PQMD Rare Diseases Guidelines:
Access to Rare Disease Medicines Programs

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I. Introduction

One of the PQMD strategic pillars is "fostering the exchange of ideas on healthcare donations and system strengthening". Many of the PQMD members from both the private and public sector are engaged in programs that provide patients living with rare diseases (PLWRD) with necessary treatment and care. As such, there is a need for the partners engaged in such activities to have tools that would allow them to be thoughtful and systematic on how they approach providing such access.

In 2021, PQMD was the steward of resources to develop both the operational framework for GARDaccess and the guidelines that serve as the standard for stakeholders engaged in providing humanitarian assistance to PLWRD. In 2024, GARDaccess was established as an independent 501(c)3 non-profit organization based in Maryland. PQMD has maintained the stewardship of the Rare Diseases Guideline as this is its core competency. These Rare Diseases Guidelines will be reviewed, assessed, and revised by the Rare Diseases Working Group as needed.

II. Background

A rare disease is defined as a medical condition that affects a small percentage of the population. The exact definition of rare diseases varies by country globally. The core definition of rare disease is [... *a medical condition with a specific pattern of clinical signs, symptoms, and findings that affects fewer than or equal to 1 in 2000 persons living in any World Health Organization-defined region of the world.]*[1] There are approximately 7,000 known rare diseases and fewer than 5% of those diseases have an approved treatment.

Access to medicines is particularly challenging for patients living with rare diseases, 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 (most of whom are children) living in low-and-middle-income countries (LMICs), these challenges are further compounded as treatment options are limited due to lack of accessibility, affordability, and/or availability (Izam & McCarter, 2021)[2]. The paucity of diagnostic resources in an already frail healthcare infrastructure is exacerbated by a lack of rare disease awareness and educational opportunities amongst clinicians.

Biotechnology companies seek to implement social impact strategies by providing humanitarian access programs to resource-limited countries. Takeda's Charitable Access Program includes 199 patients from 13 countries (Mehta, 2021)[3] and Sanofi has provided 100,000 vials to be donated to patients with diseases like Gaucher or Pompe (Sanofi, 2024)[4]. Companies implementing an access program share many of the same

[1] Wang, C.M., Whiting, A.H., Rath, A. *et al.* Operational description of rare diseases: a reference to improve the recognition and visibility of rare diseases. *Orphanet J Rare Dis* **19**, 334 (2024). https://doi.org/10.1186/s13023-024-03322-7

[2] Izem, R., McCarter, R. Randomized and non-randomized designs for causal inference with longitudinal data in rare disorders. *Orphanet J Rare Dis* **16,** 491 (2021). https://doi.org/10.1186/s13023-021-02124-5

[3] Mehta A, Ramaswami U, Muenzer J, et al. A charitable access program for patients with lysosomal storage disorders in underserved communities worldwide. *Orphanet J Rare Dis*. 2021;16(1):8. Published 2021 Jan 6.

[4] Sanofi https://www.sanofi.com/en/our-responsibility. Accessed February 10, 2022.

challenges including designing, implementing, and developing a sustainable infrastructure with multiple stakeholders in cross-collaboration in each country they wish to leave a footprint. These efforts are complicated when the high value therapies in question are high-touch (i.e., cold-chain) and require enhanced logistical capabilities or highly technical expertise in administration.

While the mission and vision are clear to those company-sponsored access programs, the resources required to implement and sustain those programs are often undercut by the enormous costs required for what are often complex diagnostic capabilities, educational efforts, logistical support, and medical expert committee engagement.

Access to Medicine (ATM) Foundation reports the 2021 Index[5] 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 interventions. A sustainable access program will allow for continued supply of life-saving medications to patients, so 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 the abstract presented at WORLD 2021 presented findings of *The Impact of Providing Rare Disease Educational Programs in Resource Limited Settings*[6], Dr. Dipesalema Joel of 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. The most common disorders identified were Gaucher disease, galactosemia, mucopolysaccharidoses, and maple syrup urine disease. The most diagnoses were made in Sudan and Tanzania where very significant changes to medical education and health delivery have been initiated. This was accomplished in spite of the severe lack of diagnostic facilities.

The Challenges to Access Rare Disease Medicines

Development of treatments and therapies for rare diseases has seen significant advances in the last few decades due to the institution of orphan drug policies like the Orphan Drug Act enacted in the US in 1983. However, those novel therapies typically come with high costs, limited distribution, and complex reimbursement structures that limit availability, access, and affordability. Access is challenging in developed countries and especially in LMIC. Programs and mechanisms are needed to reduce overall costs and provide an infrastructure with an economy of scale to build sustainable access for vulnerable and underserved populations.

For the purpose of these guidelines, the two pathways for access to RD medicines outside of the standard commercial channels are donations and managed access programs (MAP). Donations are often provided free of charge and typically less structured. Donations cannot be expected to be open-ended and sustainable.

MAP and alternative access pathways on the other hand are structured programs, that at minimum, involve regulatory exemptions and oversight, payment and funding options, and treatment data collection. Early access program (EAP), named patient, and compassionate use are some examples of

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[5] Access to medicine foundation https://accesstomedicinefoundation.org/ Accessed Feb 10, 2022

[6] D. Joel, et. al. (2019) - https://www.semanticscholar.org/paper/The-impact-of-providing-rare-disease-educational-in-Joel-Ogg/bb4f144d852d58601f6333fbc20b7225e67398cd?utm_source=direct_link

MAPs.

