Rare Disease Potential for ATMP Development Framework

The Rare Disease Potential for ATMP Development Framework is composed of **3 domains**:

1- **Unmet Medical Needs**
2- **Psychosocial and Societal Impact and**
3- **Research and System Readiness**

DOMAIN 1: Unmet Medical Needs

*It assesses unmet clinical needs of a condition, considering its **severity, prevalence**, the **urgency** of intervention (linked to disease progression), the availability, benefit-risk profile, burden and patient compliance **with current treatments and care standards**.*

Criteria	Item	Item definition
Severity: *Assesses the age of disease onset as well as the clinical seriousness and variability of the condition*	**Age of disease onset**	Age of the patients when the first clinical manifestations, most commonly, appear.
	Life-threatening potential	Assesses the probability and expected age of disease-related death.
	Extent of disability	Assesses the extent and complexity of disease-related impairments, based on motor and sensory deficits, neurological or cognitive involvement, and the number and types of organ systems affected.
	Disease penetrance and clinical variability	Assesses the degree of clinical variability and penetrance of the disease among patients. This variability can be due to genetic, epigenetic and environmental factors. It reflects how predictable disease onset, presentation and progression are among patients.
Prevalence: *Evaluates how rare the disease is based on EU definitions.*	**Rarity**	Prevalence of the disease, based on European Union definitions of rare and ultra-rare diseases. In the European Union, a disease is defined as: • Rare if it affects ≤5 in 10,000 people • Ultra-rare if it affects <1 in 50,000 people (i.e., <2 in 100,000)
Urgency: *Measures the nature of the disease and how rapidly it progresses.*	**Disease nature & Speed of disease progression**	Reflects on how urgent it is to act in response to the disease. Includes the nature of the condition (acute/chronic), pace of progression, and the critical time window for effective intervention to prevent irreversible damage or death.
Available treatments: *Assesses the existence, safety and effectiveness of treatments as well as their associated burden and how that impact patient compliance.*	**Availability and access to treatments and standards of care**	Assesses whether any standard of care or treatment, approved, off-label or compassionate use programmes, exists, is available and accessible across different regions/countries.
	Safety and efficacy of available and accessible treatment and standards of care	Evaluates the safety and efficacy – ranging from symptom management to curative - of available treatments and standards of care.
	Burden of available treatments and standards of care	Evaluates how demanding current treatments and standards of care are in terms of complexity, frequency, invasiveness, side effects, and how it impacts patients' compliance.

DOMAIN 2: Psychosocial and societal impact

*It encompasses the impact of the rare disease on the **individual and family**, in terms of **social participation**, **health-related quality of life and well-being**. It includes the **broader societal impact** the rare disease has on healthcare, social security systems.*

