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Canadian Inborn Errors of Immunity National Registry – an observational, longitudinal research study design for a Rare Disease Registry Model with Governance Framework and Enhanced Interoperability

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Abstract

Background

Inborn errors of immunity (IEI) are individually rare but collectively affect an estimated 30,000 Canadians. Their genetic and clinical heterogeneity, combined with limited disease-specific data, presents challenges in diagnosis, management, and evaluation of treatment outcomes. A national registry with standardized longitudinal data collection is needed to better characterize disease manifestations, support clinical research, inform healthcare planning, and improve care for individuals with IEI across Canada.

Methods

A national steering committee comprising 13 clinician-researchers from 3 adult and 8 pediatric centres across 9 Canadian provinces established the Canadian Inborn Errors of Immunity National Registry (CIEINR). Development was informed by an environmental scan of existing rare disease registries and consultations with bioinformatics experts and patient representatives. A multidomain electronic case report form (eCRF) was developed using Research Electronic Data Capture (REDCap), hosted at the University of Calgary, to systematically collect demographic, genetic, clinical, treatment, and outcome data.

Results

Between 2021 and 2025, the CIEINR governance framework, research protocols, and standardized data model were developed and peer-reviewed. The eCRF incorporates ontology-based medical terminologies to facilitate standardized characterization of clinical manifestations, data harmonization, and interoperability. The RareLink framework was adapted to support internationally standardized data linkage and generation of Global Alliance for Genomics and Health (GA4GH) Phenopackets, enabling structured, machine-readable representation of clinical and genomic information. Registry governance documents, policies, and data models are shared through an open-access GitHub repository to promote transparency, reproducibility, and collaboration.

Conclusions

The innovative CIEINR provides a national infrastructure for standardized, longitudinal collection of diagnosis, disease course, treatment, outcomes, and genomic data ac across the spectrum of IEI. High-quality, standardized, machine-readable, and interoperable data will enable Phenopacket analysis, support research on new therapies, and foster international collaboration. By openly sharing its governance framework, policies, and data model, CIEINR establishes a reproducible approach to rare

disease registry development while advancing evidence-based clinical care, patient advocacy, and healthcare policy.

Background

Inborn errors of immunity (IEI) are a heterogeneous group of more than 500 disorders characterized by susceptibility to infection, malignancy, immune dysregulation, or autoinflammation(1). IEIs affect an estimated 1 in 1,200 individuals,(2) equating to at least 30,000 Canadians. A 2004–2010 Canadian survey estimated the incidence of severe combined immune deficiency (SCID) to be twice that in the United States, with a disproportionate number in First Nations/Métis/Inuit (FNMI) population(3). Canada is also home to a large Low German Mennonite population who carry founder pathogenic variants in several IEI genes, including *CD3D, ZAP70, ADA*, and *ATM*(4). Despite this unique and substantial burden, Canada lacks comprehensive national data. Insufficient epidemiologic characterization of IEI across Canada, including FNMI, diverse population groups, and newcomers, complicates service planning and equitable resource allocation, especially in remote and rural regions(5). Improved knowledge of the landscape of IEI is expected to advance care, as seen with the identification of a pathogenic *IKBKB* founder variant in remote FNMI communities that led to targeted population screening, revised immunization policies, and expedited treatment, with improved survival(6).

In recent decades, registries have emerged as valuable tools to better characterize rare diseases, with a transformative impact on diagnosis and management. The European Society for Immunodeficiencies Registry (ESID-R) has generated critical epidemiologic and disease-specific insights, directly informing clinical practice across Europe and beyond(7). While the 2021 International Patient Organization for Primary Immunodeficiencies (IPOPI) report recognized Canada's strengths in IEI patient care, it highlighted the absence of a national registry as a key gap(8). Here we describe the development of the Canadian Inborn Errors of Immunity National Registry (CIEINR) as a model for a rare disease registry, with the incorporation of standardized ontologies amenable to machine learning and the creation of comprehensive governance frameworks. CIEINR will improve understanding of the IEI landscape in Canada, provide insights into treatment effectiveness, highlight the strengths and challenges of patients and healthcare providers, facilitate patient advocacy, and ultimately drive more equitable, data-informed care across Canada.

Methods

Study protocol development and implementation

A Steering Committee comprising 13 members of the Clinical Immunology Network – Canada (CINC)(9) from 11 Canadian academic centers (3 adult and 8 pediatric), a project manager, and research trainees developed the CIEINR through monthly virtual meetings from 2021 to 2025.

The registry development involved:

1. Environmental scan and literature review of rare-disease registries (Appendix Table 1a and Fig. 1b), research articles, government reports, registry websites, and guidelines.
2. Guidance from Canada's Drug Agency for Rare Disease Registries(10) and RareKids-CAN Pediatric Rare Disease Clinical Trials and Treatment Network, Registry Sub-platform(11).
3. Input from the Canadian IEI national patient organization (ImmUnity Canada)(12) and initiation of a patient and caregiver registry advisory group.
4. Development of regulatory and ethical frameworks: study proposal, consent forms, patient surveys, legal and financial agreements.
5. Design of multidomain electronic case report forms (eCRFs) in Research Electronic Data Capture (REDCap), harmonizing questions with the ESID-R(13) and the United States Immunodeficiency Network (USIDNET)(14). A single-center REDCap platform (University of Calgary) was selected due to its compliance with Health Canada and International Council for Harmonization Good Clinical Practice (ICH GCP) standards. It provides secure, web-based data capture with built-in validation features, as well as free access for multi-site collaboration. Multidomain eCRFs and data entry were piloted in 20 patients with variable forms of IEI (Appendix Table 2).

