Enabling a more effective ecosystem of innovation and care for rare diseases

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Foreword

For some time now, it has been evident that there is a pressing need to strengthen India's policy framework to promote the development and accessibility of treatments for rare diseases. This imperative formed the central focus of the National Conference on Advancing Clinical Trials in Rare Diseases, held on July 25–26 in New Delhi, where stakeholders from across the ecosystem—including patients, clinicians, scientists, regulators, and industry representatives—came together to deliberate on the challenges and opportunities in this critical domain.

The meeting was jointly organised by Dr Rakesh Mishra (Tata Institute for Genetics & Society), Prof Alok Bhattacharya (World Without GNE Myopathy), Prof Y. K. Gupta (Y. K. Gupta Academy), and Prof Satyajit Mohapatra (AIIMS Guwahati). The conference was supported by the World Without GNE Myopathy (WWGM) and the Organisation for Rare Diseases India (ORDI), with the Indian Council of Medical Research and the Indian Society for Clinical Research serving as knowledge partners.

The meeting was conducted in a hybrid format, with speakers and panellists participating in person, while the majority of participants joined via a video conferencing platform. A limited number of participants were also invited to attend in person. We hope that the discussions and recommendations captured in this document will contribute meaningfully to shaping future policies for rare disease drug discovery, regulatory approval, and improved access for patients.

This report summarises the key deliberations and recommendations that emerged from the meeting. We gratefully acknowledge the contributions of Prof Y. K. Gupta and Prof Satyajit Mohapatra in conceptualising and organising the conference. We also thank the many participants for their valuable suggestions and insights. Finally, we extend our appreciation to Prof Sudha Bhattacharya (WWGM), the staff of the Indian National Science Academy (INSA), and the Tata Institute for Genetics & Society (TIGS) for their support in preparing this document.

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Abbreviations

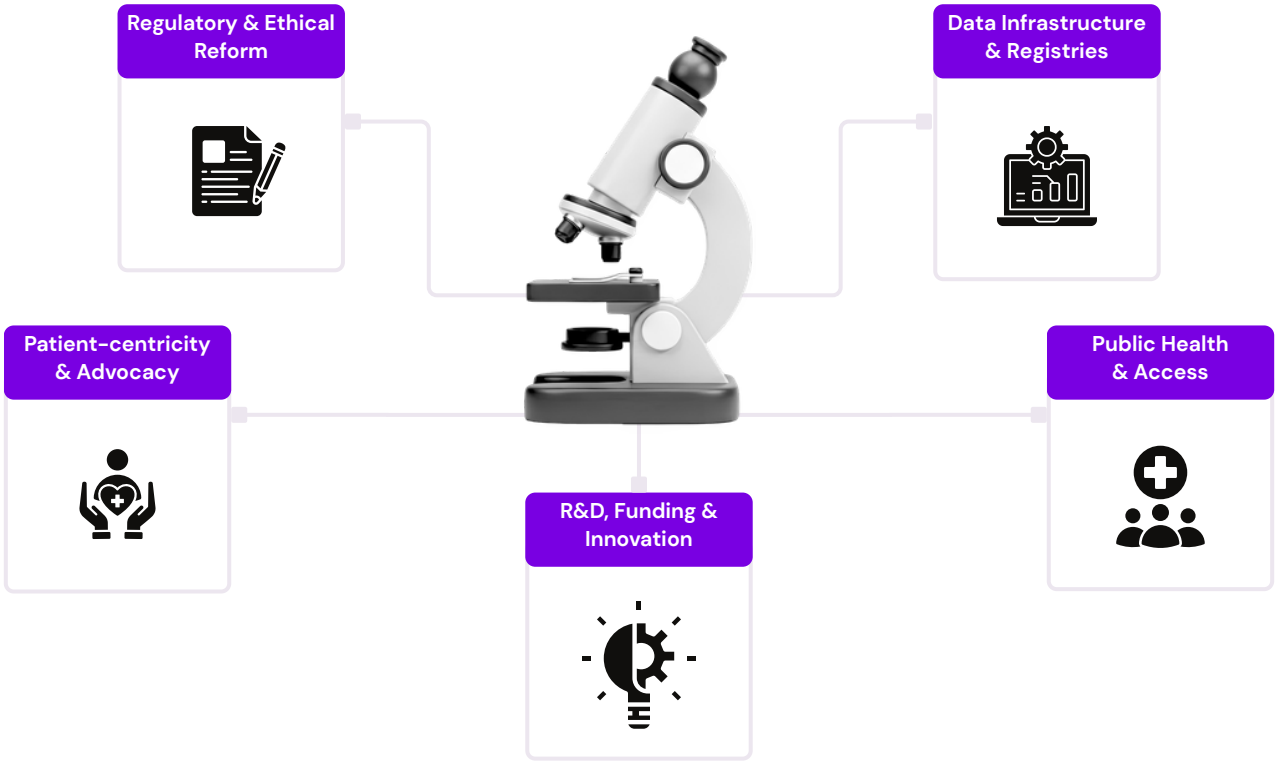
Acronym	Expanded Form
AAV	Adeno-associated virus
ABHA ID	Ayushman Bharat Health Account ID
AI	Artificial Intelligence
AIIMS	All India Institute of Medical Sciences
ASO	Antisense oligonucleotides
BIRAC	Biotechnology Industry Research Assistance Council
CDSCO	Central Drugs Standard Control Organisation
CME	Continuing Medical Education
CoE	Centre of Excellence
CRISPR	Clustered regularly interspaced short palindromic repeats
CRO	Clinical research organization
CTRI	Clinical Trials Registry-India
DBT	Department of Biotechnology
DCGI	Drug Controller General of India
DHR	Department of Health Research
DMD	Duchenne muscular dystrophy
DSMB	Data and Safety Monitoring Boards
DTAB	Drugs Technical Advisory Board
EMA	European Medicines Agency
EMR	Electronic Medical Record
ERDRI	European Rare Disease Registry Infrastructure
EU	European Union
FDA	Food and Drug Administration
GoI	Government of India
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GST	Goods and Services Tax
HMSC	Health Ministry's Screening Committee
IBDC	Indian Biological Data Centre
ICMR	Indian Council of Medical Research
IEC	Institutional Ethics Committee
IND	Investigational New Drug
INTENT	Indian Clinical Trial and Education Network
IP(R)	Intellectual Property (Rights)
iPSC	Induced Pluripotent Stem Cell
ISCR	Indian Society of Clinical Research
IT	Information Technology
LLM	Large Language Model
MAMS	Multi-arm, multi stage

Acronym	Expanded Form
MHRA	UK's Medicines and Healthcare Products Regulatory Agency
MoHFW	Ministry of Health and Family Welfare
NBS	Newborn screening
NCBI	National Center for Biotechnology Information
NCE	New chemical entity
NDAC	New Drug Advisory Committee
NDCT Rules	New Drugs and Clinical Trials Rules, 2019
NHM	National Health Mission
NHS	National Health Service
NIH	National Institutes of Health
NITI Aayog	National Institution for Transforming India Aayog
NLM	National Library of Medicine
NPRD	National policy on rare diseases
NRROD	National registry for rare and other inherited disorders
ORDI	Organisation for Rare Diseases India
PAG	Patient Advocacy Group
PDP	Product Development Partnerships
PK/PD	Pharmacokinetics/Pharmacodynamics
PRIP	Promotion of Research and Innovation in Pharma MedTech sector
PRO	Patient-Reported Outcome
QA/QC	Quality Assurance / Quality Control
RBSK	Rashtriya Bal Swasthya Karyakram
R&D	Research and Development
RD	Rare disease
RDEA	RD Endpoint Advancement Pilot Program
RDTMC	Rare disease treatment and management centres
RWE	Real-World Evidence
SEC	Subject Expert Committee
SGPGI	Sanjay Gandhi Post Graduate Institute of Medical Sciences
SMA	Spinal Muscular Atrophy
SoC	Standard of Care
THSTI	Translational Health Science and Technology Institute
TRL	Technology Readiness Level
UDID	Unique Disability ID
UK	United Kingdom
US	United States
USFDA	United States Food and Drug Administration
WGS	Whole-genome sequencing
WHO	World Health Organization

Executive Summary

This white paper outlines a comprehensive strategy for advancing the ecosystem for rare diseases (RDs) in India, with a specific focus on accelerating clinical trials. The document is a synthesis of discussions from the 'Advancing Clinical Trials in Rare Diseases' national conference held in July 2025, which convened a diverse group of stakeholders including patients, Patient Advocacy Groups (PAGs), scientists, industry, and Indian regulatory bodies. The white paper identifies systemic challenges, including the lack of a formal definition for RDs in India, scarce epidemiological data, low awareness among physicians and the public, inconsistent standards of care, severely fragmented patient data, and the need for trial designs in the face of the challenge of low numbers of patients with a given RD. The recommendations are structured across several key pillars, as follows: Regulatory and ethical reform; Data infrastructure and registries; Patient-centricity and advocacy; R&D, funding, and innovation; and Public health and access.

Key Pillars supporting rare disease innovation and care



1. Regulatory and Ethical Reform

This was identified as a significant bottleneck, with regulatory timelines described as lengthy and unpredictable. It was proposed that

a. the current sequential approval process (DCGI, Ethics Committee, etc.) be replaced with a parallel, single-window integrated research application system.

b. restrictive rules, such as the '50 km rule' for Ethics Committees, be amended to allow for digital supervision of remote trial sites.
c. a specialized RD clinical trial review team within CDSCO be established, and the advice given in pre-IND meetings be binding, similar to FDA and EMA practices.
d. approve innovative trial designs (e.g., adaptive, n-of-one), adopt flexible 'rolling reviews' for RD therapies, and issue clear guidance on using non-animal models (like organoids) for submissions
e. mandate that Institutional Ethics Committees (IECs) include patient representatives and receive specialized training on RD-specific issues.

2. Data Infrastructure and Registries

Patient data is currently siloed and incomplete. The white paper calls for:
a. creating a secure, national medical data platform, modeled on the UK's OpenSAFELY project, where researchers can query anonymized data.
b. upgrade the ICMR's NRROID registry to be more user-friendly and, critically, create a validation workflow to allow patients and doctors outside of CoEs to directly enter data.
c. host workshops between ICMR and PAGs to help structure the vast amount of data PAGs already hold.

3. Patient-Centricity and Advocacy

PAGs are positioned as essential partners. Key recommendations include:
a. Unify smaller PAGs to create a stronger voice and involve them into trial design, protocol development, and recruitment.
b. Mandate that trial sponsors pre-arrange and pay for patient travel and lodging, replacing the burdensome reimbursement process.
c. Establish a clear regulatory framework that mandates sponsors provide continued access to beneficial drugs for trial participants after the trial concludes.

4. R&D, Funding, and Innovation

3/41 India's RD drug development pipeline is weak. To stimulate it, the paper suggests:
a. Shift government funding focus, in the RD area, to academic labs and small startups, the primary drivers of innovation. Agencies like DBT and BIRAC should adopt a proactive 'hunt and fund' model to identify promising science in this area.
b. Establish non-profit Product Development Partnerships (PDPs) to bridge the academia-industry divide, provide industry expertise to academic labs, and train scientists in IPR.
c. Enact an Indian "Orphan Drug Act" to provide tax credits, market exclusivity, and other incentives to those developing therapeutics for RDs.
d. Move beyond animal models by creating a national, ICMR-supported bank of iPSC lines from RD patients and investing in organ-on-a-chip technologies.
e. Use AI to assist in diagnosis, drug repurposing, and creating synthetic control arms for trials, gaining CDSCO approval for this approach.

5. Public Health and Access

RDs must be integrated into the existing public health framework.

a. Utilize the National Health Mission (NHM) for RD prevention, data collection, and a continuum of care.

b. Implement a national newborn screening (NBS) program for treatable RDs.

c. Focus on cost-effective technologies like mRNA therapeutics and systematically investigate drug repurposing, creating a national portal of potential candidates. The paper concludes that while the challenges are significant, these do-able actions can position India as a global leader in RD product development. It calls for the creation of a National Apex Body to coordinate the multi-ministerial effort required for implementation.

Introduction

A national conference on "Advancing Clinical Trials in Rare Diseases" was held on July 25–26, at the Indian National Science Academy in Delhi. The conference brought together a diverse set of people, included patients, patient advocacy groups (PAGs), scientists, medical doctors, industry, policy researchers, the Central Drugs Standard Control Organisation (CDSCO), the Department of Biotechnology (DBT), the Indian Council of Medical Research (ICMR), the World Health Organization (WHO), and others. Additionally, about 400 people attended the meeting online. Over two days, various challenges facing the rare disease (RD) community stakeholders, with a particular focus on clinical trials for therapies for RDs, were discussed from different angles.

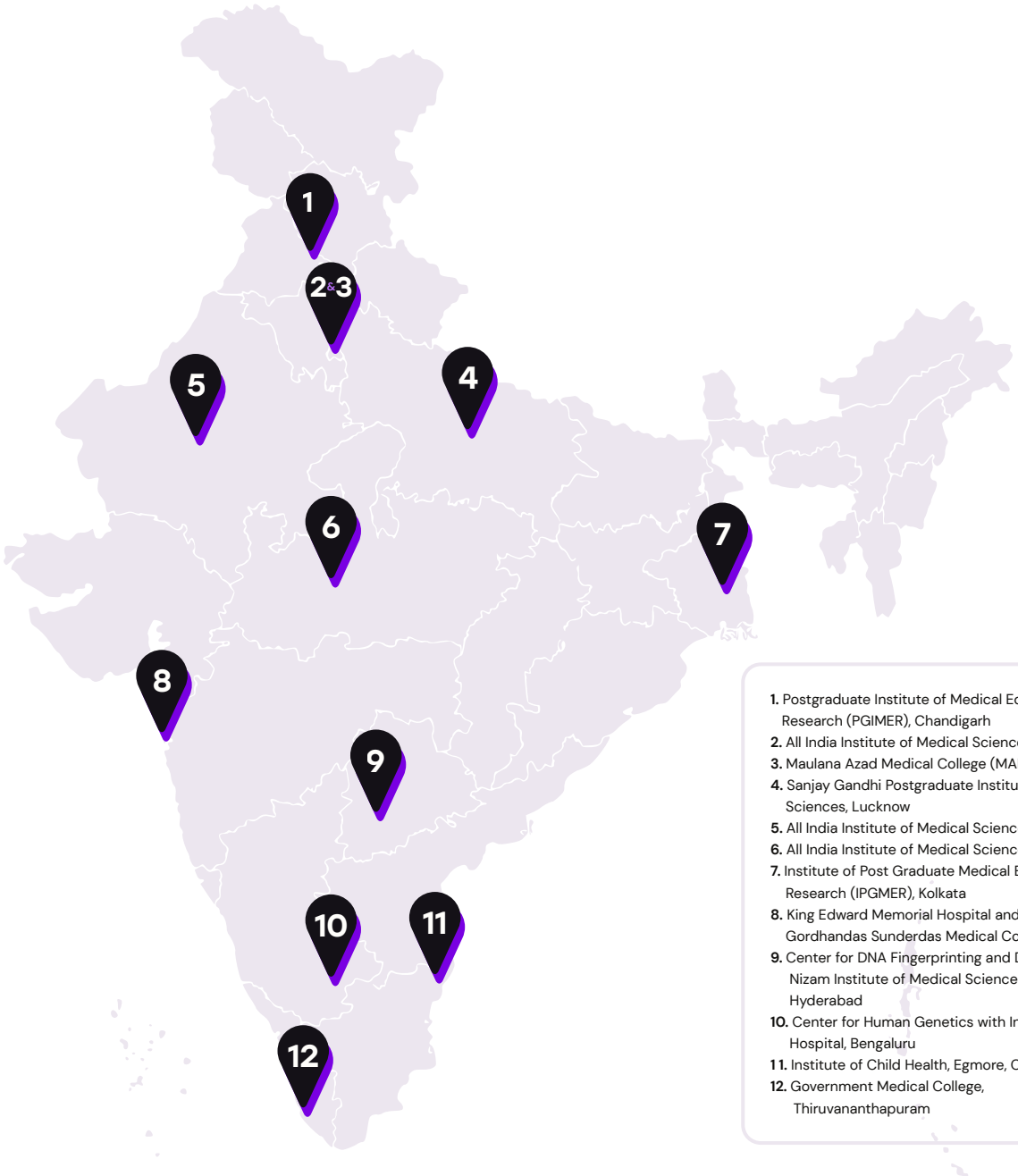
The challenges with RDs start from the very definition of such a disease or condition. Different countries do so differently. In the United States (US), a condition with up to 200,000 patients is defined as rare and in the European Union (EU) it is one in 10,000. In India, an RD has yet to be defined, due to paucity of comprehensive demographic data. This complication aside, no country knows how many RD patients it has, although some countries have better data than others.

