Adaptive Enrichment Designs Modifying Pre-specified Enrollment Criteria

ISCTM Conference

September 25, 2020

Ronald Marcus

CMO – Terran Biosciences

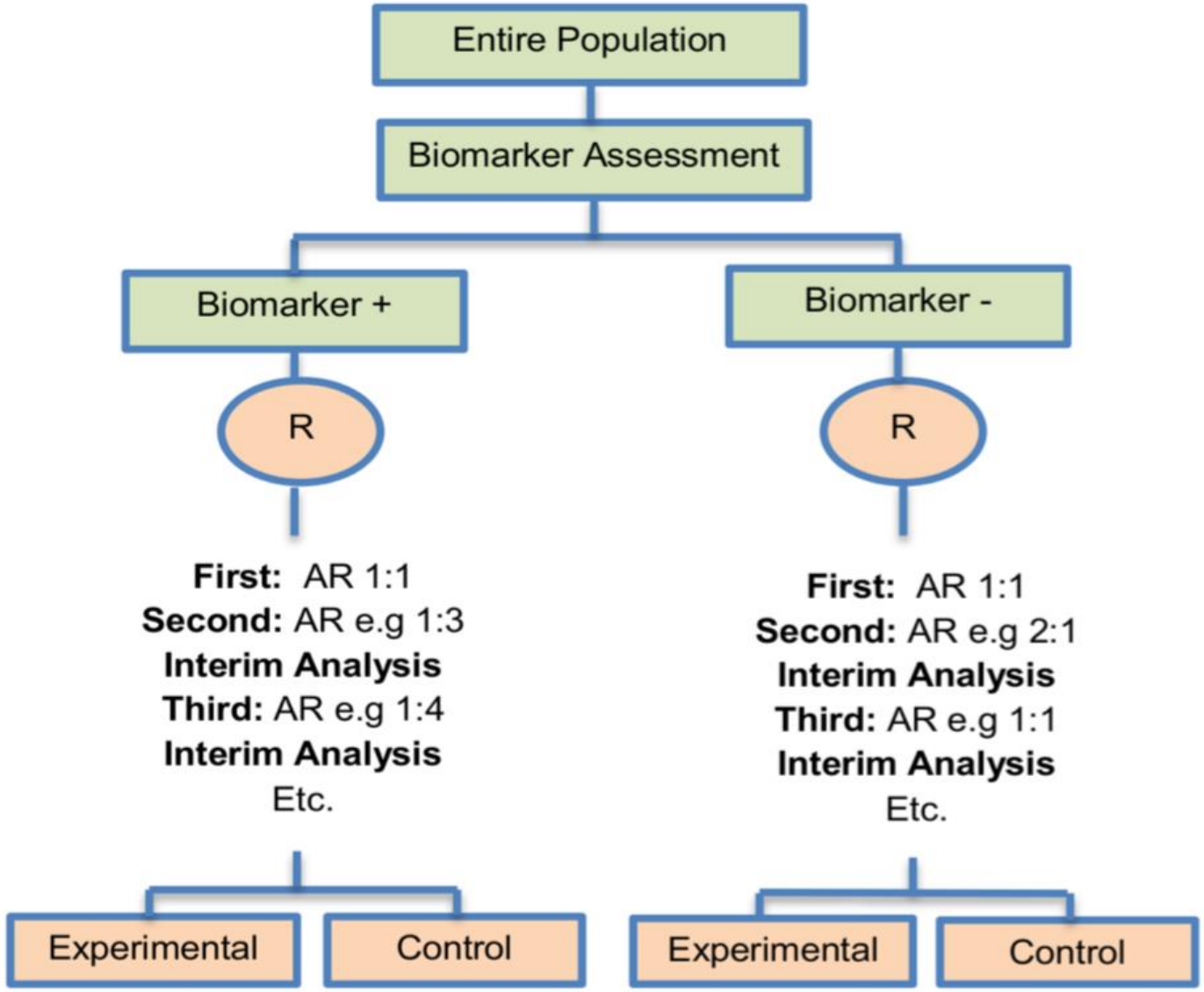
Objectives of the Presentation

- Introduce the concept of adaptive enrichment designs: randomized trial designs that adaptively change enrollment criteria during a trial
- Provide examples when adaptive enrichment designs may be useful
- Provide examples of enrollment criteria that can be modified during a trial
- Present several predictive enrichment strategies