Whether medicines are donated or made available via MAPs, when developing an access program for a specific rare disease or for the diseases more broadly, implementers need to be strategic and deliberate around the access mechanism. In addition to engagement of medicine providers, logisticians, health care professionals, and others in the healthcare delivery functions, there is also a need to include policy experts, health economists, and regulatory advisors that can address systemic barriers like financing, policy integration, and governance to ensure long-term sustainability,

III. Premises and Assumptions

1. Premises

The Rare Disease Guidelines serve the following purposes:

1. There is a significant unmet need for patients living with rare diseases that is primarily due to small patient population, geographic dispersal, high cost of treatment, unavailable or unregistered products.
2. Stakeholders willing to embark on an initiative to provide access to rare disease medicines for PLWRD living in LMIC to have a template to systematically develop a program with a clear structure that is consistent and based on evidence and best practices.
3. Support shared commitment by the global community, governments, and advocates for PLWRD and the:

    a) UN SDG on universal health coverage (WHO 2022)[7] – "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." This SDG vision of a world in which no one is left behind is central to driving health equity for PLWRD.

    b) UN Resolution (2021)[8] – adopted on the 16th of December 2021 to "address the challenges of persons living with a rare disease and their families."

    c) World Health Assembly (WHA) Resolution (2025)[9] – adopted on 24th of May 2025 "recognizing [rare diseases] as a global health priority and aiming to improve diagnosis, treatment, and care for over 300 million people affected worldwide."

4. There are different mechanisms for PLWRD in LMIC or other resource-constrained settings where the product is either not registered or cost prohibitive to access medicines and treatments for rare diseases. Products can be donated or made available via managed access programs (MAPs). The guidelines are intended to be applicable to the different mechanisms.

[7] SDG Target 3.8 | Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all
[8] n2233037.pdf
[9] Rare diseases: a global health priority for equity and inclusion.

2. Assumptions

Some assumptions before moving ahead with the development of an access to rare diseases program in LMIC include clinical, regulatory, economic, and operational considerations:

1. Treatment (the medicines and the administration regimen) and care have a basis for safety and efficacy.
2. Appropriate product/device/diagnostics/protocols exist.
3. Ancillary surgical and other interventions, if required, are available.
4. In the country where an access program is being considered, there is goodwill to provide rare disease support and commitment that extends from the MOH to the healthcare providers, local partners, and advocacy groups.
5. There is a need for rare disease solutions (including medication and education) that affect patients, and which are not available without a program.
6. The program can leverage the necessary customs and pharmacy policy expertise to enable the delivery of appropriate diagnostics and treatments.
7. Systems of surveillance and pharmacovigilance are available to support clinical needs.
8. Health literacy resources for specific diseases exist already or can be developed to serve the stakeholders of this program.
9. Due to the typical life-long chronic condition, there is a need for long term investment and strategy for sustainability.
10. Due to the typically high cost of rare disease medicines, access for PLWRD in resource-constrained settings will be receiving treatments via donations or other humanitarian avenues. However, it cannot be assumed that donations will be open-ended. In the interest of sustainability, there should always be a vision for accessibility outside of the humanitarian lens.

IV. The Rare Disease Guidelines

This Guidelines Document is meant to offer flexible recommendations based on best practices that empower stakeholders and organizations to make informed, evidence-based decisions. Due to the challenges around accessing medicines for rare diseases, especially for patients living in LMICs and other resource constrained settings, these Guidelines outline some of the key considerations when developing any program in that ecosystem. The intent is for the PQMD Rare Diseases Working Group to review, revise, and amend these Guidelines as necessary when additional information and evidence is gathered and lessons are learned.

The Guidelines are presented in the following five key sections:

1. Situational Analysis
2. Program Strategy
3. Program Design
4. Implementation
5. Sustainable Access

Each of these sections has elements that are critical considerations. The individual elements and the recommended activities and outputs are presented in tabular format for ease of navigation.

1. Situational Analysis

The first step in developing a program for access to medicines for rare diseases in LMICs is to conduct a comprehensive analysis of the existing rare diseases ecosystem and the underlying and multifaceted challenges for the specific rare disease under consideration.

Strategy and program development are wholly dependent on the data collected during this foundational phase. The information and data gleaned from a rigorous and thorough assessment will inform a multi-pronged strategy designed to address the barriers to access commensurate with the scale and scope of epidemiological and social needs. The key areas that need to be assessed are:

1. Epidemiology – disease prevalence and disease burden.
2. Legal and regulatory – existing laws and policies that support or pose challenges to patients accessing rare disease medicines because many of the key challenges in LMIC are regulatory in nature and they include:

- **Unclear or evolving regulations** governing access to **donated medicines** that are not yet registered, licensed, or commercially launched in the country. Regulatory requirements may also **change with little or no notice**.
- Healthcare providers are often **unfamiliar with the applicable regulations** for donated medicines or those made available through non-traditional pathways. They therefore often **require assistance from the sponsor or their designee** to facilitate importation and management of medicines for patients in need.
- In some LMICs, **specific regulations for donated or special access medicines do not exist**. However, sponsors can often **collaborate with the Ministry of Health (MOH)** to establish an appropriate and legal pathway for making these medicines available to benefit eligible patients.

3. Health systems – capacity, capability, and infrastructure to accommodate technical and operational needs.
4. Funding mechanisms – national health expenditures, subsidies, reimbursements, and insurance coverages to financially support a patient's access to the medicine and / or treatment regimen.
5. Patients and community – advocacy and other support structures for patients and their families.

The more complete picture of the RD landscape and the existing infrastructure that supports the RD patient community will allow the program planners to develop the strategy and plan best suited for the environment. Whether the assessment returns favorable or unfavorable findings does not dictate a go/no-go decision.

