REGISTRY PROTOCOL

National Registry for Rare and Other Inherited Disorders

(NRROID)

Indian Council of Medical Research
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Registry Initiated on	01.11.2019

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1. Background and Rationale

Global estimates suggest that approximately 7,000 rare diseases (RD) have been described. Though individually rare, these disorders collectively affect an estimated 6–8% of the world's population, and about 80% are of genetic origin. Prevalence data are unavailable for most of these conditions.

Rare diseases are defined, from a regulatory and policy perspective, as any condition affecting fewer than 200,000 individuals in the United States, or, in the European Union, a prevalence of fewer than 5 individuals per 10,000. In the United States, the Orphan Drug Act (P.L. 97-414), adopted in 1983, encourages industry and research activity in this area through tax incentives, market exclusivity, user-fee exemptions and other measures targeting orphan therapy development.

No comprehensive dataset on rare diseases is currently available from India, despite this being recognised as a pressing need. Key missing data include the prevalence and distribution of these diseases and patient, familial and disease characteristics, including natural history. While many general principles of registry planning, design and implementation apply, rare disease registries pose some unique challenges.

The WHO defines a "patient registry" as a file of documents containing uniform information about individual persons, collected in a systematic and comprehensive way, to serve a pre-determined scientific, clinical or policy purpose. The definition does not prejudge the extent of data collected, which may be minimal or extensive, but implies continuity, as distinct from a cross-sectional survey.

With increasing awareness and availability of advanced diagnostic technologies, more patients with rare diseases are being identified in India. A draft National Policy for Rare Diseases has been submitted by the Government of India and is being implemented. In this context, there is an urgent need to build databases and registries for rare genetic disorders, to help policymakers prioritise needs and to open avenues for participation in clinical trials and research.

There is no single, universally accepted definition of a rare disease. Different countries follow their own definitions based on the epidemiological data and policy perspectives. In the US any disorder affecting fewer than 200,000 individuals while in EU a prevalence of lower than 5 per 10,000 has been defined as rare (1,2) Presently more than 7000 RD are known ,80% having genetic origin ,the prevalence of many being unknown or extrapolated . The paucity of relevant knowledge, experience and diagnostic challenges particularly in the developing world with most rare diseases demands need for a holistic infrastructure and support system. Support is needed at all levels which includes identification of the quantum of the problem, awareness amongst all stake holders including public and health care workers, diagnosis, treatment and supportive care and very importantly for research. Some of these challenges can be addressed efficiently through a systematic collection of clinical, genetic, and biologic data in the form of longitudinal patient registries and other coordinated data sources. The use of observational data methods, including prospective long-term patient registries, is a critical tool in building a broad and comprehensive knowledge base for these heterogeneous diseases. Planning RD registries poses some unique challenges particularly in the developing world. Some of them are summarized as follows:

The range of stakeholders for rare diseases is inherently different from common health care issues which are better understood by the public, care takers and government which has a direct effect on implementation, governance, funding and interest in this area

Clinicians with relevant expertise and direct exposure to managing these patients are limited making patient recruitment, data collection and follow up an uphill task.

Most RD have no cure and for many absence of standards of care or treatment/management guidelines in the common use makes uniform data collection a challenge. Incomplete understanding of how these conditions should be monitored in the absence of established or widely accessible biomarkers though provide opportunities for rare disease registries to set the agenda for disease research but the task is very challenging.

Finally, patient advocacy and support groups are non existing or much smaller in number in the developing world which may help assist and take forward the agenda of RD.

Rare disease registries can be initiated by patient advocacy groups, clinicians, government's national health system, and pharmaceutical companies, individual institutions. It takes a long time before the envisaged aims of the registry are fulfilled as the registries may evolve over time. Most are initiated as hospital based, though not truly representative is an important step to begin with maturing to outreach/community based effort.

Registries can be developed to serve multiple purposes. The design of the registry depends upon the targeted objectives and future plans. The major objectives of RD registries include collection of epidemiological, clinical, laboratory, natural history data (with or without specific therapy for policy making, patient care, clinical trials and research. Collaboration between stakeholder groups is critical to the progress made (3)

Though different registries exist world over for individual diseases, there are umbrella patient organizations (e.g., NORD, the Genetic Alliance, EURORDIS) which are important to bring the groups together on a common platform which is important for these highly heterogeneous disorders and project the need to the stakeholders. In India though the movement for RD is relatively new, patient support groups are existent for some time (eg Thalassemia, Hemophilia, Muscular Dystrophy, Rett Syndrome, Lysosomal storage disorders, Immune deficiency Disorders, Cystic Fibrosis, GNE Myopathy etc.) and an umbrella registry has also been initiated (ORDI ordindia.org) Recently Government of India has submitted the RD policy which is under implementation (www) The ongoing registries in India include Birth Defects registry (website) , though not a RD registry.

An important aim of RD registries is effective in rare disease research with a collaborative approach in which multinational and multi-institutional stakeholders may combine resources. Some organizations like PARENT (Patient Registries Initiative) and the PRISM (Patient Registry Item Specifications and Metadata for Rare Diseases) are facilitating cross-border collaborations (4)

Although the creation of a single global registry for each disease (or group of diseases) particularly for ultra rare diseases is a good idea, in practice it may not always be feasible or probably not in the best interest of the stake holders. A viable alternative can be a network of registries and resources, such as TREAT-NMD (5) Similarly, multiple registries could be connected via a centralized system to provide larger sample sizes to understand disease processes and how they correlate with patient outcomes. In any collaborative research, the challenges which are inherent include who coordinates collaboration, sustainability (funding issues) and governance infrastructure and is important to be addressed before any such initiative is taken. Important data sources as indices of registries [e.g., OrphaNet7 in Europe and the new Registry of Patient Registries (RoPR) in the United States (6,7)] is helpful.

Because patient registries can collect clinical information from larger, more heterogeneous populations than those included in a clinical trial, they are becoming increasingly valuable, particularly for diseases affecting very small patient populations, such as lysosomal storage disorders and for specific populations such as children (8).

Ideally the inclusion criteria for selection of patients should be highly restrictive for correct estimates, rare disease registries often have more liberal criteria for inclusion. This may be due to lack of classification criteria limited knowledge and expertise very small patient population etc. With some exceptions, rare disease registries typically do have broad inclusion criteria and attempt to enroll most, if not all, eligible patients within a targeted geographical area. Though this approach may be practical, may overestimate the numbers which may affect the ultimate aim of the registry particularly, policy, clinical trials and research as for these purposes accurate diagnosis is the corner stone.

A major step in the development of any registry is the selection of the data elements. This task can be time consuming and resource intensive and depends on the objectives of the study and should not be so extensive and not feasible to collect as to limit participation in the registry. A critical component of developing the data set is defining the data elements and standardize the data collection for rare diseases, as the understanding of the disease is likely to be limited Common data elements (CDEs) may offer a potential solution to some of these issues. A CDE can be defined as "a data element that can be consistently collected across all registries (9). CDEs include standard definitions, code lists, and instructions so that the data are collected and stored in the same manner by each participating site, in each study. CDEs may be general, e.g., demographics or disease-specific by using CDEs, registries may be able to reduce the time and effort involved in developing a dataset and to enable the registry data to be linked or compared with data from other studies using the same CDEs. CDEs are particularly important for rare disease research. CDEs may lower the cost of developing a new registry, making registries more accessible for diseases where funding is limited. CDEs may also enable data from multiple small registry projects to be linked or compared to increase knowledge about the disease. Recognizing the potential value of CDEs, NIH funded the PRISM project. The objective is to develop a library of standardized questions that will be relevant to a broad mix of rare diseases and that can be used to develop new registries or to update existing registries. Ultimately, the project aims to develop tools that will support the rapid implementation of new rare disease registries, the revision of existing registries, and interoperability between rare disease registries and other data sources (4,10). There are important ethical considerations in collecting data on RD as the population is considered vulnerable and under-resourced and because such populations are smaller, it is important to plan for registry data access and communications. Important issues to consider and included before taking the initiative of Rd registry include data ownership access, sharing communication, publication rights and above all transparency.

Written registry policies and procedures are encouraged and required by many regulatory entities (e.g., institutional review boards).

The increasing interest in rare disease patient registries by a range of stakeholders will likely lead to the development of many more patient registries. However, the development of each individual registry requires significant effort and resources. Some efforts are underway to develop linked networks of registries for rare diseases. For example, the NIH has put forth the idea of creating a federation of Internet-based registries for rare diseases. The goal of this effort is to reduce the costs of developing and running a registry (11)

Because the rare disease population is considered vulnerable and under-resourced, ethical considerations around data ownership, access, sharing, communication, publication rights and transparency must be addressed before initiating any such registry. Written registry policies and procedures, as set out in this protocol, are required by most regulatory and institutional review bodies.

This protocol describes a registry for rare diseases in India, beginning with a defined group of relatively common, treatable or potentially treatable disorders. The dataset has been designed to be minimal, essential, feasible and meaningful.

2. Need for the Registry in India

India lacks a comprehensive, systematically collected dataset on rare and inherited disorders. Establishing such a registry is necessary to:

- Generate nationally representative burden-of-disease data to inform health policy and resource allocation.
- Support the implementation of the National Policy for Rare Diseases.
- Build a patient base that can support future clinical trials and research on orphan products.
- Strengthen diagnostic and data-management capacity at participating centres across the country.

