Background and Rationale of the National Data Stream (NDS): In Switzerland, over 85,000 children are born annually, contributing to a current population of 1.7 million inhabitants aged under 20 years. Every year, over 100,000 children require admission as inpatients to hospitals. Many more are seen in outpatient clinics and emergency wards. At present, the evidence-base for most pediatric diagnostic and therapeutic procedures is either absent, of low-quality (data from small cohorts), or inferred from adults. Due to the unique epidemiology, developmental physiology, and high vulnerability of children, there is urgency to continuously improve health care provision based on pediatric data. In 2020, the life expectancy at birth in Switzerland was 81 years for males and 85 for females. Adverse effects related to diseases, treatments, environmental exposures, and lifestyle during early childhood will affect children, their families, and future offspring for many decades, exponentially increasing the associated costs for society. New therapies and progress in social and preventive health have reduced the morbidity and mortality caused by previously prevalent conditions such as infections, cancer or trauma. Consequently, modern pediatrics in high-income countries like Switzerland deals with a conundrum of rare diseases which present as unique and often life-threatening phenotypes and which require highly personalized approaches. To date, multiple registries for pediatric patients in Switzerland coexist, with limited data links across institutions, hindering effective collaborations. In addition, common problems such as obesity-related morbidity and chronic respiratory conditions frequently result in whole-of-life trajectories that are still far from being overcome. Furthermore, patients and parents have intimate knowledge of their disease and needs but remain poorly integrated into health care planning and research. Finally, due to Switzerland's small population size and regional fragmentation, there is a mismatch between the excellent academic capacity of research institutions, and the difficulty of rapidly acquiring and processing the data required for clinical research and evidence generation. The digital transformation represents a unique opportunity to shape a data-driven, agile, learning health care system that will deliver better, more efficient, and more personalized care to children and their families.

Goal of the NDS: SwissPedHealth proposes to set up a joint pediatric NDS to make routine clinical data from pediatric hospitals in Switzerland interoperable, standardized, quality-controlled, and ready for research and trials, health-policy creation, and clinical audits. SwissPedHealth will implement a harmonized, FAIRified, modular, and scalable data stream across a network of University hospitals, non-academic clinics, research institutions, biobanks and registries in Switzerland. It will enable links with government departments. It builds on SwissPedData, a national pediatric core dataset defined through a Swiss Personalized Health Network (SPHN) infrastructure development project. SwissPedData is based on routine data that is regularly collected during clinical encounters. This pediatric core dataset has the potential for enrichment with patient-reported outcomes, population-based and administrative data, specialized disease registries, and high-density data from advanced clinical diagnostics and research projects such as omics technologies. By developing re-usable and expandable informatics, logistical, governance, regulatory, and training resources in close collaboration with the clinical data warehouses (CDWs), Biomedical Information Technology (BioMedIT), and other SPHN funded projects, SwissPedHealth will make data from routine care available for analysis. This will enable investigation of research questions, benchmarking, and improvement of quality of care, thereby implementing the infrastructure for a learning national pediatric health system. The potential of this NDS will be showcased through a first-of-its-kind multi-omics lighthouse project on rare diseases, and nested projects using electronic health care record (EHR)-derived data on common health problems which demonstrate how SwissPedHealth will contribute to 1) highly innovative personalized care, 2) readiness for clinical trials, 3) evidence-based policy making, and 4) benchmarking and quality improvement.

Structure and Governance of the NDS: A multi-site, multidisciplinary Steering Committee, representing all partner sites and disciplines (both SPHN and Personalized Health Related Technologies; PHRT) will lead the consortium. The program consists of five work packages: 1) Implementing SwissPedData in children's hospitals, designing data flows and regulatory and governance documents, 2) nested research projects using a structured core dataset of readily available data, 3) the lighthouse project, 4) bioethics, patient and public involvement (PPI), and 5) management and program coordination. The SwissPedHealth governance structure and Ethical, Legal and Social Implication (ELSI) documents build upon existing agreements and infrastructures developed in national pediatric collaborative studies through the Swiss Research Network of Clinical Pediatric Hubs (SwissPedNet) and SPHN templates to provide an overarching regulatory and legal framework for health-related pediatric data in Switzerland.

