Confidential Information

The information contained in this protocol is confidential and is intended for the use of clinical investigators. It is the property of University of British Columbia or its subsidiaries and should not be copied by or distributed to persons not involved in the clinical investigation PDE, unless such persons are bound by a confidentiality agreement with University of British Columbia or its subsidiaries.

The International Pyridoxine-Dependent Epilepsy Registry

Principal Investigator:

Dr. Clara van Karnebeek, Department of Pediatrics, University of British Columbia & Centre for Molecular Medicine and Therapeutics, BC Children's Hospital Research Institute Vancouver, BCCanada (Lead Canada)

Co-Principal Investigators:

Dr. Levinus Bok, Máxima Medical Center, Veldhoven, The Netherlands (Lead Europe)

Curtis R. Coughlin II, M.S., M.Be., Department of Pediatrics The Children's Hospital Colorado University of Colorado School of Medicine

Dr. Emma Foottit, UCL Institute of Child Health, London, UK (Lead UK)

Dr. Sidney M. Gospe, Jr, M.D., Ph.D., University of Washington, Seattle Children's Hospital, Neurology, Seattle, Washington, USA (Lead U.S.A)

Dr. Pasquale Striano, MD, PhD, Pediatric Neurology and Muscular Diseases Unit, DINOGMI-Department of Neurosciences, Rehabilitation, Opthamology, Genetics, Maternal and Child Health, University of Genoa, "G. Gaslini" Institute, Genova, Italy (Lead Italy)

Dr. Mohammed Almuqbil, MD, Boston Children's Hospital, Boston, USA and King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia (Lead Middle East Region)

Co-Investigators: Dr. Sihoun Hahn, Department of Pediatrics, Biochemical Genetics Program, University of Washington School of Medicine, Seattle Children's Hospital, Seattle, Washington, USA

Dr. Hans Hartmann, Hannover Medical School, Hannover, Germany.
Dr. Keith Hyland, Medical Neurogenetics, Neuromuscular & Neurogenetic Disease, LLC, Atlanta, GA
Dr. Barbara Plecko, University Children's Hospital, Neuropediatrics/Children Neurology, Zurich, Austria
Dr. Eduard A. Struys, Metabolic Unit, Clinical Chemistry, VUmc Medial Center, Amsterdam, The Netherlands.
Dr. Sylvia Stockler, BC Children's Hospital, University of British Columbia, Canada
Dr Johan Van Hove & Dr. R. Gallagher, University of Colorado Denver, University of Colorado Health Sciences Center at Fitzsimmons, Aurora, USA
Dr. Walla Al Hertani, Montreal Children's Hospital, McGill University Health Centre, Montreal, Canada
Dr. Joy Yaplito-Lee, Metabolic Genetics, Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, Australia

Collaborators:

Dr. Philippa Mills, UCL Institute of Child Health, London, UK

L.A. Tseng, MD, Department of Pediatrics, Amsterdam University Medical Centers, Amsterdam, The Netherlands

Funding: BC Rare Disease Foundation, CFRI Establishment Award

Table of Contents

1. Introduction:

1.1 Background

Pyridoxine-dependent epilepsy (PDE, MIM #266100) is an autosomal recessive epileptic encephalopathy characterized by resistance to conventional anti-epileptic drugs but responsiveness to pharmacological dosages of pyridoxine (Mills et al. 2010). In 2006, the underlying genetic defect was identified as deficiency of α-aminoadipic semi aldehyde dehydrogenase (antiquitin), which is involved in cerebral lysine catabolism (MIM #107323) (Mills et al. 2006). Antiquitin (ATQ) deficiency results in the accumulation of intermediates arising from lysine degradation proximal to the deficient enzyme activity including α-aminoadipic semi- aldehyde (AASA), Δ-1-piperideine-6-carboxylate (P6C), and pipecolic acid (see Figure 1). Inactivation of pyridoxal phosphate (PLP) via chemical reaction with P6C is the pathophysiological mechanism of pyridoxine dependency.

The pharmacological treatment of choice for pyridoxine dependent epilepsy includes lifelong supplementation of pyridoxine (Stockler et al, 2011). Lysine restricted diet is recommended in addition to pyridoxine based on the pathophysiology of the disease to reduce the accumulation of lysine derived intermediates and help improve cerebral function including neurodevelopment, cognition, and behaviour (Van Karnebeek et al, 2014).

