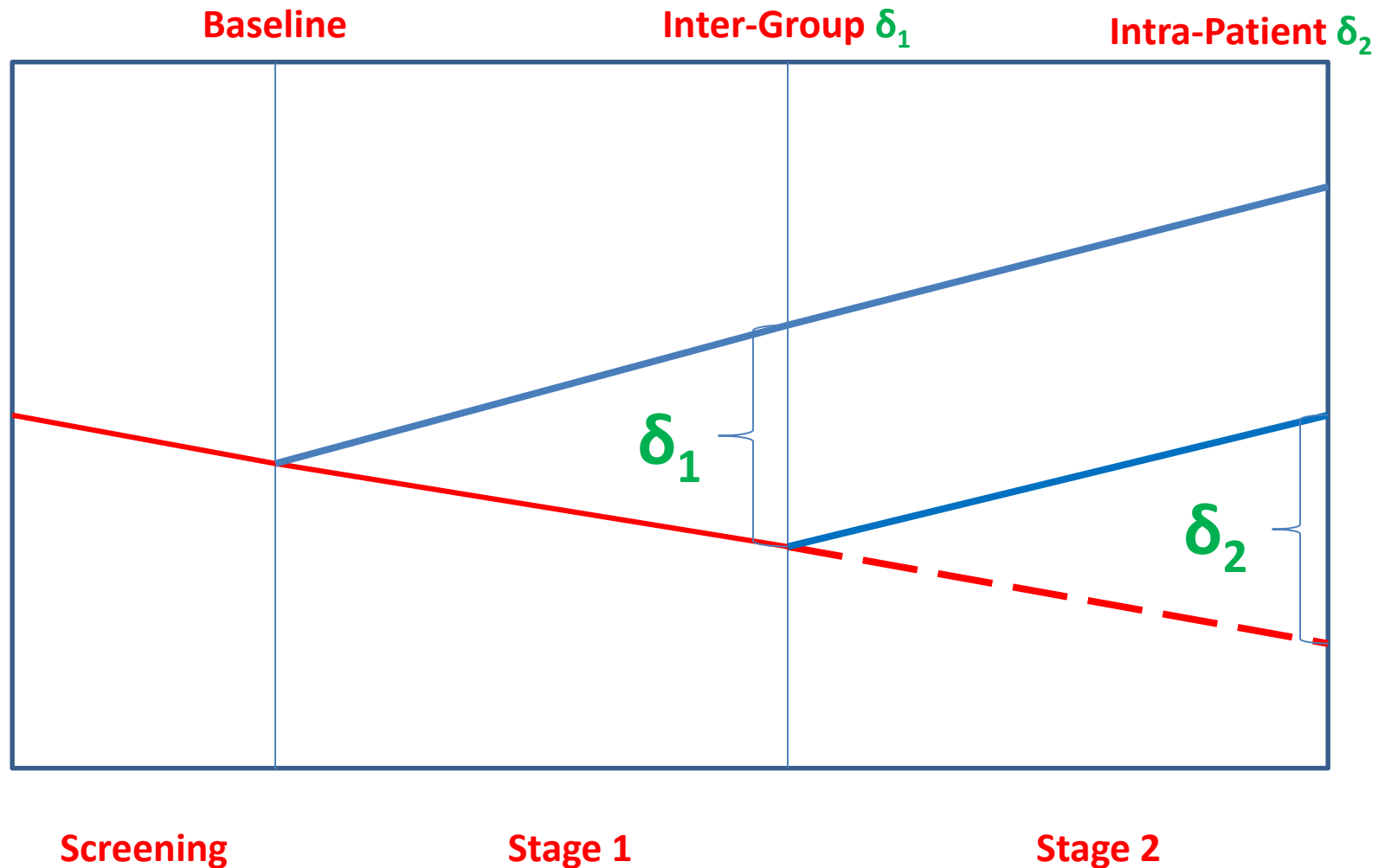
RWE Randomized Enrichment Design (RWE RE-Design)



Randomized Delayed-Start Design (RDS-Design)



Randomized Delayed-Start Design (RDS-Design)



Part III

Intra-Patient Comparisons

- **Patient-Centric Approach**
- **Individual Effects**
- **Definition**
- **Innovation with Intra-Patient Comparisons**

Patient-Centric

- **Woodcock (Sept 2019) at the Breakthrough in Medicine Conference**

“We need the whole system to evolve and change if we’re going to do what we set out to do: help every patient feel better and live longer ...”

