Guidelines for the Global Alliance for Access to Rare Diseases

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Introduction

GARDaccess will overcome the challenges and obstacles inherent in single-focused access programs to create a strategic, integrated operating model for global access to rare disease therapies, evolve guidelines to ensure safe and quality products and services for patients with rare diseases globally while raising awareness and supporting education in Low and Middle-Income Countries (LMIC).

Mission

Accelerate patient access to quality medicines, treatments, and services for rare diseases by harnessing the collective expertise of partners with shared values.

Vision

Every patient living with a rare disorder has equitable access to quality healthcare.

Four strategic pillars

1. **Build GARDaccess organizational capacity and reputation** as a leader with multiple partner stakeholders to collaboratively achieve sustainable impact on patients living with rare disorders.
2. **Catalyze partnerships** to leverage collective resources to accelerate implementation of efficient and effective access programs.
3. **Collaborate in education, awareness, and advocacy** to elevate rare diseases as a global health priority.
4. **Develop and maintain a technology platform** to make GARDaccess guidelines, tools, and performance data available to drive operational excellence.

Background

Access to medicines is particularly challenging for patients living with rare disorders, even in high-income/developed countries, and even after these life-saving treatments have been approved by regulatory authorities and are commercially available. For those individuals (mostly whom are children) with rare disorders living in LMICs, these challenges are further compounded as treatment options are limited due to lack of accessibility, affordability, and/or availability (Izam & McCarter, 2021). The paucity of diagnostic resources in an already frail healthcare infrastructure are exacerbated by a lack of rare disease and continued medical educational opportunities amongst clinicians.

Biotechnology companies seek to implement social impact strategies by providing Charitable Giving Programs to resource-limited countries. Takeda's Charitable Access Program includes 199 patients from 13 countries (Mehta, 2021) and Sanofi has provided 100,000 vials to be donated to patients with rare

diseases (Sanofi, n.d.) Companies implementing a Charitable Giving Program share many of the same challenges including designing, implementing, and developing a sustainable infrastructure with multi-stakeholders in cross-collaboration in each country they wish to leave a footprint. Further complexities are added when the therapies in questions are considered high-touch (i.e., cold-chain) and high-value products requiring enhanced logistical capabilities.

While the mission and vision are clear to those company-sponsored Charitable Giving Programs, the resources required to implement and sustain Charitable Giving Programs are often cannibalized by the enormous costs required for increased diagnostic capabilities, educational efforts, logistical support, medical expert committee travel; and what remains is a small voice to implement policy change for greater program sustainability.

Access to Medicine (ATM) Foundation reports the 2021 Index finds that many of the world's poor countries still do not benefit significantly from pharma companies' access strategies (Access to medicine foundation, n.d). It is imperative to develop a sustainable access strategy, outside of donations and charitable access. A sustainable access program will allow for continued supply of life-saving medications to children, and governments can proactively prepare and budget accordingly for these high-cost medicines.

Through various organizations and initiatives championing rare disease education for physicians, there will be a marked increase in specialists able to identify, manage and monitor children with rare diseases. In a recent abstract at WORLD 2021 presented findings of *The Impact of Providing Rare Disease Educational Programs in Resource Limited Settings.* D Joel, MD., Sir Ketumile Masire University Hospital, Botswana concluded that based on a 3-day educational initiative for 41 delegates representing 10 African countries, a total of 70 confirmed cases of rare disorders were identified one year later, despite the severe lack of diagnostic facilities. The most common disorders identified were Gaucher disease, galactosemia, mucopolysaccharidoses and maple syrup urine disease. The most diagnoses were made in Sudan and Tanzania and very significant changes to medical education and health delivery have been initiated.

In a publication by Lopez-Garcia et al. (2019), patients presenting with primary distal renal tubular acidosis (dRTA), a rare genetic disorder, demonstrated a significant ($p<0.001$) difference in achievement of adequate metabolic control in countries with high Gross Domestic Product (GDP) compared with those with lower GDP.

