Protocol Title	**Global Prader-Willi Syndrome Registry**
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I. Objectives

The primary objectives of the Global Prader-Willi Syndrome Registry are to:

- Provide a convenient online platform for participants (or caregivers) to self-report cases of PWS and to be offered the option of providing consent to be contacted for research studies and clinical trials.

- Accelerate and facilitate in the planning clinical trials by locating potential research participants quickly and efficiently.
- Characterize and describe the PWS population as a whole, enhancing the understanding of global PWS prevalence and PWS phenotype.
- Assist the PWS community with the development of recommendations and standards of care.
- Be a case-finding resource to be used by researchers who seek to study the pathophysiology of PWS, retrospectively collate intervention outcomes, and design prospective trials of novel treatments.

II. Background and Introduction

Prader-Willi syndrome (PWS) is a complex neurodevelopmental disorder resulting from disruption of an imprinted region of chromosome 15 (15q11.2-q13). PWS has an estimated incidence of 1:10,000-1:30,000 births worldwide, and equally affects males and females of all ethnicities. PWS is characteristically associated with feeding difficulties and failure to thrive in infancy and early childhood, followed by the development of excessive eating (hyperphagia), intense food seeking behavior, and morbid obesity. Additional features of PWS include poor muscle tone and strength (hypotonia), hypogonadism, osteoporosis, scoliosis, infertility, delayed motor and language development, impaired cognition, sleep abnormalities, behavioral challenges including tantrums, obsessive compulsiveness and skin picking, and psychiatric illness in adulthood. The phenotype exhibits a broad spectrum of severity.

Patients with PWS are identified by clinical diagnosis with genetic confirmation by DNA methylation analysis. Additional genetic testing is available to distinguish among the three PWS genetic subtypes (paternal deletion, maternal uniparental disomy, or imprinting defect).

There are a broad range of available current therapies and applicability is dependent upon each individual clinical presentation. These include feeding assistance in infancy and early childhood, physical therapy, speech therapy, human growth hormone therapy, vitamin supplementation, and a variety of medications directed at behavioral manifestations of PWS. Hyperphagia is a intractable problem to date. There remains a great need for novel medications and therapies to improve quality of life for those with PWS.

III. Study Design

The Global Prader-Willi Syndrome Registry is an international registry for patients with Prader-Willi syndrome (PWS). It will be hosted by NORD (National Organization of Rare Diseases). The registry will collect information from families/participants who are affected by PWS and who are interested in participating in future research. The registry will utilize a web-based interface to maximize accessibility to participating families and clinicians world-wide and no experimental intervention is involved. Patients may receive information on the most up to date standards of care relation to their disease and may be invited to participate in relevant clinical trials. Participants will be invited to update their data and information will be stored indefinitely, or until a participant requests that their data be removed. The initial design and implementation of the registry, as well as annual maintenance, will be funded by FPWR. Registry participants will automatically be enrolled in the Global Rare Disease Registry (GRDR), and their de-identified information aggregated with information from other rare diseases. The purpose of the GRDR is to enable analyses of data across many rare diseases and to facilitate clinical trials and other studies.

IV. Duration of study

This registry will be open to registration indefinitely. There is no date of termination or closure.

V. Eligibility and Recruitment of Participants

a. Inclusion Criteria

All patients with a confirmed PWS diagnosis (or pending diagnosis) are eligible for inclusion. The registry will recruit patients of all ages who have a diagnosis consistent with PWS.

b. Exclusion Criteria

You will be excluded from this registry if you do not meet inclusion criteria. Information may be excluded if the submitting person is not the participant or legally authorized representative of the participant.

c. Sample Size

There is no upper limit for the number of participants for this registry.

d. Recruitment of Participants

Information about the existence of the registry will be communicated to interested members of the PWS community including patients, physicians and researchers. In addition, information about the registry will be disseminated through clinical, professional, research, patient foundations and support groups including but not limited to:

- Foundation for Prader-Willi Research: http://fpwr.org
- Foundation for Prader-Willi Research Canada: www.fpwr.ca
- Prader-Willi Syndrome Association (USA): www.pwsausa.org
- Global Rare Diseases Patient Registry and Data Repository: http://grdr.info
- International Prader-Willi Syndrome Organization: www.ipwso.org

The initial launch of the registry may also be associated with the purchase of a "Google" advertisement that will inform internet users of the Global Prader-Willi Syndrome Registry when relevant keywords are searched using the Google search engine.