The team tasked with the situational analysis should, at minimum, include rare diseases experts, organizations with country and program experience and/or that have access to country and national level information, healthcare and clinical professionals with expertise in the treatment and the disease under assessment.

Areas to be assessed	Key Components
1.1 Epidemiology	Epidemiology data is necessary to provide quantitative and statistical information regarding disease distribution, prevalence, and risk factors that allows for strategically planning, implementing, and evaluating any

Areas to be assessed	Key Components
	initiatives undertaken to improve access to necessary medications. The evidence-based estimate of the global point prevalence is also critical to inform public policy that affects access.[10] a) isease profile and mapping – prevalence of disease, demography, and geography. b) urden of disease – socioeconomic burden (Taruscio et al, 2014)[11], quality of life, and impact on education, occupation, and family and other support structure. c) aseline indicators of the disease include contributing to morbidity/mortality. d) ocumentation of the unmet medical needs.
1.2 National laws and regulatory and health policies	Legal and regulatory requirements and healthcare capacities vary widely between countries, especially LMICs. Legislation and policies around rare diseases and their treatment regimens must be considered in the design of an access program for rare diseases. For instance, importation pathways for donated medicines, diagnostics, or other ancillary products (registered or not registered) are usually governed by ministries of health, finance, and/or social welfare. Their endorsements will be critical to the success of the program. Adachi, et. al. provides a comprehensive summary of global and regional practices, policies, and regulations, as well as challenges and barriers that need to be inventoried and evaluated in contemplating strategies to achieve equitable access to medicines for PLWRD.[12] a) Legal – program operations ● Requirements for program operations (inc. program license) ● Program staff, employment, and compensation ● Implications on intellectual property (IP) b) Regulatory – product and supply ● The medicine – registration or exemptions for donated or

[10] Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, Murphy D, Le Cam Y, Rath A. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet. 2020 Feb;28(2):165-173. doi: 10.1038/s41431-019-0508-0. Epub 2019 Sep 16. PMID: 31527858; PMCID: PMC6974615.

[11] Taruscio, D., Mollo, E., Gainotti, S. *et al.* The EPIRARE proposal of a set of indicators and common data elements for the European platform for rare disease registration. *Arch Public Health* 72, 35 (2014). https://doi.org/10.1186/2049-3258-72-35.

[12] Adachi, et. al. (2023), Enhancing Equitable Access to Rare Disease Diagnosis and Treatment around the World: A Review of Evidence, Policies, and Challenges. Int. J. of Env. Res. and Pub. Health. 20, 4732. https://doi.org/10.3390/ijerph20064732.

Areas to be assessed	Key Components
	unregistered products, importation licensing, labeling requirements, quality assurance and other product documentation, pricing, etc. ● Supply chain – storage and handling requirements c) Regulatory – policies for patient treatment ● Treatment guidelines ● Regulations for non-registered products ● Existing access programs and policies with special dispensation allowing companies with medicines to provide access to patients in need. (e.g., early access, compassionate use, managed access, etc.) ● Patient data privacy and consent ● Patient registries
1.3 Health systems capacity, capability, and infrastructure	Health system capacity, capability, and infrastructure impact everything from initial diagnosis to long-term treatment of rare diseases. Capacity refers to the resources and funding available, while capability includes the workforce's skills and the ability to conduct complex diagnostics and evaluations. Infrastructure encompasses the physical and digital systems needed, like specialized centers and data management systems, to effectively implement treatments and manage patient care. a) Capacity of healthcare provider or other healthcare workers to identify disease, refer for diagnosis, and/or subsequently provide treatment and care. b) Clinical and diagnostic capacity of healthcare infrastructure and professional workforce to identify disease, confirm diagnoses, treatment, and manage rare diseases. c) Existence of patient registries to collect data to track and monitor rare disease patients. d) Supply chain capability and capacity to manage any distribution channels for medicinal products, especially for those requiring special handling and/or storage conditions. e) General healthcare infrastructure (e.g., national / district level network of healthcare capable facilities, patient accessibility, and interoperability). (e.g., national / district level network of healthcare capable facilities, patient accessibility, and interoperability). f) Availability of health-related technologies like telemedicine and other technology can improve access through remote monitoring, consultation, and delivery of initial and follow up treatment and care.

Areas to be assessed	Key Components
1.4 Funding and reimbursement mechanisms	The cost of rare disease medicines and treatment regimens is typically quite high compared to common diseases and most likely required for the life of the patient. As such, there needs to be an understanding of how any access to the medicine program will be funded. The program funding calculus will need to include input from all interested stakeholders as well as existing or available reimbursement mechanisms. a) National funding appropriations for rare diseases. b) National health coverage, health insurance programs, subsidies, or other financing mechanisms. c) Public and/or private funding sources or patient assistance programs. d) Alternative innovative financing mechanisms (e.g., blended finance models that combine public and private funding available to expand access to rare disease interventions). e) Overall affordability and pricing.
1.5 Patient and community – advocacy and support	Patients, caregivers, and community organizations are pivotal in affecting policy changes, providing valuable patient-reported data, helping to enroll patients in clinical trials, and offering support and information to those affected. This assessment on the state of patient-centricity is vital because it provides information on resources available to support the access program and rare disease patients that the initiative is intended to serve. a) Strength and reach of patient advocacy organizations in representing and supporting rare disease patients and families. b) Availability of patient support programs, including disease and genetic (where relevant) counseling, social support, and educational resources. c) Organizations capable of supporting the institution of a rare disease medicines access program and advocating for necessary policy changes to facilitate that endeavor.

