Cerebral Palsy Research Network (CPRN) Patient Registry: An infrastructure to capture patient/caregiver outcomes over the long-term

Cerebral Palsy Research Network

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PROTOCOL TITLE:

CPRN Clinical Registry: Characterizing Patient Populations, Interventions and Outcomes in the Cerebral Palsy Research Network (CPRN)

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Executive Summary

The Cerebral Palsy Research Network (CPRN) is a group of clinician-scientists and patient advocates collaborating to improve treatments and outcomes for people with Cerebral Palsy (CP). CPRN's vision is that every clinician caring for persons with CP can offer the best, most current treatment available, proven through high quality research conducted through CPRN. CPRN consists of up to 45 Clinical Centers and a Data Coordinating Center (DCC). The centers contribute to a clinical data registry. The CPRN Registry is the foundation of a Learning Health Network, which seeks to align research and clinical cultures for continuous improvement and clinical innovation and knowledge generation as a by-product of clinical service delivery.

Registry Elements (REs) have been developed to obtain data from multiple disciplines that treat CP, including pediatrics, physiatry, neurology, orthopedics, neurosurgery, and physical, occupational, and speech therapy. The ongoing maintenance of the CPRN Registry serves two main purposes: (1) it will help investigators understand the variability, progression, and current treatment practices for CP in children and adults, with an ultimate goal of better guiding and assessing therapeutic interventions and providing recommendations on patient care and; (2) it will provide pilot and descriptive data necessary for hypothesis generation and study design (i.e. preliminary power analyses, recruitment projections) for studies under development by the CPRN. This multi-institutional database will be maintained throughout the lifetime of the CPRN or until such time that care is standardized across CPRN network sites, and will be useful for tracking trends in CP over time. The CPRN Registry will be an invaluable resource to the CPRN and will help stimulate new research protocols, identify potential need for future expansion of the network to incorporate additional patient populations, including but not limited to those at risk of developing CP, and provide a descriptive understanding of children and adults with CP cared for within the network.

As basic and translational science networks such as CP Alliance's IMPACT CP or Canada's Childhood Cerebral Palsy Integrated Neuroscience Discovery Network develop new therapeutic interventions, CPRN will provide the clinical trial infrastructure to rapidly and safely test new interventions. The many universities participating in CPRN will enable a new level of collaboration between basic scientists and clinical researchers, helping focus research on solving the most important questions for the CP community.

Registry Title	CPRN Registry
Sponsor	Cerebral Palsy Research Network
Subject Selection Criteria	All patients with documented cerebral palsy
Sample Size	50,000 patients with related clinic and hospital visits, procedures and patient reported outcome measures.
Registry Objectives	1. To describe the number and characteristics of cerebral palsy(CP), hypoxic ischemic encephalopathy (HIE), or those at risk for CP receiving care at CPRN Clinical Centers including demographics, etiology, diagnostic information, surgical and medical management and patient reported outcomes. 2. To provide these data to CPRN investigators to support hypothesis generation, study design development for future studies and practice variation for quality improvement initiatives.
Registry Procedures	Patients will be entered prospectively in the Electronic Data Capture (EDC) or Electronic Health Record (EHR) system at the time of clinic visits, Emergency room, hospital visit and surgical management. Subject data will include retrospective, quality of life, outcomes and follow-up information as available. Subjects will be followed prospectively and each hospital or clinic visit or event will be captured as it occurs.
Data Management and Statistical Analysis	A web-based data capture system or an EHR based capture will be used to collect and report Registry Data. The web-based EDC system will be set up for remote data entry. Data extractions from EHR data will be securely transmitted to the DCC for integration in the CPRN Registry database. Reports of specific data points can be requested and statistical analysis generated at the DCC as needed.