Recently other innovative treatment options have been tried which include supplementation of arginine, which will further modulate cerebral lysine influx when added to the current treatment regimen of a lysine-restricted diet. For the past 10 years, arginine fortification has proven to be a safe add-on treatment and is effective in improving outcomes in GA1 (Kolker et al, 2011; Kolker et al, 2012).

1.2 Rationale

Little is known about PDE, especially in adulthood, as the genetic basis has only been elucidated in the previous decade. This research will allow us to substantiate existing observations of the effectiveness of treatments such as lysine-restriction and other dietary interventions and to gain further

insight into the pathophysiology and treatment outcomes. Our proposed international observational registry will include PDE patients of all ages, gender and ethnicity.

With the PDE online registry, one of our aims is to describe the clinical course of PDE in adulthood. To gain more insight in the clinical course and impact of this disorder, we will include questionnaires on quality of life and participation in society.

2. Objectives:

2.1. Primary Objective

- To enhance the understanding of the variability, progression, and natural history of Pyridoxine Dependent Epilepsy with the ultimate goal of better guiding and assessing therapeutic interventions

2.2. Secondary Objectives

- To provide recommendations for monitoring patients and to provide reports on patient outcomes to help optimize patient care
- To evaluate the effectiveness of treatments both pharmacologic and innovative (lysine restricted diet, arginine supplementation etc.)
- Facilitate in the planning of clinical trials.

3. Study design

The PDE Registry is an international prospective observational cohort study. Only patients with a confirmed diagnosis of PDE due to ATQ deficiency at selected centers will be enrolled. This study will last 10 years or longer pending additional funding.

4. Eligibility criteria

4.1. Inclusion Criteria:

- All patients with a confirmed PDE due to *ATQ* deficiency (defined as elevated AASA in body fluids and at least 1 disease causing mutation in the ATQ gene) are eligible.

4.2. Exclusion Criteria:

PDE patients without molecularly confirmed *ATQ* deficiency will be excluded from this registry.

5. Outcomes:

- Level of biochemical markers in plasma, urine, and/or CSF: α-aminoadipic semi-aldehyde (AASA) & pipecolic acid
- Neurocognitive development
- Seizure frequency: clinical and neurophysiological (EEG)
- Neurological deficits
- Safety of treatments: plasma lysine and branched chain amino acid levels, peripheral sensory neuropathy
- Quality of life and participation in society: questionnaires and via PROMIS
- Behavioral/psychiatric comorbidity: clinically assessed and via PROMIS

6. Sample size:

Due to the rare nature of PDE/ATQ deficiency, an international multicenter study including centers across North America and Europe is essential to facilitate the sufficient number of patients within a 10-year time frame. Published data for PDE vary widely, a birth incidence of 1:396,000 is reported in the Netherlands [10] and an estimated prevalence of 1:100,000 in children under 16 years age in a German region [11]. Based on more recent data from the Netherlands, where patients with unexplained neurological problems are rigorously screened for inborn errors of metabolism, the estimated birth incidence is 1:200.000 [L. Bok, *personal communication*]. According to this incidence we expect that in a 10-year time frame about 120 patients should be recruited from North America and Europe and approximately 8 million newborns. We expect a conservative estimate of 30-50 patients within the first year and additional 10 patients each following year.

7. Recruitment

Subjects will be recruited by the Principal and Co - Investigators on this study who are members of the PDE consortium, many of whom have patients or are aware of people with PDE due to ATQ deficiency. According to local rules, the subjects will be recruited either by the physician or by a study

coordinator who will explain the purpose of the study and the contents of the consent form. Patients might become aware of the PDE Registry database on their own, due to a self-initiated web search. The website (www.pdeonline.org) has information regarding the patient registry and database. Patients will be advised to consult with their physician who should then direct him/her to one of the Co-Investigators for enrollment.

8. Methods

We will approach patients with PDE age 18 years or above via their clinician. Informed consent will be obtained. Questionnaires will be administrated via an online survey on KLIK (ww.hetklikt.nu). personalized log-in codes will be provided to the patients. Registry subject IDs will be used to code the questionnaires. We aim to administer three questionnaires and use PROMIS [17]. The questionnaires used are the WHO Disability Assessment Schedule 2.0 (WHODAS 2.0)and the Community integration questionnaire (CIQ) specified below. For the WHODAS and CIQ, patients with an IQ estimated above 70, the self-administration version would be administered. For patients with an IQ <70, we administer a proxy version which can be filled out by someone who knows the patient well.. As the registry includes patients from over the world, these questionnaires have been chosen because they are used in multiple countries and are internationally known. In addition they are available in multiple languages. If the required language is not available, we will translate the questionnaire.

