Research Protocol

1.0. INTRODUCTION

Angelman Syndrome (AS) is a severe neurodevelopmental disorder caused by disruption of the maternally inherited proportion of chromosome 15q 11-13 of the UBE3A gene (Clayton-Smith & Laan, 2003; Knoll, Nicholls & Lalande, 1989). There are four known genetic mechanisms which account for this dysfunction (Jiang, et al., 1999; Louise et al., 2001):

1. Deletion on the maternally derived chromosome 15q 11-13;
2. Uniparental disomy;
3. An imprinting defect; or,
4. A mutation in the UBE3A gene.

Children and adults manifest symptoms of neurodevelopmental delay (100%) with associated features of broad happy smile, jerky hand movements/ tremulousness, expressive language delay (often severe), motor delays, seizure disorders, and sleep disorders. There is thought to be some correlation between the type of genetic disruption and symptom severity with those with the deletion having more severe difficulties and those with the mutation having a less severe outcome. However, between 5-20% of individuals with characteristic physical and behavioural features show no identifiable abnormalities in the 15q 11-13 region (Clayton-Smith et al., 2003; Laan et al., 1998; Lossie et al., 2001; Williams et al., 2001).

Recent research has highlighted the progress made in the molecular genetics of AS with significant research pointing towards large scale clinical trials in the very near future. Dr Edwin Weeber has received an NIH grant trialling three different treatment modalities in the AS population and is reporting positive results. Currently the lack of an international registry inhibits people with AS from participating in clinical trials as identifying and contacting potential participants represents a significant challenge and cost to researchers.

2.0. OBJECTIVES

The key objective of the Global Angelman Syndrome Registry is to set up a parent/ caregiver driven registry to collect information about children and adults with Angelman Syndrome. This will allow for researchers conducting clinical treatment trials and other studies into Angelman Syndrome to recruit participants more easily. The registry will also serve other objectives including:

- Improving understanding of the natural history and impact of Angelman Syndrome across the lifespan;
- Focus further research into the study of this condition; and
- Inform future service planning for people with Angelman Syndrome and their families.

3.0. ELIGIBILITY AND RECRUITMENT

Parents/ caregivers of a child or adult with Angelman Syndrome are eligible to participate in this registry. The individual must have a diagnosis of Angelman Syndrome confirmed by genetic testing results (or a pending diagnosis).

Information about the registry will be communicated to members of the Angelman Syndrome community by syndrome organisations such as FAST Australia at http://www.cureangelman.org.au/

The registry will be launched in September 2016 to coincide with the **5th Angelman International Scientific Conference** in Lisbon.

4.0. REGISTRY PROGRAMME

The Global Angelman Syndrome Registry is an international registry for patients with Angelman Syndrome. No experimental intervention is involved in participation. Participants will receive electronic newsletters with updates on the registry including aggregated descriptive information about the patient data uploaded into the registry and invitations to complete new modules. Participants may also receive information about participating in relevant studies and clinical treatment trials. Once uploaded into the registry, participants may receive request to update data periodically. The data provided will be stored in the registry unless participants wish to withdraw their child/ adult's information from the study.

5.0. DATA COLLECTION AND SUBMISSION

The data will be collected via a series of "modules" within the registry. These modules will take approximately 1.5 hours to complete depending on the complexity of child/ adult with Angelman Syndrome's history. However, the data does not need to be input all at once as it is possible to log out and resume data input at a later time.

Modules cover the following demographic, health and medical, developmental and behavioural domains:

- Module 0: Demographics
- Module 1: Newborn and infancy history
- Module 2: History of diagnosis and results
- Module 3: Illnesses and medical problems
- Module 4: Medical history
- Module 5: Behaviour and development
- Module 6: Epilepsy
- Module 7: Medications and interventions
- Module 8: Sleep
- Module 9: The sleep disturbance scale for children (SDSC)
- Module 10: Pathology and diagnostics

Additional modules and measures may be added to the registry to document changes in children/ adults with Angelman Syndrome over time.