3. Registry Objectives

Primary Objectives

- To establish an Indian registry for rare genetic disorders for the assessment of the burden and to integrate their care through the available new and existing public health programs and policies to achieve “health for all”
- To collect demographic and phenotypic data for selected rare genetic disorders (Laboratory & clinical)
- To learn the natural history, evolution, and outcomes of specific diseases with/without treatment

Secondary Objectives

- To support research on genetic, molecular, and physiological basis of rare diseases
- To establish a patient base for evaluating drugs, medical devices, and orphan products
- To connect affected patients, families, and clinicians

4. Study Design

It is a prospective, hospital-based, multicentric observational registry.

5. Registry Setting

Central Coordinating Centre

ICMR Headquarters, New Delhi, serves as the Central Coordinating Centre, with overall responsibility for project coordination, data storage, maintenance and analysis.

Nodal Centres

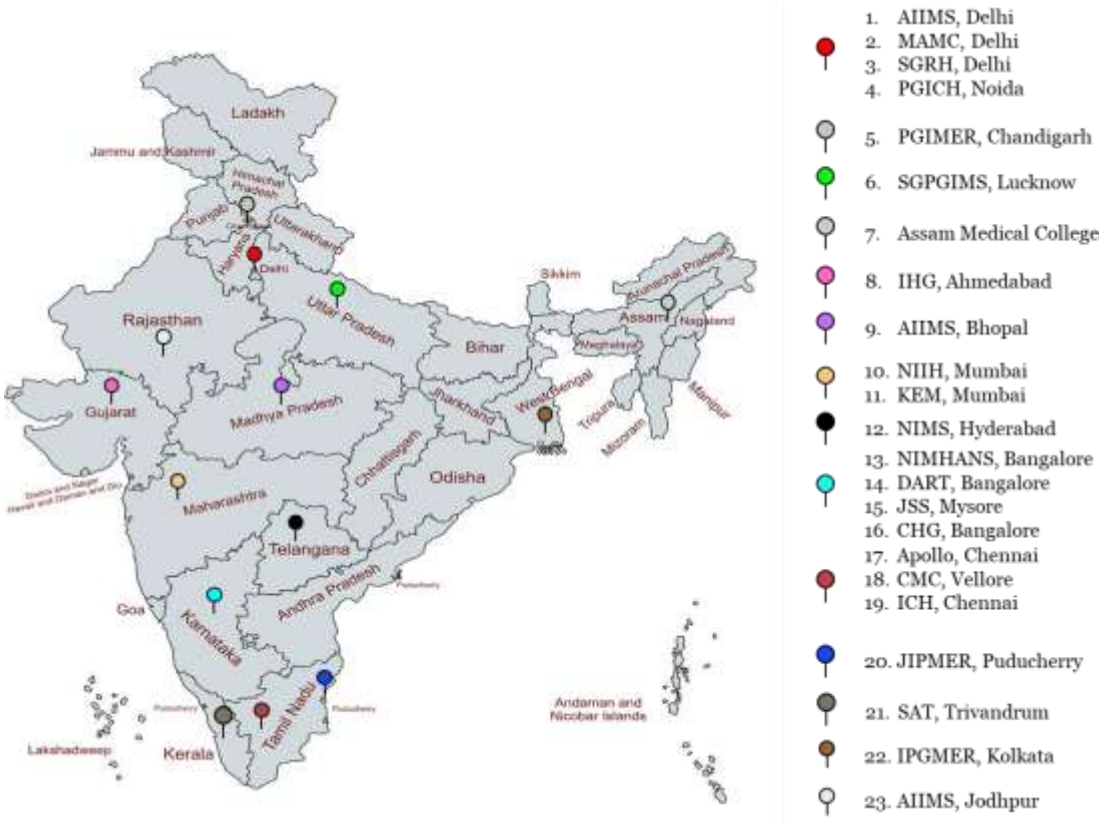
Of the participating centres, seven are designated as Nodal Centres, each responsible for disease-specific QA/QC based on their expertise. Nodal Centres perform disease-specific quality checks on anonymized data shared by ICMR through a dedicated QA/QC web-portal login.

Participating Centres

The registry is facility-based at tertiary centres recruited through an open call for Expression of Interest (EOI), screened by an expert committee against the site-selection criteria as mentioned below.

- Availability of a clinical geneticist or an interested pediatrician at the site
- A reasonably high number of cases diagnosed at the site
- Availability of basic diagnostic and counselling facilities

Currently, 23 centres are actively contributing to the registry:



One institute/centre may contribute to more than one disease condition covered under the registry.

6. Diseases Included in the Registry

The registry initiated in 2019 with six disease groups, selected as relatively common and treatable, or potentially treatable, rare and inherited disorders. As the National Policy for Rare Diseases (NPRD, 2021) has notified additional diseases as rare, the registry's scope has subsequently been expanded to nine groups, aligning disease coverage with NPRD notifications over time.

Original Disease Groups (2019)

Group	Disease Category	Disorders Included
I	Storage Disorders (LSDs & GSDs)	Gaucher disease, MPS I, MPS II, MPS IV, MPS VI, Pompe disease, Fabry disease, Hereditary Fructose Intolerance (HFI), GSD I & III
II	Small Molecule Inborn Errors of Metabolism	PKU, HCU, Tyrosinemia, Citrullinemia, OTC deficiency, MSUD, MMA, GA1, Galactosemia and related disorders
III	Hematological Disorders	Hemophilias, Thalassemias, Sickle Cell Disease
IV	Skeletal Dysplasias	Osteogenesis Imperfecta, Achondroplasia
V	Primary Immunodeficiencies (PID)	SCID, Pan-hypogammaglobulinemia, CVID, X-linked Agammaglobulinemia, Chronic Granulomatous Disease
VI	Neuromuscular Disorders	Duchenne Muscular Dystrophy (DMD), Spinal Muscular Atrophy (SMA), Limb-Girdle Muscular Dystrophy (LGMD)

Expanded Disease Groups

The following groups are added to align registry coverage with disease categories notified under the NPRD:

Group	Disease Category	Disorders Included
III	Hematological Disorders	Glanzmann Thrombasthenia
V	Primary Immunodeficiencies (PID)	Hereditary Angioedema
VII	Renal Disorders	Atypical Hemolytic Uremic Syndrome, Autosomal Recessive Polycystic Kidney Disease, Autosomal Dominant Polycystic Kidney Disease, Cystinosis, Primary Hyperoxaluria
VIII	Endocrine Disorders	Growth Hormone deficiency, Turner syndrome, Noonan syndrome, Laron Syndrome, Hypophosphatemic rickets, Congenital Adrenal Hyperplasia, Congenital Hyperinsulinemic Hypoglycemia, Familial Homozygous Hypercholesterolemia, XY Disorder of Sex Development (5-α-reductase deficiency), Partial Androgen Insensitivity Syndrome
IX	Miscellaneous	Cystic Fibrosis, Prader-Willi Syndrome

The disease list will continue to be reviewed and updated as new disorders become notifiable under the NPRD.

7. Eligibility Criteria

Inclusion Criteria

Confirmed diagnosis as per the diagnostic criteria for individual disorders.

I. **Group 1 (Lysosomal storage Disorders)** – Confirmed diagnosis based on suggestive phenotype enzyme assay with or without molecular confirmation. GSDs I & III with confirmed molecular diagnosis only

II. **Group II (Inborn Errors of Metabolism/Small Molecule Diseases)** – Confirmed diagnosis based on biochemical work up (TMS/GCMS/HPLC) with or without molecular confirmation with suggestive phenotype

III. **Group III (Hemophilias, Thalassemias, Sickle cell Disease)**- Patient diagnosed to have beta thalassemia, sickle cell syndrome, other hemoglobinopathy based on results of Cation exchange HPLC, capillary zone electrophoresis or molecular methods will be included in the study.

Patients diagnosed with any bleeding disorder based on results of coagulation tests, factor assays, platelet aggregation, platelet recepters and/ or genotype (variant with ACMG-AMP classification)

Glanzmann Thrombasthenia Diseases:

Bleeding from any site at the time of diagnosis + Diagnosis based on genotype (variant with ACMG-AMP classification)

OR

Bleeding from any site at the time of diagnosis + Platelet receptors

IV. **Group IV (Skeletal Dysplasias - Achondroplasia)** – Suggestive phenotype & Skeletal survey with or without molecular confirmation

V. **Group V (PID -SCID, Pan hypogammaglobulinemia CVID)** i) Predominantly antibody deficiencies ii) Immunodeficiencies affecting cellular and humoral immunity iii) Combined immunodeficiencies with associated syndromic features iv) Congenital defects of phagocyte number, function, or both v) Defects in Intrinsic and Innate Immunity. Detailed inclusion / diagnostic criteria for selected diseases under each of these conditions is enclosed in Annex 1.