VI. Process of Obtaining Consent

Submission of information by participant or their representative: Registry participants will be asked to read an online consent form explaining the purpose of the Global Prader-Willi Syndrome Registry and agree to the use of their personal and medical information, including identifying information. Additional information in the online consent form will explain that de-identified information will be shared with the Global Rare Disease Registry. Individuals providing consent will be asked to confirm that s/he is the participant or legally authorized representative

of the participant. Consent from a legally authorized representative is required for participants who are minors or who are over the age of 18 but unable to provide informed consent. Because individuals with PWS have some degree of intellectual disability, the ability to provide consent will depend on the cognitive ability of the individual. The participant will also be asked if they consent to future contact by the registry staff to clarify data entry should questions arise or by future investigators seeking participants for research studies. They will be informed that by participating in the registry and/or consenting to contact they are in no way obligated to participate in any future studies. Their informed consent for participation will be documented by an electronic signature mechanism whereby the individual providing the informed consent checks a box after reading the electronic informed consent document online. There will be no hardcopy written informed consent with standard signature associated with this online registry. There will be no discussion of the elements of the informed consent with participants unless clarification is requested by the potential participants. In that case, clarifying information may be provided by email or by telephone contact with study staff. Consent of one parent or legally authorized representative is considered sufficient for participation of a minor in this registry.

Registry participants will be asked to provide their permission for the use of registry information for retrospective research studies by registry investigators and staff, as well as by third parties granted access to registry data.

Registry participants will be asked to provide their permission to allow registry administrators and staff to contact them to ascertain interest in participation in future research studies and/or clinical trials. Interested registry participants contacted for possible participation in future research studies will undergo a separate informed consent process for each such research study.

Please see Appendices A and B for the information that will be requested of participants (A= Consent Form; B=Registry Questions)

VII. Data Analysis and Reporting

Statistical analyses will almost exclusively focus on simple characterization of the registry. Basic descriptive statistical measures will be calculated to summarize registry information. Specifically, frequencies, percentages, means, medians, ranges, etc. will be generated. Subgroup analyses may also be performed to further delineate registry data. These analyses may include t-tests / Wilcoxon rank-sum tests and Pearson correlation / Spearman correlation for continuous measures; for categorical variables, chi-square and Fisher exact tests may also be performed.

VIII. Data Requests and Release

It is anticipated that the Global Prader-Willi Syndrome Registry will be a valuable resource for current and future research. A Global Prader-Willi Syndrome Registry Advisory Board will ensure proper evaluation of protocols to use registry data and/or contact registry participants. To promote use of the repository, aggregate, de-identified information about database contents will be updated quarterly or semiannually and made available to the public. Such information may include number of registrants, prevalence of individual common diagnoses of registrants, demographic information, and percent willing to be contacted for future research. Investigators wanting to use the registry or contact participants will need to apply to the Advisory Board. The application will require information concerning: Principal Investigator, aims and hypotheses of

the proposed research, and where the research will be performed, and how the research will be funded.

After the Advisory Board approves the scientific/technical merit of a registry use request, the following approach will be applied:

Scenario 1: Registry investigators. Registry investigators will have access to all database elements for analysis and publication; any publication of data will be done so as to protect the confidentiality and the identity of individual registrants. Personal Health Information (PHI) will not be shared with others outside of the registry staff. Registry investigators may not contact registry participants for new research (work that goes beyond the data collection specified in this protocol) without project-specific IRB approval for the new research project.

Scenario 2 - De-identified and coded data requested. This scenario addresses the need of researchers to scan the registry and view aggregate data on the registered population. The researcher will request as part of the application process the types of research or preparation for research that will be conducted with the data. Registry Investigators may enter specific search criteria into the Global Prader-Willi Syndrome Registry and provide reports to researchers. Alternatively, upon unanimous Advisory Board approval, researchers may be granted login access to de-identified registry data to perform their own searches. No information that would directly link the data to the registrants will be included in the output data. This data could be used for publication, or as preliminary data for a grant or IRB proposal.

Oversight Requirement - No project-specific IRB submission is needed. The Advisory Board will review the request, and if needed, obtain clarifying information during the approval process. A data transfer agreement will be distributed along with the data specifying the agreed upon scope of research to be performed on with the registry data and specifying that no attempt may be made to identify the registry participants.

Scenario 3: An outside investigator would like to contact registry participants to recruit them for other research. The general mechanism by which this contact can be made is that the registry staff would contact the participants on behalf of the outside researcher, and give the participant contact information about the researcher, so that the participant can decide whether s/he would like to participate in the new research. Thus, after Advisory Board approval of the application for registry use, an IRB approved recruitment flyer will be requested from the researcher offering details about their planned study. This flyer will be reviewed by the Advisory Board for appropriateness and then sent by mass to all registry participants along with contact information for the researcher.

Oversight Requirement – Requests for recruitment from the registry will only be fulfilled after Advisory Board approval of the application. A project-specific IRB approval from the researcher's institution must also be provided.

IX. Facilities and Performance Sites

The Global Prader-Willi Syndrome Registry data will be stored on secure severs located at NORD (https://www.rarediseases.org/patient-orgs/registries). Data entry may be performed world-wide via web-interface.