Abbreviations

CP: Cerebral Palsy
CPRN: Cerebral Palsy Research Network
CDM: OMOP Common Data Model
CDISC: Clinical Data Interchange Standards Consortium
DCC: Data Coordinating Center
EDW: Enterprise Data Warehouse
EHR/EMR: Electronic Health Record/Electronic Medical Record
EVA: ETL Virtual Appliance
HIE: Hypoxic Ischemic Encephalopathy
HIPAA: Health Insurance Portability and Accountability Act
IRB: Institutional Review Board
NIH: National Institutes of Health
ODM: CDISC Operational Data Model.
OMOP: Observational Medical Outcomes Partnership
SSL: Secure Socket Layer
RE: Registry Elements
REB: Research Ethics Board

REDCap: Research Electronic Data Capture
VPN: Virtual Private Network

Introduction, Background and Significance

A workshop sponsored by the National Institutes of Health (NIH) in 2014 identified critical advances needed to improve outcomes for CP patients.[1] Their recommendations included: (1) the need for a national registry for CP; (2) the importance of comparative effectiveness research; and (3) importance of research into long-term outcomes for adults with CP. An opportunity to conduct such research is presented through the newly established Cerebral Palsy Research Network (CPRN) infrastructure. CPRN has been established by philanthropic funding to conduct multi-institutional research (clinical trials, observational studies and quality improvement) on CP. Multi-institutional longitudinal studies are necessary to generate adequate sample sizes to study clinical problems in CP because of the heterogeneity of the population. The success of the CPRN requires expeditious planning, implementation, completion, and publication of research that addresses important issues in the care of children and adult with CP. The CPRN currently consists of multiple Clinical Centers and a Data Coordinating Center (DCC).

Purpose

In order to engage in collaborative studies within the CPRN, basic epidemiological information about CP patients and events is needed from each participating institution. The ongoing maintenance of the CPRN Registry serves two main purposes: (1) it will help investigators understand the variability, progression, and current treatment practices for CP, with an ultimate goal of better guiding and assessing therapeutic intervention and providing recommendations on patient care; and (2) it will provide pilot and descriptive data necessary for hypothesis generation and study design (i.e. preliminary power analyses, recruitment projections) for studies under development by the CPRN. Each Clinical Center will place CP patient visit and event information into the centralized CPRN Registry maintained by the DCC. The DCC will provide access to the database to all CPRN investigators to support CPRN activities. The CPRN Registry supports observational descriptive research within the CPRN network that will continue throughout the life of the network or until such time that care is standardized across CPRN network sites. It includes ongoing data collection and analysis of CPRN Registry data at each Clinical Center within the network.

Procedures

The overall objective of the CPRN Registry is to establish and maintain a retrospective (from 2016 forward), prospective, longitudinal, multi-intuitional clinical database for the Clinical Centers of the CPRN, a research network newly established to investigate clinical management of CP. The list of condition Registry Elements is available here: https://cprn.org/research/cprn-registry-elements/. General registry elements can be found here: PCORnet data elements from

[1] "Report of a Workshop on Research Gaps in the Treatment of Cerebral Palsy," Codrin Lungu, Deborah G. Hirtz, Diane Damiano, Paul Gross, and Jonathan W. Mink, Neurology, unpublished.

PCORnet-Common-Data Model Specification Version 7.0 https://pcornet.org/data-driven-common-model/

The data collected include a range of clinical care data, including the following: non-identifier demographics (e.g., race, ethnicity, sex), period of data capture (e.g., enrollment start and end dates), clinical encounters (e.g., medical and surgical history, diagnoses, discharge dates and dispositions, payer type), procedures (e.g., de-identified results of imaging, lab results, etc.), vital signs and other clinical observations (e.g., height, weight, range of motion, strength), medication prescribing, administration and dispensing (e.g., prescriptions filled), patient condition (e.g., quality of life, function, durable medical equipment use, and other patient-reported conditions and outcomes), mortality information (e.g., death date and cause), privacy-preserving linkages or hash tokens (i.e., to match patient records across DataMarts for social determinants of health and other data points), and immunizations (i.e., administered and reported). The registry is expected to include up to 75,,000 participants over time; however, data collection is open-ended and will continue for the duration of the CPRN Network.

Patient Eligibility

Inclusion Criteria

1. Diagnosis of cerebral palsy (CP), Hypoxic Ischemic Encephalopathy (HIE), or identified as at risk for CP and seen at a CPRN Clinical Center 2016 forward for the duration of the existence of the CPRN Registry.