The data gathered in the situational analysis should be confirmed and validated with the country MoH and other key stakeholders. This assessment is subsequently used to inform strategy development and programmatic design to arrive at a sustainable solution.

2. Program Strategy

The program strategy defines “what” the program will accomplish and how it is intended to be impactful. The strategy for access to medicines programs typically addresses various aspects including clinical and regulatory considerations, funding, and patient support.

Dependencies

1. The thorough situational analysis is supportive of moving to the next phases of program development.
2. Key management and decision makers have been informed of the findings and have given endorsement for the project to proceed.
3. Expert representation from key areas identified and assembled to form the strategy development team. Though not always feasible to have full participation and representation, it would be good for the strategy team to include the following representatives:
   - Industry partner
   - Rare disease experts both in general and resident in the target country / geography
   - Country ministry of health or senior health systems representative
   - Medical expert / expert committee
   - Medical ethicist
   - Program partner – International NGO or organization with knowledge and experience in the geography responsible for on the ground implementation and rollout of the program.
   - Patient advocates

Strategy development is an iterative process and foundational to the entire access to rare diseases medicines program. A clearly articulated strategy with succinct vision, mission, goals and objectives is critical for program design, rollout, and used to garner the support necessary for success. It helps to align teams and functions to work towards common strategic objectives and serves as a compass for decision making. With a clear strategic vision that conveys a compelling and aspirational goal, stakeholders will have a clear understanding of the expectations and their commitments.

The elements included in these Guidelines to consider in strategy development are:

2.1 Due diligence
2.2 The strategic plan
2.3 Sustainability strategy
2.4 Buy-in and endorsement from key stakeholders

Elements of Program Strategy	Key Components
2.1 Due diligence	Due diligence exercised in developing rare disease medicine access programs allows the stakeholders to gain a thorough understanding of the target disease landscape. The evidence and data contribute to designing a plan that mitigates significant risks and navigates the unique challenges of rare diseases with sound, viable, and feasible strategies. a) Thorough analysis of the data from the assessment outlined above. The synopsis will provide details on what exists and what is needed to develop the strategy and plan for a successful program. Additional

Elements of Program Strategy	Key Components
	data may need to be collected, or research conducted to support strategy development. b) Risk assessment, risk management, gap analysis, and contingency planning. Methodologies may include SWOT (Strength, Weakness, Opportunities, Threats), NOISE (Needs, Opportunities, Improvements, Strengths, Exceptions), SOAR (Strengths, Opportunities, Aspirations, and Results), or other analytical frameworks and scenario planning. c) Estimate program costs – perform a thorough and detailed itemization of program costs to ensure that adequate funding is allocated for execution and minimize risks of unexpected expenses that will compromise achievement of the program goals. ● Develop funding strategy. ● Inform program design (scale and scope limitations) and other program decisions. ● Produce cost benefit analysis.
2.2 Strategic plan	The strategic plan defines the scope and purpose of the program and is the roadmap for decisions and actions. Based on the agreed upon vision and mission of the program, the plan provided direction and details of the specific goals, actions, and stakeholder responsibilities. a) Program strategy – Clear vision, mission, goals, and objectives needed to arrive at scale and scope. b) Identifying disease and diagnostics strategy - Being able to accurately and expeditiously confirm a patient's rare disease state is the critical first step. ● HC professionals must be trained to identify the disease. ● Laboratory and other applicable diagnostic technology must exist for confirming the diagnosis. ● Lab technicians must be properly educated and trained on any necessary diagnostic tools and technologies. ● If the country does not have the necessary diagnostic tools, the strategy needs to integrate the necessary tools into existing health systems. ● The goal of the strategy is to expand the overall capacity and capability of the national health system labs and facilities. ● The diagnostic needs must be accessible and affordable as it is needed for confirmation and perhaps for follow-ups and to monitor treatment efficacy. c) Medical and clinical supply chain ● Product specifications – required documentation (including Clinical Outcome Assessments (COAs), Clinical outcome certificates (COCs), and Certificate of Pharmaceutical Products

Elements of Program Strategy	Key Components
	(CPPs), language appropriate inserts, quality and other requirements) ● Logistics planning (global and in-country) – includes production planning, production, shipment, importation, customs clearance, and staging within and distribution from central medical stores. ● Inventory management includes cold chain (if necessary), chain of custody (ship, receipt), traceability, security (diversion and counterfeit), stock reconciliation, and processes for compliance and destruction / disposal. d) Stakeholders and resources ● An access program in LMIC will most likely require the creation of a public private partnership with many different stakeholders. ● The individual stakeholders will be required to commit time and resources for the program to be successful. The strategy developed through this phase will dictate what is needed. ● The strategy needs to detail the stakeholders to be engaged in the program as they will be involved in developing the implementation plan. e) Funding strategy that addresses how the program leverages different sources to finance the different components of the access program. ● Program cost (including product, program management, training, surveillance, and other health systems costs). ● Patient costs (including end-to-end patient journey cost from diagnosis through treatment, ancillary treatment needs, and aftercare). ● Available funding sources (including national health expenditure, public, private, philanthropic, multilateral, developmental, insurance, or out-of-pocket.) f) Metrics and criteria for success – establish SMART goals for performance and process indicators that are crucial for decision making and continuous improvement.
2.3 Sustainability strategy	Rare diseases typically require life-long treatment. Therefore, there is a need for long-term commitment and strategy to ensure equitable and affordable access. It is ideal to have both a 3-5 plan and a 5–10-year plan. If the program entails compassionate use, donation, or other access pathways, there should be a systematic and ethical transition strategy and program exit. Because sustainability is such an important consideration for an access to rare disease medicines program, see Section V.7. for a more detailed discussion on considerations and approaches.
2.4 Buy-in and endorsement	Leaders and decision makers of the initiative need to agree on and endorse the strategy. The collective leadership will be utilizing the

Elements of Program Strategy	Key Components
	strategy to garner resources and support. a) Endorse and approve strategic plan ensuring it is: ● Patient centric ● Feasible ● Viable ● Data-driven for success and risk mitigation ● Sustainable b) Approve provisional budget and funding strategy c) Establish formal and informal agreements with key partners on collaboration and funding commitments.