The Government of India (GoI) has a list of RDs, and ICMR has a list of priority RDs that it is focused on, including Duchenne muscular dystrophy (DMD), Spinal muscular atrophy (SMA), and Gaucher's disease. This priority list has been created based on experts' opinions and the availability of treatment. Participants also pointed out that the official government list of RDs needs to be updated and a new group created for all those RDs with a recognized patient population and active drug-discovery research programs. There are a few glaring omissions. For example, effective, lowcost treatments that already exist in India for conditions like pemphigus vulgaris and scleroderma. However, these conditions are not on the NPRD list of RDs.

Centres of excellence

India now has 12 Centres of Excellence (CoEs) for RDs, that include, for instance, the All India Institute of Medical Sciences (AIIMS) in Bhopal, Delhi and Jodhpur, the Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGI) in Lucknow, the Centre for Human Genetics with the Indira Gandhi Hospital in Bengaluru, and the Center for DNA Fingerprinting & Diagnostics with the Nizam Institute of Medical Sciences in Hyderabad. Each CoE is in a top public sector tertiary hospital, sometimes partnered with research labs, with facilities for routine and high risk screening, diagnosis, prevention and treatment of RDs. In addition, it is engaged in education and training at various levels, and in research geared to low-cost diagnostics, therapeutics and, in some cases, the mechanistic understanding of RDs.

Centres of Excellence(CoE) for rare diseases in India



1. Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh
2. All India Institute of Medical Sciences, New Delhi
3. Maulana Azad Medical College (MAMC), New Delhi
4. Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow
5. All India Institute of Medical Sciences, Jodhpur
6. All India Institute of Medical Sciences, Bhopal
7. Institute of Post Graduate Medical Education & Research (IPGMER), Kolkata
8. King Edward Memorial Hospital and Seth Gordhandas Sunderdas Medical College, Mumbai
9. Center for DNA Fingerprinting and Diagnostics with Nizam Institute of Medical Sciences, Hyderabad
10. Center for Human Genetics with Indira Gandhi Hospital, Bengaluru
11. Institute of Child Health, Egmore, Chennai
12. Government Medical College, Thiruvananthapuram

There was a call to strengthen these CoEs with more funding and create a mission-mode project, with a common portal, to attract foreign companies to conduct clinical trials in India. Alternately, research networks should be created that would serve the same function.

Among other things, these centres should have a centralized, permanent 'research cadre' to eliminate the delays caused by hiring and training new staff for each project. It should also be ensured that qualified genetic counsellors are available at all the CoEs.

In summary, action points are as follows:

1. Strengthen the CoEs.
2. Establish a centralized, permanent 'research cadre' to eliminate delays caused by project specific hiring and training.
3. Ensure the availability of qualified genetic counsellors at all CoEs.

Awareness

There needs to be increased awareness about RDs, among the general public and among physicians, in particular. A patient advocate shared a powerful anecdote about how a single workshop for 100 neurologists led to a spurt of patients connecting with his organization, proving the high impact of educating clinicians. Therefore, creating awareness among physicians is most important. If courses are organized, physicians can gain Continuing Medical Education (CME) points. Together with SGPGI, ICMR is already running a one-month certified course on genetics for pediatricians. This course is much appreciated and heavily oversubscribed. The course could be offered more often, and could be developed for other specialties. The National Academy of Medical Sciences should be encouraged to organize these workshops.

And the increased awareness needs to be about various issues, such as the disease can manifest at any time from a few days after birth to late in life. A public awareness campaign is also needed to help patients and the public recognize clinical trials as a legitimate, health care pathway

In terms of mechanisms of raising awareness, some methods are already at play and others were suggested. For example, RD webinar series is currently being implemented and the recordings of these webinars are also available that can be leveraged for further outreach. Many PAGs are also organizing workshops at multiple locations helping to increase awareness. There is a need to increase such activities and Government media can help in spreading the message further. It was also felt that unlike TV talks, the use of short, engaging social media messages on platforms like Instagram and YouTube may be more effective in capturing the attention of today's audience. One scientist has found that students are good ambassadors to talk to patients or other young people, and spread the word.

In summary, action points are as follows:

1. Launch targeted awareness campaigns about RDs for both the general public and physicians.
2. Develop CME accredited courses and workshops for physicians to improve diagnosis and management of RDs.
3. Increase the frequency of successful existing training programmes, like the ICMR-SGPGI certified genetics course, and adapt them for other medical specialties.
4. Educate the public and healthcare professionals that while common in children, RDs can also manifest later in life, including in the elderly.
5. Promote clinical trials as a legitimate and essential healthcare pathway through a dedicated public awareness campaign. 6/41
6. Leverage existing digital content, such as webinar recordings, for wider outreach and educational purposes.
7. Create short, engaging social media messages for platforms like Instagram and YouTube to effectively reach a modern audience. 8. Use Government media to spread awareness about RDs.
8. Engage students as ambassadors to help spread awareness among their peers and the community.

Diagnosis: Biomarkers and endpoints

Medical doctors are unlikely to have encountered an RD (particularly the ultra rare ones), and several years may go by between the identification of a medical problem and a correct diagnosis. This is true around the world. Also, for a given RD it is not always clear what the criteria for diagnosis should be. It could be molecular, biomarker-based or based on clinical symptoms.

Further, the biomarkers in use may not be validated. There is a need to use registry or natural history data to conduct research specifically to validate biomarkers across disease progression. It is also important to develop non-invasive biomarkers, that is, to shift away from invasive procedures like muscle biopsies and focus on developing biomarkers from blood, plasma, tears, etc. It was also argued that patient-reported outcomes (PROs) be used when reliable biomarkers are lacking. Further, biomarkers could be combined with digital endpoints (e.g., based on data derived from wearable sensors) and PROs to capture the progression of a condition in real time.

Early diagnosis is important both for treatment and for enrolling patients in clinical trials within a reasonable time. However, for trials, aside from the lack of validated biomarkers, there is a lack of established endpoints. India should create its own RD endpoint development programme, similar to the RD Endpoint Advancement Pilot Program (RDEA) of the US' Food and Drug Administration (USFDA), to define endpoints relevant to Indian communities. Although the ICMR National Registry for Rare and Other Inherited Disorders (NRROID) has started to collect progression data. It will take time before it would be possible to formulate disease progression models. It is quite apparent now that natural history studies help to correlate endpoints with clinical outcomes and are necessary to advance clinical trials on RDs. To be noted, the natural history of a particular RD may be very variable and unpredictable, making it difficult to assess the efficacy of a candidate drug molecule. This will require collaborative research between scientists and clinicians on specific RDs. Drawing from the RDEA programme, India should also adopt surrogate biomarkers (e.g., hemoglobin normalization in Gaucher disease) as primary endpoints for phase 2/3 trials. It should integrate real-world data from COEs to validate surrogates, enabling conditional approvals. This will reduce reliance on large randomized controlled trials.

Clinicians need to be trained via ICMR programmes on alternate trial designs and endpoint standardization, ensuring reproducibility with statistical power trials. This will boost data quality in India’s diverse settings, aligning with global adaptive endpoint strategies.

In summary, action points are as follows:

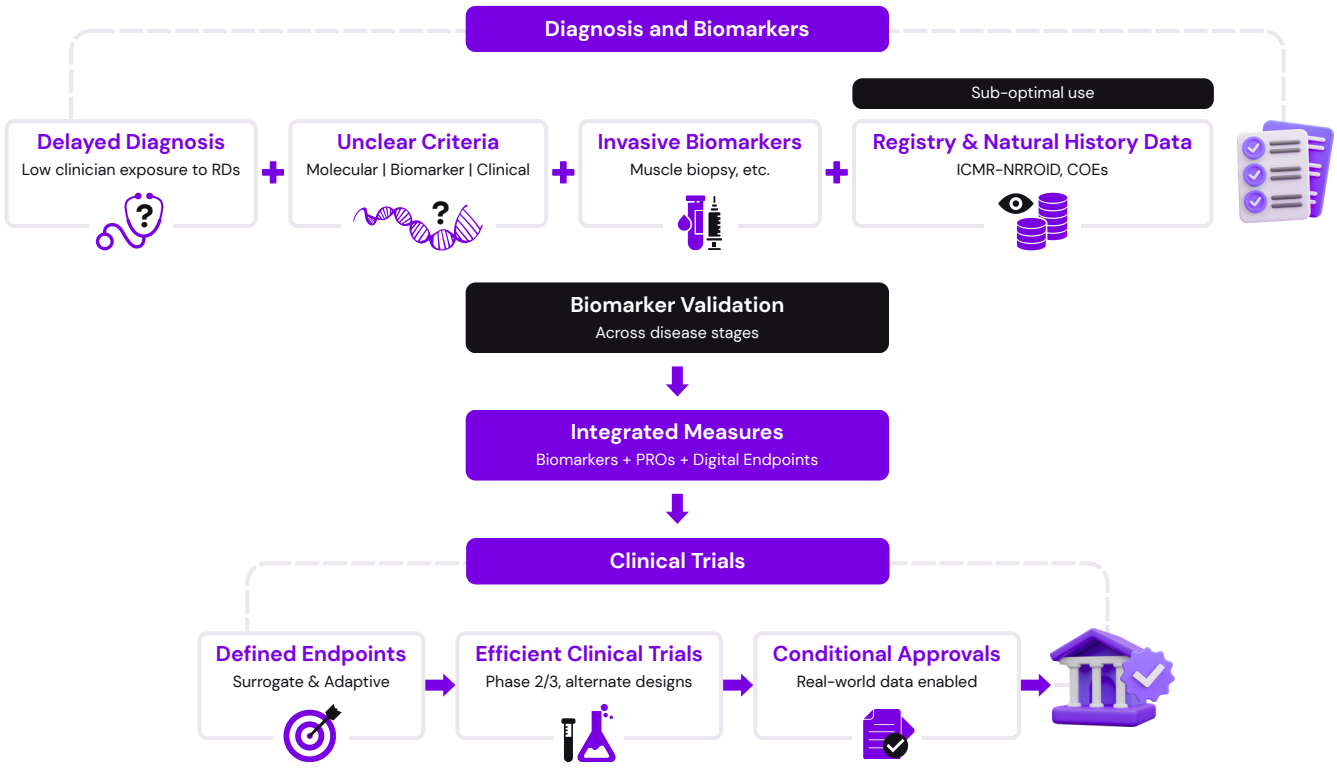
Diagnosis and biomarkers

1. Validate biomarkers across different stages of disease progression by conducting targeted research using registry data.
2. Prioritize the development of non-invasive biomarkers from sources like blood, plasma, and tears to replace invasive procedures like muscle biopsies.
3. Integrate PROs and digital endpoints (e.g., from wearable sensors) with traditional biomarkers to better capture real-time disease progression.

Clinical trials and endpoints

4. Establish an Indian Rare Disease (RD) endpoint development programme, similar to the USFDA's RDEA, to define trial endpoints relevant to local communities.
5. Use natural history data to correlate new endpoints in lieu of standard clinical outcomes.
6. Adopt surrogate biomarkers as primary endpoints for Phase 2/3 trials to accelerate drug evaluation and enable conditional approvals based on real-world data.
7. Foster research collaborations between scientists and clinicians to better understand the variable and unpredictable nature of specific RDs. 8. ICMR should run programmes on alternate trial designs to ensure reproducible, high-quality data collection in decentralized trials, and clinicians should be trained through these programmes.

From Diagnosis to Clinical Trials in Rare Diseases: Gaps and Solutions



Standard of care

For many RDs, there is no standard of care (SoC), with different hospitals following different protocols. Therefore, there should be efforts to expedite the finalization and dissemination of the national SoC documents to all the COEs to ensure treatment protocols are uniform across the country. Lack of standardized SoCs hamper clinical trial design and approval.

In summary, action points are as follows:
1. Accelerate the finalization of national SoC documents for as many RDs as possible, and their distribution to all CoEs
2. Implement these standardized protocols uniformly across the country to ensure consistent patient care.

Patients and PAGs

Across the world, RD patients, their families and their supporters have formed active and effective PAGs. There are about 600 PAGs in the US alone. It was noted that while in the US there is usually only one PAG per RD, sometimes there are multiple PAGs for a disease in India. These could be unified to avoid duplicating efforts.

As a first step, PAGs help to spread awareness about a particular RD, and reduce the associated stigma.

Then, there are various ways in which PAGs can help clinical trials for RDs. Companies often fail to find RD patients for trials because they use traditional clinical research organizations (CROs) instead of connecting with PAGs who know where the patient communities and specialist doctors are. Therefore, PAGs can connect sponsors to patients. Establishing well-defined patient cohorts is a critical step that must happen before a drug is ready for trials. PAGs are essential for building these cohorts. As part of a patient-centric approach, PAGs should be empowered for advocacy and recruitment, and improving participant retention for the entire duration of the trial.

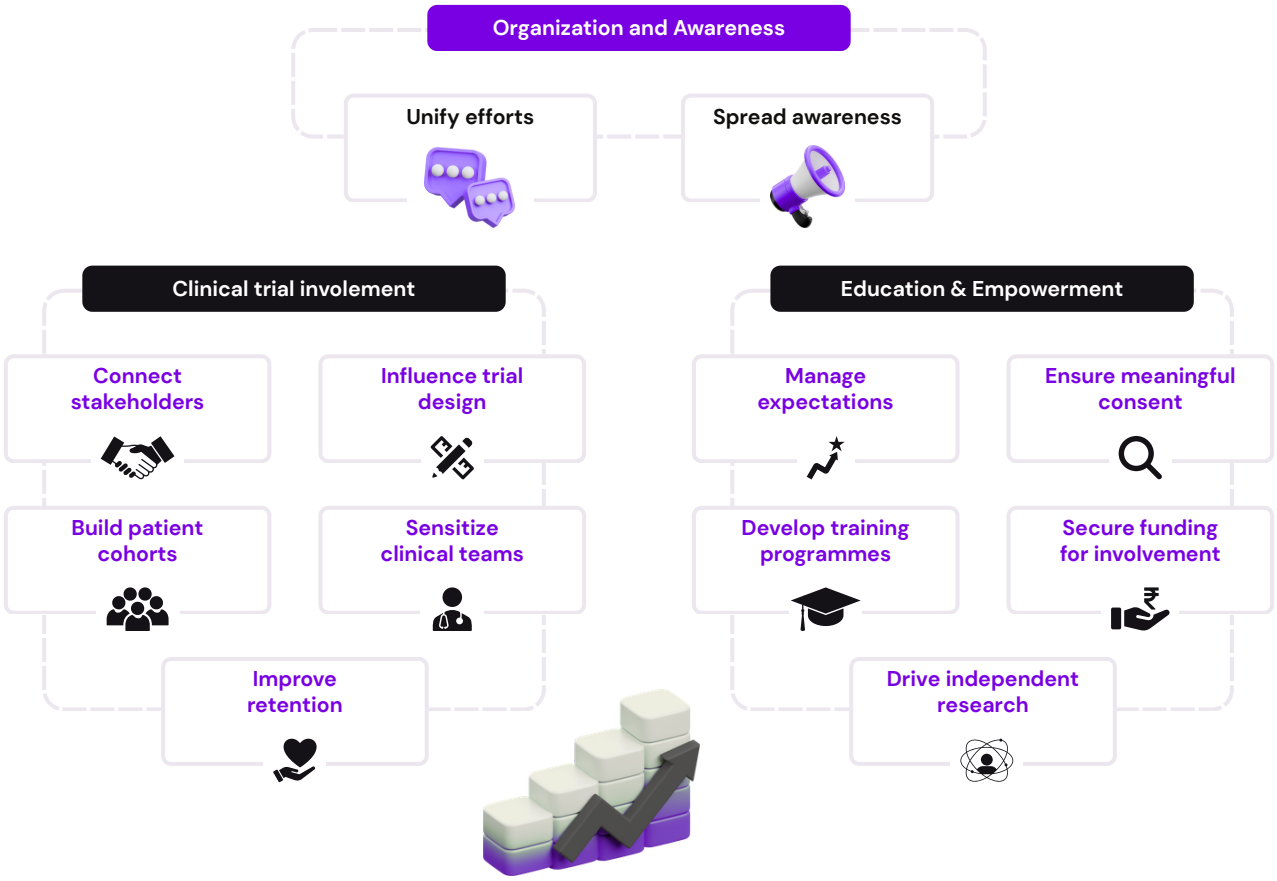
PAGs should be involved in site-level training to help sensitize the clinical team to the specific needs and sensitivities of RD patients and their families. They must also be involved during the trial design phase, including protocol development and the selection of meaningful PROs.

