Welcome!

Outcome Measures and Infrastructure for Phase III Studies in Batten Disease (JNCL)

December 6-7, 2013
Rochester, NY USA

MEDICINE *of* THE HIGHEST ORDER

UNIVERSITY *of* ROCHESTER MEDICAL CENTER

Disclosures and Acknowledgments

Thank you…

- Dan Parr, Magda Ramzy, Alyssa Thatcher, Sara Defendorf (Admin. Support)
- All participants, from near and far!
- Parents – Lori Sikorra (California, USA) & Ellen Bletsoe (Thrapston, UK)
- Advocacy Groups – BDSRA (Chris Leonard) & BBDF (Lisa Beth Furstenberg)
- NIH Program Officers - Danilo Tagle, John Porter, Jill Morris
- University of Rochester Batten Center Team

Acknowledgments - A Strong Foundation

International Conference on NCL

- 12th Hamburg, Germany (2009)
- 13th. London, England (2012)
- 14th. Córdoba, Argentina (2014)

First International Education Conference on Batten Disease Örebro, Sweden (2006)

Drug Discovery in JNCL Conf. Beyond Batten (2011)

Neurobiology of Disease Symposium – Child Neurology Society meeting South Beach, CA, USA (2012)

NCL (National Contest for Life) Congress. Annual, Hamburg, Germany

NCL RESOURCE - A GATEWAY FOR BATTEN DISEASE

http://www.ucl.ac.uk/ncl/meetingspast.shtml

1980: International Symposium on Human and Animal Models of Ceroid-lipofuscinosis, Røros, Norway

1st Worldwide Meeting of Batten Disease International Alliance (BDIA)

Background: Juvenile Neuronal Ceroid Lipofuscinosis (CLN3)

- **Childhood – onset**
- Inherited, **neurodegenerative**, lysosomal storage disease
- **Diverse symptoms**, including vision loss, seizures, loss of motor and mental abilities
- **Slow progression** (10-15 + years)
- A **rare disease**: estimated worldwide incidence: 0.2 to 7:100,000

Background

Table 2. Neuronal Ceroid Lipofuscinosis Clinical Trials Registered on www.clinicaltrials.gov.

NCL type	Intervention	Sample size	Trial phase	Design	Current status	Clinicaltrials.gov identifier
LINCL	Gene transfer vector (AAV2CUhCLN2)	11	I	Single-group, open-label	Ongoing, not recruiting	NCT00151216[32]
LINCL	Gene transfer vector (AAVrh.10CUCLN2)	16	I	Parallel-group, open-label	Ongoing, recruiting	NCT01161576[33]
LINCL	Gene transfer vector (AAVrh.10CUCLN2)	8	I/II	Parallel-group, open-label	Ongoing, recruiting	NCT01414985[34]
JNCL	Mycophenolate mofetil (CellCept)	30	II	Randomized, placebo-controlled, crossover	Ongoing, recruiting	NCT01399047[35]
INCL, LINCL	Cysteamine (Cystagon) + *N*-acetylcysteine (Mucomyst)	10	II	Single-group, open-label	Ongoing, not recruiting	NCT00028262[36]
INCL, LINCL	Human CNS stem cell transplantation	0	Ib	Single-group, open-label	Terminated	NCT01238315[37]
INCL, LINCL	Human CNS stem cell transplantation	6	I	Single-group, open-label	Completed	NCT00337636[38]

Abbreviations: AAV, adeno-associated virus; CNS, central nervous system; INCL, infantile neuronal ceroid lipofuscinosis; JNCL, juvenile neuronal ceroid lipofuscinosis; LINCL, late-infantile neuronal ceroid lipofuscinosis; NCL, neuronal ceroid lipofuscinosis.

Augustine et al. Clinical Trials in Rare Disease: Challenges and Opportunities. JCN 2013, 28: 1142

Background:

- "need to develop new tools to **more rapidly assess the effects** of potential therapies" [1]

- **Sensitive, responsive**, "well-defined and reliable endpoint measures [are] particularly important in rare diseases where sample sizes are limited"[2,] in order to assess a **clinically meaningful change** in response to intervention.

Meeting Objectives

To bring together clinical research experts in JNCL and rare diseases to focus on establishing common ground for outcomes and infrastructure in support of Phase III Clinical Trials in Juvenile Batten Disease.

Aim 1: To identify potential clinical trial endpoints for Juvenile Neuronal Ceroid Lipofuscinosis (JNCL, CLN3 disease, Batten Disease)

Aim 2: To advance the infrastructure for NCL patient registries and further develop registries as a tool to support international clinical trial development, and development of clinical trial endpoints.

Aim 3: To enable junior investigators in JNCL to learn about and participate in the clinical research development process.