Hereditary Angioedema:

- Clinical criteria:
  1. Episodic, non-pruritic angioedema without urticaria

     ± Suggestive family history
  2. Recurrent abdominal pain without any other identifiable cause
  3. A family member diagnosed with HAE

- Laboratory Evaluation:
  - C4 levels
  - C1-INH antigenic levels
  - C1-INH functional assay

- Genetic testing and family history

VI. **Group VI (Neuromuscular- DMD, SMA, LGMD)**

The minimum inclusion criteria for each of the disorders would be as follows

1. DMD - clinical + CPK + genetic tests - MLPA of 79 exons showing deletion/ If deletion negative, muscle biopsy with IHC suggestive of DMD

2. SMA - clinical + minimum - genetic tests showing exon 7 / 8 deletion

3. LGMD - clinical + muscle biopsy with IHC / genetic tests confirming the diagnosis

VII. **Group VII (Renal Disorders)**

a) <u>Atypical Hemolytic Uremic Syndrome (AHUS):</u>

Bagga, et al. Pediatric Nephrology 2019	
Microangiopathic hemolytic anemia **AND**	Anemia (hemoglobin < 10 g/dl, hematocrit < 30%) AND Schistocytes ≥ 2% AND Elevated lactate dehydrogenase (> 450 IU/l) or undetectable haptoglobin
Thrombocytopenia **AND**	Platelet count < 150,000/µl
Acute kidney injury	Increase in serum creatinine by 50% over baseline level
Exclusion of TTP, DIC, dengue malaria, scrub typhus, leptospirosis required	

b) <u>Autosomal Recessive Polycystic Kidney Disease:</u>

Guay Woodfort, et al. J Pediatrics 2014	
Positive family history with characteristic hepato-renal involvement on **USG** **OR**	Kidneys: 1. Enlarged 2. Echogenic 3. Loss of cortico-medullary differentiation Liver: 1. Hepatic fibrosis 2. Hepatomegaly 3. Increased liver echotexture Splenomegaly 4. Portal hypertension 5. Cholangiopathy
Pathogenic variant in **genetic testing**	*PKHD1, DZIP1*

c) <u>Autosomal Dominant Polycystic Kidney Disease:</u>

KDIGO 2025	
At risk individuals (**positive family history**) with following no. of cysts on **USG** **OR**	<15 years: ≥ 1 cyst 15-29 years: ≥ 3 30-39 years: ≥ 3 40-59 years: ≥ 2 in each kidney >60 years: ≥ 4 in each kidney
Pathogenic variant in **genetic testing**	Major genes: *PKD1, PKD2* Minor genes with definitive-to-moderate evidence of disease involvement: *DNAJB1, GANAB, ALG9, ALG5, IFT140, NEK8* Suspected monoallelic PKD genes with limited evidence of disease involvement or not assessed: *ALG6, AKG8, PKHD1*

d) <u>Cystinosis:</u>

Emma, et al. Nephrol Dial Transplant. 2014	
Suspicion at signs and symptoms of proximal tubular dysfunction	Polyuria, polydipsia, failure to thrive, phosphaturia, glucosuria, proteinuria, normal anion gap metabolic acidosis, hypokalemia
Confirmation with any one of the following	Measurement of leukocyte cystine levels; reference as per local lab (levels are >2 nmol ½ cystine/mg protein in affected individuals) Corneal cystine crystals in slit lamp examination Pathogenic variant in *CTNS* gene

e) <u>Primary Hyperoxaluria:</u>

A. Clinical criteria for suspecting a case where renal function are preserved

o Calcium oxalate stones in children, recurrent calcium oxalate stones or history of stones prior to age 21 yrs in adults, or nephrocalcinosis
o Predominantly calcium oxalate stones
o Family member with childhood stones, recurrent calculi, or unexplained CKD/kidney failure
o Family member with PH

Laboratory work up

1. Urine oxalate >0.5 mmol (45 mg)/1.73 m7/24 Hours

OR

Random urine oxalate/urine creatinine > normal

Note: **Rule out secondary etiology e.g. Malabsorption/ faulty diet like very high oxalate and low calcium diet/ premature infant**

2. Confirm high urine oxalate with repeat testing and measure urine metabolites if available (glycolate, L-glycerate, 4-hydroxy-2 oxoglutarate)

3. Genetic testing to confirm

B. Clinical criteria for suspecting a case where established Chronic kidney disease

- Calcium oxalate stones
- Calcium oxalate tissue deposits
- Examine any kidney or other biopsy for calcium oxalate crystals with polarized light
- Nephrocalcinosis

Laboratory work-up

1. Measure plasma oxalate

OR

If residual kidney function, measure 24-hour urine oxalate* (or oxalate creatinine ratio in young children)

2. Urine oxalate >0,5 mmol/mol Cr or 45 mg/1.73 m2/24 Hours and/or Plasma oxalate >20 umol/L

3. Genetic testing to confirm

VIII. **Group VIII (Endocrine Disorders)**

a) <u>Growth Hormone deficiency:</u>

Auxologic criteria for growth hormone deficiency

1. Short stature defined as Ht. Z score < -2SD

2. Delayed bone age

3. Other common causes of short stature are ruled out or adequately treated (thyroid disease, celiac disease , chronic liver disease, chronic kidney disease, Turner syndrome in females, no apparent skeletal dysplasia)

4. Low serum IGF 1 levels for age and gender

GH deficiency should be diagnosed using any one of the following criteria:

1. Peak Growth hormone Levels are <10ng/ml on provocative testing on 2 separate occasions in a patient fitting auxologic criteria for growth hormone deficiency

OR

2. A patient possessing all of the following three conditions

a. auxological criteria

b. hypothalamic-pituitary defect (such as major congenital malformation [ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk], tumor or irradiation,

c. deficiency of at least one additional pituitary hormone.

OR

3. GHD in congenital hypopituitarism be diagnosed in a newborn with hypoglycemia

a. if he/she does not attain a serum GH concentration above 5 ng/mL at the time of hypoglycemia

b. deficiency of at least one additional pituitary hormone and/ or the classical imaging triad (ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk)

b) Turner syndrome:

Female phenotype with a karyotype containing one X chromosome and complete or partial absence of the second sex chromosome, associated with one or more typical clinical manifestations of TS.

Any of the given karyotypes

1. 45,X Monosomy X
2. 45,X/ 46,XX Mosaicism with 46,XX
3. 45,X/47,XXX; 45,X/46, XX/47,XXX Mosaicism with 47,XXX
4. 45,X/46,XY Mosaicism with 46,XY
5. 45,X/46,X,r(X) Ring X chromosome
6. 46,X,i(Xq); 46,X,idic(Xp) 15 Isochromosome Xq Isodicentric Xp;
7. 46,XX,del (p11) Proximal deletion of Xp
8. X-autosome translocation unbalanced

c) Noonan syndrome:

Feature	**A (Major)**	**B (Minor)**
Facial	Typical facies (facial features of NS vary over time and may have only subtle differences). Expert assessment is therefore required.	Suggestive facies
Cardiac	Pulmonary valve stenosis and/or hypertrophic cardiomyopathy	Other cardiac defect
Height	<3 centile	<10 centile
Chest wall	Pectus carinatum/excavatum	Broad thorax
Family history	First-degree relative with definite NS	First-degree relative with features suggestive of NS
Other	Mild developmental delay, cryptorchidism, and lymphatic dysplasia	Mild developmental delay, cryptorchidism, or lymphatic dysplasia

Definitive clinical NS diagnosis is possible for individuals meeting:

Criterion 1A + (one of 2A through 6A or two of 2B through 6B)

OR

Criterion 1B + (two of 2A through 6A or three of 2B through 6B)

d) Laron Syndrome:

The diagnostic criteria for Laron syndrome include presence of five out of seven of the following criteria:

- height SDS < -3SD,
- basal GH > 2.5 ng/ml,
- basal IGF-1 < 50 ng/ml,
- IGFBP-3 < -2SD,
- IGF-1 increase post IGF-1 generation test <15ng/ml,
- IGFBP- 3 increase post IGF generation test <400 ng/ml and
- GH binding (%GH bound) < 10% [ref: Savage et al].

Confirmatory Genetic diagnosis by sequencing the GHR gene is mandatory before embarking on treatment with recombinant IGF-1 which is expensive and prolonged.

e) Hypophosphatemic rickets:

All should be fulfilled

1. Refractory rickets: no response clinical, radiological or biochemical response to conventional therapy for rickets (vitamin D and calcium)
2. Evidence of primary urinary phosphate wasting in the presence of normal PTH (Low maximum tubular reabsorption of phosphate TMP/GFR for age)
3. High FGF23 levels
4. Genetic confirmation of hereditary hypophosphatemic rickets or tumour induced osteomalacia (high FGF23 with pathological confirmation of tumour)
5. Indication for Burosumab (Anti-FGF23 therpay): Failure to respond to conventional treatment of hypophosphatemic rickets (oral phosphate and calcitriol) or development of secondary hyperparathyroidism.

f) Congenital Adrenal Hyperplasia (CAH):

1) **Clinical criteria:**

- Ambiguous genitalia in a newborn, particularly virilization in genetic females (46,XX).
- History of adrenal crisis in neonatal period (e.g., vomiting, dehydration, hypotension, hyponatremia, hyperkalemia).
- Family history of CAH or unexplained neonatal death.

2) Hormonal Evaluation

- Random serum 17-hydroxyprogesterone (17-OHP): Markedly elevated levels are diagnostic of classic 21-OHD.

- Newborn screening: Elevated 17-OHP used as a screening tool.
- ACTH (cosyntropin) stimulation test (gold standard):
    - Performed using 250 μg cosyntropin IV.
    - Measure 17-OHP and Δ4-androstenedione at baseline and 60 minutes.

