ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Finding the Signal:

Strategies for achieving participant-centric trials in the face of participant-introduced validity challenges

Chairs:

- **Tim Mariano, MD, PhD, MSc** – Medical Director, Sage Therapeutics; Instructor, Dept. of Psychiatry, Harvard Medical School
- **Siân Ratcliffe, PhD** – VP & Head of Medical Writing, Clinical Development & Operations, Pfizer
- **Kari Nations, PhD** – Senior VP, CNS Clinical Development, Syneos Health; Clinical Assistant Professor, Dept. of Psychology, University of Texas at Austin

Wednesday, February 20, 2019

Potential Conflicts

- **Tim Mariano, MD, PhD, MSc** – Employee at Sage Therapeutics, Inc. Past consulting: Janssen Pharmaceuticals Inc. & Ad Scientiam SAS
- **Siân Ratcliffe, PhD** – Employee and shareholder at Pfizer
- **Kari Nations, PhD** – Employee and shareholder at Syneos Health

Risk Mitigation in Trial Design – The Imperative

- **Risk mitigation is driven by sponsor motivation to maximize signal detection and minimize safety risks**

- **ICH E6 (R2) now requires that sponsors identify "risks critical to trial process and data," and implement quality control activities that are "proportionate to the risks inherent in the trial and the importance of the information collected."**

E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry (March, 2018). U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research, (CDER), Center for Biologics Evaluation and Research (CBER)

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Patient/Site Risks & Mitigation Strategies (just a few!)

Medication Adherence	Ratings Accuracy/Reliability	Subject Selection	Protocol Compliance	Placebo Response
Medication adherence technology, e.g., facial recognition	Training to maximize ratings accuracy and calibrate on conventions	Central medical agreement on subject eligibility	Patient and caregiver engagement techniques and technology	Trial designs to exclude potential placebo responders before randomization
PK assessment for IP levels	Training to promote the importance of neutrality in subject interaction	Verification of agreement between clinician assessment and patient self-assessment	Subject registries to identify participation in other trials (concurrently or too recently)	Trial designs to minimize the impact of placebo responders on the final analysis
PK assessment for prohibited medication levels	Subject training on the importance of providing accurate history	Psychiatric interview and eligibility determination by 3rd party clinician	Subject selection enrichment strategies for those most likely to be compliant	Masked protocol entry and progression criteria
Smart pills, smart caps	Electronic check of data anomalies	Verification of agreement between clinician and electronic algorithm	Between-visit phone calls	Entry criteria to enrich for those less likely to respond to placebo

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

And…We as Trial Designers Often Create Our Own Risks

- **Complexity:** number of assessments and burden of mitigation methods; compromise to site and patient engagement
- **Speed:** timeline pressure leading to poor subject selection; protocol amendments aimed at speeding up recruitment lead to sample and signal dilution
- **Scale:** increasing geographic reach of study without careful consideration of risks (e.g., small N countries, multi-national operational costs that could otherwise be invested in increasing sample size/power)
- **Underfunding:** budget limits that compromise sites' ability to dedicate adequate time and resources; underinvestment in training; inadequate sample size.

Are We Pressure Testing EVERY Element of our Trial Design?

- **What is the evidence for and/or against the underlying assumption for a given design feature?**
- **Is that evidence spurious, or is it replicated and convincing?**
- **What is the potential impact of the design element to cost?**
- **What is the potential impact to recruitment?**
- **What is the potential impact to site engagement?**
- **How could it affect the drug/placebo separation?**
- **Would the regulators support the design feature in a pivotal trial?**

Recent and Real Examples

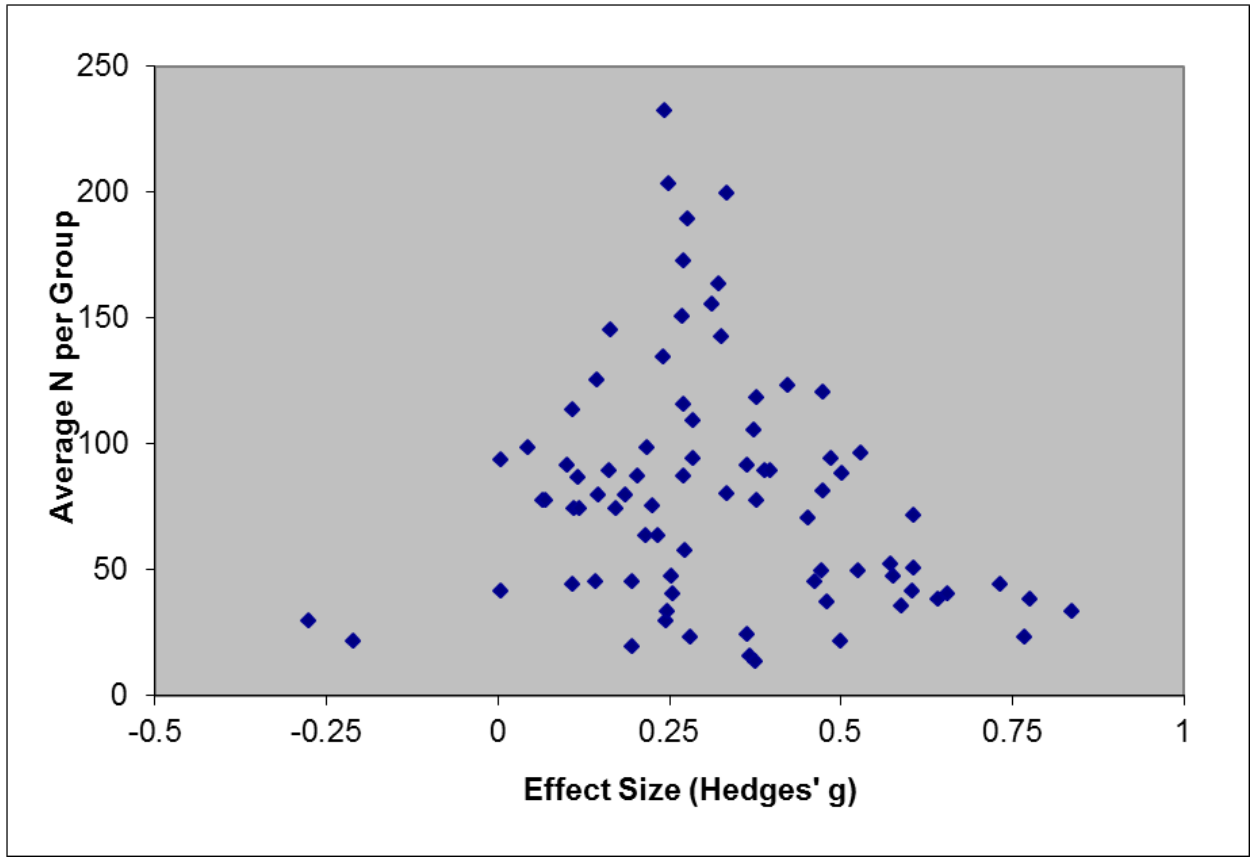
Sponsor 1: *"Our drug is going to have a large effect, so we can keep our sample size small."*

