Protocol Title	**Global Prader-Willi Syndrome Registry**
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Confidentiality Statement: Information contained within this document is not to be disclosed in any way without the prior permission of the Principal Investigator.

I. Objectives

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

- Provide an online platform for participants (or their 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 and completion of 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 the full spectrum of the PWS phenotype.
- Better understand the natural history of PWS, including medical complications and behavioral aspects.
- Facilitate the development of best practices, management guidelines and recommendations to optimize care and improve quality of life.
- 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 if food intake is not strictly controlled. 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, anxiousness, 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 main 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 an intractable problem to date, although several potential treatments are in clinical development. 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 (the “Registry”) is an international registry for patients with Prader-Willi syndrome (PWS). It is hosted by NORD (National Organization of Rare Diseases) on the “IAMRARE” registry platform. The registry collects information from families/participants who are affected by PWS and who are interested in participating in research. The registry uses a web-based interface to maximize accessibility to participating families and clinicians world-wide. No experimental intervention is involved.

In the Registry, “Respondents” refers to those individuals who establish an account and enter data, while the “Participant” is the person with PWS. In most cases, the Respondent is the parent and/or legally authorized representative (LAR) of the person with PWS. In situations where the

individual with PWS is over the age of 18 and capable of providing consent, they may serve as both the Participant and the Respondent.

Respondents and Participants in the Registry may receive educational information on PWS care and research and may be invited to participate in relevant clinical trials and studies. Respondents are invited to update their data at regular intervals and the Participant's information is stored indefinitely, or until the Respondent/Participant requests that their data be removed. Most data collected will be about the Participant, but some questions will be personal to the Respondent (e.g. Pregnancy History). The initial design and implementation of the registry, as well as annual maintenance, is funded by FPWR.

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.

Patients may also have a diagnosis of Schaaf-Yang syndrome (SYS), a disorder caused by mutations in the MAGEL2 gene, which is located in the PWS region of chromosome 15.

b. Exclusion Criteria

Participants will be excluded from this registry if they 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 Registry will be communicated to interested members of the PWS community including patients, parents, 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
- International Prader-Willi Syndrome Organization: www.ipwso.org

At times, 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 legally authorized representative (Respondent): Registry participants or their LAR (Respondent) 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. Individuals providing consent will be asked to confirm that s/he is the participant or legally authorized representative of the participant. Consent from an LAR 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 Respondent will also be asked about contact preferences for themselves and the Participant. 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, but a copy of the informed consent will be emailed to the Respondent upon completion. 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 respondents/participants will be asked to provide permission for the use of their Registry information for retrospective research studies by Registry investigators and staff, as well as by third parties granted access to deidentified registry data.

Registry respondents/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, and or for biospecimen donation. Interested Registry participants contacted for possible participation in future research studies will have the option of contacting the research staff associated with the study, and 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 focus on simple characterization of the Registry data. 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

A Global Prader-Willi Syndrome Registry Advisory Board has been established to ensure proper evaluation of studies that wish to use Registry data and/or contact Registry participants. To promote use of the Registry, aggregated, de-identified information about database contents will be updated on a regular basis and shared with the PWS community and 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 analyze Registry data or contact Registry participants will need to apply to the Advisory Board, in accordance with the written policies established by the Advisory Board. The application requires information concerning: Affiliation and qualifications of the Principal Investigator, aims and hypotheses of the proposed research, and where the research will be performed. Documentation of review and approval by an appropriate Institutional Review Board is required.

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

Scenario 1: **Analysis of data by 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 respondents/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: **Use of the Registry to recruit research participants**. An outside investigator may seek to inform Registry respondents/participants about a research opportunity, to recruit them for that research. The general mechanism by which this contact can be made is that, upon approval of the recruitment application by the Advisory Board, the Registry staff will contact the participants on behalf of the outside researcher and provide information about the study so that the respondent/participant can decide whether s/he would like to participate in the new research. Registry staff will share IRB approved recruitment information, with details about their planned study; typically, a recruitment flyer. This flyer will be reviewed by the Advisory Board for appropriateness and then sent by mass email to all Registry participants who have indicated a preference for receiving such communication in their contact preferences. The recruitment information will include contact information so that interested participants can directly contact the researcher.

Oversight – 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 as appropriate.

Scenario 3 - **De-identified and coded data requests by qualified researchers**. This scenario addresses the need of researchers to analyze data on the Registry population. Qualified researchers may request data through an application process, in which the purpose of the study, and the specific data requested will be detailed, in addition to how the data will be used. The

application will be reviewed and approved by the Global PWS Registry Advisory Board. Registry investigators or administrators will download the applicable data in a report, and the downloaded data will be reviewed by two Registry investigators/administrators to ensure that no identifying information is included (using the safe harbor method of de-identification, https://www.hhs.gov/hipaa/for-professionals/privacy/special-topics/de-identification/index.html). No information that would directly link the data to the registrants will be included in the output data. A Data Transfer and Use Agreement will be established prior to release of the data. This data could be used, for example, for publication, to support regulatory filings, or as preliminary data for a grant or IRB proposal.

Oversight – Requests for patient level data 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 as appropriate. Preparation of data for transfer will be in accordance with an approved Standard Operating Procedure.

Scenario 4: **Conducting research through the Registry.** A qualified investigator who wishes to conduct research through the Global PWS Registry, e.g., develop a survey or surveys to address specific research questions, will submit an application to the Global PWS Advisory Board that includes a description of the goals of the study, target population, plan for analysis and anticipated timeline. After review and approval by the Advisory Board, the researcher will work with Registry staff to develop new questions or surveys as needed. A Data Transfer and Use Agreement will be developed prior to release of data if the researcher wants to receive patient level data for analysis. All data will be de-identified prior to transfer (as in Scenario 3).

Oversight – Requests for conducting research through 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 as appropriate.

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 and prospective studies may be of future benefit to patients with PWS. In addition, respondent/participants in the Global Prader-Willi Syndrome Registry will be informed of PWS research studies 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, Co-investigators, and Registry staff 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. 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 Global PWS 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 Registery, when they are contacted to update their record.

XIV. Data Safety Monitoring Plan

The Advisory Board will meet at least 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 investigators as deemed appropriate by the Advisory Board.

XVI. Payment for Participation

There will be no reimbursements made to participants of the Registry. At times, gift cards may be used to incentivize completion of Registry surveys.

XVII. References

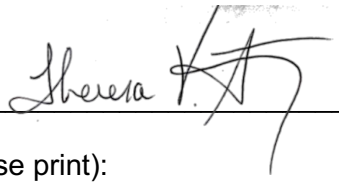
Driscoll DJ, Miller JL, Schwartz S, et al. Prader-Willi Syndrome. 1998 Oct 6 [Updated December 14, 2017]. In: Pagon RA, Bird TD, Dolan CR, et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1330/

XVIII. Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Sponsor agrees to conduct the research in compliance with approved protocol.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the research without the prior written consent of the Sponsor.

For and on behalf of the Study Sponsor

Signature: 

Date: 02 /01 /2022

Name (please print):

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