Patient engagement and autonomy are important issues. Informed consent must be meaningful, and not a mechanical process. For complex issues like genomic data, it is difficult for patients to grasp the social and legal risks involved. This needs to be handled thoughtfully. Also, PAGs must manage patient expectations, as trials may take several years and may not succeed. It was suggested that PAGs partner with the Indian Society of Clinical Research (ISCR) to create training programmes for patients and advocates.

It was noted that over 50% of recent FDA approvals are for drugs for RDs, and these trials often involve collaboration between sponsors and PAGs. In effect, patient representatives should be included at all levels of the clinical trial and drug development process including regulatory approval. To enable the involvement of PAGs, research budgets must include line items for recruitment strategies, such as advertisements, patient promotional materials, and stipends to pay for the time of patient advocates and caregivers who attend meetings.

A crucial question pertains to the following: If industry is not interested in developing a promising drug molecule, is it possible for patient groups to raise money and fund the trial themselves by working with a company or academic center? It was felt that even in such a situation, a legal entity like a company is needed to take the drug forward with regulatory bodies. So, PAGs need to find a company whose work they will fund.

Empowering rare disease patient advocacy groups (PAGs)



In summary, action points are as follows:

Organization and Awareness

1. Unify Efforts: Consolidate smaller, disease-specific PAGs into a single group to avoid duplicating work and to create a stronger collective voice.

2. Spread Awareness: Act as a primary channel for spreading awareness about a specific RD to the public, scientists, and the medical community, helping to reduce the associated stigma and accelerating the time to diagnosis.

Clinical Trial Involvement

3. Connect Stakeholders: Serve as the crucial link connecting trial sponsors with patient communities and specialist doctors, streamlining patient identification and recruitment.

4. Build Patient Cohorts: Collaborate directly with clinicians to establish well-defined patient cohorts before a drug is ready for trials.

5. Influence Trial Design: Participate actively in the trial design phase, providing critical input on protocol development and the selection of meaningful PROs.

6. Sensitize Clinical Teams: Engage in site-level training to help sensitize the clinical staff to the specific needs, challenges, and sensitivities of RD patients and their families.

7. Improve Retention: Develop and implement strategies to improve patient retention for the entire duration of a trial.

Education and Empowerment

8. Develop Training Programmes: Partner with professional organizations such as the ISCR to create formal training programmes for patients and advocates.
9. Ensure Meaningful Consent: Work to make the informed consent process meaningful by helping patients understand complex topics and the associated social or legal risks.
10. Manage Expectations: Proactively manage patient expectations regarding the long timelines, potential for failure, and uncertainties of clinical trials.
11. Secure Funding for Involvement: Advocate for the inclusion of specific line items in research budgets to pay for PAG activities, including promotional materials and stipends for the time of patient advocates.
12. Drive Independent Research: For promising drugs ignored by industry, form partnerships with a company or an academic center to legally fund and advance the research and subsequent approval process.

Registries

ICMR has set up the clinical trial registry, Clinical Trials Registry-India (CTRI), that currently has almost 1 lakh records. This is a laudable initiative that will help in drug development in the long run. The collection of data in this registry is a long-term process and requires a stable administrative and financial model. CTRI suffers from incomplete reporting and compliance. While trial registration is mandatory, full reporting of results on the CTRI is not always enforced or complied with. In other registries, such a situation has been found to lead publication bias, where only trials with positive outcomes are reported, while those with negative or inconclusive results are often hidden from public view. There is also a need to update data as the trial progresses.

ICMR's registry for RDs is called NRROID. This registry collects crucial data on the demography, phenotype, and outcomes of rare diseases through 19 collaborating institutes. The registry categorizes disorders into broad groups, such as lysosomal storage diseases, inborn errors of metabolism, skeletal dysplasias, and neuromuscular disorders. Not all diseases diagnosed in India may be reflected in the registry. While the registry has made progress, it has faced challenges in its development and accessibility. Moreover, large number of patients (particularly from outside the collaborating institutes) are not included. Also, many ultra rare diseases may not be included if they fall outside the broad categories defined for inclusion. It was felt that there should be a stable administrative structure, long term funds, and a widening of the data collection strategy.

Also, NRROID needs to be more user friendly for patients, researchers, clinicians and the public. Further, the registry needs to be periodically audited to ensure that the data being collected is adequate to support future clinical trials, especially for use as historical or external controls. The registry must collect the right data points, including determinants of equity and relevant clinical endpoints. It was proposed that the registry be made even more comprehensive, with the capturing of natural history and real world data. The registry platform should state its data sharing policies and play a key role in facilitating recruitment for trials.

Patient advocates argued for the ability of patients to enter their own data into this national registry to increase data availability. This suggestion was received well, with a recommendation that a workflow be created such that data can be entered by a patient or doctor or anybody else, but that such data is marked 'suspected' for a particular RD, until validated by a CoE. Once validation is complete, the data should be passed on, for inclusion in the registry. ICMR has planned to take up this process.

NRROID is a hospital-based registry and also government bodies like ICMR face lengthy validation processes before publishing data. Therefore, it was suggested that another, PAG-enabled nationwide, privacy-protected RD registry be created, to which patients or doctors could add data. This registry would be online, cross-sectional, longitudinal, and dynamic. It could act as a 'work in progress' platform for the consortium's findings without bureaucratic delays. Later, data could be transferred to NRROID. If comprehensive, this registry would, for instance, enable government policy making, industrial research and development (R&D) decisions and insurance decisions. Also, it is challenging to use external controls in Indian trials primarily due to the sub

optimal status of medical records, particularly data-collection, maintenance, and integration with clinical data management systems.

A registry should be made a hub of data collection of RDs in India. It should conduct natural history studies so that we have clinical trial-ready cohorts of RD patients. Natural history data will help to conduct clinical trials on smaller numbers of patients, so that one can do away with the placebo arm of a trial.

Although often the data in such registries would be submitted by sponsors, which have validated it, patient-reported data tends to be unstructured. One of the concerns is that patient reported data is not considered as authentic data as it is self reported. Therefore, it may suffer from recall bias, or other forms of bias. If the data were structured and validated, Artificial Intelligence (AI) might help in further enhancing the utility of that data.

In summary, action points are as follows:

Enhance the Existing ICMR Registry, NRROID

1. Create a Stable Administrative Structure: Provide long term funds, and create a stable administrative structure.
2. Improve User-Friendliness: Make the NRROID more accessible and easier to use by researchers, clinicians, and the public.
3. Conduct Periodic Audits: Regularly audit the registry to ensure that the data being collected is high-quality and sufficient to support clinical trials, especially for use as historical or external controls.
4. Expand Data Collection: Upgrade the registry to comprehensively collect natural history and real-world data, including key variables that demonstrate population representation and equity.
5. Facilitate Recruitment: Clearly outline the registry's data-sharing policies and actively use it as a tool to help recruit patients for trials.

Decentralize Data Entry and Validation

6. Enable Patient-Entered Data: Create a system that allows patients, their families, and doctors to directly enter data into the national registry, thereby including patients from outside the collaborating institutes, and patients suffering from ultra rare diseases that currently may not be included.
7. Implement a Validation Workflow: Develop a process where new, user-entered data is marked as suspected' until it is formally validated by a CoE, after which it is integrated into the main registry.
8. Adopt a PAG-Enabled Model: Transition from a purely hospital-based registry to a decentralized model that is enabled and supported by PAGs, using a standardized framework.

Improve Data Utility and Accessibility

9. Create 'Placeholder' Platforms: Use non-governmental websites as dynamic 'work-inprogress' platforms to host data quickly, bypassing bureaucratic delays before it is officially transferred to the ICMR database. 10. Develop a New Dynamic Registry: Consider creating an additional online, nationwide, privacy-protected registry. It should be dynamic, longitudinal, and accessible to patients and doctors. Such a registry will support policymaking, industrial R&D, and insurance

decisions.

10. Establish Registries as Research Hubs: Position registries as central hubs for conducting natural history studies to create clinical trial-ready cohorts, potentially reducing the need for placebo arms in future studies.
11. Leverage AI for Data Quality: Apply AI and data structuring methods to validate patientreported data, correct for potential biases like recall bias, and enhance its overall utility.

Data

Aside from the RD database of ICMR, it is a top priority that a database of patient medical data be created. For this, it would help if a project similar to OpenSAFELY in the United Kingdom (UK) were to be created in India. This is a project that has been appreciated by both privacy advocates and transparency advocates. In it, all the health records of almost every resident in the UK are available to researchers, but the records cannot be viewed directly. Only code can be used to query the database to obtain the desired information. Due to the highly fragmented nature of the medical system in India, it may seem impossible to create such a system here. It may require involving NITI Aayog to find ways to persuade hospitals to contribute data, which would help identify patients, track natural history and identify patient cohorts, while maintaining patient confidentiality. Any system that captures patient data must have extremely robust methods for data collection, encryption, de-identification, and secure sharing to protect patient privacy. DBT-supported the Indian Biological Data Centre (IBDC) in Faridabad is aiming to create a such a data centre. Currently, the Centre holds data related to nucleotides, structural biology, metabolomes, proteomes, biological images and crop phenomes. Its holdings could be expanded to include patient data.

There is a proposal to have a health card which is blockchain based data collection for every person throughout their life. This needs to be protected against deep fakes. Once validated, blockchaincertified data attached to an ID that migrates with a patient throughout their life if available, it will, for example, enable the creation of digital twins.

Not just hospitals, but private genetic testing laboratories also hold vast amounts of patient data, and could be encouraged to feed it into a central registry. Although this is legally complex, possibly a meeting with these companies could be convened to discuss the matter.

It was suggested that there should be an effort to build on ICMR's registry for RDs by creating interoperable digital platforms for patient identification, similar to EU's European Rare Disease Registry Infrastructure (ERDRI).

Although there was a request to make RDs notifiable, calling a disease notifiable itself is a long process, because a case of 'suspected disease' is not sufficient to notify it. And in the case of RDs, the diagnosis may be complex and uncertain. It was also proposed that since GoI had created a platform for COVID-19 data collection, the same technology could be repurposed for RDs. This would create a national database without getting stuck on the complex process of officially declaring diseases notifiable. PAGs have a lot of data. However, it is unstructured.

PAGs felt that ICMR could guide them on how to structure their data, into a standardized, meaningful format, making it easier to integrate with other databases later. It was proposed to have a meeting entitled 'Consultative meeting of the rare disease patient groups: Registries and patient data' where PAGs illustrate what data they have and ICMR and other scientists would provide inputs on consolidation, evaluation, and the creation of a standardized format for patient data. This meeting took place subsequently, on 17 Oct 2025.

AI algorithms will be able to do a lot with patient data provided it is reasonably complete. Currently because of the fragmented nature of the data concerning a given patient, which may be in different hospitals at different times, comprehensive data is not available for this purpose. So organizing that data is important. Even within a hospital, data is stored in different databases, such as those for inpatients, out-patients, radiological imaging and genomics. Some hospitals are working to integrate these so that there is once source for the data of a given patient.

It was noted that currently India is often just a donor of biological samples and data for international studies, without the resulting scientific breakthroughs directly benefiting the country. Researchers should ensure that data sharing is mutually beneficial. Given the large number of patients, and in some RDs, the high prevalence, India could be a global leader in RD research, while being open to global trials and collaborations to learn from others. Specific guidelines are needed to enable data sharing for the RD population, to facilitate international collaborations.

Other issues concerning data included the following:

a. It was noted that there is some mistrust of Indian trial sites due to concerns about data integrity and inconsistent SoCs, which needs to be addressed. And

b. It was strongly argued that trial data must be shared with families participating in trials, in near real-time. Investigators and clinicians have the power to push sponsors to make this happen.

In summary, action points are as follows:

Establish a National Data Infrastructure

1. Create a Centralized Platform: Develop a secure, national medical data platform, modeled on the UK's OpenSAFELY project, that allows researchers to query anonymized health records without directly viewing them.

2. Incentivize Data Contribution: Engage with high-level bodies like NITI Aayog to create strategies that persuade hospitals and other parts of the healthcare ecosystem to contribute data to such a centralized platform, legally and ethically.

3. Repurpose Existing Technology: Adapt the technology and infrastructure from the successful COVID-19 data collection platform to create a national RD database, bypassing the lengthy process of making diseases officially "notifiable."

4. Build Interoperable Systems: Create interoperable digital platforms, similar to the European Rare Disease Registry Infrastructure (ERDRI), to ensure different databases and registries can communicate with each other.

Integrate Siloed Data Sources

5. Standardize PAG Data: Host a brainstorming workshop between the ICMR and PAGs to guide PAGs on structuring their data into standardized, meaningful formats.

6. Integrate Hospital Data: Encourage hospitals to consolidate their multiple internal databases (e.g., in-patient, out-patient, radiology, genomics) into a single, comprehensive source for each patient's records. Promote Ethical and Collaborative Data Sharing

7. Develop National Guidelines: Create specific national guidelines for data sharing for the RD population to ensure that international collaborations are mutually beneficial and that India is a genuine partner, and not just a donor of samples.

8. Build Trust in Indian Data: To build trust with lobal partners, actively address and resolve concerns about data integrity and inconsistent SoCs at Indian trial sites.
9. Share Data with Patients: Mandate that investigators and sponsors share clinical trial data in near real-time with the patients and families participating in the trials.

Leverage Advanced Technology

10. Prepare Data for AI: Prioritize the consolidation and organization of fragmented patient data to enable the effective application of AI algorithms for research.
11. Explore Blockchain Health Records: Investigate the feasibility of a blockchain-based health card for every citizen to ensure a secure, validated, and lifelong record of health data that can enable concepts like "digital twins."

AI and digital tools

AI has proven useful for drug repurposing, such as suggesting the drug tretinoin for Ehlers-Danlos Syndrome, with a detailed scientific rationale. It was noted that 70% of the biologics now identified at Sanofi had some AI component to the drug discovery process. AI was also used to design a new nanobody for asthma and identify a new potential use (Type 1 diabetes) for an existing multiple sclerosis drug. However, it was pointed out that when AI is used in drug discovery or drug repurposing, typically, the company providing the AI owns the resulting intellectual property (IP), since the AI is treated as a 'software as a service' and the agreement does not include IP sharing. It is therefore important that IP has to be very clearly defined in any kind of agreement for a collaborative project, especially one that involves AI.

The question arose as to whether AI does a good job in finding the off-target effects of a drug in development? In terms of small molecule, it would do so for around 85–90% cases, and for biologics, around 60–65%. AI helps with safety assessment as well, identifying common safety issues with about 85% precision.

AI has also proven useful for diagnosis. Although the human mind cannot find linkages across a vast array of data, AI may be able to suggest, for instance, that a composite of three particular endpoints is helpful in identifying a particular RD. Another example is where AI can predict a tumor's genetic mutation status directly from a CT scan, providing a cheap and non-invasive surrogate biomarker.

If there was a comprehensive list of the symptomatology of various RDs, an AI could probably outperform primary care physicians, who may struggle to diagnose the RD. In fact, an AI system has been shown to do as well as, if not better than, primary care physicians on diagnostic accuracy and empathy for the patient. To the extent that a given disease label may be the result of either 'lumping' (of different conditions) or 'splitting' (of a given condition), AI can create more precise disease labels for a given condition.

Today, with modern foundational models, one does not need massive amounts of data for every specific task. These models have a broad pre-existing understanding, so they can be fine-tuned for RDs with smaller, more focused datasets. A practical challenge in India is that even major Indian institutions like AIIMS Delhi are not yet fully digitized, creating a large data gap, and making largescale data analysis impossible. However possibly AI itself can be used to solve this problem by capturing patient walking by video, summarizing conversations with audio, and digitizing handwritten notes. Further, even different units within AIIMS will have different digital databases.

Again, AI could provide the bridge between them, providing a solution to this siloization of data. Notably, AI can be designed to handle noisy or imperfect data.