Adaptive Enrichment Designs

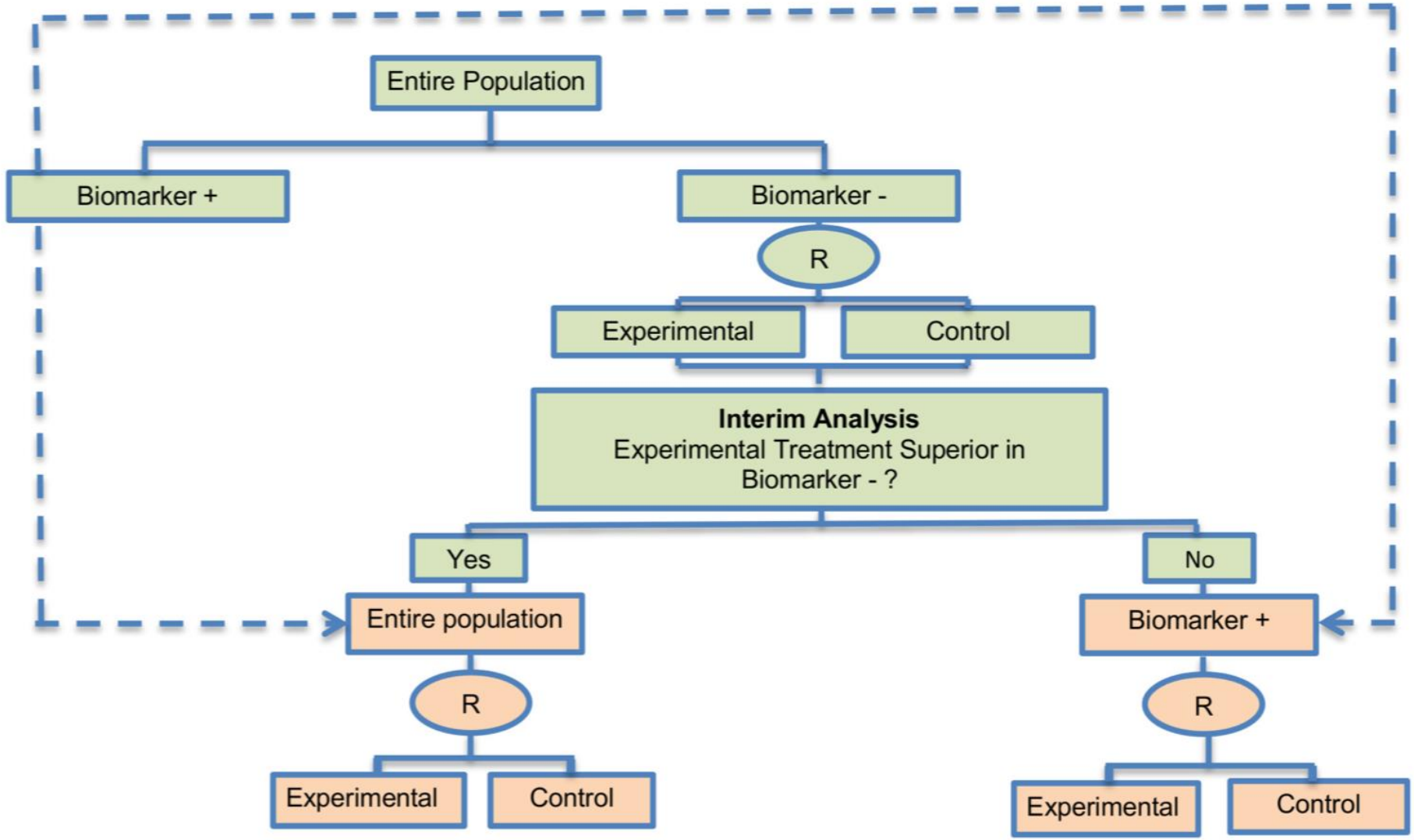
- Designs with prespecified rules for modifying the enrollment criteria based on data accrued in an ongoing trial are called adaptive enrichment designs (prognostic or predictive)
- Predictive enrichment strategies
  - Choosing patients more likely to respond to the drug treatment than other patients with the condition being treated, leading to a larger effect size (both absolute and relative) and permit use of a smaller study population
  - Selection of patients could be based on a specific aspect of a patient's physiology or a disease characteristic that is related in some manner to the study drug's mechanism, or it could be empiric

Outcome Based Adaptive Randomization Design



R=Randomization
AR=Adaptive randomization

Adaptive Patient Enrichment Design



R=Randomization

Strategic Adaptive Enrichment plan in Migraine

- The two-stage adaptive design trial is a global placebo-controlled two-arm trial in pediatric migraineurs with and without aura aged 12 to 17 years
- All prior pediatric migraine efficacy failed to demonstrate efficacy due to high placebo response rates
- The primary efficacy endpoint is pain freedom rate at two hours post-dose
- “Responder” in Stage 1 = mild to no pain (15 minutes post dose)
- “Non-responder” in Stage 1 = moderate to severe pain (15 minutes post dose)

Ho TW, et al. Efficacy and tolerability of rizatriptan in pediatric migraineurs: results from a randomized, double-blind, placebo-controlled trial using a novel adaptive enrichment design. Cephalalgia. 2012 Jul;32(10):750-65.