The product from this phase of program development is the program strategic plan. It will serve as the set of guiding principles and parameters for program design and implementation. As such, there must be buy-in from all key stakeholders on the proposed strategy.

3. Program Design

Implementing any health program or sets of health interventions is a resource intensive and complex process. The complexity is compounded in the case of rare diseases because of the inherent medical, scientific, financial, and regulatory challenges. Therefore, rare diseases require the holistic, patient-centric approach outlined in the strategic plan that accounts for small patient populations, diagnostic delays, and complex, expensive treatments.

The Program Design Team should include key internal and external stakeholders, opinion leaders, and health and medical experts with practical country knowledge and experience and representation from country government and health systems. In addition, it is critical that, where feasible, the program leverages existing health systems infrastructure and integrates the activities within the existing national health frameworks.

Dependencies

- Stakeholders buy into the proposed strategy and program goals and objectives.
- Program design team, whose composition will depend on the program type and strategy. Considerations for typical teams may include:
    - Industry
    - Public sector
    - National ministries
    - Beneficiary representatives
    - Independent medical expert
    - Prospective funders
- Scale and scope of program is conditionally agreed upon
- There is provisional approval of the budget

The elements of program design are:

3.1 Program parameters
3.2 Partnerships and alliances
3.3 Management structure and governance
3.4 Implementation strategy
3.5 Monitoring and evaluation
3.6 Communications
3.7 Program Budget

Elements of Program Design	Key Components
3.1 Program Parameters	Maintaining focus on the program goals and objectives will ensure that the activities are designed to achieve those goals. Targets and goals outline the scale and scope of the program (i.e., number of patients, specific health facilities with capacity and competency, reasonable geography, etc.) The goals should be measurable and attainable.
3.2 Partnerships and alliances	Achieving sustainable access to medicines in resource constrained settings requires input from many stakeholders and creative use of their resources. Each disease, treatment, patient(s), and geography may require novel and innovative approaches that require engaging different sets of partners. a) Identify and confirm the key stakeholders with the capacity and capabilities necessary for program implementation and sustainability are committed, informally and formally (including MOUs or more formal agreements). The stakeholders to be considered in an access to rare disease medicine program include patients and caregivers, patient advocacy organizations (PAOs), pharmaceutical companies, non-governmental organizations (NGOs), healthcare professionals (HCPs), payers (insurance providers), government agencies (ministries of health, finance, etc.), and academic researchers. b) The key partners need to be engaged to agree on the specific goals and targets and confirm that the resources exist to execute the program properly.
3.3 Management and governance	Management focuses on the day-to-day operations, planning, and execution of the program whereas governance provides the overarching framework, strategic direction, and accountability structure, while within that framework. The cadre of actors that need to be involved is incumbent on the processes outlined in the program design. a) Develop and document program management matrix - Composition, role, and structure for all the players. b) Establish clear roles and responsibilities (RACI driven – **R**esponsible, **A**ccountable, **C**onsulted, and **I**nformed). c) Transparent decision-making process.

Elements of Program Design	Key Components
	d) Install policies around conflict of interest. e) Compliant with all legal, regulatory, and ethical guidelines. f) Where applicable, establish a broad oversight structure (e.g., advisory committee, board, or expert committee).
3.4 Implementation strategy	An implementation strategy is a detailed plan that outlines the steps, resources, and timeline needed to put a program design into action. It translates the program's goals into actionable tasks and specified timelines. It also outlines coordination and communication processes among team members to achieve the desired outcomes. a) Phasing decision – A pilot phase is a widely used approach to identify design flaws and implementation issues before full-scale deployment to ensure successful deployment. However, in the case of rare diseases, a "pilot" may only apply to a handful of patients. In that case, decisions on whether to phase the implementation will have to be made as to whether data gleaned from the phasing exercise can effectively benefit the program in rolling out to a larger RD community or to the entire national RD cohort / community. b) Preparations ● Where to start – what healthcare facility or part of a country, district, municipality as clinical and technical competencies for rare diseases are not necessarily pervasive. ● Patients to be reached – criteria for confirmed diagnosis, eligibility for treatment, and enrollment. ● Administrative checklist – legal, regulatory, education / training, funding, etc. ● Operational checklist – necessary diagnostics (hardware, software, components, and expertise) established and available, product procured and staged, and other logistics. c) Information from the situational analysis needed to inform the approach and strategy for training and capacity building because of the unique and often unfamiliar territory around treatment and care for PLWRD, there may be a need to develop tailored training regimens and materials for these programs. ● The goal is, where feasible, to integrate any newly introduced rare disease program's training and capacity building with that of existing health care system resources and educational structures. Key groups to be trained include stakeholders involved in rare disease medicine access (e.g., healthcare providers, pharmacists, patient advocacy groups, regulatory bodies, researchers, patients, caregivers). ● Donors to develop training and education materials relevant to