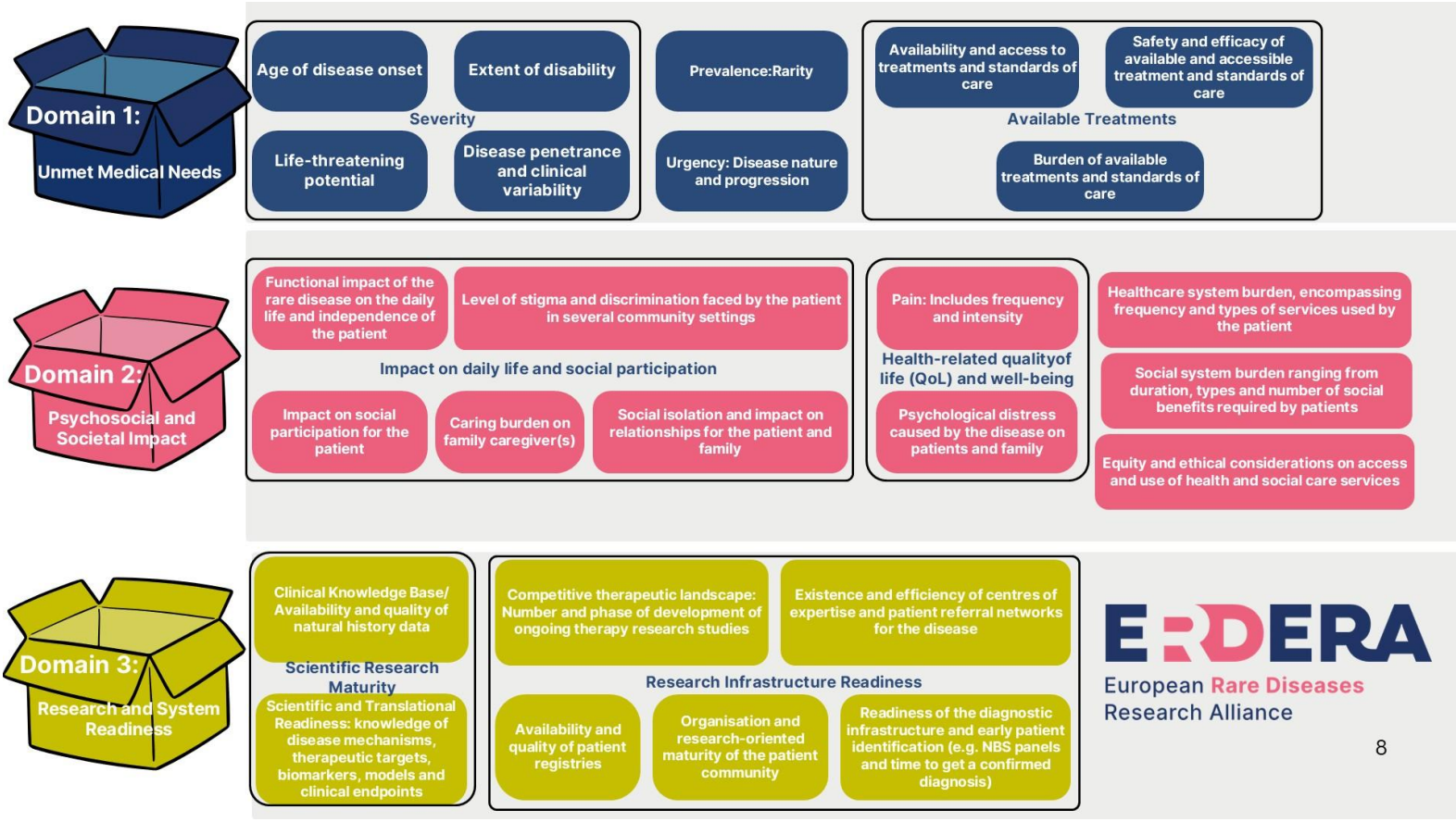
Criteria	Item	Item definition
Psychosocial impact (individual and family): *Impact that living with a rare disease has on the daily life and social participation of the patients and their families. It encompasses aspects such as functional impact, autonomy and independence, caring burden, stigma and discrimination, pain, psychological distress, work, school, leisure and cultural participation as well as social isolation and impact on relationships.*	**Impact on daily life and social participation**	**Functional impact** (**person living with a rare disease**): Describes the degree to which the disease causes specific impairments in functional abilities, encompassing communication, walking, seeing, hearing. self-care, and remembering. It reflects how well a person can perform activities of daily living as well as the degree to which the person's autonomy and independence are impacted.
		Degree of exclusion or limitation from normal participation in work, school, sports, travel, or cultural life (**people living with a rare disease**): • **Work participation** (unable to work, part-time work, early retirement) • **School participation** • **Leisure and culture participation** (go on holidays, do sports, enjoy cultural events).
		Social isolation and impact on relationships (for both **people living with a rare disease and family members**: Effect of the condition on personal relationships and the risk of social withdrawal or breakdown in social networks (e.g., divorce).
		Caring burden (**family members**): The (direct and indirect) emotional, physical, and financial cost of care borne by family members or other informal caregivers, including time commitment, employment disruption, unreimbursed costs and caregiver burnout.
		Stigma and discrimination (people living with a rare disease): Degree to which the condition causes exclusion, marginalisation, or discriminatory experiences in education, work, healthcare, or community settings.
	Health-related quality of life (QoL) and well-being	**Pain (people living with a rare disease):** Intensity, frequency, and duration of physical pain directly associated with the rare disease.
		Psychological Distress (**people living with a rare disease and family members**): The mental health burden on patients and family carers resulting from the rare disease. It can include anxiety, stress, depression, post-traumatic stress disorder (e.g. linked to a near death experience) and guilt (e.g. of having passed on a condition).
Societal impact: *Broader impact on healthcare and social systems, including healthcare and social service utilization, financial strain on public budgets, and societal values related to health and social care equity and ethics.*	**Healthcare system burden**	Healthcare system utilisation, encompassing frequency and types of services used (e.g. specialised and inpatient care) by patients as well as associated costs for healthcare systems.
	Social system burden	Social system utilisation, ranging from duration, types and number of social benefits and support required by patients as well as associated costs for social systems.
	Equity and ethical considerations in access and use of health and social care	Degree of societal inequity faced and moral imperatives (e.g., treating ultra-rare children) in access and utilisation of healthcare and social system services. It considers how difficult and inequitable the access by patients to health and social care is.