X. Potential Benefits

Because PWS is a rare genetic disorder, effective research into the phenotype, pathophysiology, effectiveness of treatments, etc., requires the accumulation of data from a large cohort of participants. There are no direct benefits associated with participation in the Global Prader-Willi Syndrome Registry and individual participants should not expect a direct benefit. The Global Prader-Willi Syndrome Registry will facilitate collaboration between investigators at multiple sites as well as assist in recruitment of participants for clinical trials. Potential benefits include the potential for future studies that will significantly increase understanding of therapeutic options for PWS patients. The use of information contained within the Global Prader-Willi Syndrome Registry for retrospective research analyses may be of future benefit to patients with PWS. In addition, participants in the Global Prader-Willi Syndrome Registry will be informed of future research studies involving PWS for which they may be eligible. Certain participants may directly benefit from inclusion in future treatment studies that result from the registry and for which separate informed consent will be obtained.

XI. Potential Risks, Discomforts, Inconveniences, and Precautions

Participation in the Global Prader-Willi Syndrome Registry presents minimal risks to its participants. The greatest risk is loss of confidentiality of personal health information.

XII. Risk/Benefit Analysis:

The Global Prader-Willi Syndrome Registry is a minimal risk study without direct benefits to the individual. There are no risks of physical harm associated with participation in the Global Prader-Willi Syndrome Registry. Participation in the Global Prader-Willi Syndrome Registry does involve the potential risks of a breach of confidentiality of medical information and associated privacy of the participants. Such risks will be minimized by 1) removing direct participant identifiers from information and data shared or released from the registry; 2) limiting access to linking codes assigned to the Global Prader-Willi Syndrome Registry information; 3) and limiting access to information contained within the Global Prader-Willi Syndrome Registry to registry Investigators and Advisory Board-approved researchers. 4. Maintaining the Privacy and Confidentiality of Registry information as described below.

XIII. Privacy and Confidentiality:

Participants' privacy and confidentiality will be safeguarded by using modern database management techniques and informed consent. As part of consent, participants will have the ability to state whether future contact is acceptable and by what means this contact may take place, i.e. mail, email, phone, etc. Registry personnel may contact such participants to clarify data entry. Confidentiality will be protected by limiting access to data and keeping PHI data password protected on a secure server. Access to PHI in the database will be limited to the Registry Principal Investigator and Co-investigators via password protected security measures. Data will be maintained on the NORD platform, which meets or exceeds current guidelines for maintaining security of PHI.

Aggregate, de-identified data will be shared with the public as general descriptive statistics regarding database contents. De-identified data will be shared with the GRDR. PHI will be associated with a unique identifier that is assigned by registry staff. The file linking the unique identifier and the PHI will be kept in a separate password protected database.

Third parties may seek access to data in the Global Prader-Willi Syndrome Registry. Third parties may include, but are not limited to, researchers or companies conducting retrospective

studies or conducting research and/or clinical trials on new therapies (see "scenarios", above). Third parties will only be granted access to registry information upon review and approval of the Advisory Board. Such approvals shall be obtained prior to providing access to registry information; shall be based upon considerations of scientific quality and validity; shall be granted for research studies related to PWS; and shall be documented. Third parties seeking access to registry information for retrospective studies will only have access to anonymous information identifiable only by the assigned unique identifier. Third parties seeking access to registry information for the purpose of determining eligibility for participation in a research study or clinical trial must demonstrate evidence of IRB approval of the research study for which access is being requested. Registry staff would contact the participants on behalf of the outside researcher, and give the participant contact information about the researcher, so that the participant can decide whether s/he would like to participate in the new research.

The PHI associated with this study will be retained indefinitely. There is no plan to destroy data or the key since this is an open-ended registry with no planned completion date. If a participant contacts the registry staff or investigators and requests in writing that they be withdrawn from the registry, their data will be removed and destroyed. However, any research use of participant information prior to the date that consent is formally withdrawn cannot be retrieved and will not be destroyed. Participants will be reminded that they may remove their data from the register on a yearly basis, when they are contacted to update their record.

XIV. Data Safety Monitoring Plan

The Advisory Board will meet twice per year and review aggregate registry data and the utilization of this registry. No stopping rules apply. The Advisory Board will also review any protocol or confidentiality deviations on a case by case basis and report any such deviations to the IRB for their consideration. Protocol violations or unanticipated problems will be handled per: 45 CFR part 46 HHS Regulations for the Protection of Human Subjects; 45 CFR parts 160 and 164 Health Insurance Portability and Accountability Act (HIPAA) Regulations for Standards for Privacy of Individually Identifiable Health Information; and 21 CFR part 50 FDA Regulations for the Protection of Human Subjects

XV. Cost of Participation

There is no cost to participants of the registry. Initial design and implementation of the registry will be funded by FWPR. Expenses for cost of data retrieval and analyses may be passed on to future investigators as deemed appropriate by the Advisory Board.

XVI. Payment for Participation

There will be no reimbursements made to participants of the registry.

XVII. References

Driscoll DJ, Miller JL, Schwartz S, et al. Prader-Willi Syndrome. 1998 Oct 6 [Updated 2012 Oct 11]. In: Pagon RA, Bird TD, Dolan CR, et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1330/