Elements of Program Design	Key Components
	the stakeholder tailored for target audiences to achieve the overall goals of the program. ● Address specific knowledge gaps and training requirements related to rare diseases, diagnostic procedures, treatment options, access pathways, and related support systems. ● Diagnostics for rare diseases may be quite complex. Therefore, if necessary, there should be focused strategy and attention on instituting laboratory or other advanced diagnostic technology training. ● Whenever possible, training materials should be developed in the local language. ● Prioritize training topics based on urgency and impact. ● Leverage existing resources and expertise within and outside the program.
3.5 Monitoring and Evaluation	Selecting a Monitoring and Evaluation (M&E) tool requires special consideration of the unique challenges associated with small, geographically dispersed patient populations and limited natural history data. The ideal tool must be flexible, patient-centric, and capable of gathering high-quality data despite these constraints. a) Standards of M&E Data – regardless of the methodology(s) the evaluation team chooses, some key principles M&E methodology should abide by include: ● SMART indicators (specific, measurable, achievable, relevant, and time-bound) for tracking program progress. ● Measure for impact and outcomes ● Credible data source ● Assured data quality. Employ procedures for ensuring the accuracy, reliability, and validity of data. ● Objective analytical methods, interpretation of data, and drawing meaningful conclusions. a) Considerations around data challenges for rare diseases ● Small dataset (establishing statistical significance may be a challenge with small sample sizes). ● Patients are often geographically dispersed. ● Limited historical patient health and medical data. ● Limited disease baseline data. ● Culture and language barriers. b) Metrics and indicators – With rare disease specific challenges, the evaluator should employ a comprehensive data collection strategy to establish what data will be collected, how it will be stored and managed, and how it will be used for program evaluation and improvement.

Elements of Program Design	Key Components
	● Capture specific patient reported outcomes. ● Minimize burden on patients and caregivers. ● Supplement with observer-reported outcomes, if necessary, in cases of limitations in patient cognitive capacity and capability. ● Observe standard technical and ethical considerations on health-related patient data. ● Real world data (RWD) is especially important for M&E in rare diseases to understand patient journey and assess treatment effectiveness. c) Methodologies to consider ● Quantitative (e.g., diagnostic, scientific, and outcome data, surveys, routine and specific data from HMIS, government agencies, etc.) ● Qualitative (e.g., patient reported outcomes, group discussions, interviews, case studies, etc.) ● Framework (e.g., logic model, results framework, etc.) **Note:** Because of the small sample size, it may be preferable to conduct direct quantitative impact evaluations, as opposed to developing a complex evaluation framework. The evaluation team may also opt to take the mixed method evaluation approach, using both quantitative and qualitative methodologies.
3.6 Communications – internal and external	After the program design is formulated, there are multiple levels of communication that need to take place between the "program" stakeholders that are involved and the patients and relevant affected parties and beneficiaries of the program. a) Communications objectives ● Advocate for national health care policy development related diseases (link to SDGs; look for the alignments) ● Build awareness among HCPs, patients/caregivers, advocacy groups of government guidelines for product donations - local laws, regulations, procedures, and challenges (especially when imported) ● Build awareness among patients/caregivers of advocacy organizations, help lines, and patient communities – include links to existing resources. ● Build awareness of donor programs through donor & supplier communication platforms (e.g., websites, social media, face-to-face (F2F) interactions), and advocacy organizations. b) Internal – Develop a communication plan for stakeholders to ensure regular and clear communication about the program's progress, challenges, and outcomes c) External – outreach to patients and beneficiaries on the existence of

Elements of Program Design	Key Components
	the program, its objectives, and its impact. d) Ensure transparency in all aspects of the program and share information readily and openly with stakeholders to build trust and foster collaboration.
3.7 Program budget	Cost of ownership is a critical consideration for any global health program. In the case of rare diseases, this is especially important because of the high cost of individual treatments, often the inability of patients in LMICs to pay out-of-pocket, and the long-term treatment regimen. Therefore, it is imperative for these types of access initiatives that the full accounting of the cost of ownership is taken into consideration. This would ensure that the benefactor and other stakeholders appreciate the expense of the effort and that the estimates accurately project what it costs to administer such a program and to ensure sustainable impact on the patient. The recommendation is to develop the budget for the full scale and scope of the initiative – set 3-5- and 5-10-years projections. a) Total cost of ownership – include product, diagnosis, treatment administration, ancillary and supportive services, follow-up, other patient costs, etc. b) Realized program cost offsets (e.g., national healthcare expenditures and appropriations for rare disease treatments, duty exemptions, patient out-of-pocket payments, subsidies insurance coverage and reimbursement, etc.) c) Other cost responsibilities and cost sharing – detailed allocations to ensure all partners and patients have clear expectations of what and how much they would be expected to contribute to realize the benefits of the initiative.

The program design developed outlines the parameters of the program and the roadmap for implementation. It is intended to be developed at a high level. The next program implementation phase will include details around how to actually roll out the program to realize the goals and objectives.

4. Implementation Planning

Implementing a health intervention is highly complex and not straightforward. Complexity is compounded with rare diseases due to the limited and geographically dispersed patient population, poor understanding of the diseases, difficult diagnosis, and significant financial hurdles. Therefore, the considerations outlined in this section for program implementation are intended to highlight those specific challenges to minimize unexpected obstacles and to facilitate and smooth the implementation path. However, the list is by no means exhaustive. It is important to be flexible within the actual implementation and have contingency plans in place.

Dependencies

- Program design has been endorsed by key stakeholders.
- The budget has been approved and secured for the term of the program.
- Processes are in place and agreed upon to address the legal and regulatory requirements for the medicines (registration and licensing, treatment, health systems, etc.)
- Approval has been secured for product and therapy administration (physicians with skills and technical knowledge) and ancillary needs.
- Financing mechanisms are in place for end-to-end treatment administration and follow-up care for patients.
- Schedule and timing of the implementation of the program design is agreed upon.

