ISCTM
International Society for CNS Clinical Trials and Methodology

Orphan Diseases Working Group

Thursday, September 12, 2024

San Diego, CA

Chairs: Joan Busner, Ph.D. and Gahan Pandina, Ph.D.

Disclosures

- Dr. Busner is a full-time employee of Signant Health, in which she may hold stock/equity.

- Dr. Pandina is a full-time employee of Janssen Research and Development, LLC, and holds stock in Johnson & Johnson

Agenda

- Welcome and introductions
- Exciting developments!
  - Our Half-Day Session at ISCTM 2025 (February 19-21, Mayflower Hotel, Washington, DC)
    - Our session is on Thursday, February 20: 2-5:30 pm
  - Manuscript Development
    - Results of interest survey
- Next steps

Our Half-Day Session at ISCTM 2025

Day 2 of ISCTM Meeting: Thursday, February 20; 2:00 - 5:30

21st Annual Meeting

19-21 February 2025

The Mayflower Hotel, Washington DC

Current Agenda for Half-Day Session

2:00-5:30	**Session 3A: Using novel biomarkers and advanced analytics to optimize measurement, endpoint selection, and signal detection: Lessons for the broader neuroscience community from orphan disease trials** • **How can we enable and enhance drug development approaches using novel tools (digital, biomarkers) and analytic approaches (composite endpoints) in neurology and neuropsychiatry, particularly in Phase 2 / PoC.** • **Provide examples from large population studies and, for rare diseases, compare and contrast with how these problems have been solved in larger populations.**	**Joan Busner** **Gahan Pandina**
2:00	Session Intro	TBC
2:05-2:25	Talk 1 – What are Digital Outcomes in Neuropsychiatry and Neurology? • Objective measures of behavior or digital signals: EMA, actigraphy, EEG, • Relationship of digital outcomes to functioning or disease outcomes of interest (feels, functions, survives) • Should include relationship of clinical meaningfulness and changes in outcome • How did we analyze the data? Regulatory path	Gahan Pandina, PhD

Current Agenda for Half-Day Session

2:25-2:35	**Discussion**	
2:35-2:55	Talk 2 - Novel digital endpoints in rare disease, examples of "success" DMD (stride veolocity) and Myotonic Dystrophy (muscle strength, respirometry) • Stride velocity accepted as primary endpoint for DMD in the EU (https://www.ema.europa.eu/en/documents/scientific-guideline/qualification-opinion-stride-velocity-95th-centile-primary-endpoint-studies-ambulatory-duchenne-muscular-dystrophy-studies_en.pdf) • Skyclaris – Friedreich's Ataxia – used secondary data as a marker of supportive secondary data. • Givinostat (Duvyzat) – approved for DMD Outcome analysis approach	Laurent Servais at Oxford University. (Re DMD measures ActiMyo and Stride Velocity)
2:55-3:05	Discussion	
3:05-3:25	Establishing clinical meaningfulness and MID in Rare/Orphan Disease endpoints • CGI here – design (# of items) and use as potential primary or co-primary. Also include PGI • Patient-defined clinical meaningfulness	TBC
3:25-3:35	Discussion	

Current Agenda for Half-Day Session

3:35-3:50	**Break**	
3:50-4:10	Composite endpoints and analysis? • Clinical rating scales are actually composites as well, to capture various aspects of disease (MADRS, PANSS, ABC etc.). • Long regulatory precedent for use of these scales, because of the "agreement in the field and large validation databases"	TBC
4:10-4:20	Discussion	
4:20-4:50	Talk 5 – analytic approaches • Practical analytic approaches to interpret data • Using permutation testing • Autism example with ML • Ability scores • What is the burden of evidence required in rare disease? Model details required up front, which may be challenging. May require negotiation (due to high level of evidence requested) • Can you use pre-programmed statistical composite approach for Ph3 programs?	TBC

Current Agenda for Half-Day Session

4:50-5:25	**Panel Discussion** **FDA and EMA panelists to respond to potential questions**	**https://www.fda.gov/news-events/fda-voices/fda-rare-disease-innovation-hub-enhance-and-advance-outcomes-patients** **~~Patrizia Cavazzoni?~~** **Peter Marks?** **New director to be hired?**
5:25pm	Session Wrap-Up	
5:30pm	Session adjourns	

Manuscripts

CGI

Maria	Acosta	NIH- NHGRI-UDP	acostam@nih.gov	x
Cristan	Farmer	NIMH	cristan.farmer@nih.gov	x
Joe	Horrigan	Duke University/AMO Pharma	jphorrigan5@gmail.com	x
Naomi	Knoble	FDA	naomi.knoble@fda.hhs.gov	x
Tom	Macek	Cybin	tommacek@yahoo.com	x
Marcela	Roy	Signant Health	marcela.roy@signanthealth.com	x
Frank	Sasinowski	Hyman, Phelps & McNamara, PC	fsasinowski@hpm.com	x
Marc	Walton	Indpendent Consultant	icnivad909@comcast.net	x

Measuring Cognition As An Outcome in Rare Disease Studies

Maria	Acosta	NIH- NHGRI-UDP	acostam@nih.gov	x
Cristan	Farmer	NIMH	cristan.farmer@nih.gov	x - lead
Meg	Grabb	NIMH/NIH/HHS	mgrabb@mail.nih.gov	x
Naomi	Knoble	FDA	naomi.knoble@fda.hhs.gov	x
Tom	Macek	Cybin	tommacek@yahoo.com	x
Ronald	Marcus	BMS	ronmarcus99@gmail.com	x
Kemi	Olugemo	Korro Bio	kemi.olugemo@gmail.com	x
Marc	Walton	Indpendent Consultant	icnivad909@comcast.net	x

Ethics of Clinical Trials in Rare Diseases

Maria	Acosta	NIH- NHGRI-UDP	acostam@nih.gov	x
Joan	Fallon	Curemark	Joan.Falllon@curemark.com	x
Cristan	Farmer	NIMH	cristan.farmer@nih.gov	x - lead
Meg	Grabb	NIMH/NIH/HHS	mgrabb@mail.nih.gov	x
Joe	Horrigan	Duke University/AMO Pharma	jphorrigan5@gmail.com	x - lead
Naomi	Knoble	FDA	naomi.knoble@fda.hhs.gov	x
Kemi	Olugemo	Korro Bio	kemi.olugemo@gmail.com	x - lead

Development of Endpoints for Disease Modifying Therapies (example: Rett Syndrome)

Maria	Acosta	NIH- NHGRI-UDP	acostam@nih.gov	x
Larry	Alphs	Larry Alphs Consulting	larryd349@comcast.net	x
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Ronald	Marcus	BMS	ronmarcus99@gmail.com	x
Frank	Sasinowski	Hyman, Phelps & McNamara, PC	fsasinowski@hpm.com	x
Marc	Walton	Indpendent Consultant	icnivad909@comcast.net	x

Other Manuscript Ideas Submitted

Meg	Grabb	NIMH/NIH/HHS	mgrabb@mail.nih.gov	biomarkers as early indicators of drug/biologic action
Frank	Sasinowski	Hyman, Phelps & McNamara, PC	fsasinowski@hpm.com	confirmatory evidence -- key to single study approvals

Next Steps

- Manuscript leads need to be assigned
- Outline of manuscript should be submitted to group
- Ideas for speakers should be submitted – may or may not contact them; need ISCTM SC approval first