3) Confirmation through Genetic Testing

g) Congenital Hyperinsulinemic Hypoglycemia:

In a critical sample- take at the time of blood glucose < 50mg/dL

Evidence of excessive insulin action at the time of hypoglycemia as seen with 2 or more of the following

1. Suppressed plasma β-hydroxybutyrate (<1.8 mmol/L)
2. Suppressed plasma free fatty acids (<1.7 mmol/L)
3. Inappropriately large glycemic response to glucagon (≥30 mg/dL [≥1.7 mmol/L])
4. Increased glucose infusion rate required to maintain euglycemia above normal for age

   >8 mg/kg/min for neonates

   >3 mg/kg/min for adults

Evidence of excessive insulin secretion/inadequate suppression of insulin secretion at the time of hypoglycemia (these are less definitive than evidence of excessive insulin action)

1. Plasma insulin >1.25 μU/mL (8.7 pmol/L)
2. C-peptide >0.5 ng/mL (>0.17 nmol/L)

In newborns diagnosed before 72 hours of life, the diagnosis should be confirmed once again after 72 hours

f) Familial Homozygous Hypercholesterolemia:

Criterion A	Total cholesterol levels > 290 mg/dl (> 7.5 mmol/l) in adults Total cholesterol levels > 260 mg/dl (> 6.7 mmol/l) in children aged less than 16 years **OR** LDL-C > 190 mg/dl (> 4.9 mmol/l) in adults LDL-C >155 mg/dl (> 4.0 mmol/l) in children aged less than 16 years

Criterion B	Tendon xanthomas in the patient or tendon xanthomas in a first or second-degree relative
Criterion C	DNA-based evidence of an LDL-receptor mutation, familial defective Apo B-100, or a PCSK9 mutation
Criterion D	Family history of myocardial infarction before the age of 50 years in a second-degree relative or before the age of 60 years in a first-degree relative
Criterion E	Family history of elevated total cholesterol > 290 mg /dl (> 7.6 mmol/l) in an adult first or second-degree relative Family history of elevated total cholesterol > 260 mg/dl (> 6.7 mmol/l) in a child, brother, or sister aged 16 years or younger
Diagnosis: Definitive A and B or C Possible A and D or A and E	

g) XY Disorder of Sex Development due to 5 alpha reductase deficiency, partial androgen insensitivity syndrome:

Diagnostic Criteria for 5 alpha reductase deficiency 2:

1. No definite diagnostic criteria
2. Phenotype- Small Phallus, unfused labioscrotal folds, Bilateral palpable gonads in labioscrotal folds, Perineoscrotal , hypospadias
3. Stimulated T:DHT ratio- >20
4. Genetic diagnosis is definitive

Diagnostic Criteria for Partial Androgen insensitivity Syndrome:

1. No definate diagnostic criteria
2. Phenotype- Small Phallus, unfused labioscrotal folds, Bilateral palpable gonads in inguinal/ labioscrotal folds, Perineoscrotal hypospadias
3. Stimulated T:DHT ratio- <20
4. Genetic diagnosis is definitive

IX. Group IX (Miscellaneous)

a) Cystic Fibrosis:

Compatible clinical features + Two positive sweat chloride

OR

Compatible clinical features + Mutation positive

b) <u>Prader-Willi Syndrome:</u>

Category	Criteria	Points
Major Criteria	Neonatal/infantile hypotonia with poor suck	1
	Feeding problems in infancy (special techniques, poor weight gain)	1
	Rapid/excessive weight gain (12 mo–6 yrs) → central obesity	1
	Characteristic facial features (≥3: dolichocephaly, narrow face, almond eyes, small mouth, thin upper lip, downturned corners)	1
	Hypogonadism (genital hypoplasia, delayed puberty, incomplete maturation)	1
	Global developmental delay (<6 yrs) or mild–moderate intellectual disability (>6 yrs)	1
	Hyperphagia/food obsession	1
	Genetic abnormality (15q11–13 deletion or maternal disomy)	1
Minor Criteria	Decreased fetal movement/infant lethargy/weak cry	0.5
	Behavioral problems (≥5: tantrums, compulsive, oppositional, rigid, manipulative, stubborn, perseveration, stealing, lying)	0.5
	Sleep disturbance/sleep apnea	0.5
	Short stature by age 15 (without GH therapy)	0.5
	Hypopigmentation (fair skin/hair vs family)	0.5
	Small hands (<25th percentile) and/or feet (<10th percentile)	0.5
	Narrow hands with straight ulnar border	0.5
	Eye abnormalities (esotropia, myopia)	0.5
	Thick, viscous saliva	0.5
	Speech articulation defects	0.5
	Skin picking	0.5

Diagnosis:

- **Birth–3 years:** Five (5) total points are required, of which four (4) must be from the major criteria list.
- **≥3 years to adulthood:** Eight (8) total points are required, including at least five (5) from the major criteria list.

Exclusion Criteria

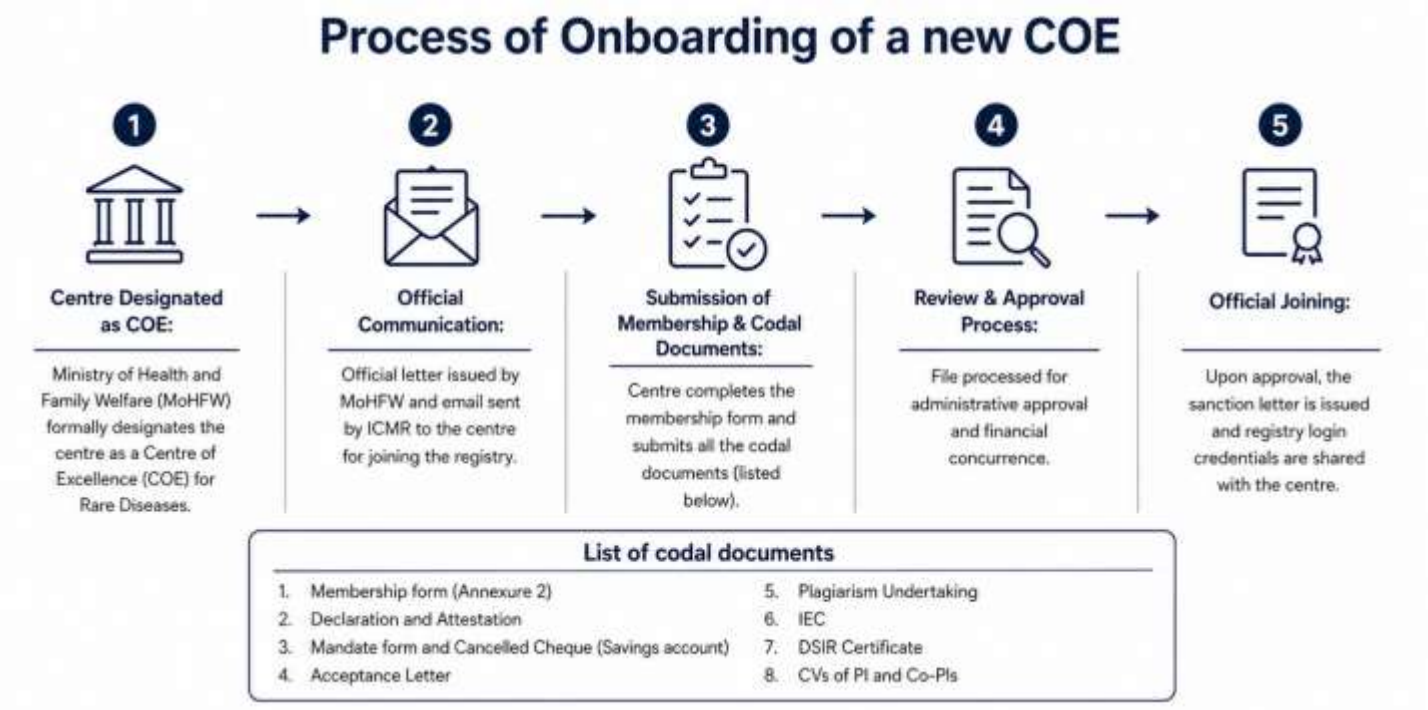
- The patient, family member/caregiver, or guardian does not provide consent to participate in the registry.
- Suspected cases without a confirmed diagnosis.

Site Inclusion:

At present, as per the mandate of the Ministry of Health and Family Welfare and Competent Authority of ICMR, all the Centres of Excellence (CoE) for Rare Diseases as and when designated by the government are added to the registry.

Site Exclusion:

If a site remains dormant for 6 months or more (i.e. without entering any case in the registry), it is removed from the study after reminders issued at 2-monthly intervals.



8. Study Population and Case Enrollment

- Enrollment into the registry is carried out only after the diagnosis is confirmed as per the relevant group-specific criteria.
- At enrollment, data is collected on socio-demographic information, clinical and laboratory investigations, and final diagnosis, using a predesigned proforma.
- One institute/centre may participate in more than one disease condition covered by the registry.
- Each participating centre is responsible for the timely collection and online submission of data.
- A unique ID is generated for each diagnosed case to avoid duplication.

9. Data Collection

The patient information is collected using two structured components. A common socio-demographic form, based on standardized Common Data Elements (CDEs), is applied across all disorders to ensure uniformity. In addition, disease-specific forms are developed by the respective steering groups, each designed to capture the minimum essential dataset required to meet registry objectives.

These forms record patient information in two parts: common socio-demographic information and disease-specific clinical information covering:

- Clinical features and family history, including pedigrees and consanguinity status
- Diagnostic delay (time from symptom onset to confirmed diagnosis)
- Molecular, hematological and biochemical diagnostic test results
- Treatment details — both definitive and supportive
- Quality-of-life and functionality indicators
- Sources of expenditure for diagnosis and treatment

All forms are piloted in paper form before deployment in the web database.

10. Follow-up Plan

Purpose of Follow-up

To understand the longitudinal progression and outcomes of rare and inherited disorders, follow-up data is systematically collected for all patients enrolled in the registry. This enables the assessment of clinical progression, response to treatment and management, and overall patient outcomes over time.

Eligibility for Follow-up

All patients enrolled in the registry, including both previously enrolled and those being enrolled prospectively, are eligible for follow-up.