An advanced data-capture framework was integrated to ensure methodological consistency and interoperability through data sharing. In collaboration with bioinformatics researchers who developed RareLink, a novel rare-disease common data model (RD-CDM), a REDCap rule set with embedded computational ontologies (e.g., Monarch Disease Ontology MONDO) was integrated into the REDCap data elements and value sets(15). Forms were annotated to include relevant IEI disease extensions, infections, clinical conditions, vaccinations and laboratory values with 14 medical ontologies. The 2024 International Union of Immunological Societies (IUIS) IEI classification of disease names was encoded in MONDO(1, 16–18). An additional 46 of the 698 IEI not-yet-represented entities were added through collaboration with the Monarch Initiative. Data entry for 9 diverse patients was piloted successfully.

6. Creation of governance framework components, including terms of reference, policies and standard operating procedures (SOPs) for data access and management, communication and reporting, training and support, decision-making for collaborations, funding and sustainability oversight, and industry engagement.
7. Quality improvement and assurance based on tailored PubMed search strategies ('register'/exp OR 'register') AND 'rare disease' AND ('quality control'/exp OR 'quality control'), examination of the Registry Evaluation and Quality Standards Tool (REQueST)(19, 20), gray literature, Canadian Drug Agency best practices(10), and relevant webinars and consultation with the RareKids-CAN research team(11).
8. Funding was obtained via the Immunodeficiency Canada Chaim Roifman Senior Investigator award, the Barb Ibbotson Chair for Pediatric Hematology, the Alberta Children's Hospital Foundation, and industry investigator-initiated grants for costs related to Registry site establishment and data collection. Participating sites were awarded start-up and per-patient enrollment funds.

Manuscript figures were generated with the help of ChatGPT.

Results

Currently, the CIEINR comprises 25 centers with confirmed or pending participation (Fig. 1). Site-specific research ethics approvals have been secured at 13 sites, with data transfer and financial agreements finalized at 9; the remaining applications are pending. The general structure of the CIEINR is demonstrated in Fig. 2.

Study Design and Regulatory Package

CIEINR is a registry designed to collect retrospective and prospective longitudinal data, including patient-reported outcomes, diagnosis, diagnostic results, and disease course, with a strong emphasis on genetic variants, therapeutic modalities, and disease outcomes. The registry collects only de-identified patient data, as defined by Alberta Health Services' non-identifying health information privacy standard, including only month and year of identifying dates(21). Participants are assigned a unique study identifier, and each site will keep a confidential, site-only master list of consented individuals, linked to name and local medical number. A policy has been developed to ensure assignment of a unique study identifier that remains with each participant across centres, including during inter-institutional transitions.

Inclusion criteria are known or suspected IEI by IUIS classification, carriers of pathogenic variants causing IEI, and infants with congenital T-cell lymphopenia identified by newborn screening. Individuals are excluded if the immunodeficiency is secondary to HIV infection, chemotherapy, or other immunosuppressive therapies unless there is evidence of an underlying genetic IEI. Registry participation requires written, informed consent and age-appropriate assent from all participants or legal guardians. Consent will be routinely re-evaluated at time of annual patient surveys. Sites have access to their own data; the CIEINR will thereby also serve as a local registry for participating sites, which may publish research with pre-approval from the Steering Committee.

Patient Survey and electronic case report form development

Multidomain electronic patient surveys and eCRFs were developed in REDCap at the University of Calgary (Fig. 3). This platform ensures daily onsite backups to network-attached storage and nightly offsite replication to secure S3 cloud storage. Access is controlled through two-factor authentication and role-based permissions.

Patient- and proxy-reported initial and annual surveys were developed with the Collaborative Immunology Program, Alberta Health Services. Surveys capture family history, treatment experiences and quality-of-life metrics using the Patient-Reported Outcomes Measurement Information System (PROMIS®). Adolescents complete a transition-readiness questionnaire created by University of British Columbia collaborators. A patient engagement strategy for survey evaluation, supplementation, and feedback is in development.

The eCRFs collect de-identified data on demographics, infections, organ-specific manifestations, diagnostic testing, and genetic variants. This facilitates precise documentation of molecular findings and enables robust genotype-phenotype correlation, essential for advancing disease characterization and improving prognostic accuracy. Interventions, including supportive care, immunoglobulin replacement, immunomodulators, hematopoietic cell transplant (HCT), and gene therapy, are also documented (Fig. 3).