Study Methods

Overview

Each Clinical Center will enroll all persons who are assessed or treated at the Clinical Center and who meet inclusion criteria. The enrolling Clinical Center will transfer clinical data to the DCC in one of two ways: (1) via electronic extract from the EHR, or (2) through manual entry into a database via a secure web portal (see Section on Data Security on page 16 for system security information) where the patient will be coded with a unique identifier.

Data Collection Via EHR Extract

The majority of Clinical Centers will collect data to populate the registry in their respective EHR systems in the course of routine care delivery. The data will be extracted using site-specific solutions that reflect whether the sites rely on vendor-provided solutions for extracting data from these EHR systems, whether they have a mature Enterprise Data Warehouse (EDW) or other operational data stores and/or infrastructure like i2b2. The DCC has developed an ETL Virtual Appliance (EVA) solution for common EHRs like Epic, Cerner, Sunrise, Meditech and others and for platforms like i2b2, available under a limited distribution. EVA will feature workflows to extract data from common EHRs, and to transfer them to the DCC automatically and securely using Secure File Transfer Protocols.

Data Collection Via Manual Entry

Certain sites may not possess the infrastructure or the resources to develop their own mechanisms for point of care structured clinical documentation and would have to rely on alternative approaches. The DCC will offer EDC using Research Electronic Data Capture (REDCap) software to such sites. This approach will require engaging Research Coordinators at the respective sites to perform chart abstraction on qualified patients' retrospective medical record data and enter the various data points using REDCap forms hosted by the DCC. Of note, REDCap is 21 CFR 11 capable when configured and used correctly.

Protection of Privacy

Data will be acquired from hospital computer systems and medical records. The primary potential risk to subjects is improper disclosure of medical information. Data collected do not include direct identifiers; however, limited data set elements (such as dates of birth, dates of clinical encounters, and zip code) are included and will be protected in accordance with HIPAA regulations.This will be accomplished with the following actions:

- All data will be maintained on secure servers.
- The patient log containing the patient's identifying information and unique identifying number produced by the EDC will be stored in a secure locked location. It is recommended that two copies of this record be retained in two different formats in two different physical locations.
- All data transmission will be encrypted, as described in the Data Management Section
- The PI and Research Coordinator at the Clinical Center and the DCC will provide documentation of human subject protection and research ethics prior to enrolling any subjects.
- All DCC staff work under strict confidentiality agreements.
- All analyses and reports will be presented in aggregate fashion.
- No identifiable data, either patient, clinician or site-specific, will be released by the CPRN through the DCC at any time. Requests for data will go through the CPRN and all aggregate data will be de-identified for site, subject and clinician. No collection or submission of data will occur at any specific Clinical Center until IRB/REB review has been completed at that site.

The Clinical Center is responsible for maintaining a log of patient name and medical record and generating a corresponding subject ID number that will be sent to the DCC. The DCC will at no time have access to the subject's name or medical record number. Participating Clinical Centers may retain the ability to reidentify individuals through locally maintained linkage files for purposes permitted under local IRB approval, including clinical care or separate, IRB approved research activities; the CPRN Registry and Data Coordinating Center do not perform reidentification or initiate participant contact.

The DCC will assign each institution a unique Center Identifier (referred to as a Data Access Group, or DAG) so centers will not be identified by name within the database. Each participating center will also keep a log of clinician name and unique identifying number generated at the site. This unique number will be the only clinician identifier throughout the database and neither the DCC nor other CPRN clinical centers will be able to identify the clinician within the database.

Subjects can be entered into the CPRN Registry at several different points of care: at the time of diagnosis, at annual or follow-up clinic visits, during a pre-op clinic visit, or after other medical/surgical procedures for the management of CP. A subject can have multiple entries correlated with the procedures performed at each intervention. It is the goal of the CPRN Registry to capture as many CP-related clinical events, procedures, and encounters as possible to provide descriptive information regarding the management of these patients.