8.1 Questionnaires:

1. WHODAS 2.0 (www.who.int) [14] – a general assessment instrument for health and disability, which can be used for all diseases. It covers the following domains: cognition (understanding and communicating), mobility (moving and getting around), self-care (hygiene, dressing, eating and staying alone), getting along (interaction with other people), life activities (domestic responsibilities, leisure, work and school) and participation (joining in community activities). The WHODAS contains 36 questions (5-20 minutes).
2. Community integration questionnaire [15, 16]– an assessment for participation in community. It includes the following domains: participation/integration at home, social

participation/integration and productivity. The CIQ contains 15 questions (15 minutes). One question should be adapted as it includes "traumatic brain injury" (question 10).

PROMIS is a set of person-centered measures that evaluates and monitors physical, mental and social health in adults and children. The adult assessments are self-report measures for functions, symptoms, behaviours and feelings. PROMIS measures provide a common metric, the T-score, with a mean of 50 and standard deviation of 10, adjusted to the country of origin of the respondent. PROMIS works, among other types of measures, with Computer Adaptive Tests (CATs), where items (questions) are dynamically selected for administration from an item bank base upon the respondent's previous answers. CATs are beneficial as they are usually quick to answer; 4 – 12 items, which can be completed in under a minute. It is precise and provides tailored content; only relevant questions are asked. In addition, it covers a wide range of function or symptoms.[17, 18]

Estimated number of patients who will fill out the questionnaires: 40-50

9. Data Management

Database Software: A research database will be set up using REDCap® software (see below) and a user ID and password will be required for access. Data elements collected will include diagnostic, clinical, family history, treatment and monitoring information. All subject data will automatically be de-identified by a computer-generated code, which only the physician entering the data and the study coordinator will be privy to. The physician will have the code on his protected patient webchart and the research coordinator will have the code on the signed consent form stored in a locked cabinet within the secured office of the Principal Investigator.

Location: Clinical and laboratory data from each recruited subject will be entered (by the clinical investigator or a study coordinator) into a secure, limited access, digital database created by the NeuroDevNet instance and hosted within the private network of BC Children's Hospital Research Institute (BCCHR) and is protected by BCCHR firewall. Physical access to the data is monitored by electronic access cards and security cameras. BCCHR IMIT and DM monitor the database and application logs for abnormalities. Monitoring of equipment is completed by BCCHR IMIT based on

our BCCHR Systems Security Policy and BCCHR Data Center Policy. The data centre (on-premise) is a physically secured and protected area. Physical access to this room is limited and is controlled by BCCH Research IT and security personnel through a process of authorizing and granting access linked to identification cards. A record of access rights is kept by both the BCCH Research IT and security personnel. The data centre is also patrolled by on-site security personnel, monitored by surveillance cameras, and protected by a fire suppression system. **Security**: All of the data for this study will be entered electronically and coded into the database using REDCap®, specialized software specifically designed for medical data collection. REDCap® is web-based, uses 128-bit data encryption, and provides role-based security requiring a user ID and password for access to the database, aside from the entry made by the attending physician. Upon consent, the relevant subject data is typed in directly into the PDE Registry in a manner that does not require the entry of the patient's name or address. No data resides on the computer used by the physician entering the data. Regular maintenance happens bi-monthly at the minimum or when there is a release by the vendor (REDCap Consortium). Backups of the network is set to run daily and are stored on Backup Servers. The backup retention schedule is currently set at 6 months.**Data form:** After extensive consultation and discussion amongst our investigators, collaborators and panel of experts (PDE Consortium), we designed a comprehensive dataset that fully encompasses the necessary phenotypic, biochemical, genotypic and treatment related information needed to make scientifically robust analysis. This will include de-identified MRI images. (Dataset see Appendix 1). A paper version of the data form will also be made available to make data collection easier for some. Each physician using the paper based data form will send these de-identified forms to the central study coordinator located at BC Children's Hospital who will enter the data for them if required. Questionnaires will be distributed via an online survey on KLIK (www.hetklikt.nl). Personalized log-in codes will be provided to the patients. Registry subject IDs will be used to code the questionnaires.