Integration of an advanced electronic data capture framework for machine-readable analyses

Interoperability, the reliable exchange and comparison of data, is essential for rare disease research(22). With the aim of utilizing systems to semantically exchange information with other IEI registries, we integrated RareLink(23). This novel REDCap-based framework embeds the ontology-driven rare disease common data model at its core and links registry data to global health data standards, notably the Global Alliance for Genomics and Health (GA4GH) Phenopacket schema(15, 24). We adopted the Linked Data Modeling Language(25) to represent the model in a machine-readable, version-controlled format and leveraged RareLink's command-line interface and engine to automate exports to Phenopackets(15). Globally standardized ontology codes such as MONDO, the Human Phenotype Ontology (HPO), and Systematized Nomenclature of Medicine Clinical Terms (SNOMED) were embedded, enabling exported data to include diagnoses, phenotypes, and laboratory values as standardized digital codes. This framework ensures semiautomated transfer of high-quality, interoperable, machine-readable Canadian data to downstream analytic algorithms and multi-registry collaborations. Examples of ontology coding are demonstrated in Fig. 3.

Embedding disease ontologies required updating MONDO codes for all IEI(18). In collaboration with the European Network for Rare Immunodeficiencies – Rapid Identification of T-cell Abnormalities (ENR-RITA), the Berlin Institute of Health at the Charité, and the Clinical Genome Resource (ClinGen) USIDNET initiative, we are contributing to new MONDO and HPO code annotation and curation to update our model with the missing codes.

To enhance transparency and community use, our complete data model is published under an open-source Apache 2.0 license on GitHub(26) which is a free, cloud-based Microsoft platform for storing, managing, and sharing developers' code: https://github.com/P2GX/cieinr/tree/develop

Development and Advancement of Governance Framework Components of CIEINR

The following governance components were developed:

1. Terms of reference: description of governance structure, Steering Committee purpose, structure, roles with descriptions, functions, reporting relationships; Co-Chair and Committee member election

and responsibilities, research and authorship guidelines, guiding principles.
2. Ethics/Privacy Policies and comprehensive SOP manuals and standard templates, including consent forms, data-use agreements, investigator declaration forms, publishing policy, data breach procedure, exit policy/legacy planning.
3. Registry Initiation Package for each site.
4. Data access and data dissemination plan.
5. Communication and reporting policies for annual reports, transparency, and communication plan.
6. Collaboration policies, including patient advisory, engagement of clinicians, patient organizations, industry, and decision-making for future collaborations.
7. Training and support for personnel, including training videos, data collection manuals, technical support and online consultation.
8. Transparent funding and sustainability oversight.

Quality Improvement and Assurance Framework in CIEINR

The Quality Assurance subgroup conducted a registry governance literature review and informed by the Registry Evaluation and Quality Standards Tool (REQueST)(19) and Canada's Drug Agency best practice guidelines(10), reviewed the protocol and supporting documents. Policies addressing gaps in governance, data access and maintenance, external collaborations, data sharing, publications, funding, exit procedures, auditing, and dissemination were developed (Appendix Table 3) and operationalized through SOPs, a comprehensive data dictionary, and revised Steering Committee Terms of Reference defining key roles, including project manager, and leads for finance, quality assurance, scientific review, and Diversity, Equity, and Inclusion (DEI). The registry is supported by a financial management plan, collaboration protocols, transparent decision-making and data-sharing frameworks, study monitoring procedures, and publication and funding mechanisms. A data entry training webinar and public registry information on the CINC website(9) will support ongoing engagement and consistency.

Discussion

The CIEINR collects standardized, ontology-coded data on patients with IEI across Canada, allowing improved understanding of the epidemiology, management and outcomes. The registry will support health care decision-making and advocacy, provide real-world data to regulatory bodies, including Health Canada and the Canada's Drug Agency, and help identify barriers to care, especially for underrepresented populations and those in rural or remote areas. Ongoing patient engagement and collaboration with patient organizations will ensure specific concerns of this population are addressed. We are enrolling patients and collecting data to enhance research, including translational, clinical and knowledge transfer projects, similar to USIDNET, ESID, and the Primary Immune Deficiency Treatment Consortium (PIDTC), which have been impactful in improving diagnosis and management for patients with IEI(27–29).

The CIEINR integrates advanced machine-learning analytic tools via RareLink, incorporating phenotypic data alongside standardized ontologies. This combination represents an innovative approach to genetic research and the modernization of rare disease registries(23, 30, 31). These tools will help link phenotypes associated with new pathogenic gene variants, uncover clusters of patients with similar clinical trajectories, facilitate genotype-phenotype correlations, develop predictive algorithms for biomarkers, signs of disease progression, treatment response, and risks of morbidity and mortality. USIDNET, ESID, the Latin American Society for Immunodeficiencies (LASID) Registries, and others are also exploring the incorporation of ontology coding, which will improve efficient data sharing. Standardized ontologies will enable international IEI registry interoperability, facilitating semiautomated data exchange and substantially enhancing collaborative analytical power(23). The CIEINR provides a blueprint for embedding standardized ontologies across other rare disease registries.

A scoping review by RareKids-CAN revealed a notable lack of governance and regulatory template documents for registry developers. We have created a robust framework for registry development and sustainability that is readily adaptable to other rare diseases and jurisdictions. Our governance framework meets the pan-Canadian guidance standards for best practices and collection of information about patients with rare diseases(10), and aligns with international recommendations for improving data transparency, content, and quality(32). By sharing the data model in an open-source GitHub public repository and all governance documents, quality assurance policies, the foundational work presented here can be adapted for use in other registries. Our documents are publicly available as a template for other rare disease registries:https://github.com/P2GX/cieinr/tree/develop/governance

Despite its strengths, CIEINR has limitations that warrant consideration. It collects data only from diagnosed, consented patients, so it cannot provide an exact IEI incidence or prevalence. Some patients may not be referred if their phenotype isn't recognized as immunological or if no immunologist is available locally. Pediatric data will give us insight into the volume of undiagnosed or uninvestigated adults.