THE UNMET NEED

There is a significant unmet need for the advancement of access programs under one umbrella to reduce overall costs and provide an infrastructure with economy of scale to build sustainable access programs in LMICs. Additionally, there is a need for a comprehensive business plan that brings key stakeholders in global rare disorders (diagnostics, education and logistics) together around one united mission. There is a growing need for a comprehensive program to combine the technical expertise of the rare disease industry community and provide long-awaited access and sustainability to those patients living with rare disorders in resource-limited geographies.

GARDaccess Guidelines

The guidelines are based on the following premises:

Support for the World Health Organization Universal Health - Universal Health Care

"Universal health coverage means that all people have access to the health services they need, when and where they need them, without financial hardship. It includes the full range of essential health services, from health promotion to prevention, treatment, rehabilitation, and palliative care" (WHO, 2022)

Support for the United Nations resolution adopted on the 16th of December 2021 to address the challenges of persons living with a rare disease and their families by:

- reaffirming the commitment to strengthen efforts to address rare diseases as part of universal health coverage.

The GARDaccess initiative has created a set of high-level guidelines which were developed by drawing on input from the literature and workstream members' experiences followed by thirty-one stakeholder interviews and networking evaluations.

The **7 guidelines** outline the general principles to help create partnership and alliances for persons and their families living with rare diseases. These guidelines focus on efforts to improve the process for access to treatments for persons living with rare disease in low-and middle-income countries (LMICs) including training and capacity sharing efforts.

The 7 Guidelines include:

1. Assessment
2. Partnership/Alliance
3. Implementation
4. Governance
5. Training & Capacity Sharing
6. Sustainability
7. Monitoring & Evaluation

1. Assessment

The essential first step is to conduct a general assessment to determine if the effort is appropriate (at this time) and viable. There are different types of health assessments: population assessment (national, regional, community); needs assessments (community needs), and health assessments (health status or disease specific). Overall, the process should be evidence based and begins by defining the problem and assessing the health status and needs of the person(s) with the rare disease. There should be a confirmed diagnosis and the testing/lab/ infrastructure available in the target LMIC country to support the required

treatment. Assessment includes both A. Preapproval and a preliminary review of B. Strategy development and program design.

A. Program Pre-Approval

Geographic scope

- Target countries (LMIC, LIC, subset or region within) (Taruscio et al, 2014)
- Estimated prevalence or identified need in target country
- Growth trend/Future need in target country
- Specific demographic (e.g., disease, time period and geographic area)
- Suggested baseline indicators of (Rare Disease) RD surveillance and socio-economic burden
- Surveillance: contribution of RD to morbidity/mortality:
    - Prevalence/incidence per disease and global
    - Number of RD actually diagnosed (and recorded) per country and per centre
    - Age at disease onset
    - Age at death
    - Life expectancy at diagnosis
    - Disability profile
    - Hospital admissions
    - Number and type of surgeries (or transplants) recorded
- Socioeconomic burden (Taruscio et al, 2014)
    - Health-related quality of life index
    - Number of patients treated per OD (Orphan Drug) per year
    - Other cases in the family
    - Impact on education and occupation

Regulatory pathway for access

- Review:
    - Strategy for regulatory approval (EUA or regulatory approval in a stringent regulatory authority)
    - Possibility for donation or humanitarian waiver in target country

External stakeholders needed to implement

- Confirm and Identify:
    - Global NGO responsible for accepting product donation & training required to support the program
    - Patient advocacy organizations (Global and Local)
    - The ability to communicate with external partnerships- physicians, MOH, patient advocates, payers, other key partners

Eligibility and selection criteria

- Patient eligibility, prioritization
- Selection criteria, number of spots/treatments available, how to manage allocation (points system, lottery)
- Will treatment require travel and is patient/physician support needed

- Internal processes, external review committees and medical expert committees

Facilitate the path to treatment and support
- Supply chain management and local infrastructure needed for delivery
- Treatment administration considerations: other supports or medicines required

Monitoring and reporting
- Safety reporting
- Country level reporting requirements
- Required level of reporting needed vs information privacy

Promote executive endorsement
- Endorsement confirmed
- Length of commitment
- Budget for COGS, partner grants, and other financial supports