Database management: The database will be managed by the WCHRI Clinical Research Informatics Core, in collaboration with the NeuroDevNet Neuroinformatics Core personnel from the University of British Columbia. The data will be collected and maintained for at least 10 years or longer pending sufficient financial support. The NeuroDevNet Neuro-informatics Core professionals are Dr. Elodie Portales-Casamar and Mr. Nicolas St -Georges. After such time should funding be longer available all

master-lists for each centre will be destroyed and the now anonymized data will be available for future analyses.

Data Source: All data inputted into the PDE Registry database will originate from the physicians private patient charts.

Data Entry: De-identified patient data with study number only will be entered by the physician and/or study coordinator through the use of an online-form (or paper form if required) and will go directly into the REDCap® database as a 'physician's computer-REDCap® database data tunnel'. The online and paper versions of the data form will only list the unique computer-generated random patient identifier.

Quality Control: The PDE Registry Central Study Coordinator will ensure that all data collected are complete and correct. In the case of missing or apparently incorrect data entries, the Central Study Coordinator will contact the site where the data entry occurred and clarify with the local Co-PI investigator. The corrections will be made by the local Co-PI or by the PDE Registry research coordinator.

Stratification of Access: Access to the Registry will be stratified according to the following hierarchies:

Steering Committee: includes the Principal Investigator, Co-Principal Investigators and all site-Lead Co-Investigators of the PDE Registry database; they will have access to all data entered. They will be able to view, add to, or edit information on the master list.

(Other) Co-Investigators and Collaborators will have access to their own data. The data will be shared only within the research team members who contributed the data to the database (e.g. PI, Co-PIs and collaborators). The data will not be shared with external or commercial third parties. Interested scientists and clinicians, members of this project, will be able to use the PDE Registry information if their request is approved by the project Steering Committee.

The requested data will already be de-identified and upon approval be provided as an excel data file. The file will be sent encrypted and password protected to the recipient investigator who will be availed of the password via a separate communication channel.

Governance: PI & CoPIs will be responsible for the establishment and maintenance of the PDE Registry as well as for data analysis and periodic data reporting to the Steering Committee every 6 months, and all co-investigators every 12 months.

10. Data Analysis

The longitudinal cohort study design allows for analysis of the data using three approaches – 1) as a complete cohort, 2) using a case–control approach and 3) using a case-cohort approach. The cohort analysis facilitates examination of the demographic and clinical information and prevalence of risk factors and a better understanding on the natural history of the condition. Case–control studies can be performed to determine the risk of specifically defined neurocognitive development, neurological deficits and whether or not these are associated with the disease progression, treatment etc. A case-cohort analysis approach can be used to test hypotheses not initially considered when the cohort was initiated or to analyze data where additional assessments have been carried out. Using this approach, a randomly selected sub-cohort of non-cases will be selected from the main cohort and used to compare risk factors for any or all adverse outcomes.

Confounding will be addressed through the use of multivariate analysis, where the sample size is adequate. Alternatively, cases and controls can be matched in order to address the potential for confounding. Subsequent analyses will therefore use paired statistical methods.

Descriptive statistics and exploratory analysis will be the primary approach for summarizing data from the PDE Registry with frequencies of outcomes with 95% confidence intervals.

Data will be analysed and reported periodically every 6 months and upon individual requests from approved researcher to assess the primary and secondary endpoints as well as to assess the quality of the information submitted by contributing sites based on pre-defined indicators (e.g. missing data fields, inconsistencies between fields). Statistical analysis will consider heterogeneity within the data set in terms of methods employed, quality of the data and other site-specific differences. This information will be used to guide clinical monitoring and management of PDE patients.

11. Ethics Approval

The PDE Registry research protocol, informed consents, and relevant supporting documents will be submitted to the Institutional Review Board (IRB) of the primary (PIs) study site (British Columbia Children's Hospital Vancouver) for review and approval. A generic '*Subject information and consent document for release of information to the international Pyridoxine Dependent Epilepsy Registry database (*or *"Generic Informed Consent Form")* will be provided to all participating sites / participating Co-PIs and Co-Investigators. This generic Informed Consent Form (ICF) will be adjusted at each site to comply with the local IRBs and returned to the Headquarters in Vancouver to be reviewed and approved. After the local ICFs are verified and approved by the Headquarters in Vancouver these will be submitted for review at the IRB or IEC. If further changes are required by the IRB or IEC these changes need to be approved by the PDE Registry coordinating center (BCCH) in Vancouver.

