ANGELMAN SYNDROME: A NATURAL HISTORY STUDY IN OXFORD

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INTRODUCTION

A Natural History study for Angelman Syndrome is important for several reasons:

- Driven by trained clinicians in a standardize form
- Characterize AS and identify demographics, genetic phenotypes, environmental impact and other variables that correlate with AS and outcomes
- Study the indications of AS and how they progress over time, potentially patterns that might otherwise go unnoticed
- Once significant natural history study data is available, it can help with patient care including best practices of care and identifying research priorities
- Help stakeholders to get a better understanding of Angelman Syndrome

An encouraging number of developments are currently in the pipeline of Angelman Syndrome therapeutics, with some of them already at clinical trial stage.

Nevertheless, clinical trial readiness is still largely immature.

STUDY DESIGN

Prospective & observational

Monocentric

40 participants
0-99 years old

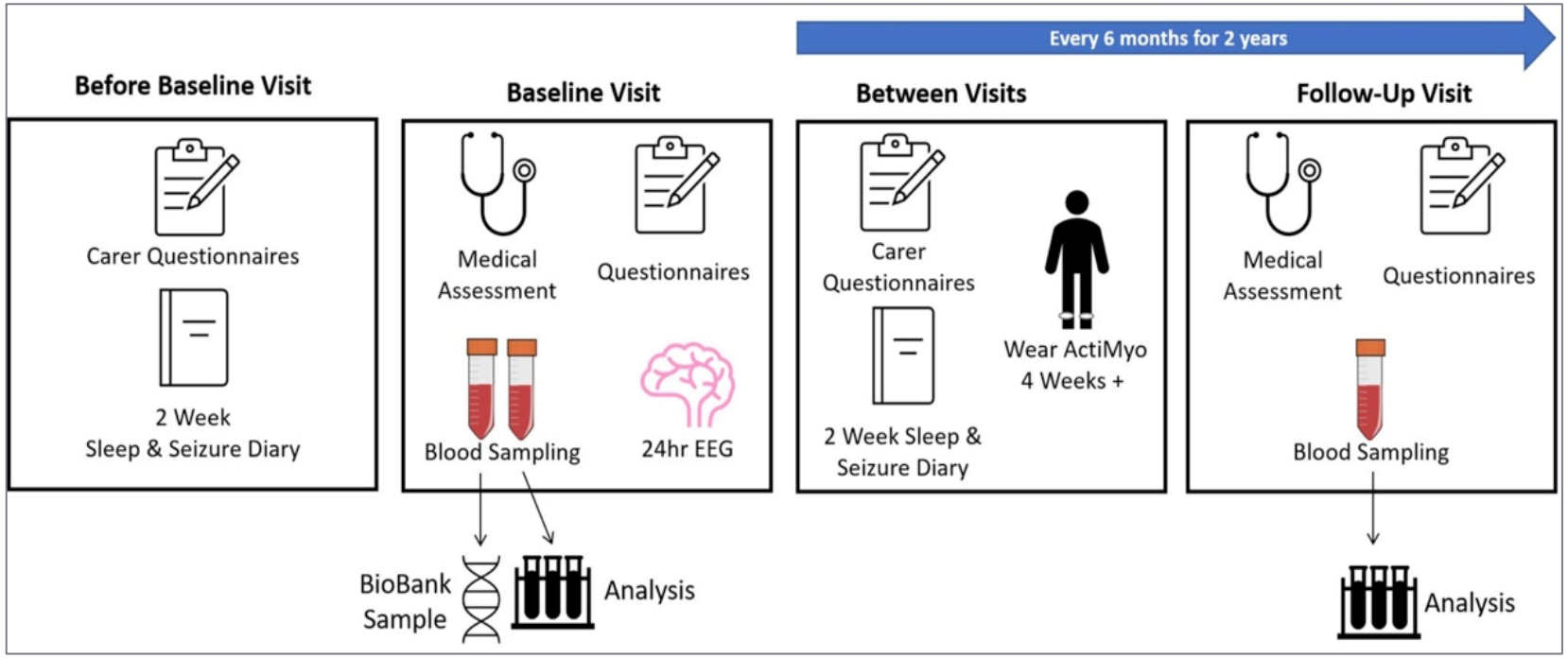


Fig. 1

ASSESSMENT VALIDATION

Motor scales
FMS, WHO motor milestones, Bayley-4

Cognition & Adaptive Behaviour
Bayley-4 & Vineland-3

Maladaptive & aberrant behaviour
ABC-C, Vineland-3

Quality of Life & Disease Burden
Peds QoL

Communication
ORCA & Matrix tools

INNOVATIVE OUTCOME MEASURES

number of falls
stride speed coefficient
perimeter of walk
strides/h

Fig. 2

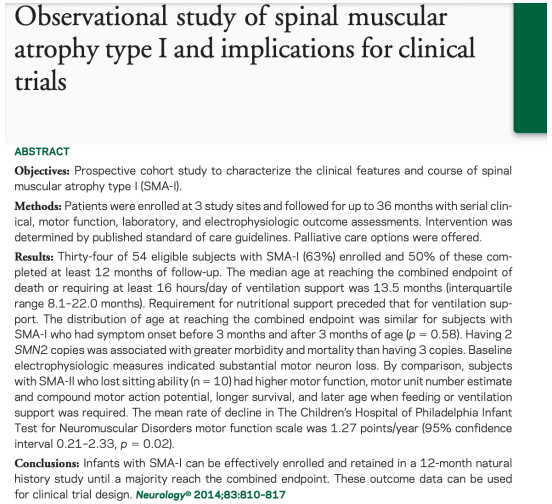
BIOMARKERS

EEG

Proteomic analysis

DNA BIOBANK

Natural history studies have paved the way to drug approval



Observational study of spinal muscular atrophy type I and implications for clinical trials

ABSTRACT

Objectives: Prospective cohort study to characterize the clinical features and course of spinal muscular atrophy type I (SMA-I).

Methods: Patients were enrolled at 3 study sites and followed for up to 36 months with serial clinical, motor function, laboratory, and electrophysiologic outcome assessments. Intervention was determined by published standard of care guidelines. Palliative care options were offered.

Results: Thirty-four of 54 eligible subjects with SMA-I (63%) enrolled and 50% of these completed at least 12 months of follow-up. The median age at reaching the combined endpoint of death or requiring at least 16 hours/day of ventilation support was 13.5 months (interquartile range 8.1–22.0 months). Requirement for nutritional support preceded that for ventilation support. The distribution of age at reaching the