Program design in the previous section details how the initiative would be rolled out to realize the vision, mission, goals, and objectives of the program. Implementation of that program adheres to the rigorous, disciplined and systematic approach of project management. It is not the purpose of the Rare Diseases Guidelines to outline the technical details around project management. This section of the Guidelines emphasizes the important elements and considerations for the project management team as they execute the program.

The elements included in this section in preparing for implementation of the program are as follows:

4.1 Implementation team (Team structure, roles and responsibilities, governance, and processes)
4.2 Detailed project plan (Gantt chart) will serve as a roadmap for implementation.
4.3 Execution
4.4 Data collection (collection, analysis, ongoing monitoring, feedback, and adaptation)
4.5 Communications – internal and external
4.6 Contingency plan / scenario planning

Elements of Implementation Plan	Key Components
4.1 Implementation team	The cohort of players needed to implement the access program is multi-sectoral. The team would include public and private sector stakeholders and international and national organizations. The team members need to have specialized technical expertise around specific rare diseases, operational management skills, and cross-functional competencies related to global health programming. The team members and their roles and responsibilities (e.g., RACI) are identified in the "Partnerships and Alliances" (Section 3.2 under Program Design).
4.2 Detailed project plan	Program manager(s) need to develop a detailed project plan using project management tools like Gantt charts, outlining itemized tasks, and specific timelines reflecting details of the program design. Key considerations that will dictate the tasks and timeline on the project plan are: a) The geographical location(s) within the country (as not all facilities have capability or capacity).

Elements of Implementation Plan	Key Components
	b) Patient access to treatment and care – includes availability of medicines and therapies, ancillary services and devices, and ability to transport patients to the facility equipped for proper treatment administration. c) Realistic estimates of timeline based on the geographical and healthcare infrastructure. d) Whether program rollout will be phased (e.g., pilot, scale-up, etc.)
4.3 Execution	The actual execution and rollout of the program is typically part of the details included in the project plan. The considerations called out here are the specific considerations critical to rare diseases and warrant more focused attention. a) Stage hardware and software (include medicines, equipment (diagnostic and therapeutic), ancillary products, consumables, training, and other support services). b) Training and education ● People, inventory, training, etc. ● Validation of program needs and planning with on-the-ground healthcare and community providers. ● Product positioning. c) Patient identification and treatment ● Confirmed diagnosis. ● Patient eligibility and prioritization. ● Patient intake – incl. registration, consent, disease confirmation, patient record, etc. ● Prep and treatment / therapy administration. ● Monitoring, observation, and discharge. ● Financial settlement – out-of-pocket, insurance, government subsidies, etc. ● Post-treatment follow-up.
4.4 Data collection	The battery of data to be collected and described in this section includes patient level clinical data and program data. a) Patient clinical data ● Patient data including real world data (RWD), patient-reported outcomes, and other patient and disease-specific information (observing all privacy requirements). ● Treatment reporting (outcomes and progression of disease). ● Other treatment data (e.g., AE reporting, surveillance, pharmacovigilance, and other product and safety data and regulatory requirements). ● Other country level reporting requirements and patient registries.

Elements of Implementation Plan	Key Components
	b) Program data for assessment and evaluation ● Progress and performance indicators ● Ancillary support ● Financial impact ● Other quality of life
4.5 Communications	Communications referenced in this section are associated with program implementation. These are primarily external facing between the program and the public and prospective beneficiaries. a) Communications package on the access program and other Public Service Announcement (PSA) for awareness building of disease and availability of treatment, engagement for government, hospital, HCP, patient, program managers, etc. b) Patient empowerment and support ● Patient and family support and education. ● Education and advocacy. ● Counselling and peer-to-peer networks. ● Telehealth and other access strategies.
4.6 Contingency planning	Due to the combination of complexity of access programs for rare diseases and the fragility of the medicines, it is advisable to develop a contingency plan and conduct scenario planning exercises to reduce setbacks and failures from unforeseen disruptions.

Implementing any global health program requires a balance of attention to details because of its complexity of rare diseases as well as flexibility because of the potentially unique nature of individual cases and paucity of real-world data.

In addition, there is a need for rigor in applying best practices in project management especially because of the small patient population, potentially limited data for and understanding of the disease, complex regulatory, legal, and logistical pathways, and financial hurdles.

5. Sustainability

In rare disease programs, sustainability necessitates a multifaceted approach that ensures the long-term viability of patient access to treatments and care. It is important to note that sustainability may be different depending on disease, treatment type, socioeconomic status, political will, and other factors.

This Rare Diseases Guidelines focus on three key elements of sustainability: 1) national and private sector commitment to provide **appropriate** treatment(s) and / or alternative treatment options; 2) operational resilience in making these complex therapies consistently and continuously **available**; and 3) social equity and inclusion policies in making the therapies **affordable** and within reach of all patients, including those in

underserved communities.

Therefore, the sustainability framework presented here is based on the three A's:

1. **Appropriate** – proper, safe, and effective treatment for the disease that includes the process from accurate diagnosis through treatment administration and follow-up care.
2. **Available** – access to all patients living with rare diseases when and where needed.
3. **Affordable** – where the total cost to the patient as the beneficiary, healthcare providers, and the system as a whole is economically viable for the long term.