12. Patient Authorisation/Consent

The patient/parent/caregiver will be required to sign a research ethics board-approved ICF prior to any entries into the database. If eligible, the subject or his/her parents/legal guardian will be approached by his or her physician if the physician is first aware of the database. Conversely, the subject or his/her parents will be contacting their physician and inform the physician about the database. Either circumstance present, the physician will download the ICF and after familiarization (including contacting the listed database principals or coordinator) the physician will go over the form with the subject or the subject's parents/legal guardian. Should the subject wish to know more about the registry and database a study coordinator will be made available to explain the goals of the study, as well as the methods (data collection and storage) and be available to answer any questions. The signed ICFs will be kept in a locked cabinet in the secured office of the Principal Investigator at each site. The date when each subject signed the ICF will be entered in the PDE Registry database. The ICF version number and/or date will also be entered in the PDE Registry database. Once consent is provided, data will be collected and stored as specified below. Should you become 18 years of age during the study period you will be contacted by the clinic investigator and given the opportunity to provide your individual consent to continue your participation in this study. Should the clinic investigator not be able to reach you, you will be withdrawn from the study.

13. Patient Confidentiality

Data Donor Privacy and Confidentiality: All data will be assigned the subject code as indicated below. There will be only one master code key which links identifiable information from the subject to their unique identifier and that will be the patient ICF. No identifiable data is used for research nor is any identifiable data disclosed for any reason. Only a limited number of investigators (Dr. Van Karnebeek, Dr. Stockler) and the research coordinator can view, add to and edit personally identifiable information in the master list. All records pertaining to the identity of subjects in the PDE Registry database will be maintained as private and confidential. Personal identifying information will only be released with the express written permission of the data donor or by IRB approval.

Allotment of Data Identifier: Due to the paradox presented by patients with rare diseases (namely, the very rarity of the disease itself allows a greater chance of identification of an individual as it is harder for these individuals to be "lost in the crowd"), we are implementing a system in which a computer program assigns a unique code to each new patient being entered into the database. The attending physician will see the code and will be able to assign that code to the patient's chart and ICF. The study coordinator will also be aware of the code with respect to the physician and the patient data being consented. Aside from the physician, the patient's name will never be known to anyone associated with the PDE Registry/database and no record of the patient's name will ever be entered to any element of the online dataset. If the physician wants to update a patient's dataset, he or she can access the database by entering the patient's unique study ID code and their month and year of birth (this information is required to calculate age as the patient's return for follow up and additional data must be entered at a later date in order to calculate age each time data is entered). The patient's name will never appear on the dataset and the only record of the patient's name will be on the written consent form, which will be secured in the principal investigator's office or in the office of the co-investigator who is collecting and entering the data with informed consent.

Duration of data storage: As the described study is a prospective longitudinal study, we have targeted a 10 year time frame to capture the medical data of as many people with PDE patients as

practicable. At the end of the study we will retain the data for a further 5 years. If there continues to be financial support the study will continue beyond 10 years. At the completion of this study all data will be destroyed, including the master lists.

14. Patient Discontinuation

Patient participation is voluntary. The patient may decline to participate or withdraw consent for their data to be stored on the register at any time without prejudice.

15. Internet-based Information

The PDE consortium website, with domain name www.pdeonline.org (searchable via multiple keywords for the disease), will serve as an information hub for the PDE community as a whole and will be used: 1) to inform patients about participation in the research database; 2) to disseminate knowledge about PDE due to ATQ deficiency; and 3) to connect patients through social media. Nowadays, patients (or their families) with rare diseases are avid web-users and their familiarity with the internet will no doubt play a role in advertising the presence of the portal and cross-pollinate knowledge amongst patients, interested parties and researchers alike. Finally, the website will be regularly updated to address feedback and new developments.

16. Facilities and Role Descriptions

The main project activities will be carried out using the facilities of the Division of Biochemical Diseases, Department of Pediatrics, at BC Children's Hospital (BCCH) in Vancouver, BC. The Division will provide space for a research coordinator hired for this project and access to the hospital's telecommunication facilities. The research coordinator will work with Dr. van Karnebeek and will have primary responsibility for setting up the databases, communicating with stakeholders (physicians, patients, and advisory board), organizing meetings and teleconferences, producing reports, and performing statistical analyses. The server hosting the databases will be provided and maintained by NeuroDevNet, a Canadian network of centres of excellence. The PDE website is maintained by Mr. Roderick Houben (Health2Media). Mr. Houben has already created several websites for TIDE-BC and also was involved in establishing the TIDE Data Registry.