combined endpoint was similar for subjects with SMA-I who had symptom onset before 3 months and after 3 months of age ($p = 0.58$). Having 2 *SMN2* copies was associated with greater morbidity and mortality than having 3 copies. Baseline electrophysiologic measures indicated substantial motor neuron loss. By comparison, subjects with SMA-II who lost sitting ability (n = 10) had higher motor function, motor unit number estimate and compound motor action potential, longer survival, and later age when feeding or ventilation support was required. The mean rate of decline in The Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders motor function scale was 1.27 points/year (95% confidence interval 0.21–2.33, $p = 0.02$).

Conclusions: Infants with SMA-I can be effectively enrolled and retained in a 12-month natural history study until a majority reach the combined endpoint. These outcome data can be used for clinical trial design. *Neurology*® 2014;83:810-817

Understanding of natural history, event free survival and CHOP intend validation

ORIGINAL ARTICLE

Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

Richard S. Finkel, M.D., Eugenio Mercuri, M.D., Ph.D., Basil T. Darras, M.D., Anne M. Connolly, M.D., Nancy L. Kuntz, M.D., Janbernd Kirschner, M.D., Claudia A. Chiriboga, M.D., M.P.H., Kayoko Saito, M.D., Ph.D., Laurent Servais, M.D., Ph.D., Eduardo Tizzano, M.D., Ph.D., Haluk Topaloglu, M.D., Már Tulinius, M.D., Ph.D., et al., for the ENDEAR Study Group*

FDA NEWS RELEASE

FDA approves first drug for spinal muscular atrophy

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Succesful phase 3 design

Benefits of the Natural History for clinical trials are mainly to enable a smoother transition to clinical trial and improve chances of success

- Identify potential trial endpoints and help plan the trial
- Identify potential sites and establish early relationships to gauge suitability
- Engage patients ahead of clinical trial recruitment
- Engage with potential Biotech and leverage resources

CONCLUSION

With your help and the support of the AS UK community, we hope that this study will achieve the following main endeavours:

- Help characterize Angelman Syndrome
- Help with patient care including best practices of care and identifying research priorities
- Contribute to clinical trial readiness for Angelman Syndrome

Let's make it a resounding success!

We welcome collaboration with all associations, research teams or prospective natural history studies.

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