B. Strategy Development & Program Design

Include cost/benefit analysis (reimbursement)
- Country specifics abilities/assessment (trained physicians, lab, ability to store) is the product commercially available (approval vs. locally)
    - Availability of treatment centres within the existing health services
- Country specifics abilities/assessment (trained physicians, lab, ability to store) is the product commercially available (approval vs. locally)
- Consider types of rare diseases within a country (available reporting) and the potential location of treatments for example in many countries there might only be two hospitals where rare diseases are treated. This can help direct the population assessment.
- Procedure for the coding and collection of patient information for clinic, research, and administrative purposes to improve planning and patient access to healthcare pathways www.rd-code.eu
- Establish program management, design and structure
    - Assemble extended project and program team
    - Document organizational management matrix (it would be in the hospital)
    - Establish clear roles and responsibilities
- Develop a process map and project plan
- Confirm / document regulatory requirements and strategies
    - Country specific regulatory requirements vs. product and therapy administration (physician ad technical knowledge and skills) needs and requirements
    - Develop country(s) regulatory strategies
    - Agreement from national government ministries and industry partner(s) on approach and means to satisfy regulatory requirements – registration, licensing, and training.

Conduct risks and benefits SWOT (strengths, weaknesses, opportunities, threats) or NOISE (needs, opportunities, improvements, strengths, exceptions) analyses

Engage government and country(s) stakeholder(s) to gain consent and agreement on implementation plan

- Full operational perspective and plan (end-to-end)
- Establish formal contracts / MOUs and other informal agreements (private sector, NGO, government, patient communities, and other stakeholder commitments, and reimbursements)

Funding and resource allocations for start-up and continuing operations

- Detailed cost accounting of end-to-end intervention cost per patient (including detection, confirmatory diagnoses, wrap-around treatment cost, post-treatment follow-ups, frequency of treatments x prevalence of disease in target community = total projected program cost
- Overall program cost to include program management, surveillance, and other health systems costs
- Financing strategy
- Detailed accounting of funding sources – national health expenditure, public, private, philanthropic, multilateral, developmental, insurance, or out-of-pocket.
- Risk and gap analysis based on committed vs. uncommitted funding
- Funding schedule and requirements for 5-10 year plan
- Funding transition and transition strategy - need to be tied to ethical considerations for the transition and exit

Communications strategy – internal and external (Global, Multiple levels of government and patient community)

- Validation of program needs and planning with on-the-ground healthcare and community providers – gain feedback and amend plan as necessary

Develop project implementation and rollout (Pilot, launch and scale-up phases if applicable) plan (output should be detailed project plan and Gannt chart)

- Develop checklist of requirements – what is required for effectiveness, efficiency, and properly phased (hardware, software, resource per patient / case)
    - Identify implementation team and roles and responsibilities
    - Identify and agree on eligible patients and communities and rollout phases
    - Develop supply chain strategy
        - Supply chain strategy and requirements (production to point of care cold chain (if necessary), chain of custody, and traceability)
        - Logistics planning (global and in-country) – include Shipment, importation, customs clearance, and staging within and distribution from central medical stores
        - Manufacturing forecast and fulfillment
        - Inventory management in the field (ship, receipt, administered waste disposal (environmental considerations), traceability, security (diversion and counterfeit), reconciliation, and compliance)

2. Partnership/Alliance

Once need is established, identify all key partners in the country and ascertain the commitment of all participants. The next step is to develop a formal partnership where all the parties agree on the activities. This doesn't have to be a long complex legal document, but it is very important that expectations, responsibilities and cost be clearly understood and agreed upon by all involved through the joint development of a memorandum of understanding (MOU). The importance of consultation, participation and communication is vital and the development of a MOU can support clear documentation of the nature of the partnerships and the involvement in the implementation.