Human Subjects

Each of the Clinical Centers with the CPRN network will participate in the CPRN Registry after obtaining Clinical Center Institutional Review Board (IRB) approval or Research Ethics Board (REB) approval for the project. The institution originating the protocol (Nationwide Children's Hospital, Columbus Ohio) will obtain IRB approval at Nationwide Children's Hospital prior to submission of the protocol to the other CPRN clinical centers and the DCC. Other CPRN sites that are part of PEDSNet or the Pediatric Research Alliance may have the option of leveraging Nationwide's IRB approval as the IRB of record for the reliance model.

Recruitment Methods

A waiver of consent and authorization is requested because the registry data constitute a HIPAA Limited Data Set, in which all direct identifiers are removed and only permissible elements such as dates and zip code remain.

HIPAA Privacy Rule Criteria for Waiver of Authorization

1. The use or disclosure involves no more than minimal risk to the privacy of individuals

First, the nature of the research, which is designed to document ongoing care practices in CP clinics around the country, as is done routinely in quality initiatives, poses minimal risk to the welfare or general well being of treated persons and is limited to confidentiality and privacy. The care delivered to persons with CP is in no way linked to study participation.

Second, the registry has an adequate plan to protect identifiers from improper use or disclosure, which significantly reduces the risk to confidentiality and privacy. Key identifiers are maintained exclusively at Clinical Centers and neither reused or disclosed to others, except as required by law, as necessary for the oversight of the research, or as permitted by the Privacy rule for other research. The DCC will at no time have access to the subject's name or medical record number.

2. The research cannot practicably be conducted without the waiver

First, requiring prior authorization for entry into the CPRN registry will likely result in selection bias and perhaps other biases in the data obtained, compromising the scientific validity of the study. Studies suggest major differences in care and outcomes between those who are enrolled in consenting registries and those who are not,[2] [3] [4] which results in the gathering of data of limited usefulness, and, consequently, undue burden on those who participate. Inclusivity and universality are key elements of an effective registry.

Second, due to the broad inclusion/exclusion criteria, the multiple potential points of entry into the study, and the variable set of clinical service contacts made by persons with CP, it is challenging to obtain the prior authorization of everyone who may qualify for the study (1) without the nuisance of multiple offers to participate, and (2) in a manner that ensures equitable opportunity to participate. Importantly, the care received by persons with CP is in no way connected with participation in the study.

3. The research cannot be practicably conducted without access to, and use of, the health information

By nature, the research, which is designed to document ongoing care practices in CP clinics around the country, cannot be practicably conducted without access ongoing care practices.

The Common Rule

1. The research involves no more than minimal risk to subjects

Per above, the risk is minimal.

2. The waiver will not adversely affect the rights and welfare of subjects

Per above, the care received by persons with CP is in no way connected with participation in the study.

3. The research cannot practicably be carried out without a waiver

Per above, requiring consent will likely result in selection bias and perhaps other biases in the data obtained, compromising the scientific validity of the study and resulting in undue burden for those who choose to participate.

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[2] Tu, J. V., et al. Impracticability of Informed Consent in the Registry of the Canadian Stroke Network. N Engl J Med 2004;350:1414-21.

[3] Dudeck J. Informed consent for cancer registration. Lancet Oncol 2001;2:8-9.

[4] Chertow GM, Pascual MT, Soroko S, et al. Reasons for nonenrollment in a cohort study of ARF: the Program to Improve Care in Acute Renal Disease (PICARD) experience and implications for a clinical trials network. Am J Kidney Dis 2003;42:507-51.

4.

Direct patient contact is not required for registry participation. Any re-identification or subsequent contact with individuals is performed under separate IRB approvals. Information regarding the registry is made publicly available through CPRN communications and materials on the website https://cprn.org .

Risks and Side Effects

This is a minimal risk study without direct patient intervention. The goals of this study are primarily descriptive of the CPRN patient population and internal network capabilities. Data will be acquired from hospital computer systems and medical records, and the primary potential risk to subjects is improper disclosure of medical information. The risk is minimized by the data management steps outlined.