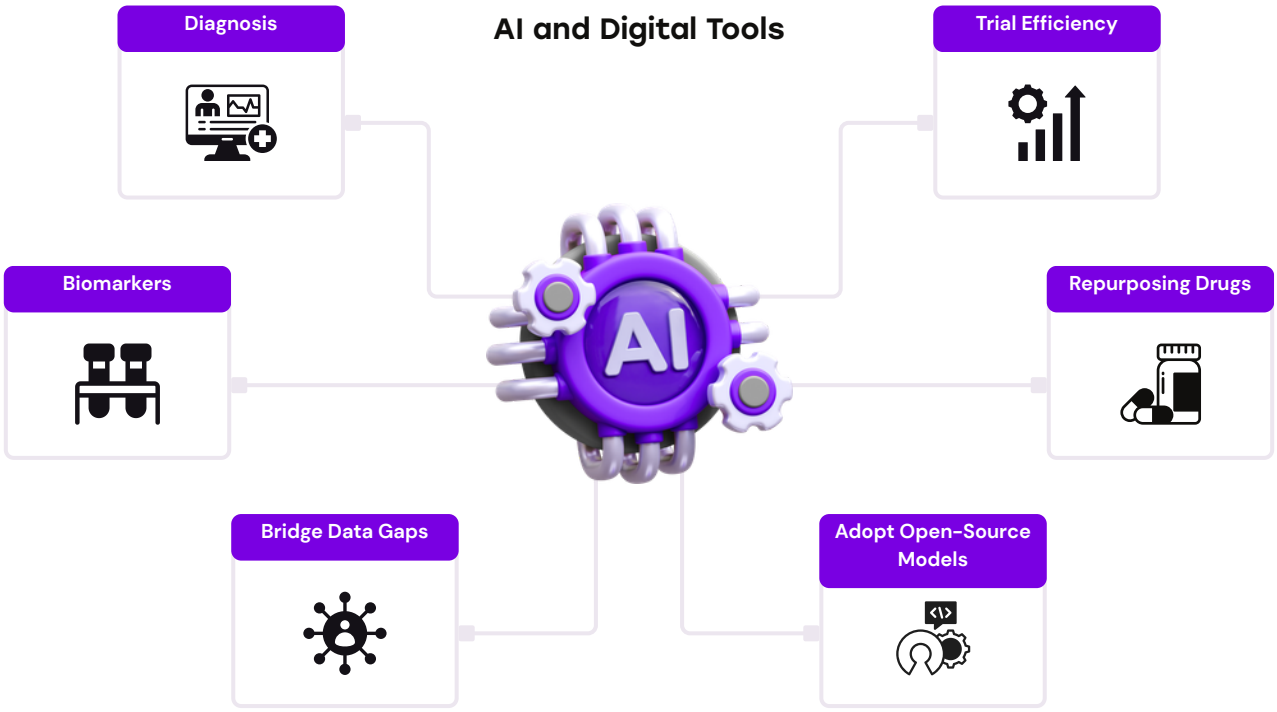
In terms of clinical trials, AI is being used to generate draft trial protocols. It is also being used to create a 'digital twin', that is a virtual model of a patient based on their lifelong health data, to run virtual trials. An agency in Singapore has used AI to identify, based on social media posts, where

particular patients live, and thereby can help speed up the identification of possible participants in trials. As mentioned above, if particular data is combined to produce an endpoint, and the regulator is convinced that this composite is a better endpoint than individual isolated data points, then fewer patients will be required for a trial, an important issue for RDs. In order to address the issue of small patient numbers, AI-generated synthetic data has been used by companies. The European drug regulator, the European Medicines Agency (EMA), has approved this approach, and CDSCO is also agreeable to doing so. It was pointed out that it is ironical that on the one hand we are talking about personalized medicine but on the other the regulators, even internationally, ask for large numbers of trial participants, whom it is a challenge to identify. Ideally, AI should be able to use a person's health records, and predict the expected progression of the condition, and therefore be able to measure any improvement due to an intervention.

On the administrative side, AI has drastically sped up of trials, reducing database lock time from six to two weeks, and the writing of the final report from four months to two weeks.

It was agreed that it was crucial that engineers and medical professionals work together through the entire process of designing Electronic Medical Records (EMRs) and AI tools designed to help doctors. There are now training programmes for doctors in AI to enable this. In fact, the National Academy of Medical Sciences has recently started a three months programme for AI, particularly for health professionals, run by the International Institute of Information Technology, Hyderabad, the idea is that doctors should be fully aware of how AI tools are made.

Finally, we must keep in mind that whereas AI can be extremely useful, it is not cheap. A new AI driven drug discovery company in the US needed to raise $300 million. Probably the best way forward for India is to work with downloadable open-source Large Language Models (LLMs), finetuning them to our specific scenarios, and creating versions that are owned by people who fine-tune the model. However, for some tasks in India, training humans is more cost-effective.



In summary, action points are as follows:

Strategic and Collaborative Framework

1. Secure IP Rights: Clearly define and secure IP rights in all collaborative agreements involving AI, to ensure ownership of discoveries made using these tools.

2. Foster Collaboration: Mandate close collaboration between engineers and medical professionals through the entire process of designing, building, and deploying AI-powered healthcare tools and EMRs.

3. Train Medical Professionals: Expand AI training programmes for doctors and health professionals, like the one offered by the National Academy of Medical Sciences, to ensure they are well-versed in how AI tools are developed, and can contribute effectively to their development.

AI in Diagnosis and Drug Discovery

4. Use AI for drug repurposing for RDs.

5. Deploy AI for Diagnosis: Develop and deploy AI tools to assist primary care physicians in diagnosing RDs by analyzing complex symptom patterns and creating more precise disease classifications.

6. Identify Surrogate Biomarkers: Use AI to analyze real world and natural history data to find easily measurable, non-invasive surrogate biomarkers, such as a serum parameter or muscle strength.

7. Assess Drug Safety: Utilize AI to, with high precision, predict off-target effects and assess common safety issues for new drug candidates, improving the safety profile of therapies in development.

Modernizing Data and Clinical Trials

8. Bridge Data Gaps: Use AI to solve the problem of incomplete digitization by capturing and structuring data from handwritten notes, audio conversations, and video, and by integrating the different databases within a hospital.

9. Enhance Trial Design: Leverage AI to draft clinical trial protocols, identify novel composite endpoints to reduce patient count, and create "digital twins" of patients to run virtual trials.

10. Use Synthetic Data: Gain regulatory approval from CDSCO to use AI-generated synthetic data to supplement small patient cohorts in RD trials, following the precedent set by the EMA.

11. Accelerate Trial Administration: Implement AI tools to drastically reduce administrative timelines for critical tasks like database locking and final report writing.

India's National Strategy

12. Adopt Open-Source Models: Focus on adapting and fine-tuning open-source LLMs for India-specific healthcare needs. This strategy promotes cost-effective innovation and allows for local ownership of the customized models.

Funding for R&D

Given the often-exorbitant price of drugs for RDs, sometimes the only way to make them affordable is to develop therapies from scratch for conditions that are prevalent in India. Although the situation is improving, there has been a dearth of funding for RD research, and therefore research is often in better funded areas such as oncology. It was felt that clinicians and scientists must work together to create joint proposals, as their combined perspectives are essential for success. In any case ICMR now encourages team-based proposals. Although ICMR cannot fund industry, it can fund industry's academic and clinical collaborators. Globally, innovation comes from academia and small startups, not big pharma companies. India must shift its focus to supporting these smaller entities, which could later out-license their products to large companies.

DBT proposed a 'hunt and fund model' of funding academic research, wherein the funding agencies would look for researchers working in particular areas and then fund them for particular projects. The Biotechnology Industry Research Assistance Council (BIRAC) also reiterated this mode of searching for fundable projects in an RD area of interest. To be noted, there may be novel ways of obtaining funding. For instance, in order to research sickle cell disease, scientists had accessed funding through the Ministry of Tribal Affairs. It was felt that there should be government cofunding models that match private investment for clinical trials in high-priority RDs, especially for therapies developed by local academic labs and startups.

In summary, action points are as follows:

1. Prioritize Local Drug Development: Fund the development of affordable therapies from scratch for RDs that are prevalent in India.
2. Mandate Collaboration: Require clinicians and scientists to work together from the start, and submit joint, team-based proposals to funding agencies like ICMR.
3. Support Startups and Academia: For RDs, shift the primary focus of government funding towards academic labs and small startups, as they are the main drivers of innovation globally.
4. Adopt a 'Hunt and Fund' Model: Task funding agencies like DBT and BIRAC to proactively search for and fund promising projects in high-priority RD areas.
5. Create Co-Funding Mechanisms: Establish government co-funding models that match private investment to de-risk and encourage clinical trials, especially for therapies developed by local startups.
6. Explore Novel Funding Sources: Encourage researchers to seek funding from nontraditional but relevant sources, as was done by approaching the Ministry of Tribal Affairs for research on sickle cell disease.

Academic research

RDs are a challenging area, and academic often hesitate to work on them. For instance, often there are no suitable animal models. It was argued that there is a need to develop disease-specific collaborative groups for RDs. Each group should have clinicians, scientists, and patient representatives dedicated to a particular RD. These should become active hubs of research in that RD. The mandate would be to develop disease models relevant to Indian disease phenotypes, assess biomarkers and endpoints, and develop and test potential drugs. Common pathways affecting multiple diseases should be studied for suitable drug targets of processes like mitophagy, endoplasmic reticulum stress, protein misfolding etc. There is a need to establish a network of highquality, ethically governed biobanks to store samples from RD patients, providing a critical resource for biomarker discovery and translational research for RDs. It was also agreed that we need to push forward with natural history studies to understand disease progression, which are vital for trial design. PAGs should be involved to assist patient participation in the entire process.

Needless to say, there is a need for more scientific research towards finding the mechanisms of various RDs to help expedite drug discovery. To be noted, ICMR is now funding RD research well.

It has included RDs in its priority area of research for all extramural grant calls. It is already funding a few projects in all categories of grants including a number of Centres for Advanced Research in the RD area, ICMR also encourages a co-development model with industry, wherein ICMR attempts to de-risk the clinical development of a therapy by directly funding trial sites and also providing all support related to dossier preparation and documentation in cases of regulatory approvals. Additionally, ICMR helps researchers to file patents.

BIRAC is also interested in supporting the development of therapies for RDs. It was proposed that BIRAC conducts a landscape analysis to determine which research groups in the country are working on what, and fund relevant groups. One could try to engage a high-level government coordinating body like NITI Aayog to bring together all necessary government departments (CDSCO, DBT, ICMR, etc.) to streamline oversight for complex national projects in this space. However, it was pointed out that one has to vet collaborators diligently. Due diligence is necessary to ensure that a technology being developed is truly scientifically superior.

In this area, where it is hoped that academic research will translate into medical products, it was stressed that such research must be conducted with regulatory scrutiny in mind. It is important to collaborate with labs/institutions that have GLP facilities right from the beginning of product development. It will help to maintain proper documentation, crucial for research to be scalable and accepted by industry and the regulator. In order to increase awareness among scientists, there needs to be a mechanism to transfer knowledge about regulatory standards to academia.

It was argued that academic researchers who have done very relevant RD work should be incentivized to take the work forward toward the clinic. The scientist could hold a stake in a company, that would incentivize his/her research. It was averred that currently there is no

mechanism to enable this. This may encourage researchers to "pass on the baton" by collaborating with domain experts for different stages of the development value chain rather than trying to do everything themselves. In this regard, there was a call to establish non-profit Product Development Partnerships (PDPs) —groups with industry-level expertise in manufacturing, regulations, and clinical development—to help academic labs advance their discoveries, allowing scientists to focus on science. However, currently there is a deep lack of trust between academia and industry. A company may spend years navigating the bureaucracy of an academic institute, without a positive outcome. Also, there is no transparent mechanism to transfer academic IP to a company.

Due to the low number of patients to conduct clinical trials, the use of in silico methods, both for drug repurposing (for regulatory submission) and for simulation of clinical trials (control arm, different genetic sub-populations of India etc.) could be incentivized and developed. Policy initiatives are required to incentivize the development of these methods for India, specifically for the RDs, for which the cost of treatment is very high and/or no treatments are available.

In summary, action points are as follows:

Foster Collaborative Research Ecosystems

1. Establish Disease-Specific Groups: Create dedicated research groups for RDs, ensuring that each group includes clinicians, scientists, and patient representatives to act as a hub for research. It may be helpful if a group of diseases that target the same tissue are taken together. For example, all muscle degenerative diseases, or those affecting red blood cells, could be grouped together.
2. Incentivize the Development of Animal Models for RDs.
3. Create a National Biobank Network: Establish a network of high-quality, ethically-governed biobanks to store samples from RD patients, providing a critical resource for translational research.
4. Prioritize Natural History Studies: Push forward with natural history studies to understand disease progression, which is vital for designing effective clinical trials, and involve PAGs to facilitate participation.

Implement Proactive Funding and Coordination

5. Understand the biology of RDs: Promote research into the mechanisms of RDs.
6. Conduct a National Landscape Analysis: Rather than waiting for grant applications, task an agency like BIRAC with conducting a thorough analysis to identify all active RD research groups in the country, and proactively funding promising ones to help them move their discoveries toward commercialization.
7. Engage a High-Level Coordinating Body: Involve a body like NITI Aayog to bring together all necessary government departments and agencies (CDSCO, DBT, ICMR, etc.) to streamline the oversight of complex national RD projects.

Bridge the Academia-to-Industry Gap

8. Train Academics on Regulatory Standards: Create a mechanism to transfer knowledge about industry-level documentation and regulatory standards to academic researchers to ensure their work is scalable and accepted by regulators.

9. Incentivize Scientist-Entrepreneurs: Develop a system that allows academic researchers to hold a stake or equity in a company that commercializes their discoveries, encouraging them to advance their work toward the clinic.
10. Establish PDPs: Create non-profit PDPs that provide industry-level expertise in manufacturing, regulations, and clinical development to help academic labs translate their scientific breakthroughs.
11. Streamline IP Transfer: Develop a transparent and efficient mechanism to transfer IP from academic institutions to industry partners, removing bureaucratic hurdles and building trust.

Promote Innovative Methodologies

12. Incentivize In Silico Methods: Develop policy initiatives to encourage the use of computational methods for repurposing drugs and for simulating clinical trial arms, especially for RDs with very few patients.

Model systems

Animal models often fail to recapitulate the disease characteristics or phenotypes which are observed in humans. Therefore, the heavy reliance on animal data for efficacy has been questioned, and it has been suggested that one should move quickly from cell-line studies to human trials, especially for repurposed drugs. Although animal models have been necessary to test a drug's efficacy for a new condition (even if it is a repurposed drug already proven safe in humans), there has been a recent amendment to the Indian regulations that now accepts validated alternatives to animal models for safety and efficacy testing if such an alternative is used anywhere in the world.

Coming to human-relevant model systems, new, complex in vitro disease models (such as human based organoids and induced pluripotent stem cells, or iPSCs) have provided unique insights. For example, for cystic fibrosis, a lung-on-a-chip has been developed, which is like a microfluidic chip lined by bronchial epithelial cells of patient or normal humans. This chip recapitulates several aspects of CF. For some diseases, the pathophysiology has been 90% recapitulated in iPSC-derived organoids. And iPSCs have been used to model the specific mutations found in patients of Osteogenesis imperfecta, where different mutations within the same gene lead to varying drug efficacy, and different outcomes.

It was strongly felt that India should create a centralized, ICMR-supported bank of well characterized iPSC lines from patients. This would make validated models accessible to researchers and prevent duplication of effort.

However, it was noted that at present, organoids are more expensive and time-consuming than animal models to both develop and use[1]. As a pragmatic approach, animal models could continue to be used for safety studies, while in vitro cell models could be used to show efficacy and molecular function. Such work would have to be disease specific, and based on what is scientifically doable. If a disease can be modeled in a dish, then that should be allowed, and there should be clear guidelines that if the in vitro model meets certain parameters, then the drug candidate, for instance, can be taken forward for a human trial. In particular, clinical trials of repurposed drugs should be facilitated where efficacy has been demonstrated in model systems. Meanwhile, the supply chain for all the necessary inputs to the creation and use of such in vitro models needs to be established to bring down the cost.

We need to establish CoEs to focus on such model systems, nurturing skills that are in short supply, and having programmes to develop new technologies. The CoEs would also have tie ups with industry. There needs to be funding for such programmes, and relevant financial and other policy incentives to build these technologies in India.