Key Partner	**Commitment**
Hospitals/Hospital Pharmacy	Ensure that medicine supply can be received and maintained compliantly within correct storage conditions and only goes to patients approved for the program. Also, it is important to confirm that the institution has capabilities to appropriately diagnose and provide the level of treatment required for each medicine, including administration of supporting medicines / therapies and treatment of side effects and adverse events.
Physicians	Helpful to have one physician take responsibility for the program at each hospital with focus to make sure patients understand treatment regimen, are properly diagnosed and treat on-label, remain compliant with dosing, perform drug safety reporting as agreed with the NGO or sponsor, and collect outcome information like reason for discontinuation. If a **disease registry** exists, ensuring that **patient data** are appropriately and compliantly included.
Professional Organizations	National, professional organizations can provide essential resources and training to physicians, nurses, residents, and students (and allied health providers for example dieticians, physiotherapists, and occupational therapists). Additionally, they typically provide local advocacy for their members and the patients they provide care and services for.
Patient Advocacy/Support	People with personal experience of a disease, condition, or service, their caregivers or family members, and people representing a collective group of patients are strong representatives and advocates (Guidelines International Network, 2021). It is important to have in-country representatives who can help identify patients and can provide additional information and support to the patients. Could be a local NGO (with a similar mission or focus or support such as a community health worker.
Ministry of Health	Ensure that medicine can be imported into the country, ideally without minimal levels of additional duties paid.

Local Distributor	Assist with securing local import permission, engagement with local customs authorities and provide last mile delivery to point of care. If these are not donations, understanding and securing local funding pathways. Consider buying products locally.
Global NGO	Depending on the operating model, a global NGO could be used in some cases if a sponsor wished to make the initial donation to a non-profit organization allowing for a possible tax write off.
Pharma Company Regional Affiliate	Depending on the complexity of the treatment it may be necessary to have medical resources available for training and to address questions coming from physicians seeking to use the medicine.

3. Implementation

Implementing any health program or sets of health interventions is a resource intensive and complex process. Leveraging the best expertise in global health from public and private sectors is key to conducting a full and thorough analysis in order to develop the implementation plan. The objective is to implement a set of interventions in LMIC to address rare diseases. The target country or community may or may not have medical expertise or interventions for that particular disorder. Regardless, it is not the intent to introduce a vertical intervention. It is critical that the program leverages existing health systems infrastructure and plans to integrate the activities within the existing national health frameworks.

Implementation includes the following sections:

1. Assumptions based on initial assessments that details the existing health infrastructure and program strategies around how to effectively integrate the specific rare disease intervention
2. Developing the implementation plan that will serve as a roadmap to that integration.
3. The actual launch of the program may entail a phasing in process to achieve program objectives and scale
4. Transition to national ownership in support of country specific health system planning

Assumptions before moving to the implementation phase

1. Assessment and detailed documentation of existing health systems and rare disease intervention capacity and capabilities is complete – supported by detailed data and is evidence base
2. Key program stakeholders identified and engaged to review, validate, and endorse the assessment. Often this would include a Medical Expert Committee (MEC).
3. Scale and scope of program is conditionally agreed upon
4. Ethical transition and exit strategy agreed upon (if applicable)

5. Has "Go" decision – consensus among stakeholders is the project is viable and has the green light.

   Scaling up any health intervention in a large population is highly complex and not straightforward by any means. Therefore, implementation planning is intended to minimize unexpected obstacles but is by no means guaranteed to account for all eventualities. It is important to be flexible within the actual implementation and program launch and have contingency plans in place. It is also important to agree on whether the implementation is to be phased and how (i.e., pilot, launch, and scale-up).
6. Program management team agrees on launch sequence, timing, and phasing

   A pilot phase is a widely used approach to identify design flaws and implementation issues before full-scale deployment and is therefore highly recommended to ensure successful deployment. The following implementation sections are high level guidelines and dependent on the details of the plans to be thorough in the different stages. In developing the implementation plan for each of these stages of pilot, launch, and scale-up, all the considerations outlined in the guidelines on implementation planning above are important to consider.
7. Pilot phase (if applicable)
    a. Develop pilot plan (if applicable)
        i. Pilot site
        ii. Pilot scale and scope
        iii. Pilot duration
        iv. Data and reporting on pilot outcomes and issues
        v. Review pilot data and revise future phases as appropriate
    b. Identify launch locations
    c. Identify and recruit target patient / patient groups
    d. Notifications, communications, and other Public Service Announcement (PSA) for awareness building and engagement
8. Launch phase – Execution plan
    a. National, sub-national and district level health provider engagement
    b. Agreements on phasing and timing of launch
    c. Stage hardware and software (include healthcare provider training and staging necessary equipment (diagnostic labs and therapy administration)
    d. Identify and enroll eligible patients
    e. Final implementation check
    f. Launch
    g. Record keeping and surveillance (including Adverse Event (AE) reporting and pharmacovigilance