Benefits

There are no direct benefits for study participants. This study will provide previously unavailable epidemiological information about CP patients seen throughout CPRN. This information will provide the basis for multi-institutional studies to be carried out by the CPRN that may ultimately improve the clinical care for people with CP throughout North America. The continuing collection of such information serves to provide data necessary for hypothesis generation and study design (i.e. preliminary power analyses, sample size determination, recruitment projections and practice variation for quality improvement protocols).

Financial Considerations

Research subjects will not be compensated for their participation, nor will study subjects incur any costs as a result of their inclusion in the study.

Record Retention

Following the guidelines for federally funded studies subject to the Common Rule, records relating to the research conducted shall be retained for at least 3 years after completion of the research. Completion of the research for this protocol should be anticipated to include planned primary and secondary analyses, as well as subsequent derivative analyses. Completion of the research also entails completion of all publications relating to the research. All records shall be accessible for inspection and copying by authorized representatives of the regulatory authorities at reasonable times and in a reasonable manner [45 CFR 46.115(b)].

Health Information Portability and Accountability Act (HIPAA)

A waiver of consent is requested because the data forms a Limited Data Set defined by HIPAA as protected health information in which direct identifiers have been removed but potential identifiers remain such as date of birth, hospitalization dates, zip code and relevant medical information. The following direct identifiers will NOT be collected for this study:

- Name
- Postal address information, other than zip code
-
- Telephone and fax numbers

- Social security numbers
- Medical record numbers, or other account numbers
- Certificate/license numbers
- Vehicle identifiers or serial numbers, including license plate numbers
- Device identifiers and serial numbers
- Web universal resource locators (URL's) or Internet protocol address numbers
- Biometric identifiers such as finger and voice prints
- Full face photographic images or any comparable image

The CP Research Network will offer a Participation and Data Use Agreement to each Clinical Center to authorize its creation of a a Limited Data Set database for use by CPRN investigators.

Data Management

Data Set Description

The Registry Elements are available here: https://cprn.org/research/cprn-registry-elements/

Health Information

The data collected include a range of clinical care data, including the following: non-identifier demographics (e.g., race, ethnicity, sex), period of data capture (e.g., enrollment start and end dates), clinical encounters (e.g., medical and surgical history, diagnoses, discharge dates and dispositions, payer type), procedures (e.g., de-identified results of imaging, lab results), vital signs and other clinical observations (e.g., height, weight, range of motion, strength), medication prescribing, administration and dispensing (e.g., prescriptions filled), patient condition (e.g., quality of life, function, durable medical equipment use, and other patient-reported conditions and outcomes), mortality information (e.g., death date and cause), privacy-preserving linkages or hash tokens (i.e., to match patient records across DataMarts), and immunizations (i.e., administered and reported).

Protected Health Information

In addition, 3 of the 18 Health Insurance Portability and Accountability Act (HIPAA) identifiers, birth dates, dates of clinical services, and zip code will also be collected.

Data Access

The following data access and security methods will be used to transmit, manage and store the data. For a complete description of the DCC security infrastructure see Section Data Security on page 16.

- The EDC system features 128-bit SSL data encryption to ensure data security over an internet connection.
- The system is configurable for access restrictions by Site and Role base level with an audit trail.

- Hourly incremental backups and full daily backups provide a high level of protection against data loss.

Clinical Site Monitoring

In most multi-institutional studies, the DCC assigns a site monitor to travel to each Clinical Center at times appropriate to the specific study, to ensure that all regulatory requirements are being met and to monitor the quality of the data collected. The CPRN investigators recognize the importance of ensuring data of excellent quality and recognize that site monitoring is critical to this process.

Site monitoring visits are conducted to review compliance with the study methodology and adherence to Good Clinical Practice guidelines, and will be conducted as needed based on pre-defined thresholds (e.g., risk-based) established by the Steering Committee and the DCC. During site monitoring visits patient forms and original source documents will also be inspected. The primary criterion for data element verification is identification in the source document, which is the medical record. Thus, the medical record, either hard copy file or access to the electronic medical record system, must be available for review by the site monitor.