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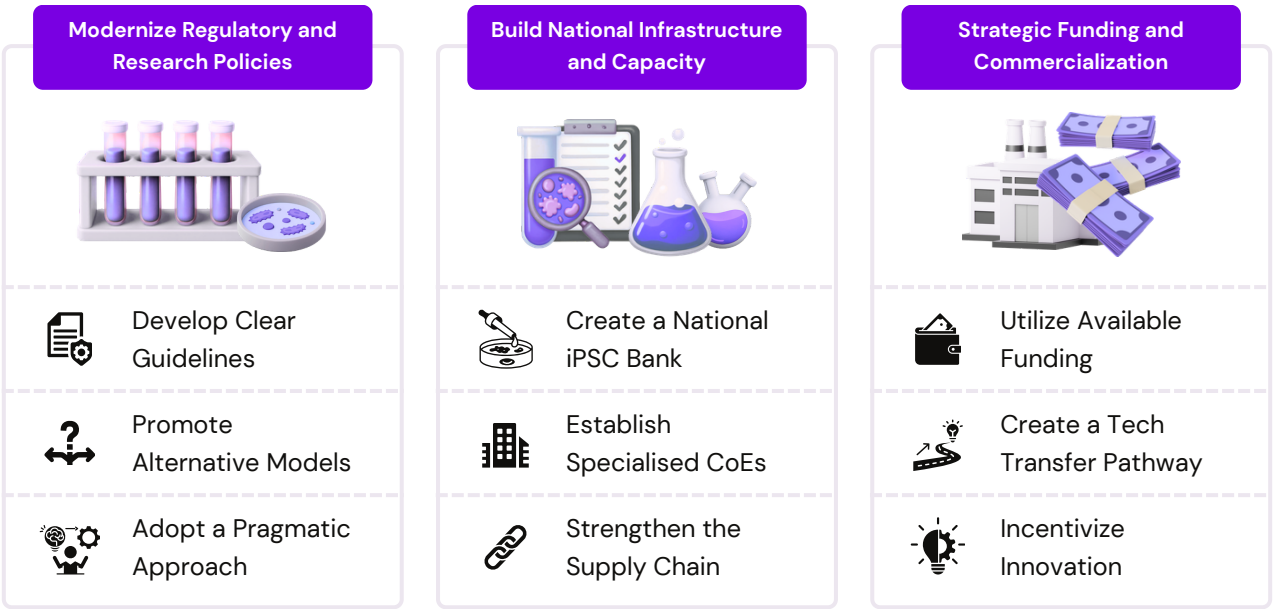
1 Mahadik K, Parvatam S, Rao NM. Pharmaceutical adoption of microphysiological systems in India is contingent on their economics among other aspects. J Biosci. 2025, 50:39. https://www.ias.ac.in/article/fulltext/jbsc/050/0039

The pathway for incorporation of such innovative methods could start from academic and smaller companies which could take them from Technology Readiness Levels (TRLs) 1–3 to 5–6 and then these higher TRL technologies could be adopted by end users such as CROs and pharma companies into the drug development pipelines (both for new drugs and repurposing of existing drug for RDs).

The Department of Pharmaceuticals has launched the Promotion of Research and Innovation in Pharma MedTech sector (PRIP) scheme with an allocation of Rs. 5000 crores, including Rs 700 crores to establish CoEs at seven National Institutes of Pharmaceutical Education & Research (NIPERs), and Rs 4250 crores to accelerate investments in the R&D ecosystem within the sector. At some of these CoEs, and also the RD CoEs, funding could be allocated to develop human-based and innovative models to test drugs for RDs that are of relevance to India, such as those for which treatment is unavailable or is unaffordable to most patients. In general, there is a need to establish funding pathways to encourage the use of innovative human-relevant technologies for RD drug development.



In summary, action points are as follows:

Here are the action points for developing and using alternative model systems for RD research.

Modernize Regulatory and Research Policies

1. Develop Clear Guidelines: Establish clear regulatory guidelines that specify the parameters an in vitro model (like an organoid or organ-on-a-chip) must meet to allow a drug candidate, especially a repurposed one, to advance directly to human trials.
2. Promote Alternative Models: Actively encourage the use of validated human-relevant alternatives to animal testing for both safety and efficacy, leveraging recent amendments to Indian regulations.
3. Adopt a Pragmatic Approach: Due to the cost factor, use animal models primarily for safety studies while prioritizing advanced in vitro models to demonstrate a drug's efficacy and molecular function.

Build National Infrastructure and Capacity

4. Create a National iPSC Bank: Establish a centralized, ICMR-supported national bank of well-characterized iPSC lines from RD patients to provide validated models to all researchers.
5. Establish Specialized CoEs: Create specialized CoEs focused on developing and validating innovative model systems. These centers should be tasked with nurturing the necessary skills and building strong ties with industry.
6. Strengthen the Supply Chain: Work to establish a robust domestic supply chain for all necessary reagents and materials required for creating and using in vitro models to bring down costs and ensure self-reliance.

Strategic Funding and Commercialization

7. Utilize Available Funding: Scientists should be encouraged to make use of the government's PRIP scheme for developing human-relevant models for RDs that are a priority for India.
8. Create a Tech Transfer Pathway: Establish a clear pathway for innovation, where academic labs and startups advance technologies to TRLs 5-6, before they are transferred to CROs and pharmaceutical companies for drug development.
9. Incentivize Innovation: Create specific financial and policy incentives to encourage the development and adoption of these new technologies within the Indian R&D ecosystem.

Clinical trials

Although many issues concerning RDs were discussed during the symposium, the focus was on how to advance clinical trials in RDs. There are many angles to be considered.

At the outset, patients lack information about relevant trials, since most trials take place outside the country. India is underrepresented in global RD trials[2] and it was argued that India should be taking a more active part. In certain cases, this could be enabled through virtual trial mode, leveraging technology. It will require harmonizing clinical trial rules with those of other countries and enhancing Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) capabilities at several trial sites. For local trials, it was noted that although ICMR recommends that trials conducted within the country sample from six zones of the country to ensure ethnic diversity, this is difficult and costly for RDs.

There are three regulatory and ethics issues pertaining to trials that need to be kept in mind for RD patients. These have been termed the 3 'C's: (a) 'counseling and consenting', which is complex with vulnerable RD patients; (b) 'control groups and standard care', which are often nonexistent; and (c) 'compensation' issues, where determining payout for trial-related injury is difficult in patients with pre-existing severe conditions. The formulas for insurance and compensation for adverse events tend to be ambiguous and not clearly defined in monetary terms, creating uncertainty for patients. There is now a publication in press, on how to calculate compensation. It also needs to be kept in mind that children are the largest number affected with RDs, and this tends to be a more complex and sensitive situation.

The design and management of clinical trials have to be tweaked for RDs. It was proposed that innovative trial designs be acceptable in India. These include adaptive designs (like multi-arm, multi stage, or MAMS), master protocols (basket and umbrella trials), and n-of-one trials, none of which are currently acceptable in the country. Such trials require fewer patients, and are faster and cheaper to conduct.

It was argued that instead of the phase-by-phase approach, a trial design with just a phase 1/2a study for determining the biological safety of the drug, the tolerability, a Pharmacokinetics (PK)/Pharmacodynamics (PD) analysis or the maximum safe dose; and a 2b/3 study for dose response, safety and efficacy, subgroup labeling, could be planned. Real-world data or real-world evidence (RWE) and historical controls could also play a big role in such trials. One should align with global best practices of using RWE for endpoints, enabling cost-effective evidence generation and regulatory decisions in resource-limited settings. Researchers can use already available or specifically generated natural history data to correlate endpoints with clinical outcomes, supporting adaptive designs and FDA-like accelerated approvals. Unfortunately, although data from western countries are available for many RDs, that from Indian populations is not.

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2 Chakraborty M, et al. Rare disease patients in India are rarely involved in international orphan drug trials. PLOS Glob Public Health 2(8): e0000890. https://doi.org/10.1371/journal.pgph.0000890 (2022)

Therefore, data generation from local patients should be a top priority. This will require collaborative research between scientists and clinicians on specific RDs. Early and continuous engagement with the regulator will also be required to ensure that the novel trial designs are acceptable.

It was pointed out that FDA guidance allows for single-arm, open-label studies (without a placebo) for RDs due to ethical reasons and the lack of SoC. Perhaps placebos could be eliminated in RD trials by using progression models based on natural history, AI and machine learning to create synthetic control arms from existing data. AI tools could also be used for simulations and endpoint optimization, to minimize costs and ethical issues in trials for diseases like Gaucher or SMA, addressing recruitment delays noted in Indian studies.

However, most statisticians would not be comfortable with some of the trial designs mentioned above. Additionally, the clinical trial data monitoring committees, ie., the Data and Safety Monitoring Boards or DSMBs need to have specific training for RD trials. It was proposed that CDSCO should create a specialized New Drug Advisory Committee (NDAC) or specialized Subject Expert Committees (SECs), that are willing to accept greater risk and side effects for treatment of life threatening RDs and debilitating RDs, as is done during the development of anti-cancer drugs. Special training of these committees might be needed, in collaboration with ICMR and CDSCO. It was suggested that the SECs for RDs should include experts who have dealt with these conditions (pharmacologists or clinical pharmacologists) and including representatives from PAGs, as is done for some oncology ethics committees. It was also proposed that the term 'risk-benefit' analysis be replaced with 'potential risk, potential benefit' analysis.

When designing protocols, especially for global or multi-centric trials, it is important to take into account the operational feasibility and local social/cultural sensitivities of the sites. One example was shared where an India-specific protocol for a global trial was decided upon by holding an investigators' meeting with local oncologists before the protocol was finalized. This model was recommended.

An issue faced by Indian trials has been that USFDA lab standards lead to misclassifying normal variations in the Indian population as severe adverse events. Therefore, there is a need to develop India-specific reference ranges for common lab tests (e.g., for liver function, or electrolytes).

There was general agreement that there is a need to build capacity at trial sites, especially at government institutions and the CoEs. This includes training for investigators, the study team, the support staff etc. A cadre of clinical trial facilitators specializing in handling RDs should also be trained. We should consider integrating genetic counselling into the clinical pathway. It was suggested that there be a brainstorming session, potentially hosted by BIRAC, to develop a network of clinical research sites for RDs by identifying and training potential highly motivated investigators. ICMR already has initiatives like the ICMR's Indian Clinical Trial and Education Network (INTENT), which could be expanded. Further, to reduce high staff turnover, there is a need to create clear career advancement trajectories for trial staff (e.g., research nurses) instead of hiring them for individual projects. It was noted that an academic centre, the M D Anderson Cancer Center in the US, has a large team of 150 people who are intensely involved in running clinical trials for candidate drug molecules. The team is very knowledgeable and efficient. It knows the regulations, and this clinical trial group is better than that of any company. It was proposed

that AIIMS can become a similar centre for India. In fact, it is essential to establish RD treatment and management centres (RDTMC) in as many locations as possible. Each centre should have a multidisciplinary team with recent technologies in clinical investigations and molecular diagnostics. To begin with, all AIIMS should be encouraged to set up RDTMCs.

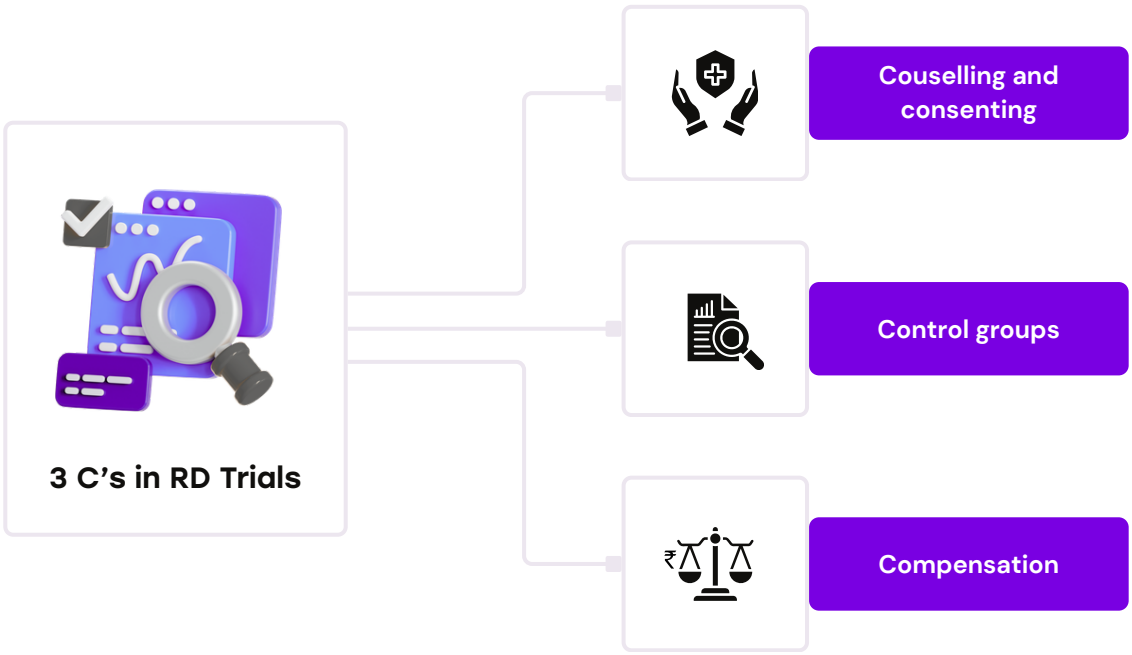
To improve access and recruitment, clinical trial sites need to include primary health centers and district hospitals. But to create effective and practical protocols, all the investigators need to participate in intensive workshops. The network of clinical trial sites could have a central coordinating center that provides shared infrastructure, such as data management systems, biostatisticians, Quality Assurance (QA)/Quality Control (QC) processes, and robust information technology (IT) and clinical data management systems to support sites that lack these resources.

Generally speaking, there is a critical lack of infrastructure, including a shortage of statisticians, with researchers often having data but being unable to afford analysis, for instance. One has to ensure that the costs for all supported investigations and analysis are built directly into the trial budget and protocol from the outset.

Patients should be made aware of the fact that they cannot be excluded from a trial for subjective reasons, outside of the pre-specified exclusion criteria, as this introduces bias and would jeopardize the entire study. A regulator will not accept a study where such exclusion has happened. But patients also need to be aware of the critical importance of honesty and strict adherence to the trial protocol (e.g., not registering at multiple sites or hiding their use of drugs available through 'compassionate use' schemes of other companies). To prevent fraud and duplication, it is important to advocate for a unique RD patient number. Currently, persons with disabilities are issued Unique Disability Identity cards (UDID). The same scheme could be extended to issue UDIDs to RD patients.

There is often a significant gap in understanding between clinicians and patients, especially those from remote areas, due to complex technical language, that needs to be bridged. It is very important to educate patients and patient groups about the nuts and bolts of clinical trials and natural history studies in a language they can understand. Also, not just recruitment but patient retention is very important. It was pointed out that beyond institutional support, the individual investigator must be personally driven and motivated to conduct research. Further, it was noted that patients may lose interest due to unclear eligibility criteria, the high cost of prerequisite genetic tests (15,000– ₹ ₹20,000), and a lack of communication about trial progress.

An industry clinician mentioned that his organization achieves around 99% retention by providing trained study coordinators at sites and budgeting for patient travel and accommodation. The latter issue was flagged by others as well. The practice of reimbursing families for travel and accommodation is not ideal. Instead, trial sponsors should hire agencies to pre-arrange all travel and lodging, sending tickets directly to families to make participation more humane and feasible, as is done abroad. There should be specific funds for recruitment, as screening can take substantial resources. Developing a specialized group of nursing professionals trained to administer homebased infusions would support patients in long-term trials as well. Finally, if trials are decentralized, and wearables used as much as possible, this would help to increase coverage and minimise patient travel, to avoid the inconvenience and cost of travelling to distant health facilities.



In summary, action points are as follows:

Regulatory and Ethics Framework

1. Increase Participation: Actively promote and increase India's participation in global clinical trials for RDs, utilizing technology for virtual trial modes where feasible. As necessary, harmonize clinical trial rules in India with those of other countries and enhance GLP and GMP capabilities at several trial sites.
2. Standardize the '3 C's': Develop clear and robust national guidelines for the complex ethical and regulatory issues in RD trials: counseling and consenting, the use of control groups, and fair compensation for trial-related injuries.
3. Establish dedicated SECs: Create specialized Subject Expert Committees (SECs) for RDs, comprising relevant clinical experts, pharmacologists, and representatives from PAGs, to ensure expert oversight.
4. Train Oversight Committees: Provide specialized training for DSMBs and SEC members on the unique aspects of RD trials, including accepting different risk-benefit profiles for lifethreatening conditions.
5. Adopt New Terminology: Shift the terminology from a 'risk-benefit' analysis to a 'potential risk, potential benefit' analysis in trial review, to better reflect the uncertainties inherent in treating RDs.