Furthermore, limiting inclusion to consented patients is ethically essential given the rarity of these conditions and the collection of detailed clinical and genetic information, which carries a potential risk of re-identification despite robust de-identification safeguards. Ensuring informed consent protects patient autonomy, supports trust, and aligns with national privacy and research ethics standards. As the IUIS classification of IEI includes over 500 diseases, eligibility may be challenging for patients without a genetically confirmed IEI diagnosis; the inclusion of less-defined immune disorders and the exclusion of secondary causes will be at the discretion of the site principal investigator and thus may compromise data quality. Sustainability is challenging with limited personnel and financial resources until sufficient data is available for competitive grant opportunities. Machine learning capability embedded within the CIEINRin addition to comprehensive government and quality assurance will hopefully decrease manpower requirements and improve long-term sustainability of the CIEINR.

Conclusions

The establishment of the CIEINR provides a comprehensive, research-driven infrastructure to improve understanding and care of IEI in Canada. Designed as both a national resource and a scalable template for other rare disease registries, CIEINR integrates advanced analytics frameworks, including RareLink REDCap and GA4GH Phenopackets, to ensure semantic interoperability, data reusability, and secure exchange, thereby supporting research collaboration, regulatory decision-making, and health system planning. As a vital source of standardized, real-world data, the registry will inform treatment effectiveness, disease trajectory, and long-term outcomes. Future directions focus on sustainability, patient partnership, and digital integration(33), including the essential active involvement of a patient and caregiver advisory committee in collaboration with ImmUnity Canada(34, 35), development of a publicly accessible website through CINC to enhance transparency and knowledge translation(36), and collaboration with IT specialists to enable structured data extraction from electronic medical records. Together, these initiatives position CIEINR as a sustainable, patient-informed national platform capable of driving innovation and improving care for Canadians with IEI.

Abbreviations

CIEINR Canadian Inborn Errors of Immunity National Registry

CINC Clinical Immunology Network – Canada

ClinGen Clinical Genome Resource

eCRF Electronic case report form

DEI Diversity, Equity, and Inclusion

ESID-R European Society for Immunodeficiencies Registry

ENR-RITA European Network for Rare Immunodeficiencies – Rapid Identification of T-cell Abnormalities

FNMI First Nations/Métis/Inuit

GA4GH Global Alliance for Genomics and Health

HPO Human Phenotype Ontology

IEI Inborn errors of immunity

ICH GCP International Council for Harmonization Good Clinical Practice

IPOPI International Patient Organization for Primary Immunodeficiencies

IUIS International Union of Immunological Societies

LASID Latin American Society for Immunodeficiencies

PIDTC Primary Immune Deficiency Treatment Consortium

RD-CDM Rare-disease common data model

REDCap Research Electronic Data Capture

REQueST Registry Evaluation and Quality Standards Tool

SCID Severe Combined Immune Deficiency

SNOMED Systematized Nomenclature of Medicine Clinical Terms

SOP Standard operating procedures

USIDNET United States Immunodeficiency Network

Declarations

Ethics approval and consent to participate:

The Canadian Inborn Errors of Immunity National Registry (CIEINR) has received research ethics approval from participating institutions, with site-specific approvals obtained prior to patient enrolment. Written informed consent is obtained from participants or their parents/legal guardians, as applicable, with assent obtained from pediatric participants in accordance with local research ethics requirements.

Consent for publication:

Not applicable. This manuscript describes the development, governance, and data infrastructure of the CIEINR and does not contain identifiable individual patient data.

Availability of data Material:

Data model and all governance documents, quality assurance policies, the foundational work shared in an open-source GitHub public repository. Our documents are publicly available as a template for other rare disease registries: https://github.com/P2GX/cieinr/tree/develop

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Declaration of author(s) competing interests:

ASLG holds a small business in rare disease software consulting with no financial relationships relevant to this work; no income received to date.

JC received educational grants from CSL Behring and Takeda, and honoraria for consultancy work from CSL Behring, Takeda, and Alexion.

LM-F is a member of the IDMCs for Encoded Therapeutics and Regenxbio, has received honoraria for consultancy work from Takeda, Merck, BioCryst, Valeo Pharma, and Canada's Drug Agency, and has received a research grant from the Jeffrey Modell Foundation.

HC received honoraria for consultancy work from CSL Behring, Takeda and AstraZeneca Rare Diseases (Alexion).

BD is a member of a DMC for TAKEDA and received honoraria for consultancy work from TAKEDA.