The DCC may supplement on-site monitoring with remote monitoring activities. Remote monitoring involves detailed review of the data entered by the Clinical Center and telephone consultations with the Clinical Center investigator and/or research coordinator to review and verify selected data elements. This requires uploading de-identified copies of specific parts of the medical record to the DCC staff, who review those materials against the data recorded in the EDC system.

The site monitor will provide the study investigator and research coordinator with a written report and Clinical Centers will be required to follow up on any deficiencies.

Data Analysis

Primary Objective

.o describe the number and characteristics ofindividuals with cerebral palsy (CP), at risk for CP, HIE and related conditions receiving care at CPRN Clinical Centers, including patient demographics, etiology, diagnostic characteristics, interventions, and patient-reported outcomes.

Secondary Objective

To provide this data to CPRN investigators to support hypothesis generation and study design development for clinical trials and observational studies to be carried out by the CPRN. It is expected that the CPRN Registry will provide an infrastructure for the execution of future multi-institutional research, such as clinical trials and observational studies, on CP within CPRN.

Each Clinical Center will only have access to their Center's data. If a CPRN Investigator requires access to aggregate data across the CPRN, they will need to send a request to a CPRN

investigator committee responsible for the use of aggregate data. The committee will evaluate the project under consideration and will then forward the request to the DCC who will package and export the data as a de-identified data set to the CPRN Investigator.

All research publications and presentations arising from this study will be presented in aggregate form, and at no time during or after the study will any research data be released by CPRN, DCC, or private funders with patient, surgeon or center identifiable fields.

Accrual Projection and Study Duration

The registry includes the full population of eligible individuals receiving care within CPRN Clinical Centers. Data collection began retrospectively in 2016 and continues prospectively on an open-ended basis for the duration of the CPRN network. Anticipated enrollment is approximately 75,000 participants, supporting longitudinal and subgroup analyses over time. Data Safety Monitoring Plan

All procedures and interventions are conducted as part of clinical care and the range of possible study events having an important impact on risks and benefits to study participants is limited. The probability and magnitude of harm and/or discomfort anticipated in the research is not greater than that ordinarily encountered in daily life. As such, oversight of an independent Data Safety Monitoring Board is not warranted. Data safety and quality reports will, however, be compiled at the DCC at the University of Pittsburgh on a yearly basis and disseminated with the site PIs in the Scientific Steering Committee.

These reports will include: study accruals, unanticipated problems, extraction statistics, the identification of the cause of failed extracts, and any data breaches reported by Clinical Centers. The DCC staff will investigate all breaches and extract failures, collaborate with, and advise Clinical Centers on their findings to formulate appropriate solutions. Reports will be generated by DCC staff and leadership. Site monitoring activities occur under site-specific IRB approval and HIPAA authority and do not involve transfer of direct identifiers to the Data Coordinating Center.

Data Security

The Data Coordinating Center (DCC) at the University of Pittsburgh relies on the University's existing infrastructure which includes a dedicated hosting on all main campus and health sciences servers in a secure facility that conforms to Federal and Pennsylvania state standards for security. The DCC has a state-of-the-art server infrastructure, with enterprise high availability features like clustering, load-balancing, transparent failover, etc., and enterprise security features like stateful firewalls, network segmentation, intrusion detection, monitoring, and 24/7/365 support by dedicated Database, Server, Network and Security teams at the

University. Communication over public networks is encrypted with using secure socket layer (SSL) or virtual private network (VPN) technologies.

Direct physical access to the DCC server infrastructure is highly restricted, and remote access to most server infrastructure incorporates multi-factor authentication. Additionally, routine vulnerability scanning and patching is performed on a set schedule for servers hosted in DCC, and each server is additionally assigned a technical owner and a business owner, who are personally responsible for ensuring the technical security as well as adherence to University of Pittsburgh Information Security Risk Management.

The investigators and staff of the DCC and CPRN are fully committed to the security and confidentiality of all data collected for CPRN studies. All personnel at the DCC at the University of Pittsburgh have signed confidentiality agreements concerning all data encountered in the center. Violation of these agreements may result in termination from employment at the University of Pittsburgh. In addition, all personnel involved with the DCC and CPRN have completed Human Subjects Protection and HIPAA training.