17. References

1. Mills PB, Footitt EJ, Mills KA et al (2010) Genotypic and phenotypic spectrum of pyridoxine dependent epilepsy (ALDH7A1 deficiency). Brain 133:2148–2159

2. Mills PB, Struys E, Jakobs C et al (2006) Mutations in antiquitin in individuals with pyridoxine-dependent seizures. Nat Med 12:307–309 743

3. Basura GJ, Hagland SP, Wiltse AM, Gospe SM Jr (2009) Clinical features and the management of pyridoxine-dependent and pyridoxine-responsive seizures: review of 63 North American cases submitted to a patient Registry. Eur J Pediatr 168:697–704

4. Bok LA, Halbertsma FJ, Houterman S (2012) Long-term outcome in pyridoxine-dependent epilepsy. Dev Med Child Neurol 54:849–854

5. van Karnebeek CD, Stockler S, Jaggumantri S et al (2014) Lysine restricted diet as an adjunct therapy for Pyridoxine Dependent Epilepsy: The PDE Consortium Consensus Recommendations. JIMD Reports

6. Stockler S, Moeslinger D, Herle M, et al., (2012) Cultural aspects in the management of inborn errors of metabolism, J. Inherit. Metab. Dis., http://dx.doi.org/10.1007/s10545-012-9455-4.

7. Van Karnebeek CD, Hartmann H, Jaggumantri S et al (2012) Lysine restricted diet for pyridoxine-dependent epilepsy: first evidence and future trials. Mol Genet Metab 107:335–344

8. Kolker S, Boy SP, Heringer J, Müller E, Maier EM, Ensenauer R, Mühlhausen C, Schlune A, Greenberg CR, Koeller DM, Hoffmann GF, Haege G, Burgard P (2012) Complementary dietary treatment using lysine-free, arginine-fortified amino acid supplements in glutaric aciduria type I - A decade of experience, Mol Genet Metab. 107(1-2):72-80.

9. S. Kolker, E. Christensen, J.V. Leonard, et al (2011) Diagnosis and management of glutaric aciduria type I—revised recommendations, J. Inherit. Metab. Dis. 34: 677–694.

10. Strauss KA, Brumbaugh J, Duffy A, Wardley B, Robinson D, Hendrickson C, Tortorelli S, Moser AB, Puffenberger EG, Rider NL, Morton DH. (2011) Safety, efficacy and physiological actions of a lysine-Free, arginine-rich formula to treat glutaryl-CoA dehydrogenase deficiency: focus on cerebral amino acid influx, Mol Genet Metab. 104(1-2):93-106.

11. Been JV, Bok LA, Andriessen P, Renier WO, Epidemiology of pyridoxine dependent seizures in the Netherlands. Arch Dis Child. 2005 Dec; 90(12):1293-6.

12. Ebinger M, Schultze C, König S., Demographics and diagnosis of pyridoxine-dependent seizures. J Pediatr. 1999 Jun; 134(6):795-6.

13. G.J. Basura, S.P. Hagland, A.M. Wiltse, S.M. Gospe, Clinical features and the management of pyridoxine-dependent and pyridoxine-responsive seizures: review of 63 North American cases submitted to a patient registry. Eur. J. Pediatr. 168 (2009) 697-704.

14. www.WHO.int/classifications/icf/whodasii/en/

15. Willer B, Rosenthal M, Kreutzer JS, Gordon WA, Rempel R. Assessment of community integration following rehabilitation for traumatic brain injury. *Journal of Head Trauma Rehabilitation*. 1993;8:75-87.

16. Salter K, Foley N, Jutai J, Bayley M, Teasell R. Assessment of community integration following traumatic brain injury. Brain Inj. 2008 Oct;22(11):820-35.

17. Www.healthmeasures.net, HealthMeasures is the official information and distribution center for PROMIS, Neuro-QoL™, NIH Toolbox®, and ASCQ-Me®, which were developed and evaluated with National Institutes of Health (NIH) funding

18. Alonso J, Bartlett SJ, Rose M et al. The case for an international patient-reported outcomes measurement information system (PROMIS ®) initiative. Health Qual Life Outcomes 2013. 11:210. doi: 10.1186/1477-7525-11-210.