4. Program Governance

Due Diligence

- Assume the ability to treat the rare disorder exists locally
- Assess local capability/accessibility and availability to safely administer the drug and provide supportive care (for ex. intrathecal injections, access to physical therapy, and monitoring tests)

- Assess product logistics/security, cold storage capabilities, etc.
- Existence of local patient advocacy group/support group

Laws and Regulations

- Determine if a regulation exists for supporting rare disease patients locally (reimbursement program, and financial support)
- Determine local importation pathway for donations of rare disease medicines (some countries have unique pathways for rare disease treatments, some countries it could fall under general drug donation regulations) – usually governed by ministries of health, finance, and/or social welfare
- Drug manufacturers must be committed to provide relevant drug/lot certificates to meet country regulations (Clinical Outcome Assessments (COAs), Clinical outcome certificates (COCs), and Certificate of Pharmaceutical Products (CPPs)) – these are documents that only the manufacturer can produce/apply for
- Package inserts and Prescribing Information should be made available in approved/accepted languages

Legal, Ethical, or Health Role/Provider Compliance (Ethicist Input)

- Refer to WHO Guidelines for Medicine Donations
- Donated products should be made available at same treatment guidelines as in countries where drugs are commercially available
- Ensure that HCPs administering the drugs are trained in administering the drugs and aware of any potential safety events
- Determine reporting requirements and mechanisms (should not be too burdensome on HCPs) on usage/patient status
- Commitment from hospitals/HCPs to treat patients at no cost, minimal costs to cover administrative fees, or sliding scale
- For long-term/life-long treatments, commitment should be made to provide access to treatment (drug and treatment care) for long-term/life-long or with clear plan for alternative options
- What is the burden on treatment centers where there are might be limited treatment center options? (For ex. countries where there may be only 1 or 2 hospitals that can treat certain complex rare disorders)

5. Training and Capacity Sharing

The overall goal is to connect any rare new disease program's training and capacity sharing with that of the local workforce, officials, and health care system and whenever possible connect with existing educational structures such as NGOs supporting the community, professional or licensing bodies, and colleges and universities. All key partners must have an awareness of the local population, culture, and health care system.

Education – multi stakeholder responsibility

- Donor Responsibility

    - Product information/training sufficient for HCPs to determine appropriateness of treatment for their patient, educate their patients (disease, treatment, self-care), and safely administer treatment
    - Transparent communication about the duration of donation program and process for donation approval (e.g., medical review)
    - Adverse Event & Product Complaint training
    - Local language should be considered
    - Product destruction process if unused/expired
- Distributor/Supplier Responsibility – may be the Donor or Third Party (e.g., NGO, Service Provider)
    - Distribution/storage information sufficient for donor recipient to confirm and maintain quality of the product, e.g., temperature requirements
    - Educate and guide donor recipients on local procedures required to deliver product donation, e.g., importation process in accordance with local laws & regulations, and donation agreements
    - auditing
- Health Care Provider (HCP)Responsibility
    - Demonstrate thorough understanding of product information, administration requirements, donation duration to advise patient/caregiver and safely administer treatment
    - Demonstrate understanding of local procedures, including HCPs role (e.g., complete paperwork for approval) to receive product donation
    - Educate patients/caregivers to support disease understanding & health literacy, adherence to donated product treatment plan, and support self-care to manage elements of the disease (e.g., symptoms, lifestyle changes, and record keeping)
- Broader education considerations for HCP/Healthcare Institution capacity sharing
    - Impact of mentorship/fellowship programs to attract and retain specialized talent to support receipt & administration of donated products for rare diseases
    - Collaboration between major centers and under resourced/less experienced centers to advance specialized knowledge/expertise

Awareness

- Communities and unmet needs - of rare disease
- Advocacy for national health care policy development related diseases (link to SDGs; look for the alignments)
- Improve awareness among HCPs, patients/caregivers, advocacy groups of government guidelines for product donations - local laws, regulations, procedures, and challenges (especially when imported)
- Improve awareness among patients/caregivers of advocacy organizations, help lines, and patient communities – include links to existing resources.
- Define best practice for creating awareness of donor programs existence – donor & supplier communication platforms (websites, social media, Face to face (F2F) interactions), and advocacy organizations.