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Methodology; (registry design, data dictionary, REDCap/database design, standardized data-collection planning, piloting): TK, ASLG, TM, HH, MU, LS, RR, DD, ST, PNR, OB, JKG, AA, BT, NAMW, BD

Project Administration; (coordinating participating centres, ethics/regulatory processes, meetings): TK, CR, AG, NAMW, BD

Visualization;(preparation of figures, tables, flow diagrams, and data displays.): ASLG, TK, AG, TM, LMF, BT

Writing – Original Draft: TK, AG, TM, ASLG, BD, NAMW,

Writing – Review & Editing: all coauthors

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References

1. Poli MC, Aksentijevich I, Bousfiha AA, Cunningham-Rundles C, Hambleton S, Klein C, et al. Human inborn errors of immunity: 2024 update on the classification from the International Union of Immunological Societies Expert Committee. J Hum Immun. 2025;1(1):e20250003.
2. Boyle JM, Buckley RH. Population prevalence of diagnosed primary immunodeficiency diseases in the United States. J Clin Immunol. 2007;27(5):497–502.
3. Rozmus J, Junker A, Thibodeau ML, Grenier D, Turvey SE, Yacoub W, et al. Severe combined immunodeficiency (SCID) in Canadian children: a national surveillance study. J Clin Immunol. 2013;33(8):1310–6.
4. Payne M, Rupar CA, Siu GM, Siu VM. Amish, mennonite, and hutterite genetic disorder database. Paediatr Child Health. 2011;16(3):e23–4.
5. Pham-Huy A, Murguia-Favela L, Rubin T, Suresh S, Wright NAM, Derfalvi B, et al. Inborn errors of immunity in Canadian First Nations and Nunavut Inuit Children: the tip of the iceberg. Paediatr Child Health. 2025;30(1):40–7.
6. Rubin TS, Rockman-Greenberg C, Van Caeseele P, Cuvelier GDE, Kwan L, Schroeder ML. Newborn Screening for IKBKB Deficiency in Manitoba, Using Genetic Mutation Analysis. J Clin Immunol. 2018;38(7):742–4.
7. Kindle G, Alligon M, Albert MH, Buckland M, Edgar JD, Gathmann B et al. Inborn errors of immunity: Manifestation, treatment, and outcome-an ESID registry 1994–2024 report on 30,628 patients. J Hum Immun. 2025;1(3).
8. Nordin J, Solís L, Prévot J, Mahlaoui N, Chapel H, Sánchez-Ramón S, et al. The PID Principles of Care: Where Are We Now? A Global Status Report Based on the PID Life Index. Front Immunol. 2021;12:780140.
9. Clinical Immunology Network Canada: Clinical Immunology Network Canada. 2026 [Available from: www.cin-canada.org.
10. Tarride J-E, Okoh A, Aryal K, Milinkovic D, Okoh A, Aryal K, et al. Best Practices and Standards to Enhance the Quality of Rare Disease Registries in Canada. Canada's Drug Agency; 2025.
11. Registry Sub platform: RareKids- CAN: Pediatric Rare Disease Clinical Trials and Treatment Network. 2026 [Available from: https://www.rarekidscan.com/sub-platform-leads
12. ImmUnity C. ImmUnity Canada; 2026 [Available from: https://immunitycanada.ca/
13. Registry Working Party: European Society for Immunodeficiencies (ESID). 2024 [Available from: https://esid.org/working-parties/registry-working-party/
14. USIDNET. United States Immunodeficiency Network (USIDNET). United States Immunodeficiency Network (USIDNET); [Available from: https://www.usidnet.net/
15. Graefe ASL, Hübner MR, Rehburg F, Sander S, Klopfenstein SAI, Alkarkoukly S, et al. An ontology-based rare disease common data model harmonising international registries, FHIR, and Phenopackets. Sci Data. 2025;12(1):234.

16. Vasilevsky NA, Toro S, Matentzoglu N, Flack JE, Mullen KR, Hegde H et al. Mondo: Integrating Disease Terminology Across Communities. Genetics. 2025.
17. Köhler S, Gargano M, Matentzoglu N, Carmody LC, Lewis-Smith D, Vasilevsky NA, et al. The Human Phenotype Ontology in 2021. Nucleic Acids Res. 2021;49(D1):D1207–17.
18. Putman TE, Schaper K, Matentzoglu N, Rubinetti VP, Alquaddoomi FS, Cox C, et al. The Monarch Initiative in 2024: an analytic platform integrating phenotypes, genes and diseases across species. Nucleic Acids Res. 2024;52(D1):D938–49.
19. EUnetHTA. REQueST Tool and its vision paper 2021 [Available from: https://eunethta.eu/request-tool-and-its-vision-paper/
20. Allen A, Patrick H, Ruof J, Buchberger B, Varela-Lema L, Kirschner J, et al. Development and Pilot Test of the Registry Evaluation and Quality Standards Tool: An Information Technology-Based Tool to Support and Review Registries. Value Health. 2022;25(8):1390–8.
21. Alberta Health Services. 2014 [Available from: https://publicshare.albertahealthservices.ca/teams/policydocuments/1/clp-ahs-privacy-non-identifying-health-information-standard-ipo-2013-0004.pdf
22. Lehne M, Sass J, Essenwanger A, Schepers J, Thun S. Why digital medicine depends on interoperability. NPJ Digit Med. 2019;2:79.
23. Graefe ASL, Rehburg F, Alkarkoukly S, Danis D, Grönke A, Hübner MR, et al. RareLink: scalable REDCap-based framework for rare disease interoperability linking international registries to FHIR and Phenopackets. NPJ Genom Med. 2025;10(1):72.
24. Jacobsen JOB, Baudis M, Baynam GS, Beckmann JS, Beltran S, Buske OJ, et al. The GA4GH Phenopacket schema defines a computable representation of clinical data. Nat Biotechnol. 2022;40(6):817–20.
25. Moxon SAT, Solbrig H, Harris NL, Kalita P, Miller MA, Patil S et al. LinkML: an open data modeling framework. Gigascience. 2026;15.
26. BIH-CEI. Open source Apache 2.0 license on GitHub [Available from: https://github.com/BIH-CEI/cieinr
27. Pai SY, Logan BR, Griffith LM, Buckley RH, Parrott RE, Dvorak CC, et al. Transplantation outcomes for severe combined immunodeficiency, 2000–2009. N Engl J Med. 2014;371(5):434–46.
28. Haddad E, Hoenig M. Hematopoietic Stem Cell Transplantation for Severe Combined Immunodeficiency (SCID). Front Pediatr. 2019;7:481.
29. Durkee-Shock J, Zhang A, Liang H, Wright H, Magnusson J, Garabedian E et al. Morbidity, Mortality, and Therapeutics in Combined Immunodeficiency: Data From the USIDNET Registry. J Allergy Clin Immunol Pract. 2022;10(5):1334-41.e6.
30. Bridges Y, Souza V, Cortes KG, Haendel M, Harris NL, Korn DR, et al. Towards a standard benchmark for phenotype-driven variant and gene prioritisation algorithms: PhEval - Phenotypic inference Evaluation framework. BMC Bioinformatics. 2025;26(1):87.