Exclusion criteria: Those patients who refuse to give consent are excluded. The database automatically exclude the patients from the follow-up list whose outcome status at the last visit had been marked as "Dead".

Methodology

The follow-up data for all patients is collected either through an in-person visit of the patient to the OPDs, audio or video communication, or by post, at a regular interval of 6 months (±1 month) for all the disorders.

The web follow-up forms are enabled for every patient, except those having an outcome status as "Dead". A downloadable list of patients due for follow-up is available on the portal for easy access by the site teams.

For the study teams: The Site PI downloads the list of patients due for follow-up every week and share it with the team. The study team conducts follow-up of the patients either through physical OPD visits or

telephonic calls. The follow-ups is conducted in a timely manner to avoid backlogs and skipping the scheduled follow-up time.

The emergency visit data is also recorded in the follow-up if a patient visits the health facility independently or is admitted for any reason to the same facility/institute. These visits are documented with details such as date, reason for visit, and outcome.

Data Collection Forms

The standardized follow-up forms, designed as part of the registry, are used to record patient data.

Consent and Confidentiality

The recorded verbal or written re-consent is obtained at the first follow-up interaction, through a common follow-up consent form. Patient confidentiality and data privacy is strictly maintained during all follow-up activities. Communication and storage of follow-up data complies with ethical guidelines, with secure access provided only to authorized personnel.

Loss to follow-up

Attempts to reach each patient are made on three occasions over a span of 2 months apart. Each attempt includes 3 consecutive days of contact effort, using alternate numbers (if available). If all attempts fail:

The patient is considered as “Loss to follow-up” and marked as “Could not contact” on the portal.

11. Data Management System

Web Portal

A web portal for the rare disease registry has been created at ICMR Headquarters, New Delhi. The portal consists of a frontend built on a high-level Python web framework and a backend built on an object-relational database system, using open-source technologies to support dynamic evolution and interoperability with other data-collection sources. The platform has undergone a mandatory security audit and is certified as safe to host for data collection. The web-based design enables multicentric data collection and analysis, with data updated and accessed through web browsers; new tools and upgrades can be added with relative ease. Final data storage, maintenance and analysis are carried out at ICMR Headquarters.

Salient features of the platform include:

- Role-based access (DEO → Validator → Admin)
- Security and audit trail, including data encryption and a full audit trail
- Analysis and reporting: real-time dashboards
- Single-step standardisation of test panels across the network
- Data sharing and access, including integration with international systems and a defined access policy
- Full customisability and extendibility (diseases, test panels)

User Roles and Access Levels

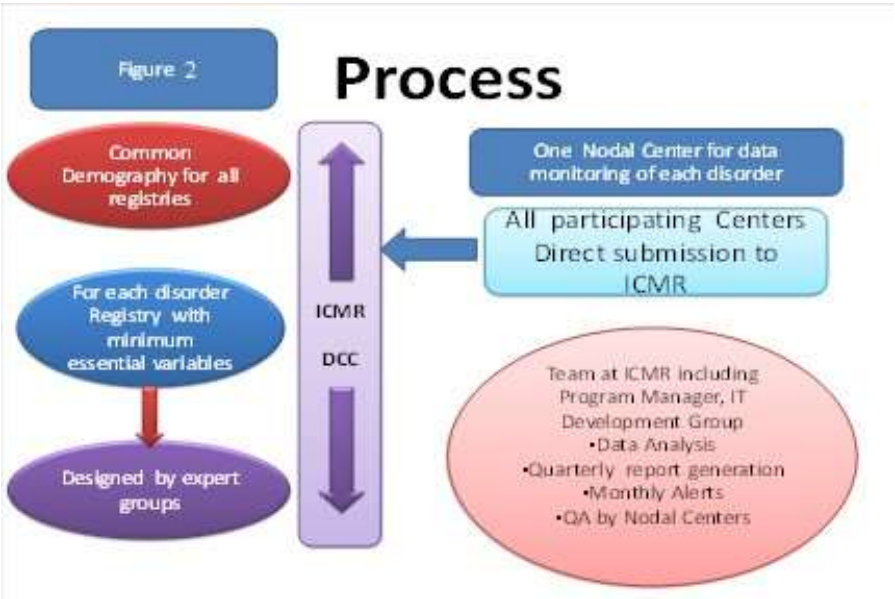
The portal operates a three-tier data security and quality-check structure:

1. Data Entry Operators at participating centres collect data and PIs perform a preliminary check of relevance and completeness, filtering obvious errors.
2. Nodal Administrators at Nodal Centres check data submitted by participating sites and pass it or fail it on the portal for quality and completeness.
3. The Super-Administrator at CCU, who controls the master database, checks the data submitted, with rights to edit data and complete the final upload to the master database.

Data Flow and Centre Registration

Each centre, selected through the EOI process, is issued a login and password for data entry on the registry portal. For quality control, Nodal Centres are responsible for checking data completeness and consistency for their assigned disease group(s), reporting this to the ICMR Data Coordinating Unit (DCU).

Figure 2: Process and work flow details from various centres



Unique ID Generation

A unique ID is generated for each diagnosed case at the time of enrollment to prevent duplication across the network.

Data Storage, Backup and Security

Data storage, maintenance and backup formats and tools are designed as part of the platform, with encryption and a full audit trail. All registry data is additionally stored securely at the study sites on password-protected systems, and physical case record forms are stored in a separate locked cabinet at each site.

12. Quality Assurance and Quality Control

Standard Operating Procedures for clinical data collection and data entry are prepared and followed uniformly by all participating centres. Ensuring the completeness, accuracy and timeliness of collected data is treated as essential to the registry, and QA/QC is built into the system at every stage, from data entry through to central review.

Levels of QA/QC

Data quality is ensured at four levels:

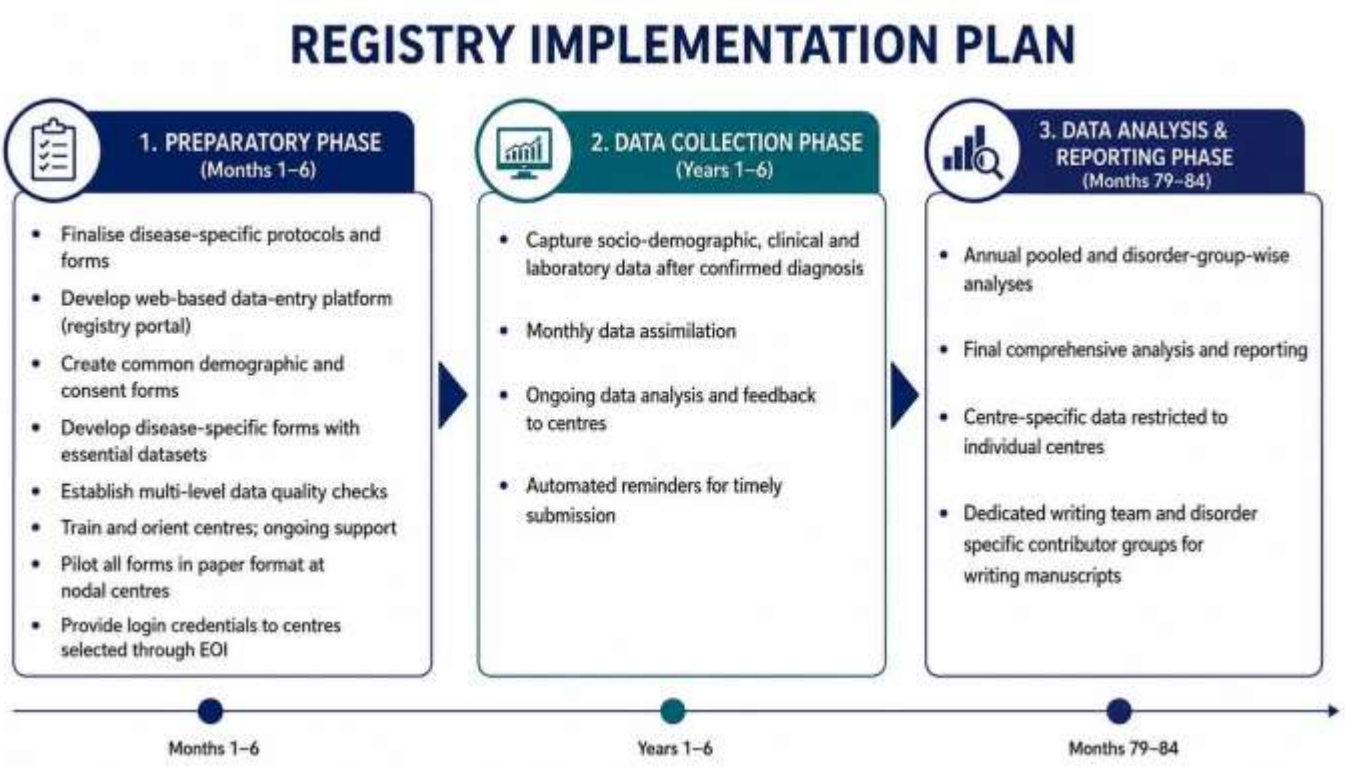
Level	Responsibility	Description
I	e-Form (electronic data entry)	Validations are built into the web-based data-entry form itself: mandatory fields, numeric value ranges, character limits, and specific format entries (calendars, numbers, multi-select/single-select options, drop-down menus). An error pop-up is displayed if any field is not filled as per the validation applied, and data entry cannot proceed until the error is corrected.
II	Site Principal Investigators (PIs)	The site PI is responsible for the accuracy and completeness of data collected and entered at their centre, and for ensuring new project staff are properly oriented to the registry's data-collection and entry procedures.
III	Nodal Centres	Disease-specific Nodal Centres are provided login credentials to a dedicated QA/QC web portal, where they check essential and mandatory fields of each rare-disease form on anonymized data shared by ICMR. The result is recorded as QA/QC “pass” or “fail”, visible simultaneously to the concerned participating site, along with feedback on any failed checks. Sites resubmit a corrected entry based on this feedback.
IV	ICMR (Central Coordinating Centre)	ICMR shares monthly/weekly reports with each site individually, highlighting the completion status of disease-wise forms and recent performance. A visual dashboard is also available to track the performance.