6. Sustainability

Training and capacity sharing can help improve national and local health efforts, but to be sustainable requires locally managed and properly funded health efforts. Long-term collaborative relationships can help move towards sustainability and a national scale-up plan might be dependent on geography, demography, and timing. Transitioning programs to the national health system is part of development and achieving sustainability. The details of the transition plan are dependent on many variables including sociocultural dynamics, economics, and technical capability and capacity to ensure equitable access and quality of care, and disease progressing and prevalence as a result of the newly introduced interventions. Therefore, what can and will be transitioned to national ownership will look different for different diseases as well as different countries.

- Commitment to country goals for example: importance of understanding the capacity within the different countries is key (leads to the identification of patients and then, treatment)
- Develop a customized support plan specific to country needs (future GARDaccess activities)
- Carefully examine the patients journey looking for ways to improve (timeframe or outcome)
- What attempts to establish collaborative joint efforts for long-term sustainability have been conducted? (for example WHO - Twinning partnerships for improvement)
- Manufacturer commitment (for ex. register product, local country support)
- Local coalition supports- sustainability is often driven by the patient community
    - Support alignment of an approach with all stakeholders (Patient advocacy and MOH)
- Guideline must support international, national, regional, and local standards (UN declaration, WHO health system strengthening, Global commission to End the Diagnostic Odyssey for Children with a Rare Disease)
- **Education and awareness** for health care providers to recognise potential symptoms of rare disease (diagnosis is key)
- **Advocacy** for newborn screening programs, diagnostic tools and technology services, infrastructure and health care provider expertise to diagnosis
    - case studies to illustrate (medicine, ancillary costs or diagnosis)
    - early access to care can slow disease progression
        - promote specialised training for physicians, and nurses
        - promote access to geneticists (genetic consultation)- referrals
- **Training and capacity sharing** (right people, right place, and right time) can help support local health efforts however, to be sustainable requires locally managed and properly funded programs
    - Support information (for example knowledge exchanges) and promote the overall awareness of rare diseases at the community level (social acceptance and culture)
- **Funding:** promote sustainable access to treatment (nutritional or medicines) once MOH is committed
    - What is the long-term commitment of the government? Have attempts to establish collaborative joint efforts for long-term sustainability been conducted?
    - Investment in resources to support diagnosis for example specific equipment requirements, trained local Nurses or a postgraduate medical college for specialist physician training
- **Policy** to support a national financing and access strategy

- Empowering patients and families
- Promote patient registries (information and data sources)
- Digital tools to improve communications among health care providers

7. Monitoring and Evaluation

Finally, there must be monitoring and evaluation of rare disease treatment including measurement of outcomes and health impact metrics. Measuring (assess, track and monitor) activities are needed to gauge progress and, equally important, help identify areas to be improved for long-term sustainability.

Here is a template for creating your own logic model for a rare disease access program:

Logic model template

While measurement methodology will differ for individual treatments and programs the basic measurement principles are summarized below along with key terms defined to guide the process.

Stakeholders are the people and organizations who have vested interest in the project.

> *For rare disease charitable access programs,* **suggested stakeholders** include Industry Manufacturers, Government (different sectors), Healthcare Providers (HCP), Physician experts, Patients, Patient advocacy organizations. International or Local NGO, Other Multi-lateral partner associations.

Inputs are the various resources available and needed for program implementation, inclusive of staff and funding.

> *For rare disease access programs*, suggested inputs are included in the chart below. Prompts to consider in identifying the program's resources include: What resources (meds, facilities, staff, volunteers, supplies, training, cash, time) contribute to the program?
>
> - Consider local government facility or provider level enablers?
> - Alignment with company and NGO programmatic efforts - any relevant resources/input?
> - Any data system or communication or promotional/awareness considerations?