Strategic Adaptive Enrichment plan in Migraine (2)

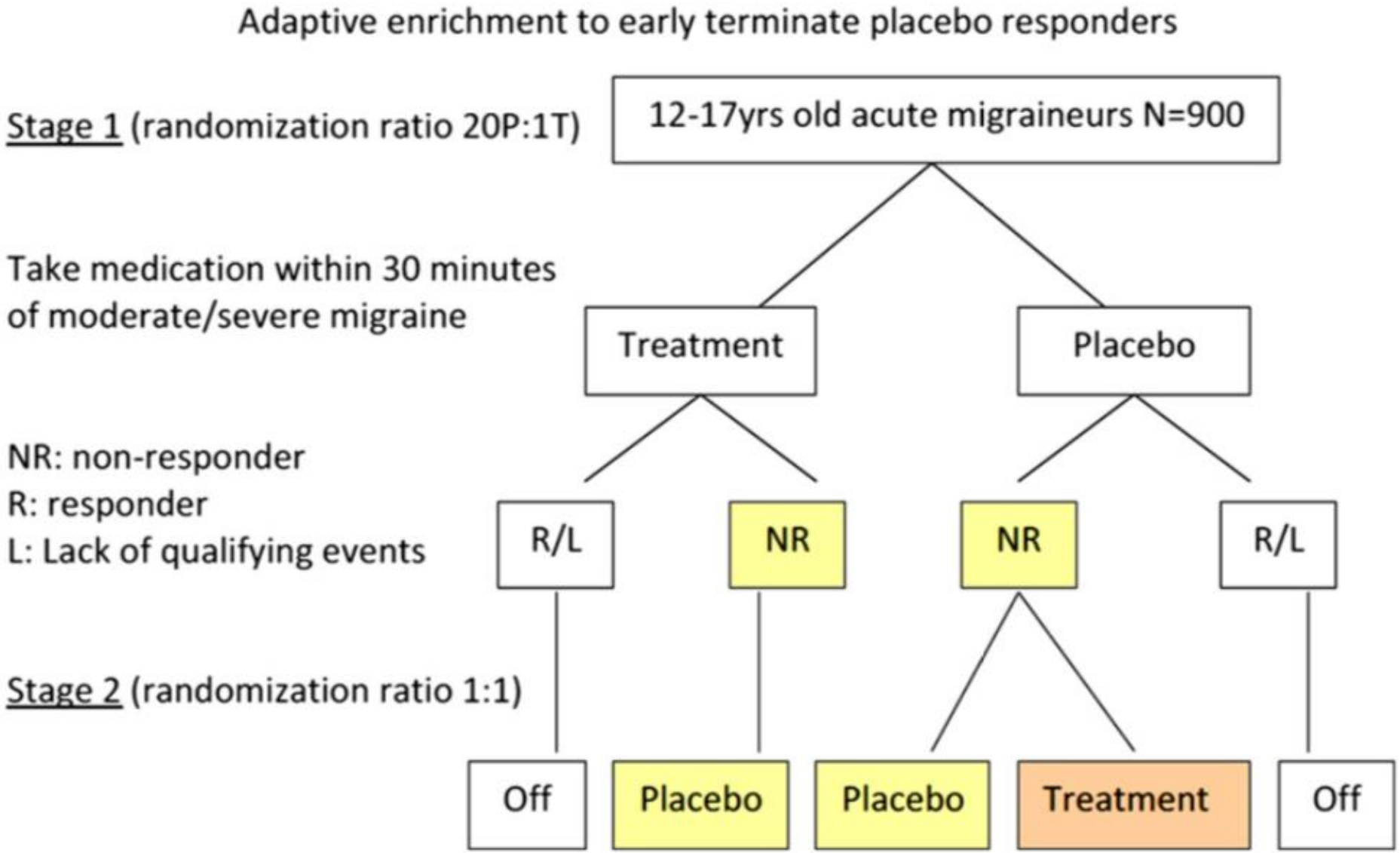
Stage 1

- 20:1 placebo to treatment randomization ratio
- Responders are discontinued from the study
- Non-responders (NR) in Stage 1 will proceed to Stage 2