Trial Design and Data Management

6. Approve Innovative Designs: Work with regulatory bodies like CDSCO to have innovative trial designs such as adaptive trials, master protocols (basket/umbrella), and n-of-one trials accepted and approved, since such trials require fewer patients, and are faster and cheaper to conduct.
7. Streamline Trial Phases: Adopt a more efficient, condensed trial approach (e.g., combined Phase 1/2a and 2b/3 studies) to accelerate drug development.

8. Leverage AI and RWE: Promote the use of AI to create synthetic control arms and utilize RWE and natural history data from registries to support trial endpoints and regulatory decisions.
9. Develop Indian Lab Standards: Establish India-specific reference ranges for common laboratory tests to prevent the misclassification of normal population variations as severe adverse events in global trials.
10. Create Unique Patient IDs: Advocate for and implement a unique patient identifier for individuals with RDs, to prevent fraudulent or duplicate trial enrollment. RD patients could be issued Unique Disability Identity cards (UDIDs), that are issued to persons with disabilities.

Capacity Building and Infrastructure

11. Establish a National Network: Develop a coordinated national network of clinical research sites for RDs, with a central hub providing shared infrastructure like data management, biostatisticians, and quality assurance.
12. Build an Expert Hub: Develop several large, knowledgeable, and efficient clinical trials group at premier institutions like the AIIMS to serve as RDTMCs, similar to the M D Anderson Cancer Center model.
13. Train a Specialized Workforce: Create a dedicated cadre of clinical trial facilitators, research nurses, and support staff specializing in RDs and integrate genetic counselling into the clinical trial pathway.
14. Create Career Paths: Establish clear career advancement trajectories for clinical trial staff to reduce high turnover and build institutional expertise.
15. Budget Appropriately: Ensure that trial budgets explicitly include costs for all necessary investigations, data analysis, and patient recruitment and retention activities from the outset.

Patient Centricity and Support

16. Decentralize trials, and use wearables as much as possible, to increase coverage and minimise patient travel, to avoid the inconvenience and cost of travelling to distant health facilities.
17. Improve Patient Logistics: Mandate that trial sponsors pre-arrange and directly cover all travel and accommodation for patients and their families, eliminating the burdensome reimbursement process.
18. Develop Home-Based Care: Create a specialized group of nursing professionals trained to administer home-based infusions and provide care to support patients enrolled in long-term trials.
19. Educate Patients: Develop and disseminate educational materials about the clinical trial process in simple, accessible language to bridge the understanding gap between clinicians and patients.
20. Ensure Fair Inclusion: Make patients aware that they cannot be excluded from a trial for subjective reasons beyond the pre-specified exclusion criteria to prevent bias.

Post-trial access

Patients in India, who participate in international trials, may have no access to the drug subsequently, if the company decides not to market it in India. Therefore, a clear framework is required that outlines the sponsor's responsibility to provide continued access to trial participants in case the drug is beneficial, until it becomes commercially available. However, it has been noted that even for a company to import a drug that was used in a small trial in India, for example for 18 patients, there are hurdles because the import license has expired. Therefore, the regulator should have a provision to enable such imports.

In summary, action points are as follows:

1. Establish a clear regulatory framework that mandates sponsors to provide continued, posttrial access to a beneficial drug for trial participants until it becomes commercially available in India.
2. Create a specific regulatory provision to streamline the process for importing these drugs for post-trial access, even after the import license for the purpose of the trial has expired.

Industry

The larger challenge is that there is very little drug development happening in India. However, GoI's PRIP scheme would fund RD drug development. It was argued that the government should provide more incentives, such as tax credits, to encourage pharmaceutical companies to invest in RD drug development. In fact, the country could enact an Orphan/Rare Drug Act, similar to the U.S. Orphan Drug Act of 1983, that offers incentives such as tax credits, grants, market exclusivity, and fasttrack regulatory approvals to promote the development of treatments for RDs.

For industry, challenges include the long and complex process of drug discovery in general, that is compounded by the small number of patients with RDs, and their wide disbursal across the country. Industry is also apprehensive of price caps that the National Pharma Pricing Authority is likely to impose. However, existing drugs could be repurposed – that would be low hanging fruit. For that there needs to be strong industry-academy partnership so that novel ideas can be shared. Industry is very knowledgeable about how trials should be done properly, including the protocol, the site readiness, the Clinical Trial Applications or CTAs, the statistical analysis and the preparation of Clinical Study Reports or CSRs. If this knowledge extends to RDs, where smaller trials are needed the knowledge should be tapped.

It was also pointed out that Indian pharmaceutical companies are unwilling to advance new molecules unless they have already been tested in humans in the US or other countries that are members of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), causing India to lose out on developing its own IP.

To bring down costs, all components of the supply chain must be manufactured in India. This requires working with companies, sometimes training their personnel, and negotiating with government to access necessary technologies.

In summary, action points are as follows:

Provide Government and Financial Incentives

1. Offer Tax Credits: Provide incentives, such as tax credits, to encourage pharmaceutical companies to invest in RD drug development.
2. Utilize Existing Schemes: Actively use government initiatives, like the PRIP scheme, to fund RD drug development projects.
3. Price caps: The government should allay fears about stringent price caps for any drug developed for an RD.

Strengthen Industry and Academia Collaboration

4. Foster Partnerships: Promote strong industry-academia partnerships to pursue low-hanging fruit, such as drug repurposing, by sharing novel ideas and resources.
5. Leverage Industry Expertise: Create platforms to tap into the pharmaceutical industry's deep knowledge of conducting efficient trials, including protocol design, site readiness, and regulatory submissions for smaller RD studies.

Promote Local Innovation and Manufacturing

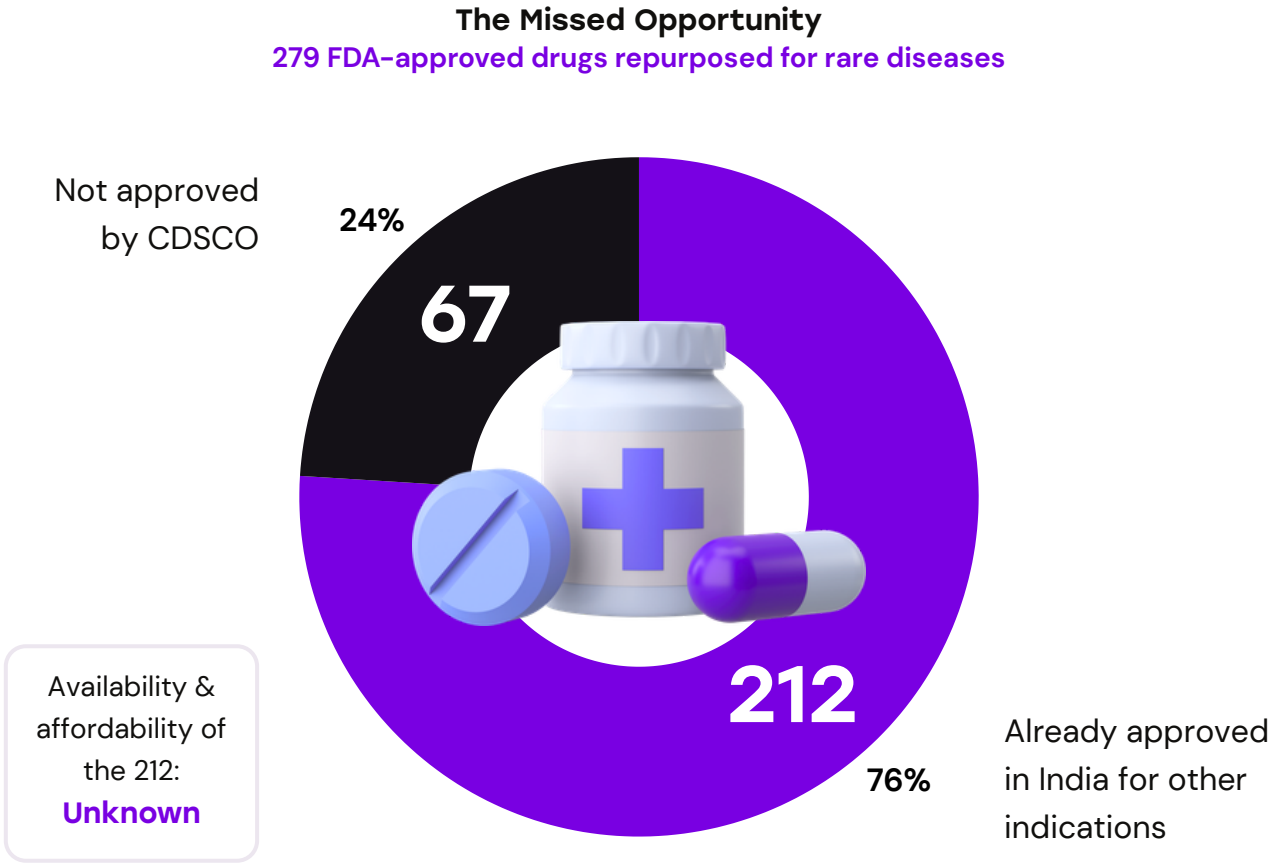
6. Encourage Local IP: Develop policies and an ecosystem that encourages Indian companies to advance novel molecules developed domestically, helping to secure local IP rather than waiting for foreign validation.

7. Establish a Domestic Supply Chain: Work to have all components of the drug supply chain manufactured in India to bring down costs, supported by personnel training and government negotiations to access necessary technologies.

Repurposing drugs for RDs

Repurposing drugs that are used for other conditions are a possible alternative for RDs due to their cost-effectiveness and reduced timeline for development. India's patent regime prevents the evergreening of drug patents, and a large generic manufacturing industry provides ample opportunity to explore the potential of repurposed drugs for treating RDs. These are known as repurposed orphan drugs. However, there is no portal or other source for information on orphan drugs which lists the drugs that are approved for marketing in India. As such there may be many drugs which are approved for repurposing by regulatory bodies such as USFDA and EMA and are off patent. These may be eligible for generic manufacturing in India but due to lack of information these drugs remain unavailable to patients in India.

A total of 279 drugs approved by the FDA have been repurposed for RDs. Most of these, 212 (76%), are approved in India for some condition[3] . However it is not known whether all of them are available and affordable in the country. The remaining 67 (24%) drugs have not been approved by CDSCO. So, there is a need to check that the 212 drugs are available and affordable in India, and to seek approval for the 67 drugs.



3 Rajueni K, Choudhury MC. Assessment of the availability of repurposed orphan drugs in India. PLOS Glob Public Health. 2023 Sep 27;3(9):e0001498. doi: 10.1371/journal.pgph.0001498.

It was noted that clinicians are hesitant to try repurposing drugs for new indications (off-label use) due to the cumbersome approval process and fear of legal action. It was clarified that off-label use is not illegal if the drug's dose and route of administration remain unchanged.

In summary, action points are as follows:

Create a National Orphan Drug Portal

1. Develop a comprehensive and publicly accessible national database of all orphan drugs. This portal should clearly list repurposed drugs approved by international bodies like the US FDA and EMA, along with their patent status and current availability in India, to facilitate generic manufacturing and patient access.

Systematically Investigate Potential Drugs

2. Launch a national initiative to systematically investigate drugs for their potential to be repurposed to treat RDs prevalent in India. This effort should prioritize the large number of drugs already approved in India for other conditions, as well as those that currently need to be imported, to find treatments for conditions where none exist or that are unaffordable.

Support and Clarify Off-Label Use

3. Issue, and widely disseminate, clear guidelines to clinicians clarifying the legality of offlabel use of drugs in treating RDs. This will help reduce the fear of legal action and encourage doctors to consider cost-effective, repurposed treatment options for their patients.

IPR

There was agreement that IP needs to be handled in a manner such that it helps both to bring out a product and reduce the cost of access. We need to conduct high-quality basic science research, in parallel with the development of therapies, to generate IP. It was noted that scientists generally lack IPR knowledge, which can delay or prevent treatments from reaching patients since IP is critical for attracting venture capital investment and industry partners, and ultimately lowering the price of the therapy. But we also need to encourage a collaborative model that discourages academic institutions from forcing mandatory IP licensing fees and royalties for RD therapies, as these practices add to the final cost. The question arose as to whether a patient group would violate IP laws if it contractmanufactured a patented drug for its members without selling it at a profit. The legality would depend entirely on the national laws of that specific country.

In summary, action points are as follows:

Develop a Balanced IP Framework for RDs

1. Create a national IP strategy for RDs that simultaneously encourages the development of new therapies by protecting discoveries while also ensuring that the final products are affordable and accessible to patients.

Empower Researchers with IP Knowledge

2. Generate Local IP: Conduct high-quality basic science research in parallel with therapy development to generate valuable, homegrown IP.

3. Provide IP Training: Implement comprehensive training programmes on IPR for academic scientists to help them understand how to protect their work and attract the investment needed to bring treatments to patients.

Promote Collaborative and Affordable Licensing

4. Encourage academic institutions to adopt a collaborative model that waives or reduces mandatory IP licensing fees and royalties for RD therapies. This will help lower the final cost of the drug for patients by reducing the financial burden on developers.

5. Have progressive interpretations of compulsory licensing provisions and licensing of IP rights to philanthropic foundations engaging in RD drug development.

6. The government should negotiate for licensing of IP rights on fair and reasonable terms on behalf of philanthropic organizations who want to manufacture and develop RD drugs for charitable purposes.

Clarify Legal Boundaries

7. Issue clear legal guidance to patient groups and other stakeholders on the specific national laws governing IP. This should clarify the rights and limitations regarding the manufacturing and distribution of patented drugs, even for non-profit, compassionate use.

Genomics and IPR for therapeutics

Currently, enzyme replacement therapies, for instance, may cost between Rs. 40 lakh and Rs. 1 crore per year per patient. There are now genome-based technologies that are being developed that could reduce these costs. For instance, mRNA therapeutics are much cheaper to make, and could cost less than Rs. 10,000 per year per patient. And although the production cost of the Moderna vaccine for COVID-19, an mRNA vaccine, was around $3–4 a dose, it could be manufactured significantly more affordably in India.

Academic institutions have taken an innovation only approach so far, without any plans for taking forward to clinical trials. Smaller companies need some concessions from the government to enter this area. It has to be economically viable for them to take up drug development for RDs. Possibly, one could identify the top three or four areas where academic research in India is ongoing (such as gene editing, antisense oligonucleotides and mRNA therapeutics), and then suggest to the government a path forward in these areas.

Although there are apprehensions about the cost of genomic screening compared to existing biochemical tests, it was pointed out that with the steep fall in the costs of genome sequencing, it is becoming increasingly affordable to use genomics to identify and manage diseases.

Currently, India deposits its biological data in global repositories such as the National Center for Biotechnology Information (NCBI), which serves as an international archive for nucleotide and protein sequences. However, NCBI does not categorize submissions by country, making it impossible to quantify India's exact contributions. Importantly, NCBI is funded and maintained by the US National Institutes of Health (NIH) and its National Library of Medicine (NLM), raising concerns about whether research outcomes generated using Indian public funds should continue to be deposited in a foreign government-funded repository. In recent years, it has become mandatory to deposit certain biological data, generated by public funds, in IBDC[4] . If IBDC were to be expanded to include basic research data pertaining to RDs, then this would be a valuable resource. ICMR's NRROID registry has data of almost 206 conditions. This data is captured in a structured manner, with all quality checks in place. At the same time, research on RDs where patient numbers are low, depends critically on global collaboration. Pooling data across countries is essential to understand natural history of the disease, progression, and mutation patterns, all of which remain poorly characterized. This raises an important question: Can WHO facilitate mechanisms for secure data collaboration, globally, or at least within its South-East Asia Regional Office (SEARO), while also ensuring that India retains sovereignty and protection over its patient data?

4 https://ibdc.dbtindia.gov.in/

In summary, action points are as follows:

Prioritize Cost-Effective Technologies

1. Champion Genome-Based Therapies: Prioritize the development and adoption of affordable, cutting-edge platforms like mRNA therapeutics, which have the potential to reduce annual treatment costs from tens of lakhs, or crores, of rupees to under ₹10,000.
2. Promote Genomic Screening: Encourage the widespread use of genomic screening for diagnosis and management, taking advantage of the rapidly decreasing costs of genome sequencing to make it a standard tool.