Intra-Patient Effects

- **Positive Individual Effects**
 - Improvement in change from baseline for stable conditions
 - Slowing down in disease progression
- **Consistency Criteria**
 - Positive inter-group effect does not imply positive individual effects
 - Positive intra-patient effect does not imply positive inter-group effects
 - RWE-RE design seeks consistent effects

Definition

- **Contemporaneous Comparisons**
 - Predicted effects had patients continued the control
 - Difference based on observed on treatment versus predicted on the control during stage 2
- **Predictive Modeling**
 - Mixed effect models with longitudinal data
 - Conditional logistical regression model for binary data
 - Conditional Cox regression model for time-to-event data

Innovation with Intra-Patient Comparisons

- **Motivations of Intra-Patient Comparisons**
 - Patient-centric approach focusing on treatment effect for each patient
 - To control various sources of bias due to heterogeneity of patient population with known and unknown risk factors
 - Improve efficiency of trial designs to bring innovative therapies to rare disease patients early
- **Key Features of Efficient Randomized Designs**
 - Randomized controlled design
 - Adequately sized control arm
 - Intra-patient comparisons as (part of) primary analysis
 - Tipping point sensitivity analysis to assess placebo effects

Part IV

RWE RE-Design

- **Main Analysis**
- **Tipping Point Sensitivity Analysis**
- **Case Example**
- **Randomization Ratio**

Main Analysis

- **Exact Conditional Intra-Patient (ECIP) Test**
 - Mean or median based test statistics
 - Exact distribution free with sign probabilities derived from control distribution
- **Tipping Point Sensitivity Analysis**
 - To assess robustness of ECIP test against potential placebo or volitional effects
 - Shift control distribution to reach a tipping point

Tipping Point Analysis

- **Concept**

- Primary intra-patient comparisons assumes no volitional effects in prediction models
- Use a single scale sensitivity parameter to alter trajectory of prediction
- Application of scale sensitivity parameter patient specific
- Tipping point is the parameter value where statistical significance is lost
- Similar to tipping point MNAR analysis of missing data

- **Interpretation**

- Review issue, not a design issue
- Magnitude of volitional effects from both **concurrent** and **historical** controls to be used to assess tipping point

Case Example

- **Design Parameters**

- Effect size **5** and SD **10**; **90%** power for intra-patient comparisons with one-sided significance level **0.025**
- **95%** power for inter-group comparisons

- **Comparisons of Efficiency**

- Inter-group comparisons requires **85** per arm with **170** total
- Intra-group comparisons requires **43** patients
- Inter-group comparisons requires **four** times of the sample size

Randomization Ratio

- **Choice of Randomization Ratio**

Randomization Ratio	Sample Size	Relative Efficiency	Consistency Criterion
5:1	52	70%	0.625
4:1	54	68.75%	0.575
3:1	58	66.75%	0.5
2:1	66	62.5%	0.4
3:2	72	58.33%	0.35
1:1	86	50%	0.25

Part IV

RDS-Design

- **Integrated Analysis of Efficacy**
- **Tipping Point Sensitivity Analysis**
- **Sample Size Example**

Integrated Analysis of Efficacy (IAE)

- **Combination Test Statistic**
 - Weighted combination test statistic to combine inter-group comparison of stage 1 and intra-patient comparison of stage 2
 - Exact conditional distribution-free procedure based on randomization test and sign probabilities
- **Two-Stage Procedure**
 - Inter-group test at stage 1 and IAE at stage 2, **both at one-sided significance level 0.025**
 - Consistency criteria to control overall type 1 error rate at the one-sided level 0.025.

Tipping Point Analysis

- **Objective and Use**

- To assess potential placebo effect of intra-patient comparisons
- Sensitivity analysis, review (not design) issue
- Applicable to settings with subjective or effort-driven endpoints

- **Procedure**

- Removing potential placebo effect from intra-patient comparison to the tipping point at which the IAE is no longer statistically significant
- Natural history data or literature

Sample Size Example

- **RDS Design**

- One sided significance level 0.025
- 28 patients per group
- Stage one, two and IAE powers are 46.5%, 97.7% and 99%

- **Parallel Group (PG) Design**

- 75, 100 and 175 per group with 80%, 90% and 99% power
- RDS requires only 20% to 45% of PG design

Discussion

- **Efficient Randomized Designs**
 - Current in use in INDs
 - Collaborative work with FDA review team and management
 - Broader collaboration in the context of rare disease consortium and forum as part of complex innovative designs and analysis methodology that could lead to paradigm shift in regulatory policies
- **FDA's Complex Innovative Design (CID) Pilot**