Activities represent the action components of the program in order for your organization to address the problem or asset (i.e. to convert inputs into outputs).

> *For rare disease access programs*, suggested activities are included in the chart below. Prompts to consider in identifying the program's activities include:
>
> - What work will need to be performed?
> - Is there different work with different stakeholders?
> - What materials/products/networks must be created/activated?

- What systems must be established or reinforced?

Outputs describe the services and goods (For example: product or trainings that have been delivered (networks, logistics measures) and dimensions of the participation in the program by different groups, (patients, HCP, facilities)

For rare disease access programs, **suggested outputs** are included in the chart below. Prompts to consider in identifying the program's *initial* results include:

- Determining which descriptive characteristics of your resources and activities (above) you want to measure? Is there a standard? (Number, value, volume)
- Consider local government facility or provider level descriptive measures?
- Were the objectives met in terms of patients, providers, (rare disease program objectives)?
- Timeliness indicators are important.

Outcomes capture changes in the target group's health status and health system functionality that is achieved through the program. They are often denoted as short-term and long-term outcomes and reflect changes in knowledge, attitudes and understanding and changes in capacity, ability, skills, and behavior. **Impact** is the longest-term outcome and reflects changes beyond the target group, at a societal level.

For rare disease access programs, suggested outcomes are included in the chart below. Prompts to consider in identifying the program's lasting results include:

- Measures of trainings - increased knowledge, increased awareness, new networks?
- Enhanced skills for providers? Parents?
- Enhanced facility capacity? Equipment availability? Maintenance or supply chains established.
- Any changes in government approach/policy to rare diseases?
- Increased funding or focus?

Input **Product / Funds / People / Technology / Partners**	**Process/Activity**	**Output**	**Outcome / Impact**
<u>Costs</u> Health products Diagnostics Funding Providers Staff/Consultants Warehousing Distribution (multiple levels) information technology services Healthcare facilities Specialized storage systems	Assess & Identify needs Engage local partners HCP & patient training/education Regulatory clearance Diagnostic &/or genotyping support Ensure supply chain functionality & compliance administration of treatment Provide services & support to patients/families/HCP (Financial or other)	Number treated per country, % population treated Patients enrolled in registry (if have one) Health outcomes for the target population – measured by pre-established criteria and/or disability adjusted life years	% of population covered Health outcomes (morbidity/mortality) Improvements in markers specific to the rare disease Economic Impact Patient satisfaction Symptom improvement Established pathway to treatment, inclusive of diagnostics

Diagnostic &/or genotyping systems Transportation	Pharmacovigilance &/or medical Oversight & reporting	-Key health markers by disease – mortality, morbidity, co-meds usage -Diagnosis rates, accuracy of diagnosis (diagnostic system established or available) -Government investment – any incremental investment, changes in local policy -Descriptive of HCP training and education -Impact on service – patient numbers treated in service, diagnostic services, genotyping services, newborn screening (where appropriate)	

Assumptions and **external factors** articulate the landscape within which a program operates. They are larger circumstances affecting the program. These can be resources or barriers; they can promote or limit success of the program.

For rare disease access programs, **suggested assumptions to consider include that** rare disease programs are in their infancy; rare disease programs are incredibly varied and specific; they will require long-term investment, they must have the support of the MOH and maintain a commitment from local partners, and the impact comes when country is at the level of education and diagnosis.

Therefore, additional assumptions to consider:

- There is good-will to provide rare disease support that extends from the MOH to the Providers and advocate groups
- There is a need for rare disease solutions (including medication and education) that they Do not have access to without a program
- The program can leverage the necessary customs and pharmacy policy expertise to Enable the delivery of the appropriate diagnostics & treatments
- Appropriate product/device/diagnostics/protocols have been developed inclusive of Appropriate packaging variations
- Established systems of pharmacovigilance can guide the programs evolution
    - Health literacy resources for specific disease exists already or can be developed to serve the stakeholders of this program
    - Health outcomes at a patient, provider and facility level exist already

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Definitions

Due Diligence is a systematic investigation of an organization prior to entering a relationship. Due diligence can be a legal obligation, but the term more commonly applies to voluntary investigations. Due diligence typically leads to more informed decisions by ensuring that the information collected in done in a complete quality organized manner.