Monitoring and Supervision

Overall monitoring and supervision is carried out by the Central Coordinating Unit at ICMR. Regular centralized and site-specific training sessions are held to maintain data-entry consistency across centres,

particularly to address the impact of staff turnover at participating sites: group and individual training sessions are conducted for new project staff as needed, the ICMR data centre team provides regular trouble-shooting support, and site PIs ensure new staff are oriented to the registry on joining.

13. Implementation Plan



14. Governance Structure and Roles

ICMR- Central Coordinating Unit and Data Management Centre:

- Responsible for the overall coordination of the registry.
- Orient sites on registry processes, web-based data entry, and troubleshooting.
- Develop and maintain the data management system and registry website.
- Issue regular reminders and updates in the form of monthly reports regarding data entry and form completion status.
- Ensure data completeness and quality by sharing highlighted datasheets with the respective sites.
- Resolve technical and operational issues related to data entry and system functionality.
- Conduct review meetings and prepare annual reports jointly with the sites.
- Ensure registry alignment with the National Policy for Rare Diseases, incorporating identified Centres of Excellence (MoHFW) and newly recognized rare diseases.

Nodal Centres: Finalize and update disease-specific data forms. Each Nodal Centre performs QA/QC for the disease condition(s) assigned to them, checking essential and mandatory fields on anonymized data and providing pass/fail feedback to the concerned participating site.

Participating Centres: Data are collected in paper form and then entered into the web-based portal.

Technical Advisory Group (TAG):

The Technical Advisory Group is responsible for overall monitoring of the project, reviewing progress and results, and making recommendations. It is composed of experts from diverse fields such as pediatrics, genetics, public health and government policy, and reviews annual registry reports together with the investigating teams at its annual meeting.

15. Ethical Considerations

Ethical Review and Approval: Ethical approvals are obtained from the Institutional Ethics Committee of each institute participating in the registry. Written informed consent is taken from the patient, family member/caregiver, or guardian before enrollment, and a participant information sheet is provided to each participant. Prior Ethics Committee approval will additionally be obtained whenever registry data is proposed for use in further research beyond the registry's core objectives.

Consent: A common consent form is used for enrollment, and a common follow-up consent form for re-consent at first follow-up.

Confidentiality: Patient confidentiality and data privacy are strictly maintained throughout data collection, storage and follow-up, with secure access provided only to authorised personnel.

Conflict of Interest: The institution where the study is conducted is responsible for ensuring there is no financial conflict of interest on the part of the investigators.

16. Data Sharing, Ownership, Publication and Intellectual Property

Data Sharing Policy: All participating sites are responsible for data collection, uploading the data on the registry portal and for sharing data with the ICMR data-management team.

Data Ownership and Custodianship: Data governance is overseen by ICMR, which ensures centralized data stewardship and is the custodian of the data collected. Patients/parents retain ownership of their own data. Site investigators may access anonymized data for research purposes with appropriate approvals; participating sites also have access to their own locally generated data. Any request for use of registry data for research purposes requires prior Ethics Committee approval; any request for external data sharing is submitted to competent authority for decision.

Publication Policy and Authorship: Publications will be made under the group name "NRROID Registry Group". A writing committee will be constituted for each disorder-specific manuscript preparation and submission, with authorship following ICMJE criteria.

Intellectual Property Rights: As per ICMR guidelines all new intellectual property viz. patents, copyright, design, etc. generated as part of the research supported by the ICMR would belong to the ICMR. Raw data (in all forms) would belong to ICMR and should be made available/accessible to ICMR at the completion of the project.

17. Statistical Analysis and Reporting Plan

Data analysis is performed periodically by the ICMR CCU:

- Analysis is performed on annual basis, both disease-group-wise and on pooled data.
- A final analysis will be conducted at the end of the registry period, with a comprehensive report prepared by a dedicated writing team.

18. Expected Outcomes

1) Registry will provide valuable information on burden of rare diseases for which systematically collected data is not available at the moment.
2) Capacity building of participating centers will be done for regular collection, entry and submission of data to a central portal
3) Based on burden of disease, further research proposal can be developed by interested group for undertaking future research

19. References

1. Institute of Medicine. Rare Diseases and Orphan Products: Accelerating Research and Development. Washington, DC: The National Academies Press; 2010.
2. Moliner AM. Creating a European Union framework for actions in the field of rare diseases. Adv Exp Med Biol. 2010;686:457–73.
3. Dunkle M, Pines W, Saltonstall PL. Advocacy groups and their role in rare diseases research. Adv Exp Med Biol. 2010;686:515–25.
4. Richesson R, Shereff D, Andrews J. [RD] PRISM library: patient registry item specifications and metadata for rare diseases. J Libr Metadata. 2010;10(2-3):119–35.
5. Bushby K, Lynn S, Straub T, et al. Collaborating to bring new therapies to the patient – the TREAT-NMD model. Acta Myol. 2009;28(1):12–5.
6. Weinreich SS, Mangon R, Sikkens JJ, et al. Orphanet: a European database for rare diseases. Ned Tijdschr Geneeskd. 2008;152(9):518–9.

7. Developing a Registry of Patient Registries (RoPR). Project Abstract. Agency for Healthcare Research and Quality, 2012.
8. Jones S, James E, Prasad S. Disease registries and outcomes research in children: focus on lysosomal storage disorders. Paediatr Drugs. 2011;13(1):33–47.
9. National Institute of Neurological Disorders and Stroke. NINDS Common Data Elements – Glossary, 2012.
10. PRISM. Patient Registry Item Specifications and Metadata for Rare Diseases. 2012.
11. National Institutes of Health. Advancing Rare Disease Research: The Intersection of Patient Registries, Biospecimen Repositories and Clinical Data. ORDR co-sponsored Scientific Conferences, 2012.

20. Acknowledgement

We acknowledge the invaluable contributions of the Disease-specific Steering Groups and the Technical Advisory Group (TAG) members, whose expertise has guided the development of protocols, disease-specific data forms, quality assurance frameworks and way forward of the registry.

Disease-specific Steering Groups:

Disease Group	Steering Group Members
Lysosomal Storage Disorders & GSDs	Dr. Madhulika Kabra (AIIMS, New Delhi); Dr. Neerja Gupta (AIIMS, New Delhi); Dr. Sujatha Jagdeesh (Mediscan, Chennai Centre of Human Genetics); Dr. Meenakshi Bhatt (Bangalore); ICMR representative; Project Monitoring Committee representative
Small Molecule Diseases	Dr. Seema Kapoor (MAMC, Delhi); Dr. Neerja Gupta (AIIMS, Delhi); Dr. Sunita Bijarnia (SGRH, Delhi); Dr. Madhulika Kabra; Dr. Ratna Puri; ICMR representative; Project Monitoring Committee representative
Primary Immunodeficiency (PID)	Dr. Manisha (NIIH, Mumbai); Dr. Surjit Singh (PGIMER, Chandigarh); ICMR representative; Project Monitoring Committee representative
Hemoglobinopathies: Thalassemia & Sickle Cell Disease	Dr. Renu Saxena (AIIMS, Delhi); Dr. Anita Nadkarni (NIIH, Mumbai); Dr. Reena Das (PGI, Chandigarh); Dr. Vikram Mathews (CMC, Vellore); Dr. Renu Saxena (Sir Ganga Ram Hospital); ICMR representative; Project Monitoring Committee representative
Hemophilia A & B	Dr. Shrimati Shetty (NIIH, Mumbai); Dr. Renu Saxena (AIIMS, New Delhi); Dr. Shubha Phadke (SGPGI, Lucknow); Dr. Alok Srivastava (CMC, Vellore); Dr. Anupam Sachdeva (Sir Ganga Ram Hospital); ICMR representative; Project Monitoring Committee representative

Disease Group	Steering Group Members
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Skeletal Dysplasias	Dr. Ratna Puri (SGRH, New Delhi); Dr. Neerja Gupta (AIIMS, New Delhi); Dr. Girisha K.M. (Manipal, Mangalore); Dr. Seema Kapoor (MAMC, New Delhi); Dr. Madhulika Kabra; Dr. Sunita; Dr. Anju; ICMR representative; Project Monitoring Committee representative

Original TAG Members

1) Dr. I.C. Verma
2) Dr. N.K. Arora, INCLEN Trust, New Delhi
3) Dr. Siddarth Ramji, Maulana Azad Medical College, New Delhi
4) Dr. R.M. Pandey, AIIMS, New Delhi
5) Dr. Harish Chellani, Safdarjung Hospital, New Delhi

Revised TAG Members

1) Dr. Shally Awasthi, Ex-Professor, Pediatrics, KGMU, Lucknow (Chairperson)
2) Dr. Sheela Nampoothiri, Geneticist, Amrita Institute, Kochi
3) Dr. Rakesh Lodha, Professor, Pediatrics, AIIMS, New Delhi
4) Dr. Praveen Kumar, Professor and Head, Neonatology, PGIMER, Chandigarh
5) Dr. Rajib Dasgupta, Chairman, Social Medicine and Community Health, JNU, Delhi
6) Dr. Najam Khalique, Professor, Community Health, AMU, Aligarh
7) Dr. Swasti Charan, Additional DDG, Dte. GHS, Nirman Bhawan, New Delhi
8) Dr. Vinod Scaria, Geneticist, Vishwanath Cancer Care Foundation, Bangalore