The drug's average effect size is not yet established. Guessing, based on mechanism (and hope), is risky!

Effect size, even for proven drugs, is highly variable with small samples. Some studies will separate, some will not.

Best to invest in a sample size that will maximize statistical power and allow for the most conclusive gate decision.

Effect size as a function of average sample size per arm for 15 registered antidepressants



M Gibertini, KR Nations, JA Whitaker (2012). International Clinical Psychopharmacology, 27:100–106.

Recent and Real Examples

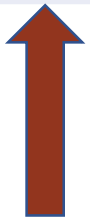
Sponsor 2: *"In our last study, Germany and France did not separate (drug/placebo), so we won't use those countries in the next study."*

- In a global trial, a single European country likely recruits fewer than 10-15% of all subjects
- Country decisions based on true drug/placebo statistical separation have a sample size problem.
- Country decisions based on effect have a effect size variance problem.
- Few subjects make an impactful contribution to the country-level (but not overall) separation.

Statistical modeling, three runs using same score range

	Large Sample (N=300)		Small Sample (N=30)	
	Pooled SD	Cohen's d	Pooled SD	Cohen's d
Run 1	8.68	0.40	7.51	0.16
Run 2	8.57	0.32	9.73	0.68
Run 3	8.86	0.42	10.09	0.03

Germany was not great in your last study, but maybe they'd be the best in your next!



Recent and Real Examples

Sponsor 3: *"We need to exclude unemployed patients, because they are less compliant and won't complete the study."*

- **What is the evidence for this assumption?** → *If no good evidence, consider examining your own past programs and evaluate discontinuation rates and effect size by employment status.*
- **Is there good evidence to the contrary** → *Perhaps unemployed patients are more motivated to return to work, more likely to be compliant. Could go either way, until you examine the evidence.*
- **What is the potential impact to recruitment?** → *Considering high unemployment rates among those with mental health issues; high mental health issue rates among those who are unemployed, you may be inadvertently prolonging your study timeline.*
- **What is the potential impact to site engagement?** → *Will cutting the potential patient pool by >30% mean that sites need more advertising budget? Will they become frustrated and refocus their attention on another study?*
- **How could it affect drug/placebo separation?** → *Are unemployed patients more severe, with more room to change?*
- **Would the regulators support the design feature in a pivotal trial?** → *Is your enrichment strategy sanctioned for Phase III?*

Recent and Real Examples

Sponsor 4: ***"Omega-3 supplements improve cognition, so we can't allow any patients taking omega-3s in the study."***

→ What is the evidence for/against? What percent of subjects in this indication take supplements? How will this impact recruitment?

Sponsor 5: ***"CGI-S and CGI-I take five minutes to administer, so there's no downside to including both."***

→ Did you pressure test your assumptions? CGI-S can be a more sensitive response measure, and dropping CGI-I can save >$500K in a single study (site grants, database build, data entry, data cleaning, etc.; Nations, Gandy, Spiridonescu et al, 2017**). Why not give that money over to your sample size?**

Sponsor 6: ***"Any subject with drug levels below the level of quantification will not be included in the final analysis."***

→ Verify you will be supported by regulators. Post-randomization data exclusion is rarely acceptable.

Sponsor 7: ***"In Phase II, our drug significantly improved symptoms. The study just didn't separate because of the response in the placebo group."***

→ → → …Don't get us started….

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Finding the Signal - Agenda

Stakeholder	Section	Speaker
Sponsors	Case studies on how sponsors influence risks and utilize evidence/data to support decisions Discussion	Stephen Brannan Éva Kőhegyi
Academia/Methods Research	Testing our assumptions: Moving from speculative to evidence-based trial design Discussion	Fabrizio Benedetti
	Break	
Sites and Patient Advocates	Site and patient perspectives: Balancing risk mitigation with site/patient burden and acceptability Panel / Audience Q&A	Lori Davis- Facilitator Sarah Atkinson, Penney Cowan, David Walling
Regulatory	Regulatory perspective on design solutions Panel / Audience Q&A	Tom Laughren Valentina Mantua
Session Chairs	Concluding remarks	Sian Ratcliffe, Tim Mariano, Kari Nations