6.0. QUALITY ASSURANCE OF DATA

The registry is hosted by the Rare Disease Registry Framework, developed by the Centre for Comparative Genomics at Murdoch University. The Rare Disease Registry Framework was built on top of Django 1.8.4, which incorporates several levels of security to protect against data loss and unauthorised access to registry information. Access to the registry is restricted to a designated curator located at the Mater Research Institute, as well as software technicians who maintain the Rare Disease Registry Framework.

7.0. STATISTICAL METHODS AND DATA REPORTING

Statistical analysis of the Global Angelman Syndrome Registry for any purpose will be overseen by a governance board to ensure that usage of information complies with relevant ethical and privacy protocols.

Data analysis will initially focus on descriptive analysis of the sample to aggregate and summarise registry data. More detailed analysis techniques such as correlational analysis, multiple regression, hierarchical regression, and cluster analysis will be used to develop an understanding of the impact of various phenotypes and genotypes or sociodemographic factors on the natural history and progression of the syndrome into adulthood within the population of individuals with Angelman Syndrome. Findings from descriptive analyses will be disseminated to parents/ caregivers in newsletters. This data may also be utilised in research reports and possibly training workshops for paediatricians and paediatric psychiatrists.

Third party researchers may request data from the registry for other purposes. Any data requests will require approval from the registry governance board (see section 9.0).

8.0. ETHICAL CLEARANCE AND PARENT/ CAREGIVER CONSENT

All research protocol, participant information and registry content documentation was submitted to the Mater Health Services Human Research Ethics Committee for review and approval.

All parents/ caregivers will be asked to read an online consent form detailing the purpose of the Global Angelman Syndrome Registry. They will be asked to confirm that they have read and understood the information sheet, particularly with respect to the voluntary nature of the registry and their ability to withdraw without penalty.

They will also indicate their agreement to several conditions related to the data that they provide. These include participation in the registry and storage of their child/ adult with Angelman Syndrome's data on the registry.

They will also be asked for permission for their clinician to be contacted to verify information, and whether they agree to be contacted by the research team for follow up. Further details are available in the participant information sheet.

9.0. PARTICIPANT CONFIDENTIALITY

Any information parents/ caregivers choose to include on the Angelman Syndrome registry will be treated with utmost care to maintain privacy and confidentiality. This will include database security measures and informed consent processes. The consent processes enable participants to state

whether they agree to further contact from the registry team and the circumstances under which contact is made. The registry is also maintained on a secure server, and access to the registry is limited via a password system to the registry curator and technical maintenance personnel.

Any registry data disseminated to the public domain will be aggregated and de-identified, as patient names, dates of birth and other information which could potentially lead to the identification of participants will be removed from analysis and replaced with a unique identification number. Names and other potentially identifiable information will be linked to these unique identification numbers in a separate file stored on a secure computer terminal at the university. This process ensures that all data is potentially "re-identifiable" should the need occur.

Third party researchers may also apply to access de-identified data. In order to do so, researchers must satisfy the requirements of the registry governance committee regarding ethical use of the data and maintaining patient privacy.

Third party researchers wishing to conduct clinical trials or other studies requiring access to identifiable information **will not** be able contact registry participants directly. As per third parties accessing de-identified data, researchers must apply for approval from the registry governance committee. They must also arrange an independent ethical review of their study. Once these requirements have been satisfied, the registry team will contact eligible members of the registry on behalf of the third party researchers.

10.0. PARTICIPANT DISCONTINUATION

Participation in this registry is voluntary. Individuals may decline to participate in the registry, or withdraw consent for the patient's data to be stored on the registry at any time.

11.0. REGISTRY SPONSOR

The Global Angelman Syndrome Registry is funded by the **Foundation for Angelman Syndrome Therapeutics (FAST**) **Australia**. FAST Australia is an organisation of families and professionals dedicated to finding a cure for Angelman Syndrome and related disorders through the funding research, education, and advocacy. Launched in 2010, the organisation is committed to assisting individuals living with Angelman Syndrome to realise their full potential and quality of life.