Create a Clear Path to Commercialization

3. Identify Priority Research Areas: Identify the top three or four RD research areas where Indian academics are most active and have promising innovations.
4. Propose a Commercialization Roadmap: Based on this analysis, propose a clear path forward to the government, that includes specific concessions and incentives to make it economically viable for smaller companies to enter the RD drug development space.

Ensure Data Sovereignty and Global Collaboration

5. Explore a National Data Repository: Investigate the creation of a national or regional (South-East Asia Region) biological data repository to ensure India retains sovereignty and control over patient data generated with public funds. Expand IBDC to include basic research data pertaining to RDs.
6. Engage with the WHO: Propose that the WHO facilitate a mechanism for secure global data collaboration. This framework should allow for the essential pooling of data for RD research while protecting the sovereignty and privacy of national patient data.

The cost of RD drugs

RD drugs can be exorbitantly expensive. In order to tackle the high prices, GoI has a multi-pronged strategy to make drugs affordable. This strategy includes the following:

a. DBT has established 12 biotech parks[5] . The Department is investing heavily in this area. For example, 1000 crores is being ₹ invested in one of the parks, Genome Valley in Hyderabad, to create platforms that small companies can use at a low cost, to enable bio-pharma scale up.

b. BIRAC and DBT are providing significant funding for joint industry-academia projects.

c. Although there will be price controls, the National Pharmaceutical Pricing Authority will allow companies to make a reasonable, but not exorbitant, profit.

d. Conducting trials in India can reduce drug development costs to as little as 1/4th or 1/5th the global cost, and steps are in place to support such trials.

e. The Production Linked Incentive scheme (10,000 crores) aims to promote local manufacturing of Active Pharmaceutical ₹ Ingredients (APIs), and reduce reliance on expensive imported molecules.

f. GoI is encouraging consortia to make bulk purchases, which can significantly lower costs.

g. Learning from the COVID-19 vaccine story, where industry manufactured vaccines at the government's request, but then were left with unused stocks, the government could provide assurance to companies that their manufactured product will be purchased, thereby reducing industry risk.

In terms of the costs of RD trials, it was noted that sometimes the cost of the comparator drug that has to be imported is 80% of the costs of a trial. Responding to the requests of patient groups, some concessions have been implemented. Integrated GST and basic custom duties are now exempt for RD drugs. It was also suggested that rather than negotiating the price of one drug at a time, there should be negotiations with multinational companies for a bundle of RD therapies. Better negotiations should lead to reduced prices. Also, India's large population should be leveraged as a powerful negotiating tool. When companies test drugs in India, they gain valuable data, which should be factored into the negotiations on pricing.

In summary, action points are as follows:

Implement Government-Led Financial Strategies

1. Take advantage of various government schemes: Leverage the multi-pronged government strategy to make drugs affordable.

2. Provide Purchase Guarantees: The government should offer purchase guarantees to companies that manufacture priority RD drugs at the government's request, de-risking their investment and ensuring supply.

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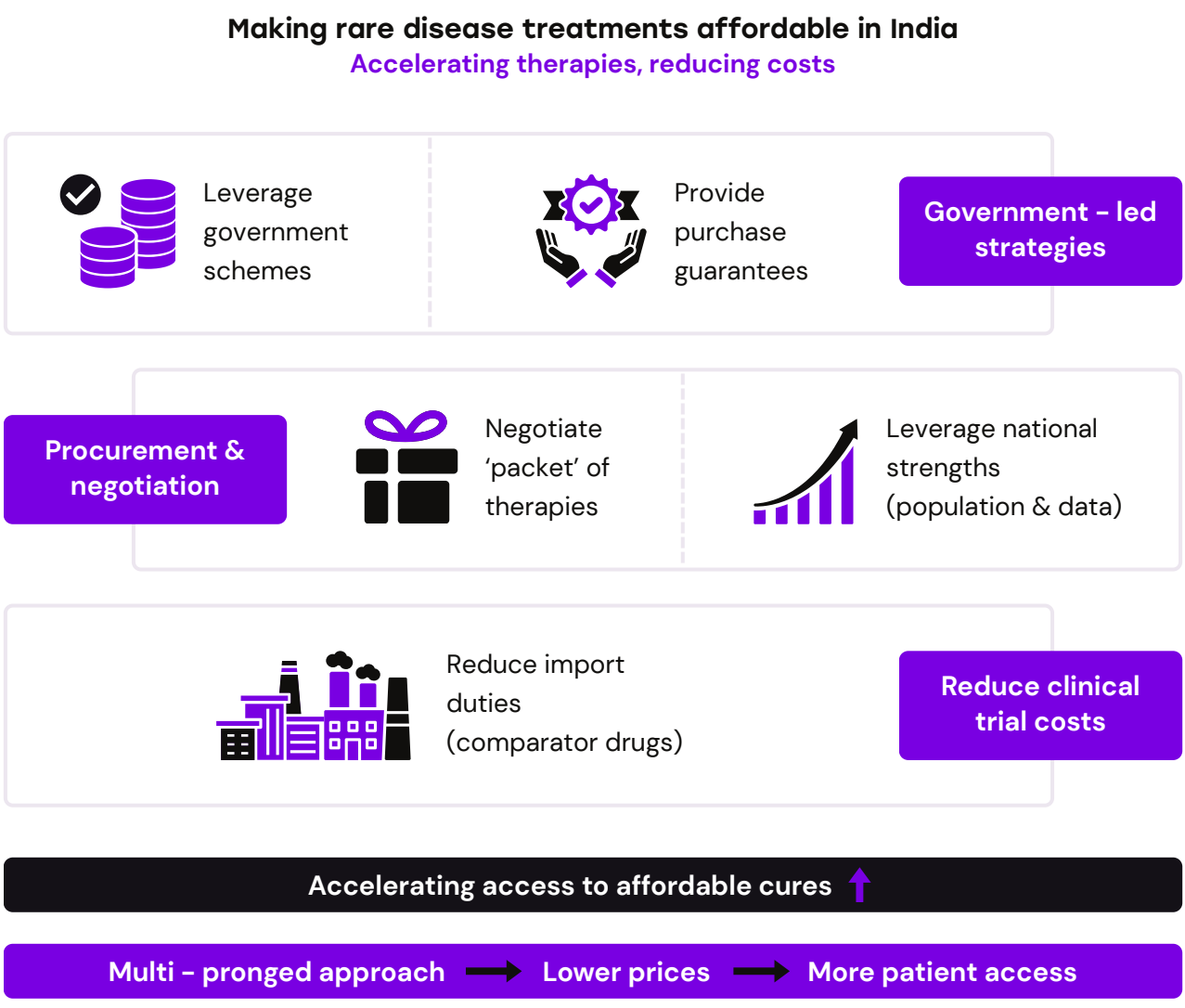
5 https://dbtindia.gov.in/scientific-directorates/bio-wealth-biosafety/biotech-park

Strengthen Procurement and Negotiation Tactics

3. Negotiate for a "Packet" of Therapies: Shift from negotiating the price of one drug at a time to negotiating for a bundle of multiple RD therapies with multinational companies.
4. Leverage National Strengths: Use India's large population and the valuable data generated from local clinical trials as a powerful negotiating tool for better drug pricing.

Reduce Clinical Trial Costs

5. Reduce Import Duties: Lower or exempt import duties on expensive comparator drugs that are imported for use in clinical trials.



Ethics

Ethics play a foundational role in research. For RDs, planning to conduct an ethical study extends through the entire research lifecycle. It is not just about obtaining informed consent. It ranges from the conceptualization of the trial, preparing for it, conducting the trial, follow-up, completion, and even post-study translation of knowledge. Comprehensive care, including counseling needs to start from before the diagnosis, and continue till after the trial. Even after approving a trial, the Ethics Committee must actively monitor the research. A comprehensive ethics plan must address equitable access and affordability; protocols for data storage, sharing, and de-identification; provision of psychosocial support; strengthening of the healthcare system; prioritization of efforts and resources; and empowerment of patients.

Although individual trial sites tend to have their own Ethics Committees, the group discussed the need for a Central Ethics Committee, managed by ICMR specifically for initiating clinical trials for RD drugs. In addition, it was felt that training members of existing Institutional Ethics Committees (IECs) on the unique issues related to RD clinical studies may be highly useful. The reviewing IEC should be required to include at least one patient representative from the RD community, especially if it pertains to their RD, and members familiar with the science of RDs.

We need to be conscious of issues of equity. Usually it is an urban, educated person from a Western nation and a well-studied ethnicity who participates in a trial. Even the goal of using technology to aid trials has drawbacks that we need to be aware of. For instance, it has been seen that whereas patients in a private sector hospital may have a smart phone, those visiting a public hospital may not even know how to use one.

Patients, and members of PAGs need to be trained on patients' rights. And the public needs to be made aware of their rights in research so they can make complaints to the IEC if necessary.

In summary, action points are as follows:

Implement Comprehensive Ethics Oversight

1. Develop a Holistic Ethics Plan: For every RD trial, create a comprehensive ethics plan that covers the entire research lifecycle—from initial design to post-study follow-up and knowledge sharing.
2. Mandate Active Monitoring: Require that IECs actively and continually monitor research throughout the trial, rather than only providing approval at the start.
3. Ensure Comprehensive Care: Provide comprehensive support, including counseling, that starts before a diagnosis, and continues long after a trial has concluded.

Strengthen Ethics Committees

4. Provide Specialized Training: Implement specialized training programmes for members of IECs on the unique ethics challenges of RD research.
5. Include Patient Representatives and Scientists: Mandate the inclusion of at least one patient representative from the relevant RD community, and a scientist in that area, on any IEC that is reviewing a trial for that disease.

6. Simplify the Ethics Committees' Functioning: Procedures should be simplified so that ethics and other committee approvals are made public within a week of the meetings, and the need for physical signatures is waived.

Promote Equity and Inclusivity

7. Design for Equity: Proactively design recruitment strategies that ensure equitable access for diverse populations, consciously avoiding biases toward the urban and educated, or specific ethnic groups.
8. Address the "Digital Divide": When using technology in trials, create non-digital or hybrid pathways to ensure patients without access to, or knowledge of, particular technologies, including smart phones, are not excluded.

Empower Patients and the Public

9. Train Patients on Their Rights: Conduct training programmes for patients and PAGs to educate them on their rights as research participants.
10. Launch a Public Awareness Campaign: Inform the general public about their rights in research and the proper channels for making complaints to an ethics committee if they witness unethical practices.

Regulatory matters

The New Drugs and Clinical Trials Rules, 2019 (NDCT Rules) contain several progressive features, including processes for accelerated approval or expedited review, and waivers for local clinical trials. However, whereas foreign-approved drugs for unmet medical needs may be given such waivers, companies must still provide data demonstrating the drug's safety and efficacy in the Indian population. Discussions are ongoing between medico-scientists and CDSCO, regarding possible amendments to the NDCT Rules, identifying areas where flexibility/waiver can be granted for RD trials while ensuring adherence to scientific and ethics standards. One of these issues is the '50 km rule', which states that a trial can only be conducted in a medical facility if there is an Ethics Committee in that facility or within a radius of 50 kms. It was argued that today, with digital means of effective supervision of sites that are further away, this rule should not apply. This is especially so for RDs, where patients may be scattered in far flung areas, and an excellent IEC may not be locally available. Such a modification of NDCT Rules could lead to an increase in the ease of conducting clinical research.

Another amendment proposed by a participant was that investigators and sites should be registered, as IECs are. It was felt that these would be very beneficial since small players sometimes lose out when this doesn't happen.

It was pointed out that the USFDA has a process to keep up with the latest developments in science. It was recommended that CDSCO could also have a dedicated division that looks at any promising area where scientific advancements are happening, whether in RDs or other areas. They could collaborate with the scientists, understand the science and also bring in international experts if it is possible, and thereby contribute very early on in the development of any potential novel product. Researchers were strongly urged to collaborate with CDSCO from the very beginning of a project. It was suggested that patients or members of PAGs be included as official members of regulatory bodies to ensure that the patient perspective is central to decision-making.

To be noted, during COVID-19, due to the emergency situation, although Pfizer was working on an mRNA vaccine, it could not conduct all the required trials, and for the first time, the USFDA performed a rolling review of data that the company submitted every few weeks, as it became available. Perhaps CDSCO could adopt such a method for RDs. Also, currently, the regulatory pathway is the same, whether it is for one patient or 2000 patients, which is a challenge in the case of RDs. It was recommended that CDSCO establish a special RD clinical trial review team, that understands the paradigm and can fast-track the approval process. In this connection, a suggestion was made that BIRAC should come up with a guidance document for CDSCO.

Since the Drugs Technical Advisory Board (DTAB) is the highest statutory body in India that advises the Central and State Governments on technical matters related to the Drugs and Cosmetics Act, 1940, a special meeting may be convened to specifically discuss RD drug development. Patients and PAGs should be part of these committees, as they are knowledgeable about diseases.

Some start-ups are developing products in the RD space. Their major challenges have been the lack of predictable timelines for various processes, such as approvals by various committees. International sponsors have also commented on the "lengthy and unpredictable" regulatory timelines in India, which deters them from running trials here. It was argued that the rules should give the company permission to proceed in case the timelines have not been met. It is appreciated that in a 2025 amendment, following recommendations from the DTAB, the Union Health Ministry has halved the timeline for trial drug manufacturing approvals from 90 to 45 working days. Also, if no communication is received from the CLA within the stipulated time, the application may be considered as deemed approved, subject to conditions.

Small steps can be extremely helpful. For example, if e-signatures were acceptable, it could cut 1–2 months off an approval timeline. In order to cut down the delays to trial initiation, it was proposed that there be a change from the current sequential approval process (for instance, from the Drug Controller General of India (DCGI) to Ethics Committee to the Health Ministry's Screening Committee (hMSC), to a system where the assessments are undertaken in parallel. It was also proposed that an "integrated research application system" be created that acts as a single window for submitting applications to multiple regulatory bodies.

Regulators should guide industry and support it in reaching first-in-human trials. Then drug development will translate into actual clinical trials and commercialization. It was proposed that a clinical trial Advancing Rare Disease Therapeutics programme be established, where researchers can have discussions with the regulators, to obtain guidance on how to develop the data for getting approval to run clinical trials. Although pre-Investigational New Drug (pre-IND) meetings with CSDCO have been initiated, trialists found that they were not very useful. They called for the advice given by the regulator during these meetings to be binding, as happens at the FDA and EMA.

CDSCO clarified that a drug manufactured under GMP, for GLP tox studies could be used in a clinical trial. Usually studies from two animal species would be required, it was suggested that if there was enough data to justify cutting it down to one species, that should be considered.

Global regulators are increasingly accepting data from non-animal models. In fact, the NIH is planning to de-prioritize funding for animal-only studies, and the FDA released a roadmap to reduce animal testing in pre-clinical safety studies. A survey found that over 60% of the 27 surveyed pharmaceutical companies use in vitro or in silico models, usually in combination with animal data, for regulatory submissions. The USFDA is in the process of qualifying a liver-on-achip for safety testing, and Sanofi has already filed an IND application for an RD based purely on efficacy data from a human-on-a-chip system. Organoids and organ-on-a-chip are still being standardize and validated for different conditions. Scientists felt that clear regulatory guidance from CDSCO is needed to build confidence, and encourage Indian researchers and companies to use these new methods for regulatory submissions.

It was also argued that we need to have international regulatory collaborations. This will make the trials more efficient, and may accelerate drug development around the world.

For gene therapies using common "vehicles" (like adeno-associated virus (AAV) vectors), it was

recommended that platform-based regulatory pathways be created where extensive toxicity studies for the vehicle do not need to be repeated for every new drug, since this would save significant time and money. It was also proposed that regulatory documents be updated to include new, more efficient scientific methodologies for product release and safety assessment.

It has been noted that regulators have shown flexibility with cutting-edge therapies. For the FDA approved CRISPR therapy, proving that edited cells could engraft in mice was sufficient, without needing a perfect animal model that replicated the entire disease. In a similar way, for RDs, CDSCO should be more flexible and evaluate submissions on a case-by-case basis.