31. Rekerle L, Danis D, Rehburg F, Graefe ASL, Bily V, Caballero-Oteyza A, et al. GA4GH phenopacket-driven characterization of genotype-phenotype correlations in Mendelian disorders. Am J Hum Genet. 2026;113(1):57–70.
32. Kodra Y, Weinbach J, Posada-de-la-Paz M, Coi A, Lemonnier SL, van Enckevort D et al. Recommendations for Improving the Quality of Rare Disease Registries. Int J Environ Res Public Health. 2018;15(8).
33. Vichare V, Kilich G, Rundles C, Onyekaba M, Abraham R. United States Immunodeficiency Network (USIDNET) Reimagined as a Semiautomated Data Extraction Method for Registry Building. J ournal Hum Immun. 2025;2(1):e20250118.
34. Manafo E, Petermann L, Mason-Lai P, Vandall-Walker V. Patient engagement in Canada: a scoping review of the 'how' and 'what' of patient engagement in health research. Health Res Policy Syst. 2018;16(1):5.
35. Klein TL, Bender J, Bolton S, Collin-Histed T, Daher A, De Baere L, et al. A rare partnership: patient community and industry collaboration to shape the impact of real-world evidence on the rare disease ecosystem. Orphanet J Rare Dis. 2024;19(1):262.
36. Mordenti M, Boarini M, D'Alessandro F, Pedrini E, Locatelli M, Sangiorgi L. Remodeling an existing rare disease registry to be used in regulatory context: Lessons learned and recommendations. Front Pharmacol. 2022;13:966081.

Figures

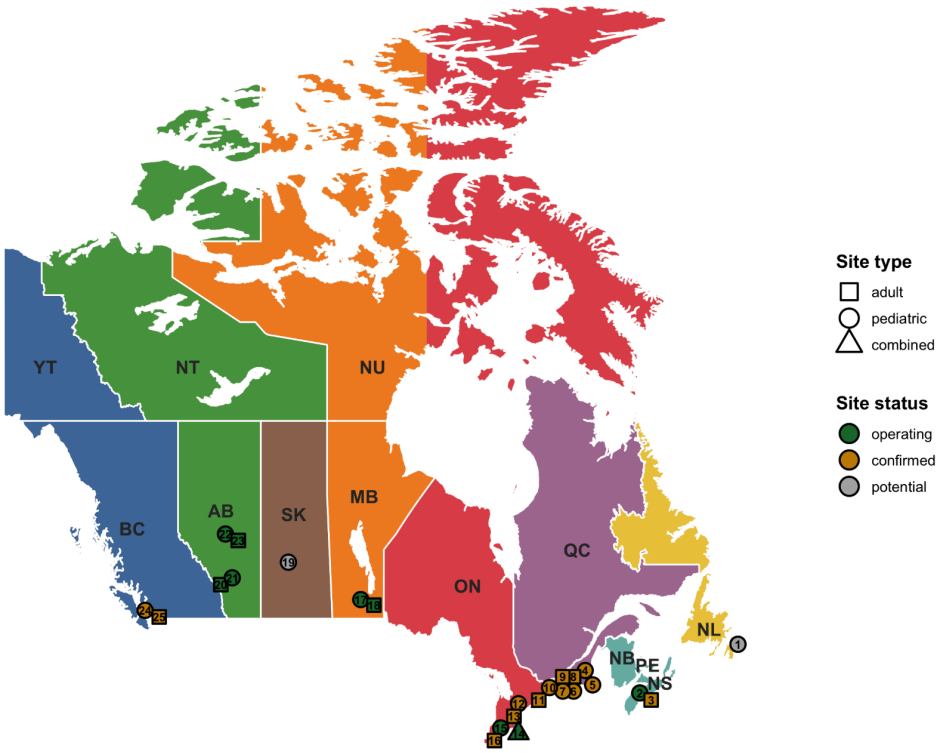


Figure 1

CIEINR sites at their geographic location.