Lighthouse Project: Multi-Omics Workflow to Diagnose Rare Diseases in Children: Rare diseases predominantly affect children, frequently causing premature death or decades of life with chronic disability. In the past decade, the rate of discovery of rare diseases has been rapidly increasing. In particular, the ability to generate and analyze genomic data with rapid turnaround times at lower cost, has led to a major paradigm shift in the role of genomics in pediatric acute care. Nevertheless, genome-dependent diagnostic rates remain low (30-50%). As the depth and speed of genome sequencing has increased, the challenge has shifted from identifying genetic alterations to defining their functional relevance. Multilayered omics technologies define relationships between genes, proteins, metabolites, and phenotypic traits, which accelerate identification of the underlying cause of rare clinical presentations. Building on a successful PHRT pilot study, we aim to develop and prospectively validate a multi-omics workflow to identify rare diseases in children with life-threatening extreme phenotypes. Using existing cohorts of children with different extreme phenotypes (N=250), we will apply an integrated approach of whole-genome sequencing (WGS), RNA sequencing (RNA-seq), proteotyping, and metabolomics, to identify rare deleterious genetic variants and demonstrate their impact at the gene, transcript, and proteome/metabolome level. We will develop novel computational methods using machine learning to integrate multi-omics data with SwissPedData and link this to intensive care minimal datasets (MDSi, b34) and the Swiss Rare Disease Registry (SRDR). This multi-omics workflow will create a diagnostic tool that can be optimized for rapid result generation and will be tested in a prospective cohort (N=140) from partner Swiss hospitals.

Nested Projects: The harmonized SwissPedData set developed in our previous SPHN Infrastructure Project is ready for implementation in hospital EHRs. The nested projects use core variables from SwissPedData, available since 2017, which can easily be extracted from university CDWs. The main emphasis in the nested projects is feasibility and relevance for routine pediatric care, thus they will only use readily available structured data such as heights, weights and diagnoses. The projects will address relevant questions in child health, on 1) anthropometric data, 2) childhood cancer, 3) pediatric respiratory diseases, and 4) decision-making around antibiotic utilization. Data will be combined with linkable data from selected national registries and cohort studies to carry out a range of data quality checks, such as consistency, accuracy, completeness, and validity. External datasets will serve as reference standards. Results will feed back to hospital clinic information systems and data cleaning routines to improve and update SwissPedData.

International benchmarking: SwissPedHealth represents worldwide the first harmonized and integrated national pediatric data stream combining routine EHR data, links with registries, and enhanced by high granularity datasets. We will partner with international research networks that align with our aims including PEDSNet, the undiagnosed disease network, and care4rare. This exchange will help to identify best practices, compare performance across countries and enhance the learning of pediatric health systems. Cross-fertilization will 1) enhance and improve the efficiency of the SwissPedHealth in terms of quality, speed, and costs, 2) enable external validation, and 3) result in highly competitive Swiss pediatric health care data for international collaborations.

Significance and Sustainability: This unique pediatric NDS will integrate clinical, federal administrative data, and research data across leading Swiss hospitals under joint governance. SwissPedHealth will thereby overcome the challenge of pediatric data being kept in local silos, in non-standardized and non-interoperable forms, highly dispersed across hospitals, and thereby not usable for translational research and clinical trials of sufficient power. Our NDS builds on existing and endurable partnership of all pediatric teaching hospitals centered around SwissPedNet. It will implement a harmonized pediatric health dataset in Switzerland, which is scalable to additional datasets and sites. The lighthouse project will serve as a high-visibility example of how this infrastructure can be enriched with high-density data to deliver cutting-edge research on personalized health. This pediatric NDS will set up a sustainable framework and infrastructure to conduct Swiss-wide observational and interventional studies, enhancing clinical trial readiness, and to develop a learning health care system driving frontier, innovative and highly patient-focused research.