In terms of drugs in development, similar to the Expanded Access programme of the USA, India does have a framework and provisions that allow for the use of unapproved drugs for rare orphan diseases. However currently it is a somewhat cumbersome and a time-consuming process. It was suggested that the consent of the patient and a certificate from an attending physician should be sufficient for approval. Moreover, the requirement of continuation of a phase III trial may be waived where the data from a phase I and II trials show minimal toxicity and significant efficacy. Since some of the provisions are embodied in Drugs and Cosmetics Act, 1940 and Rules, 1945, and others in the New Drugs and Clinical Trial Rules, 2019, a consolidated policy would be helpful.

However, even experimental drugs are likely to be extremely expensive, and providing them free of cost may be a challenge. Patient advocates argued that FDA-approved drugs for very small patient populations should be made available for local sale and distribution directly, instead of forcing patients to go through a cumbersome individual import process. A simplified, single-window regulatory process is also needed for clinicians to access unapproved medicines for critically ill patients who are not eligible for any trial.

It was argued that a regulatory framework should be created that allows accredited hospitals and academic centers to manufacture certain drugs, such as antisense oligonucleotides (ASOs) or cell and gene therapies, at small scale, for N-of-1 or small cohort use. This can be modeled on the new framework introduced by the UK's Medicines and Healthcare Products Regulatory Agency (MHRA), which permits National Health Service (NHS) hospitals to produce highly personalized medicines.

There is a need to strengthen regulatory capacity to understand complexities of innovative designs, and address associated clinical data requirements. The Translational Health Science and Technology Institute (THSTI) is planning to start formal training programmes in regulatory science to build a professional cadre that can navigate complex regulations for evolving technologies.

Although there may be flexible policies like fee waivers, tax credits, and expedited reviews for RD therapies, there is a need for a clear guidance document and simplified rules. It was argued that it is important to further strengthen regulatory incentives. CDSCO should prioritize indigenous orphan drug development through specific programmes, reducing reliance on imports and enabling faster local trials, as highlighted by recent guidance documents from the US and Europe.

Finally, the establishment of a National Apex body for RDs was mooted. It is felt that the implementation of the Government's various policies on RDs (including the provisions in the National Policy on Rare Diseases, NPRD) requires a concerted approach involving all the

participating ministries and departments (DST, Ministry of Health and Family Welfare (MoHFW), ICMR, Department of Health Research (DHR), DBT, Ministry of Chemicals and Fertilisers, CDSCO). A National Apex Body on RDs could provide policy and strategic direction, manage inter-ministerial coordination, perform monitoring and evaluation, facilitate the quick resolution of problems, and generate and organize resources. It would streamline processes, and foster innovation in this sector.

In summary, action points are as follows:

Modernize Regulatory Processes and Rules

1. Amend the '50 km Rule': For RD trials, amend the NDCT Rules to remove the requirement for an Ethics Committee to be within 50 km of a trial site, allowing for effective digital supervision of remote sites.
2. Shift to Parallel Approvals: Replace the current sequential approval process with a parallel system where applications are reviewed by CDSCO, Ethics Committees, and other bodies simultaneously, to reduce delays.
3. Create a Single-Window System: Develop an 'integrated research application system' to act as a single point of submission for all regulatory bodies involved in trial approval.
4. Introduce Predictable Timelines: Wherever possible, introduced predictable timelines in the regulatory process.
5. Accelerate Processes: Accept e-signatures to shorten approval processes.
6. Register Investigators and Sites: Create a formal system for the registration of clinical trial investigators and sites, similar to the current process for Ethics Committees.
7. Establish a National Apex body for RDs.
8. Consider RDs an Emergency. Patients are suffering, usually without any suitable drug, and therefore provisions for emergency approval should be introduced on a fast-track basis, as was done for COVID-19 vaccines.

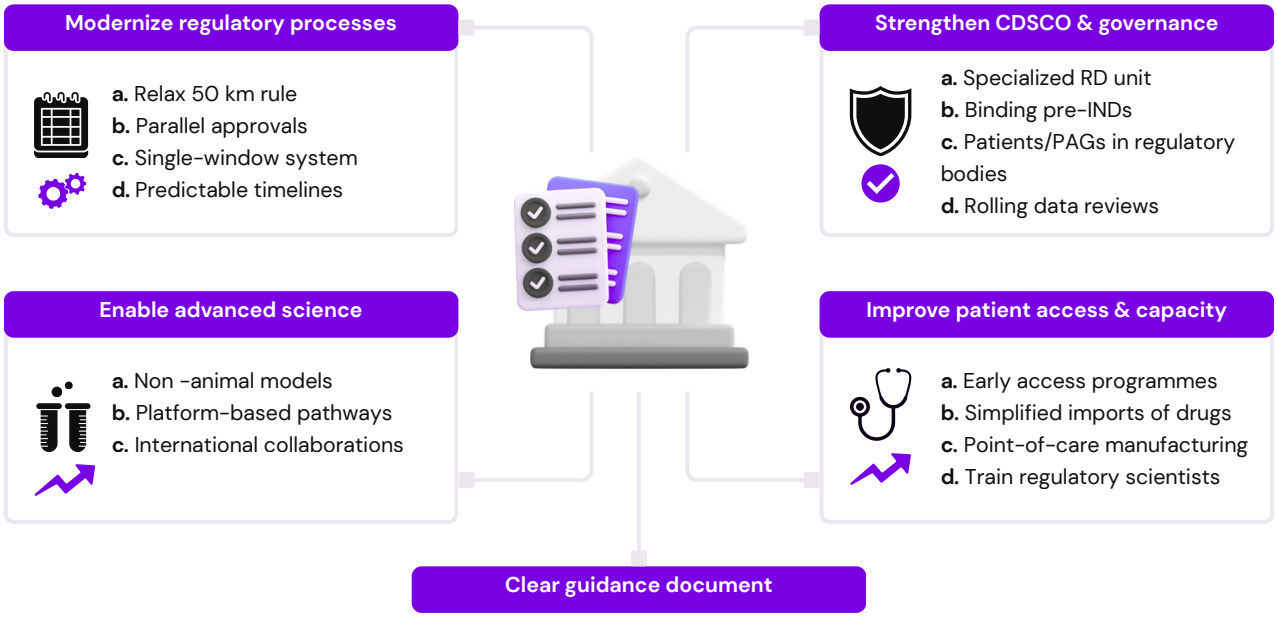
Enhance CDSCO Structure and Engagement

9. Create a Specialized RD Unit: Establish a specialized clinical trial review team within CDSCO that understands the unique paradigm of RDs and can fast-track reviews.
10. Make Pre-IND Advice Binding: Ensure that the advice given by the regulator during preIND meetings is formally binding, similar to practices at the FDA and EMA.
11. Include Patient Representatives: Appoint patients or members of PAGs as official members of regulatory bodies to ensure that the patient perspective is central to decision-making.
12. Adopt Flexible Review Methods: Implement flexible methods like a 'rolling review' of data for RD therapies, allowing companies to submit data as it becomes available.
13. Establish a Scientific Advancement Wing: Create a dedicated wing within CDSCO to stay updated on cutting edge science, collaborate with scientists early, and bring in international experts as needed, in order to be ready to regulate the most innovative therapies at the earliest.
14. A special meeting of the DTAB may be convened to discuss RD drug development.

Adopt Advanced Scientific Methodologies

15. Issue Guidance on New Model systems: CDSCO should provide clear regulatory guidance to encourage, and build confidence in, the use of non-animal models (such as in vitro, in silico, organoids and organ-on-a-chip) for regulatory submissions.

Regulatory steps to accelerate rare disease drug development in India



16. Create Platform-Based Pathways: For gene therapies using common vectors (like AAV), create platform-based regulatory pathways so that extensive safety studies on the vehicle do not need to be repeated for every new drug.

17. Promote International Collaboration: Foster regulatory collaborations with other countries to make trials more efficient, and accelerate drug development globally.

Improve Patient Access Programmes

18. Establish Early Access Programmes: For patients with life-threatening RDs, create a consolidated policy for early access to drugs in development, similar to the Expanded Access programme of the USA. Also, simplify the process for accessing such drugs in development.

19. Simplify Import of Approved Drugs: Develop a simplified, single-window process for the sale and distribution of internationally-approved drugs for very small patient populations, eliminating the cumbersome individual import process.

20. Enable Point-of-Care Manufacturing: Create a regulatory framework, modeled on the UK's MHRA, that allows accredited hospitals and academic centers to manufacture personalized medicines (like ASOs or cell therapies) on a small scale for individuals or small cohorts.

Build Capacity and Provide Incentives

21. Strengthen Regulatory Capacity: Establish formal training programmes in regulatory science to build a professional cadre of experts who can navigate complex regulations for evolving technologies.

22. Provide a clear guidance document: Although there may be flexible policies like fee waivers, tax credits, and expedited reviews for RD therapies, there is need for a clear guidance document and simplified rules.

23. Prioritize Indigenous Drug Development: Create programmes to prioritize and fast-track indigenous orphan drug development to reduce reliance on imports and enable faster local trials.

Public health

It was argued that RDs should be integrated into existing public health programmes. For sustainable care pathways for patients, an RD policy alone is not enough and it is essential to focus on strengthening and utilizing the existing public health framework for the optimal usage of healthcare resources. In this regard, the National Health Mission (NHM) is one of the crucial programmes that could be expanded to include RDs. Some of the disease-prevention initiatives of NHM do address certain RDs, and the programme can easily be expanded to manage many such preventable RDs. In addition, NHM programmes can provide a unique epidemiological data repository to strengthen NRROID. These programmes can also play an important role in providing a continuum of care for many RDs that need lifelong management. However, existing programmes have a limited scope to provide specialized RD-related treatments. Thus, considering RDs in the design of existing programmes may help to better manage RDs through prevention, data collection, and providing a continuum of care by linking it to an RD CoE.

In particular, newborn screening (NBS) should be explored. A recommendation for the implementation of NBS at least for RDs has already been made for the Rashtriya Bal Swasthya Karyakram (RBSK)[6] . Additionally, genomic screening should be a premarital requirement in order to prevent births with defect.

As a cautionary note, one should ensure that effective treatments are readily available before implementing widespread NBS programmes. The cost of whole-genome sequencing (WGS) is dropping drastically, and it is already in the range of a CT scan. It is expected to go down to at least 1/5th of the current price over the next few years. With such low prices, it will not be necessary to think of testing only a panel of genes. Instead, one can directly think of WGS. If WGS is carried out proactively for a newborn, it may help the person lifelong. And in case premarital screening is performed, it will reduce the disease burden). And at lower costs, mass screening becomes feasible. This will enable timely care of any patient with an RD, and will reduce the emotional and financial burden on families.

Any widespread NBS programme will generate unprecedented amounts of data, that will be useful for the RD field.

In summary, action points are as follows:

Integrate with Existing Public Health Infrastructure

1. Integrate RD Management into the NHM: This will ensure sustainability and efficiency, which a separate vertical may not.
2. Expand the NHM's scope: This should include RD prevention, data collection for the national registry, and providing a continuum of care.
3. Link the NHM to Specialized CoEs: Establish a clear referral pathway linking the primary and secondary care provided by the NHM to specialized CoEs for advanced treatments.

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6 Chaube P et al.. Expansion of India's national child healthcare programme, Rashtriya Bal Swasthya Karyakram (RBSK), for rare disease management : a health policy perspective. Orphanet J Rare Dis. 2023 Jun 12;18(1):145. doi: 10.1186/s13023-023-02761-y

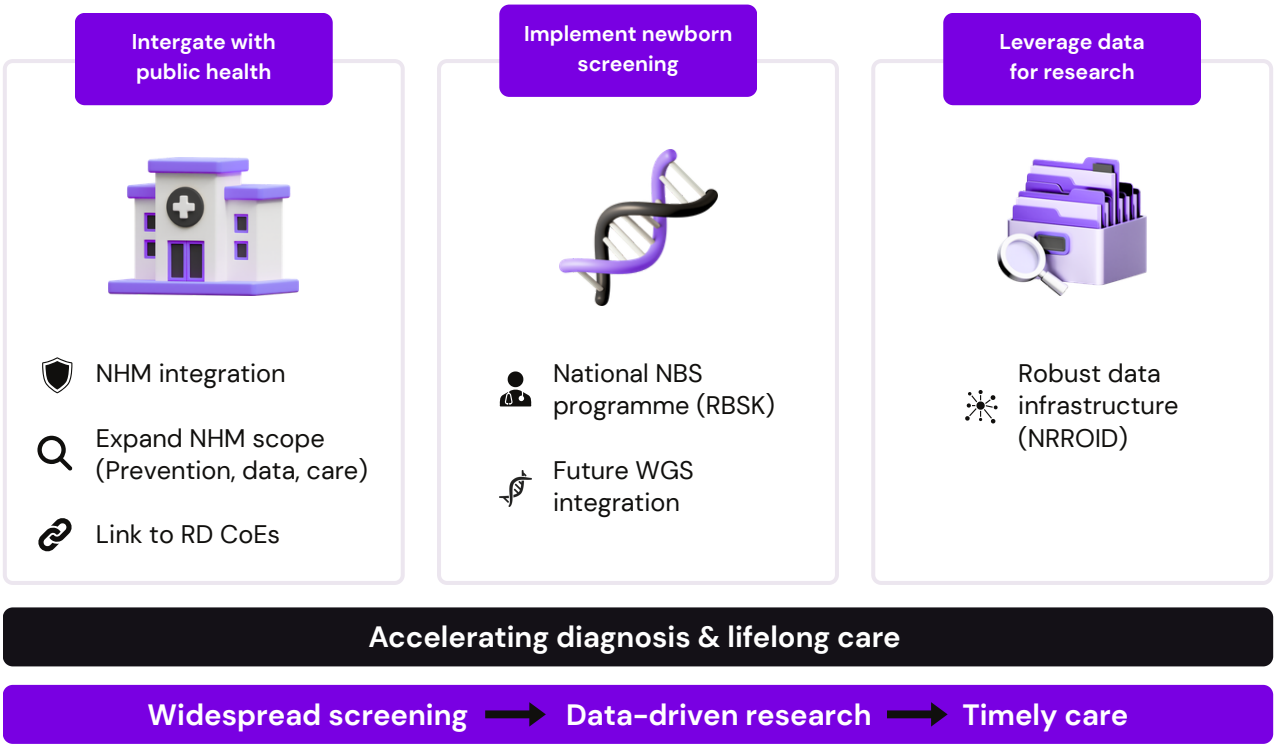
Implement Widespread Newborn Screening

4. Launch a National NBS Programme for Treatable RDs: Leverage the existing Rashtriya Bal Swasthya Karyakram (RBSK) programme for implementation.
5. Plan widespread use of WGE: Plan for the future integration of WGS into the NBS as its cost becomes comparable to other routine medical tests.

Leverage data for research

6. Develop a Robust Data Infrastructure: This is needed to collect, manage, and ethically utilize the massive amount of health and genomic data that will be generated from a national NBS to fuel research and improve treatments.

Integrating rare diseases into India's public health framework



A consortium

There was a strong call for creating a consortium between industry players and patient organizations to advance RD research, similar to what was done during COVID-19. This consortium needs to be a formal advocacy platform with power, with a say in policy making and a say in clinical trials, where it has an impact in drug development. For instance, the consortium can help with obtaining orphan indications for drugs in development. Some of these tasks are too complex for patient groups to handle on their own. There was also a word of caution, that to avoid failure, the consortium would need a clear structure, defined roles, and good funding. It is important to create a writing group to produce white papers, op-eds, and letters to government ministries and the WHO to ensure that the consortium's discussions lead to tangible results.

In May 2025, the seventy-eighth World Health Assembly adopted a resolution (https://www.who.int/news/item/24-05-2025-seventy-eighth-world-health-assembly---dailyupdate--24-may-2025) that, among other things, stated that RDs are a global health priority, and countries should integrate RDs into their health planning. This should include improving diagnostics, and advancing research and access to affordable care. WHO is going to define a 10-year global action plan for RDs, and the consortium should provide concrete inputs to that plan.

Final comments

India has an enormous population of RD patients, for most of whom there are no effective drugs or other therapies. Both for its own patients, and because it has this large pool of patients, India could aim to be the world leader in RD product development. For that to happen, a large number of steps need to be taken, that include improving regulations and the process of regulating; increased funding for relevant research; enabling increased participation by patients or patient representatives in many steps of the treatment paradigm and of drug development; and so on. All of these are very do-able, and are listed in the form of action items above. India can improve the lives of RD patients, around the world, if such actions are taken.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