21. Annexures

Annexure	Content
1	Detailed Diagnostic Criteria – Group V (PID)
2	Membership Form

Annexure 1 (Group V: Primary Immunodeficiency)

In absence of molecular confirmation, diagnostic criteria to be adopted for PIDs enlisted in the registry

i) Immunodeficiency affecting cellular and humoral immunity

Disease	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if criteria are not completely fulfilled)
Severe combined immunodeficiency (SCID)	At least one of the following: • invasive bacterial, viral or fungal/opportunistic infection • persistent diarrhoea and failure to thrive • affected family member **AND** manifestation in the first year of life **AND** HIV excluded **AND** 2 of 7 T cell criteria fulfilled : • low or absent CD3 or CD4 or CD8 T cells • reduced naive CD4 and/or CD8 T cells • elevated gamma delta T cells • reduced or absent proliferation to mitogen or TCR stimulation • reduced or absent expression of CD132 • absent or very low levels of the enzyme ADA in RBCs	For other (e.g. older) patients with T-cell deficiency, consider Combined IDs.
Omenn syndrome	Desquamating erythroderma in the first year of life **AND** one of the following: • lymphoproliferation • failure to thrive • chronic diarrhea • recurrent infections/opportunistic infections **AND** eosinophilia or elevated IgE **AND** T-cell deficiency (low naïve cells/low TRECs/ reduced proliferation/oligoclonality/abnormally elevated HLA-DR) **AND** maternal engraftment excluded **AND** HIV excluded	For other patients with severe erythroderma, please consider: • SCID • IPEX • Unclassified disorders of immune dysregulation • Unclassified defects in innate immunity

Disease	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if criteria are not completely fulfilled)
HLA class II deficiency (MHC II)	One of the following: • Recurrent and/or opportunistic infections • Autoimmunity **AND** one of the following: • Hypogammaglobulinaemia • Lymphopenia • Low T-CD4 count • absence of Ab production in response to antigens or absence of T cell proliferations in response to antigens **AND** Reduced or absent HLA DR expression at the surface of B cells and/or monocytes	Combined immunodeficiency
DOCK8 deficiency	Any one of the following: • Cutaneous viral and staphylococcal infections • Severe atopy • Recurrent and/or opportunistic infections Low IgM, reversed CD4:CD8, TEMRA expansion **AND** High Ig E **AND** Absence of DOCK8 expression	
HIGM syndromes	**At least one of the following:** • Increased susceptibility to infections (recurrent and/or opportunistic) • Immune dysregulation (autoimmunity, lymphoproliferation, sclerosing cholangitis) • Cytopenia (neutropenia or autoimmune) • Malignancy (lymphoma) • Affected family member **AND** Marked decrease of IgG (measured at least twice) **AND** Normal or elevated IgM (measured at least twice) **AND** Defined causes of hypogammaglobulinemia have been excluded **AND** No evidence of profound T-cell deficiency, defined as 2/3 of the following (mo=month, y=year of life): • CD4 numbers/microliter: 0-6mo 12y 16y 10% • T cell proliferation absent **AND** No evidence of Ataxia telangiectasia (cafe-au lait spots, ataxia, telangiectasia, raised AFP)	

	AND Absence of CD40 or CD40L expression by flow-cytometry	

ii) CID with associated or syndromic features

Disease	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if criteria are not completely fulfilled)
Hyper IgE syndrome (HIES)	Bacterial infections (boils and pulmonary infections, pneumatoceles) due to S.aureus, P.aeruginosa, P.jirovecii , or mucocutaneous candidiasis, AND atleast one of the following: • Eczema • Retained primary teeth • Skeletal abnormalities like scoliosis, fractures with minor trauma, hyperextensibility • Midline anomalies like cleft lip/palate, hemivertebrae or other vertebral anomalies IgE> 10 times the normal for age **AND** No evidence of T-cell deficiency (low T cell numbers, low naive T cells, reduced proliferation) **AND** Normal B cell numbers and no hypogammaglobulinaemia	• For patients with evidence of T-cell deficiency, please consider: Combined immunodeficiencies. • For patients with evidence of B-cell deficiency, please consider Unclassified antibody deficiency. • For other patients, please consider Unclassified immunodeficiencies.
Wiskott-Aldrich syndrome (XLT/WAS)	**At least one of the following:** • Eczema • Recurrent bacterial or viral infections • Autoimmune diseases (incl. vasculitis) • Malignancy • Reduced WASP expression in a fresh blood sample • Abnormal antibody response to polysaccharide antigens and/or low isohaemagglutinins • Positive maternal family history of XLT/WAS **AND** Male patient with thrombocytopenia (less than 100,000 platelets/mm3) (measured at least twice) **AND** small platelets (platelet volume < 7.5 fl)	

Ataxia Telangiectasia (ATM)	Ataxia **AND** at least two of the following : • Oculocutaneous telangiectasia • Elevated alphafetoprotein (tenfold the upper limit of normal) • Lymphocyte A-T karyotype (translocation 7;14) • Cerebellum hypoplasia on MRI	

	• Increased chromosomal breakage with radiation	
DiGeorge syndrome	Documented microdeletion 22q11 or 10p **AND** Signs of immunodeficiency, i.e. infections (recurrent or severe bacterial) and/or immune dysregulation	

iii) Predominant antibody deficiency

Disease	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
XLA	**All of the following** • Male patient • Recurrent severe bacterial infection • less than 2% CD19+ B cells • persistent hypogammaglobulinemia after 6 months of age **AND** at least one of the following: 1) Mutation in Btk 2) Absent Btk mRNA on northern blot analysis of neutrophils or monocytes 3) Absent Btk protein in monocytes or platelets by flowcytometry 4) Maternal cousins, uncles or nephews with less than 2% CD19+ B cells	

Common variable immunodeficienc y disorders (CVID)	**At least one of the following:** • increased susceptibility to infection • autoimmune manifestations • granulomatous disease • unexplained polyclonal lymphoproliferation • affected family member with antibody deficiency **AND** marked decrease of IgG and marked decrease of IgA with or without low IgM levels (measured at least twiceatleast 3 weeks apart; <2SD of the normal levels for their age); **AND** at least one of the following:If IgG is less than 100 mg/ d Lthen this criteria may be ignored) • poor antibody response to vaccines (and/or absent isohaemagglutinins); i.e. absence of protective levels despite vaccination where defined • low switched memory B cells (<70% of age-related normal value) **AND** secondary causes of hypogammaglobulinaemia have been excluded **AND** diagnosis is established after the 4th year of life (but symptoms may be present before) **AND** no evidence of profound T-cell deficiency, defined as 2 out of the following (y=year of life):CD4 numbers/microliter: 2-6y <300, 6-12y,<250, >12y <200;% naive CD4: 2-6y<25%, 6-16y <20%. >16y <10% • T cell proliferation absent For patients	For patients<4 years old or patients with incomplete criteria please consider "Unclassified antibody deficiency". For patients with evidence of profound T-cell deficiency, please consider Combined immunodeficiencies.

iv) Diseases of immune dysregulation

Disease	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Familial Hemophagocytic Lymphohistiocytosis syndromes (FHLH)	**At least one of the following:** • at least 1 episode of HLH (at least 5/8 criteria as defined by the Histiocyte Society) • affected family member **AND** at least one of the following: • recurrent disease (>4 weeks after initiating treatment for first episode) • partial albinism • absent or significantly decreased (<15%) Perforin expression on NK cells in flow Cytometry • at least one assay with absent degranulation (NK or CTL) or two assays with reduced degranulation • at least 2 assays with absent NK cell cytotoxicity	For patients with incomplete criteria, please consider unclassified disorders of immune dysregulation.
Autoimmune lymphoproliferative syndrome (ALPS)	**At least one of the following:** • splenomegaly • lymphadenopathy (>3 nodes, >3 months, non-infectious, non-malignant) • autoimmune cytopenia (>/= 2 lineages) • history of lymphoma • affected family member **AND** at least twoof the following: • TCRab+CD3+CD4-CD8- of TCRab+CD3+ T cells >2.5% • elevated biomarkers (at least 2 of the following): • sFASL> 200pg/ml • Vitamin B12 > 1500ng/L • IL-10 > 20pg/ml • Impaired FAS mediated apoptosis	For patients with lymphoproliferation and/or autoimmunity who do not fulfil these criteria, please consider the following diagnoses: • CVID • Combined immunodeficiencies • Unclassified disorders of immune dysregulation