Symbols: green - operating centres; yellow - centres confirmed to participate (with or without initiating a regional ethics board and legal agreement application); grey - centres with potential participation; circles - pediatric sites; squares - adult sites; triangle - combined adult and pediatric site; N# - number of enrolled patients. The same colour for provinces and territories indicates the North-to-South referral routes.

1. Janeway Children's Health and Rehabilitation Centre, St. John's, NL, 2. IWK Health/Dalhousie University, Halifax, NS, N#5, 3. Nova Scotia Health/HAAA/Dalhousie University, Halifax, NS, 4. Centre Hospitalier Universitaire de Québec/Université Laval, Laval, QC, 5. CIUSSS de l'Estrie-CHUS/Université de Sherbrooke, Sherbrooke, QC, 6. Centre Hospitalier Universitaire de Ste-Justine/Université de Montréal, Montréal, QC, 7. Montreal Children's Hospital/McGill University Health Center, Montreal, QC, 8. Immune Deficiency Treatment Center at the Montreal General Hospital, McGill University Health Centre, Montreal, QC, 9. Institut de Recherches Cliniques de Montréal, Clinique d'Immunodéficience Primaire de l'Adulte, Montréal, QC, 10. Children's Hospital of Eastern Ontario/University of Ottawa, Ottawa, ON, 11. The Ottawa Hospital/University of Ottawa, Ottawa, ON, 12. Hospital for Sick Children, University of Toronto, Toronto, ON, 13. St. Michael's Hospital/University of Toronto, Toronto, ON, 14. McMaster Children's Hospital/McMaster University, Hamilton, ON, 15. Children's Hospital at LHSC/Western University, London, ON, N#20, 16. St. Joseph's Health Care, Division of Clinical Immunology & Allergy, London, ON, 17. The

Children’s Hospital of Winnipeg/University of Manitoba, Winnipeg, MB, N#4, 18. Health Sciences Centre Winnipeg/University of Manitoba, Winnipeg, MB, 19. Saskatchewan Cancer Agency, Regina, SK, 20. Jim Pattison Children’s Hospital/University of Saskatchewan, Saskatoon, SK, 21. Foothills Medical Centre, Adult Immunology Service, Calgary, AB #73, 22. Alberta Children’s Hospital, University of Calgary, AB #26, 23. Stollery Children’s Hospital/University of Alberta, Edmonton, AB, 24. University of Alberta Hospital, Edmonton, AB, 25. British Columbia Children’s Hospital/University of BC, Vancouver, BC, 26. St Paul's Hospital/ University of British Columbia, Vancouver, BC