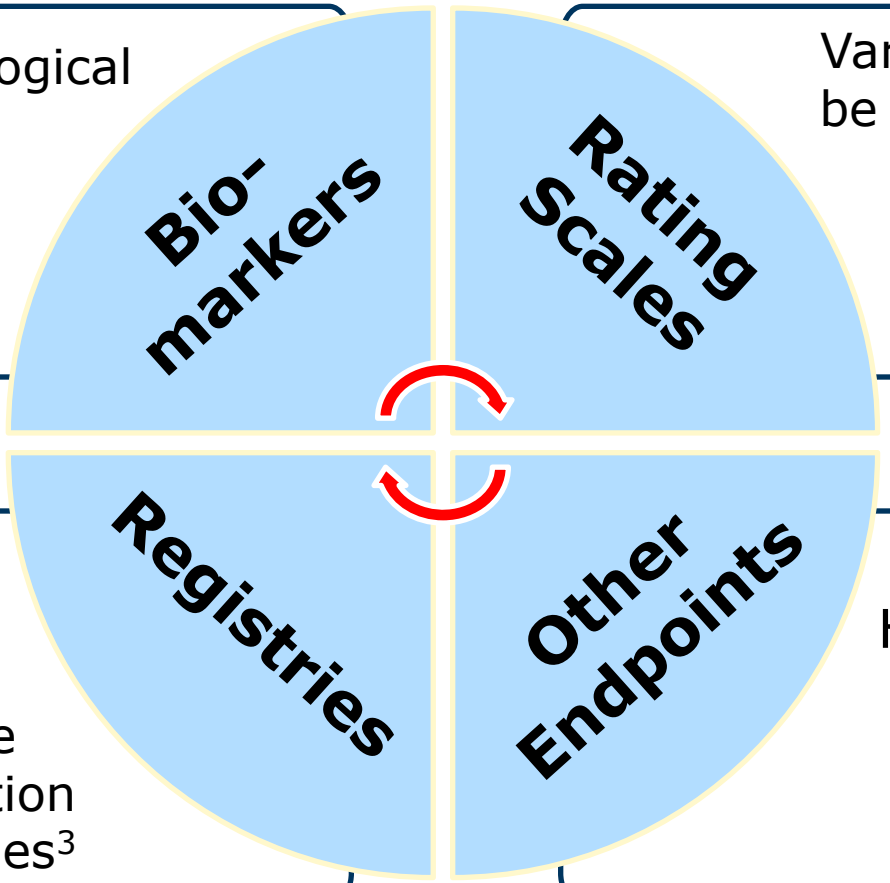
Meeting Structure: Day 1 – Formal Talks

THEMES

- Background on the NCLs
- Rare disease clinical research
  - Experimental therapeutics, Clinical trial endpoints
- Challenging ourselves…
  - Registries, Clinical endpoints, What matters to parents
  - State of the Science in JNCL, *with focus on clinical trial applications*
- Poster Presentations

Meeting Structure – Day 2: Working Groups

- Characterize biological processes
- Objective
- Quantifiable[1]



Variables that can only be indirectly measured (e.g., disability, quality of life, Well-being)[2]

- Observational
- Uniform
- Pre-planned
- Specific purpose
- Specific population
- Specific outcomes[3]

How an individual "functions, feels or survives".[4]

Day 2 – Working Groups

Working Group: Session 1

Propose endpoints / registry activities

Consider: reliable, valid, relevant, feasible

Large Group Discussion: Session 1

SUMMARY & FEEDBACK

Working Group: Session 2

Revise proposed endpoints / registry activities

Draft work plan

Large Group Discussion: Session 2

FINAL SUMMARY

Action Items

Research Priorities

Establish Consensus

Meeting Outcomes – Build a "Road Map"

1. A set of potential clinical endpoints in JNCL and a plan for their development and validation for future Phase III studies.

2. A plan for expansion of NCL Patient Registries, to incorporate clinical trial endpoint work.

3. <u>Enduring and evolving content</u>

- Manuscript of proceedings
- Website (with PDFs of Day 1 talks and reference materials to support experimental therapeutics and Phase III trials in JNCL. We hope these materials will be useful for clinical trials in the other NCLs as well.
- Maintain interactions among participants at future meetings

References

1. Strimbu K & Tavel JA. What are biomarkers? Curr Opin HIV AIDS 2010. 5(8) 463-466

2. Gliklich RE, Dreyer NA, editors. Registries for Evaluating Patient Outcomes: A User's Guide. 2nd edition. Rockville (MD): Agency for Healthcare Research and Quality (US); 2010 Sep. Available from: http://www.ncbi.nlm.nih.gov/books/NBK49444/

3. McDowell I. Measuring Health: A guide to rating scales and questionnaires, Third Edition. 2006. Oxford Univ. Press.

4. *Robert Temple, FDA; Biomarkers Definitions Working Group 2001; Institute of Medicine 2010*