Stage 2

- Placebo non-responders will have 1:1 placebo to treatment randomization ratio
- Treatment non-responders automatically receive placebo in Stage 2

Successful Adaptive Enrichment Study in Migraine



Biomarker - Adaptive Design

- Biomarker adaptive design studies have been used in Oncology drug development trials
- Biomarkers require qualification, optimal screening design, model selection and validation
- “Prognostic” means that treatment effect exists in mutually exclusive, biomarker positive versus biomarker negative patient subsets
- “Predictive” means that treatment effect primarily exists only in one of the two mutually exclusive subsets

Biomarker Adaptive Design – Why Bother?

Increase Power

- In one study (Wang et al), there was an increase of 25% to 32% statistical power, if the treatment was only effective in the positive subset whose prevalence was at most 50%
- Adaptive enrichment is more powerful than a traditional design in studies where biomarker clinical utility is predictive of treatment effect, and is as powerful as a traditional design when clinical utility of a biomarker classifier is prognostic

Alzheimer's Disease

- Early AD Progression Studies did not use biomarkers for inclusion of subjects
- Later AD Progression Studies mandated the presence of brain amyloid as an inclusion criteria and in some studies APOE4+ heterozygotes
- All of the studies failed. Why?
  - Wrong patients?
  - Wrong, individual treatment?
  - Are multiple treatment approaches required?
- One study "worked" – Multi-domain (FINGER* study) – multidomain lifestyle-based intervention delivered by dietary counseling, exercise, cognitive training, social activities, and monitoring and management of vascular and lifestyle-related risk factors
  - Positive on comprehensive neuropsychological test battery (NTB) Z score

*Ngandu T, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet 2015;385:2255-2263.

Alzheimer's Studies: Biomarkers

- There are no established biomarkers for AD for identifying individuals most likely to respond to treatments, measuring responses to treatments, and predicting clinical benefit of treatments (surrogate biomarkers)
- Current biomarker/assessments/risk factors:
  - APOE-4 status
  - Atrophy – structural MRI
  - Connectivity – functional MRI
  - Metabolism (FDG PET),
  - Amyloid pathology (amyloid PET),
  - Tau pathology (tau PET & plasma P-tau181)
  - Diabetes, hypertension, hypercholesterolemia
  - Age, diet, exercise, obesity, chronic inflammation, etc

Alzheimer's Studies: Precision Medicine

- Include biomarkers that assess biological (blood/CSF) markers, genomic structural/functional/metabolic imaging, inflammation, metabolic, cardiovascular assessments, and potentially molecular data
- Blinded study that includes multiple treatments, simultaneously
- For example, "A+B" vs observational vs multi-domain plus "A+B" vs multi-domain plus "A+B+C"
- Multi-domain (FINGER* study) – multidomain lifestyle-based intervention delivered by dietary counseling, exercise, cognitive training, social activities, and monitoring and management of vascular and lifestyle-related risk factors
- Drug/nutritional treatments (options)
  - Metformin
  - GSK inhibitor (lithium)
  - Antihypertensive drugs
  - Oxidative stress treatment*
  - Biological
  - Novel therapy

* Epigallocatechin gallate (EGCG), resveratrol, pterostilbene, curcumin, quercetin

Alzheimer's Studies: Precision Medicine

- Subjects are assessed every 3 months to ensure compliance with study
- On an ongoing basis: integrating into the model various categories of structured data and clinical measurements
- Temporally co-registering the disease trajectories of every subject, which may start at a different age with a different pace and pathophysiological pattern
- Accounting for inter-individual variability in terms of temporal patterns of disease progression, since each individual shows different anatomical/ physiological/ functional characteristics and these features will change in each patient in a different way
- Assess how each biomarker, individually, or in groups impact the progression of the disease and the "efficacy" of the treatment intervention

Alzheimer's Studies: Precision Medicine

- As the study progresses the data is analyzed and based on prespecified criteria and the enrollment will be enriched by including or excluding selected subgroups for randomization into the trial
- With a large enough dataset and enough time for progression of the illness, the biomarkers individually or collecting may predict the utility of each treatment intervention
- Randomization ratios will change if a pattern of positive or negative predictive response to treatment/biomarker/subject characteristics is achieved