Ethical Standards refers to commonly accepted principles that encourage the values of trust, fairness and benevolence. Ethical standards are broad statements, open to interpretation and not easily enforceable. However, the ethical directives by organizations such as the United Nations /World Health Organization (WHO) are generally accepted worldwide. It is every health care provider's obligation to follow and adhere to the specific regulations and professional practice standards set by their respective college or governing body by country/province/state.

Guidelines: Although the terms 'guidelines' and 'standards' are frequently used interchangeably in the literature 'guidelines' refer to "statements that include recommendations… that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options", as defined by the Institute of Medicine, and is thus a more suitable term (Tracey et al, 2022; Graham et al, 2011)

Health Services: include primary, secondary, and tertiary care, ranging from promotion and protection of health to hospital, rehabilitation and palliative care services (Stamler, Yui & Dosani, 2015).

Healthcare Systems is the organization of people, institutions, and resources that deliver health care services to meet the health needs of the population. Each nation designs and develops their individual health systems in accordance with their needs and resources.

Healthcare Training is any activity focused on teaching medical professionals and support staff on methods that can be used to analyze and improve health quality. This also include clinicians, community health workers and health managers. Healthcare 21 training is designed to improve the skills, competencies, clinical experience, required to meet the health needs of the populations they serve.

Humanitarian Organizations/NGOs are charitable entities (termed as 501 C3 organizations in the US) which provide philanthropic programs and support to help people in need. The primary purpose of humanitarian NGO organizations are efforts such as; saving lives, reducing suffering and maintaining respect to human dignity and addressing health and social economic situations.

Low and Middle-Income Country: A country reaches lower middle-income status when it obtains an income level greater than USD 1 045. The World Bank reassigns income categories on July 1 each year. Classifications are based on Gross National Income (GNI) per capita for the previous calendar year. Gross national income (GNI) is defined as gross domestic product, plus net receipts from abroad of compensation of employees, property income and net taxes less subsidies on production (OECD, n.d)

Ministry of Health (MoH) is the national government department responsible for issues related to the general health of the citizenry. Health departments also compile statistics about health issues. The head of the Ministry of Health is often called the Minister of Health

Monitor and Evaluation (M&E) is a process designed to helps improve performance and achieve results. Monitoring is the systematic and routine collection of information during a program to track and account for resources used to help make decisions on program execution. Evaluation is the assessment of a project after completion, to review and determine the relevance, effectiveness, efficiency, impact and sustainability of the program.

Partnership of Quality Medical Donations (PQMD) is a global alliance of corporations and nongovernmental organizations. PQMD is leading the development and championing of high standards in medical supply and service donations. PQMD seeks to enhance access to health care in underserved communities and in areas affected by disasters.

Rare diseases: are typically defined as conditions with fewer than 40 to 50 cases per 100 000 population or that affect a small number of patients compared with the total population (Richter, 2015)

World Health Organizations (WHO) is the specialized agency of the United Nations that is concerned with global health. The WHO currently defines its role in public health as follows:

- providing leadership on matters critical to health
- shaping the health research and disseminating valuable knowledge;
- setting norms and standards and promoting and monitoring their implementation;
- articulating ethical and evidence-based policies;
- providing technical support, catalyzing change, and building sustainable institutional capacity;
- monitoring the health situation and assessing health trends

Abbreviations

LMIC: Low and Middle - Income country
LIC: Low income country
RD: Rare disease
ATM: Access to medicine
dRTA: Distal renal tubular acidosis
GDP ; Gross domestic product
EUA: Emergency Use Authorization
NGO: Non-governmental organization
MOH: Ministry of Health
COGS: Cost of Goods Sold
MOU: Memorandum of Understanding
MEC: Medical Expert Committee
PSA: Public service announcement
COAs: Clinical Outcome Assessments
COCs: Clinical Outcome Certificates
CPPs: Certificate of Pharmaceutical Products
WHO: World Health organization
HCP: Health Care Provider
SDGs: Sustainable Development Goals
F2F: Face to face