DOMAIN 3: Research and System Readiness

*It captures how far the **scientific knowledge**, translational tools, and enabling **research-care infrastructure** for a rare condition have matured to support the rapid, large-scale development and clinical evaluation of an ATMP. It includes natural history data, validated targets, registries, patient networks, expert centres, diagnostics, and competitive whitespace.*

Criteria	Item	Item Definition
Scientific Research Maturity: *Readiness of the scientific evidence base, including the depth of natural-history data, validation of therapeutic targets, and availability of predictive disease models, biomarkers, and regulator-accepted clinical endpoints.*	**Clinical Knowledge Base**	Assesses how well disease progression in patients is reflected in practice – i.e. the dept h and quality of data on natural history of the disease and the reliability with which doctors can predict the course, complications and prognosis over time.
	Scientific and Translational Readiness	Evaluates how well the disease is understood at a mechanistic level, whether therapeutic targets are validated in relevant disease models, and how fully the biological insights are translated into usable tools for preclinical and clinical development. It is focusing on two key aspects: • **Mechanistic understanding & target validation** – depth of disease mechanisms mapping and confirmation of therapeutic targets in relevant disease models. • **Translational resources — disease models, biomarkers & endpoints** – availability of predictive disease models, validated biomarkers (measurable characteristics that indicate a normal or abnormal process, or a condition or disease), clinical endpoints and outcome measures (e.g., lab tests, functional scores, patient-reported outcomes).
Research Infrastructure Readiness: *Measures whether the supporting ecosystem for a rare-disease ATMP programme is in place. High readiness means the scientific community, health-system actors, and patient stakeholders can work together immediately to generate high-quality clinical evidence.*	**Competitive therapeutic landscape**	Assesses the extent and maturity of ongoing therapy development programmes—both ATMPs and other therapies—for the target disease. It includes academic, patient organisation and industry-led therapeutic studies. It indicates the degree of strategic whitespace for a new intervention and the risk for market saturation at launch.
	Patient registries	Availability and quality of a disease-specific registry to support clinical trials.
	Patient communities	Evaluates how well organised, resourced and research-oriented patient or stakeholder groups are – in particular their ability to identify patients, maintain or support registries, disseminate study information and enter into partnerships in therapeutic research.
	Centres of expertise & patient referral network	Evaluates the availability of accredited experts and specialised centres—together with the formal referral mechanisms that connect newly diagnosed patients to this expertise—thereby gauging the health system's overall capacity to provide timely, specialised care (with faster ATMP access as one potential downstream benefit).
	Diagnostic infrastructure & patient identification	Evaluates how quickly and equitably patients can obtain a confirmed diagnosis—considering test availability, reimbursement, newborn-screening (NBS) coverage, and the typical delay from first symptoms to diagnosis.

Figure 1 – Overall rare disease prioritisation framework for Advance Therapy Medicinal Products (ATMP) development



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