Disease	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Chediak Higashi Syndrome (CHS)	**At least one of the following:** • recurrent bacterial infections • episode of hemophagocyticlymphohistiocytosis (HLH) • progressive neurological dysfunction • Neutropenia • reduced lymphocyte degranulation/cytotoxicity • affected family member **AND** one of: • Typical hair shaft abnormalities • Presence of intracytoplasmic typical giant granules on blood or bone marrow smears	Immunodeficiency with partial albinism
Griscelli Syndrome Type 2	**At least one of the following:** • episode of hemophagocyticlymphohistiocytosis (HLH) • reduced lymphocyte degranulation/cytotoxicity • affected family member **AND** Typical hair shaft abnormalities **AND** Absence of giant granules on blood smear	Immunodeficiency with partial albinism

v) Congenital defects of phagocytic number, function, or both

Disease	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Chronic Granulomatous Disease (CGD)	**At least one of the following:** • Deep seated infection due to bacteria and/or fungi (abscesses, osteomyelitis, lymphadenitis) • Recurrent pneumonia • Obstructing/diffuse granulomata (gastrointestinal or urogenital tract) • Chronic inflammatory manifestations (colitis, liver abscess and fistula formation) • AEFI following BCG • Recurrent infections with typically catalase positive bacteria (S.aureus and gram negative bacilli, Aspergillus, Candida), Burkholderiacepacia, Chromobacterium, Nocardia, and invasive Serratia marcescens. • Affected family member **AND** absent/significantly decreased respiratory burst (NBT or DHR, measured at least twice)	
Leucocyte Adhesion Defect I	**At least one of the following:** • delayed cord fall with omphalitis • periodontitis • no pus formation, lack of inflammation observed in area of infection **AND** neutrophilic leukocytosis **AND** Absent/significantly reduced CD18/CD11a/b/c expression on neutrophils	
Congenital neutropenia	Neutropenia below 0.5 g/L measured on at least 3 occasions OR Neutropenia below 1 g/L measured on at least 3 occasions with **at least one of the following**: • deep seated infection due to bacteria and/or fungi • recurrent pneumonia • buccal and/or genital aphthous lesions or ulcerations • omphalitis • neutrophil maturation arrest • affected family member **AND** exclusion of secondary causes of neutropenia	For other patients with chronic neutropenia, please consider Unclassified phagocytic disorders.

Cystic Fibrosis	**At least one of the following:** • recurrent infections • pancreatic insufficiency **AND** Elevated sweat chloride(≥60 mmol/L)	

vi) Defects in intrinsic and innate immunity

Disease	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Predisposition to invasive bacterial infections IRAK4/Myd88 deficiency	Recurrent non-invasive bacterial infections(skin, upper respiratory tract) **AND** Molecular diagnosis	
Defects with susceptibility to mycobacterial infection (MSMD)	**Any one of the following:** Infections caused by weakly virulent mycobacteria, such as BCG vaccines and environmental mycobacteria, tuberculosis, salmonellosis, candidiasis, other intramacrophagic bacteria, fungi, or parasites, Affected family member **AND** Altered IFN-γ mediated immunity tests or Altered IL-12 mediated immunity tests	
STAT1 GOF	**At least one of the following:** • fungal, bacterial and viral (HSV) infections • auto-immunity (thyroiditis, diabetes, cytopenias), enteropathy **AND** Increased pSTAT1 MFI atleast on two occasions	

vii) Auto-inflammatory disorders

Disease	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Type I interferonopathies	**At least one of the following** • Developmental delay with basal ganglia calcification in CT/ MRI brain • Chilblain-like lesions/ peripheral gangrene • Infantile-onset interstitial lung disease **AND** Elevated type-1 interferon mRNA signature	
Familial Mediterranean fever	**At least six out of eight: Presence** • Duration of episodes, 1–3 days. • Chest pain. • Abdominal pain • Arthritis. **Absence** • Aphthous stomatitis. • Urticarial rash. • Maculopapular rash. • Painful lymph nodes.	
Hyper IgD Syndrome	Recurrent episodes of fever **AND** **Presence of at least three of six:** • Age at onset <1 years. • Gastrointestinal symptoms (pain/ diarrhea) • Painful lymph nodes. • Aphthous stomatitis. • Triggers (physiologic stressors such as vaccination/ minor trauma) • Maculopapular rash	

Cryopyrin-associated periodic syndrome (CAPS)	Recurrent/ Prolonged episodes of fever **AND** **Presence of at least two of five:** • Urticarial rash. • Cold/Stress-triggered episodes. • Sensorineural hearing loss. • Chronic aseptic meningitis. • Skeletal abnormalities (epiphysial overgrowth/ frontal bossing).	
Tumor necrosis factor receptor associated periodic syndrome (TRAPS)	**Presence of at least 3 of the 5** • Fever duration >5 days • Migratory rash • Periorbital oedema • Myalgia • Positive family history of TRAPS	

viii) Complement deficiency

Disease	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
C1 esterase inhibitor deficiency	**Presence of at least one of the following** • Recurrent episodes of non-itchy subcutaneous edema (over face/ extremities) • Recurrent episodes of abdominal pain • Suggestive family history of hereditary angioedema (autosomal dominant inheritance) **AND** Normal C3, low C4 levels, and low C1 inhibitor levels/ function	

- **Early complement deficiency (C1q, C2, C3, C4)**

Disease	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Complement component 1q deficiency (C1q deficiency)	**At least one of the following;** • Increased susceptibility to infections with encapsulated organisms • SLE like syndrome • Family history of symptomatic C1q/C1r/C1s deficiency **AND** • CH50/CH100 activity less than 10% of control value with normal AP50/AP100 activity • Normal C3, C4 levels with low C1q levels	
Disease	**Clinical criteria for a probable diagnosis (= clinical diagnosis)**	**Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)**

Complement component 2 deficiency	**At least one of the following;** • Increased susceptibility to infections (recurrent pyogenic) • Discoid lupus • SLE • Family history of symptomatic C2 Deficiency **AND** CH50 or CH100 activity less than 10% of control activity **AND** Absent C2 with normal C3 and C4 complement levels	
Complement component 3 deficiency (C3)	**At least one of the following;** • Increased susceptibility to infections (Neisseria or streptococcal) • Glomerulonephritis • Family history of symptomatic C3 Deficiency **AND** CH50/CH100 and AP50/AP100 less than 10% of control activity **AND** Absent immunochemical C3 with normal Factor H and I levels	
Complement component 4 deficiency	**At least one of the following;** • Increased susceptibility to infections (Neisseria or streptococcal) • Family history of C4 deficiency **AND** CH50 (or CH100) and AP50 (or AP100) activity less than 5% of control activity **AND** Low immunochemical C4 protein	

- **Late complement component deficiency (C5 to C9)**

Disease	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Late complement component deficiency	**At least one of the following;** • Increased susceptibility to infections (Neisserial) • Family history of recurrent Neisserial disease **AND** CH50 (or CH100) and AP50 (or AP100) activity less than 5% of control activity	

ix) Marrow failure syndromes

Disease	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Fanconi anemia	**Any one of the following:** • CNS features including microcephaly, developmental delay, café au lait spots, deafness • Skeletal features: short stature, radial abnormalities, abnormal or absent thumb • Craniofacial features: bird like facies, microopthalmia, ptosis, strabismus, large ears • Cardiac features: VSD • Urogenital anomalies: Horseshoe kidney • Skin features: Hypopigmentation, freckles **AND** Pancytopenia **AND** Increased chromosomal breakage with alkylating agents (MMC, DEB) induction	
Dyskeratosis congenital (DKC)	**At least two of the following:** • Skin pigmentation abnormalities • Nail dystrophy • Mucosal leucoplakia • Bone marrow failure **AND** Very short telomeres	

x) Phenocopies of PID

Disease	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Chronic mucocutaneous candidiasis (associated with autoantibodies)	Atleast one of the following: Persistent or recurrent CMC Endocrinopathy **AND** Autoantibodies to IL-17 and/or IL-22	
RAS- associated leukoproliferative disease	Atleast two of the following: Persistent non-malignant lymphadenopathy > 6 months Massive splenomegaly Autoimmunity AND granulocytosis,monocytosis **AND**elevated or normal DNTs **AND** defective lymphocyte apoptosis	

ANNEXURE 2: Membership Form

Nodal/Participating Center Membership Form

for

"National Registry for Rare and Other Inherited Disorders (NRROID)"

1. **Name & Address of the Institute**

2. **Name and designation of the Principal Investigator & Co-Investigators**

3. **Name of the Rare Disease diagnosed at the facility**

   i.
   ii.
   iii.
   iv.
   v.

(Please add more rows if needed)

4. **OPD Attendance on per month basis for rare diseases (mention separately for new cases and follow-up cases)**

   i.
   ii.
   iii.
   iv.
   v.

(Please add more rows if needed)

5. Diagnostic Facility Available

a. Cytogenetic workstation with software with Fluorescent in situ hybridization ☐

b. DNA Sequencer with 8 capillary sequencer ☐

c. Mi Seq next generation sequencer ☐

d. Next Seq next generation sequencer ☐

e. Real Time PCR (96 well format) for real time polymerase chain reaction ☐

f. High throughput rNA and DNA extraction systems ☐

g. Quality Check stations and microtips station ☐

h. Chromosomal Micro array platform ☐

i. Newborn Screening platfrom for fluroimmunoassay ☐

j. Antenatal screening equipment (one stop screening for pre-ecclampsia and chromosomal aneuploidies) ☐

k. Eonis tm system for DNA based newborn screening for rare disorders ☐

l. Capillary Electrophoresis system for newborn screening of hemoglobinopathies ☐

m. Multimode readers for both ELISA and fluorescent enzyme assays ☐

n. Liquid chromatography Mass Spectroscopy (Tandem Mass Spectrometry) ☐

o. HPLC (quarternery pump high Performance Liquid Chromatography) ☐

p. GCMS (gas chromatography Mass Spectrometry) ☐

q. Microfluidics platform ☐

r. Any other facility (specify name in the space provided)

_____

_____

_____

_____

6. Commitment offered

Please specify your commitment towards

1. **The number of cases of rare diseases to be entered in the portal per 6 months**

2. **Availability of free/ cheap advanced diagnostic services for patients from other centres in the registry**

Date: **Signature with seal**

Name of the PI