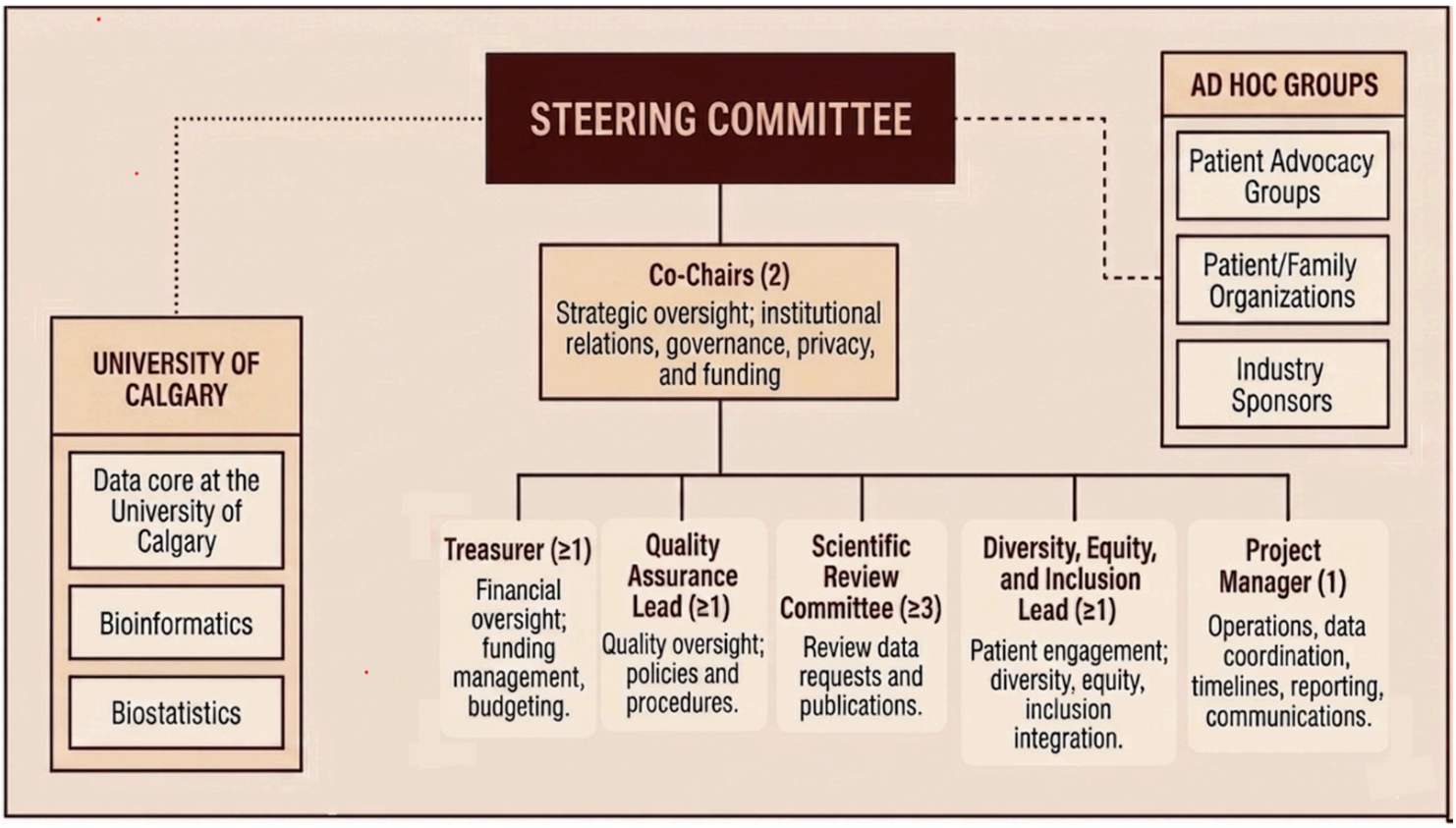


Figure 2

CIEIN Registry Governance Structure

Appendix 1a: Global Directory of Inborn Errors of Immunity Registries

World Region	Registry Abbreviation	Registry name	Founded	Number of participating sites/countries	Total Participant Number	Latest Report Year
America	USIDNET	United States Immunodeficiency Network[1,2]	1992	50 sites	5489	2025
	CIEINR	Canadian Inborn Errors of Immunity National Registry	2021	9 sites, 3 pending	128	2026
	LASID	Latin American Society for Immunodeficiencies Registry [3]	2009	17 countries: Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Paraguay, Peru, Uruguay and Venezuela	9307	2024
Europe	ESID	European Society for Immunodeficiencies [4-6]	1994	191 sites in Austria, Belarus, Belgium, Bosnia-Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Egypt, Estonia, France, Germany, Greece, Hungary, Iran, Ireland, Israel, Italy, Lithuania, Netherlands, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, United Kingdom	30,628	2024
Asia	PID	Russian Primary Immunodeficiency Registry[7]	2017	69 regional medical centers and 5 university clinics	2728	2020
	PIDJ	The Primary Immunodeficiency Database in Japan [8]	2007	13 Medical Colleges	4481	2021
	APIDN	Asian Primary Immunodeficiency Network database[9]	2011	14 Specialty Centers in China, Taiwan, Hong Kong, Singapore, Malaysia, Thailand, Philippines, Australia	2487	2024
		Singapore PID Registry[10]	1994	Not Reported	100	2006
	KPR	Korean PID Registry [11]	2001	23 Hospitals	152	2005
	PICAR	Taiwan Primary Immunodeficiency Care and Research Institute[12]	2003	Single Centre	727	2020
	ISPID	Indian Society for Primary Immune Deficiency network, in collaboration with the Foundation for Primary Immunodeficiency Diseases (FPID), USA[13,14]	2011	8 FPID-supported diagnostic & treatment centers across India (Bengaluru, Chandigarh, Chennai, Hyderabad, Lucknow, Mumbai, New Delhi, Vellore)	1539	2021
	MENA-IEI	Middle East and North Africa Registry on Inborn Errors of Immunity Registry[15]	2021	22 countries: Afghanistan, Algeria, Azerbaijan, Bahrain, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Qatar, Saudi Arabia, Sudan, Syria, Tunisia, Turkey, UAE, Yemen	17,120	2021
	KNPIDR	Kuwait National Primary Immunodeficiency Registry [16]	2004	Not Reported	314	2008
		Kazakhstan National PID Registry [17]	2009	Single National Centre	269	2025
Africa	SAPIDR	South African Primary Immunodeficiency Registry[18]	2008	National Registry at Tygerberg	396	2001
		Algerian PID Registry[19]	2008	Single National Centre	887	2021
		Tunisia PID Registry[20]	1988	Single National Centre	710	2015
		Morocco PID Registry[21]	2008	Single National Centre	421	2012
Pacific	ASCIA	The Australian Society of Clinical Immunology and Allergy Primary Immunodeficiency Registry[22]	2003	88 clinical sites in Australia and New Zealand	1209	2006

Figure 3

CIEINR Platform. Overview of the ontologies used within the CIEINR REDCap

MONDO = Monarch Disease Ontology. HPO = Human Phenotype Ontology. SNOMEDCT= Systematized Nomenclature of Medicine Clinical Terms. VO = Vaccination Ontology. NCIT = NCI Thesaurus OBO Edition. LOINC = Logical Observation Identifiers Names and Codes. GA4GH = Global Alliance for Genomics and Health, GENO = Genotype Ontology, HGVS = Human Genome Variation Society Nomenclature

Supplementary Files

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- Appendix.docx