These elements are particularly challenging for rare diseases due to small, geographically dispersed patient populations, high development costs, and a significant unmet medical need. Therefore, the recommendations in this set of guidelines are lists of key considerations as opposed to specific activities and outputs. This last section is a framework to guide stakeholders through developing a comprehensive strategy for sustainability. If an access program is initiated through donations or other special access mechanisms, the long-term vision is to transition the program and intervention activities to the national health system.

Elements of Sustainability	Key Considerations
5.1 Appropriate	The medicine or treatment regimen needs to be appropriate for and properly administered to the patient. In resource-constrained settings, detection and proper diagnosis of rare diseases are challenging due to the lack of or scarcity of properly equipped laboratories and diagnostic facilities. Appropriate in this case refers to clinical and support services throughout the patient journey. a) Diagnosis ● HCP is trained to identify the disease and make proper recommendations and referrals. ● Equipment and technology are available with trained technicians. ● Accuracy of diagnosis (i.e., considerations for diseases with genotype variants). b) Treatment ● HCP trained in proper administration and monitoring, ● Assured product quality and safety – monitoring for AE, SAE, and side–effects. ● Monitor treatment efficacy / disease progression – providing testing is technically feasible, available, and affordable. c) Consider alternative products, biosimilars, off label use, or products under development if applicable.
5.2 Available	Making rare disease medicines available in resource-constrained settings depends heavily on operational excellence to increase efficiency, reduce costs, and drive timeliness in production and distribution. Availability also refers to all the ancillary products and services needed for treatment and care along the patient journey. Lastly, because chances are the few patients are geographically dispersed, availing convenient

Elements of Sustainability	Key Considerations
	and accessible healthcare facilities with trained staff and technical capacity to all can be challenging. a) Supplies – Medicines, ancillary products, mobility devices, etc. ● Consistent supply to meet demand – proper forecasting whether purchased or donated. ● Proper supply management (cold chain and special storage). ● If donated or special access, time bound or open-ended commitment. ● Regulatory complexity – registration, importation processes, duties, exemptions. b) Capacity building and healthcare infrastructure ● HCP trained to identify and refer for diagnosis and treatment in strategic locations. ● Location of properly equipped healthcare facilities. ● Resources and services for patients needing assistance to access the proper facilities. ● Institution of telehealth infrastructure for remote counseling, monitoring, and follow-up. ● Supportive services for patients and their families.
5.3 Affordable	Making rare disease medicines affordable likely involves a combination of regulatory incentives, innovative financing, and healthcare policies favorable towards PLWRD. Driving changes will require collaborative advocacy efforts involving the public and private sectors and civil society. In addition to pricing considerations, the goal in affordability is that access to treatment and care are equitable and inclusive (as outlined in the 2025 WHA resolution)[13]. a) Costs – the following are the various costs that need to be considered for funding needs and affordability throughout the entire patient journey. ● Product – a typical approach using HTA pricing should be adaptive and account for the unique challenges of rare diseases and other non-clinical factors (e.g., unmet need, disability, and quality of life). ● Product is donated, subsidized, or procured through tiered / preferred pricing. ● Health systems – HCP time, resources, and infrastructure. ● Non-governmental programmatic support – NGOs, pharmaceutical distributors, patient support, and other groups involved in the access program. ● Patient – all out-of-pocket costs along the patient journey from identification of disease through travel to access treatment at

[13] Rare diseases: a global health priority for equity and inclusion.

Elements of Sustainability	Key Considerations
	qualified facilities and other ancillary products, support services, and aftercare. b) Funding ● National budget and subsidies for rare diseases. ● Insurance reimbursements. ● Leveraging existing clinical, technical, and administrative resources. ● Diversified funding – a mix of public funding, philanthropic organizations, industry partnerships, and other innovative funding models. ● Cost effectiveness offset – improved health outcomes that benefit HCS, patients, and society.

Driving all three elements of the three A's in this framework to achieve sustainable equitable and inclusive access to rare disease medicines relies on adoption of supporting regulatory, health, economic, and social policies. It is important to engage and empower patients and patient advocacy groups to actively participate in policy discussions and raise awareness to lobby for these policy changes. It is also beneficial to promote collaboration across countries to address the rare disease challenges globally. It is important to share best practices to effectively and efficiently replicate successful access program models to institute change.

V. Acknowledgements

These guidelines were originally developed in 2022 through a multi-stakeholder process under the GARDaccess initiative, incubated by PQMD. In partnership with external consultants and a multi-sectoral team of stakeholders, PQMD led a dedicated workstream to explore how quality rare disease programs could be designed and implemented, especially in resource-limited settings. Drawing on global literature, subject matter expertise, and in-depth stakeholder interviews, the guidelines were developed to support high-impact, sustainable access to rare disease treatments in LMICs.

As of 2024, PQMD has completed its incubation of the GARDaccess initiative, which is now an independent 501(c)(3) entity under the leadership of Ms. Harpreet Ram. To follow the ongoing work of the independent GARDaccess organization, visit www.gardaccess.org. While the new GARDaccess organization continues to advance access and equity for rare disease patients, PQMD retains ownership and stewardship of the Guidelines for Rare Disease Programs as part of its broader Guidelines portfolio.

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VI. Common Abbreviations

ATM: Access to medicine
COGS: Cost of Goods Sold
EAP: Early Access Program
HCP: Health Care Provider
HTA: Health Technology Assessment
LMIC: Low- and Middle-Income Country
MAP: Managed Access Program
MOH: Ministry of Health
MOU: Memorandum of Understanding M MEC: Medical Expert Committee
NGO: Non-governmental organization
ODA: Orphan Drug Act
PSA: Public service announcement
SDG: Sustainability Development Goal
WHO: World Health Organization