innovative health initiative

Ref. Ares(2023)7602356 - 09/11/2023

Realise D

compRehensive mEthodological and operational Approach to cLinical trIalS in ultra-rarE Diseases

and other IHI projects

Prof. Ralf-Dieter Hilgers & Dr Solange Corriol-Rohou

ERICA

12 December 2024 - UDINE, ITALY

What is a Rare Disease?

- There are about **7000 rare diseases (RDs) affecting more than 300 million people worldwide,** including 30 million in Europe*.
- There is no universal definition of rare disease
- The definition depends on legislation and policies adopted by each country and region

There is the general concept agreed

→ **Prevalence** of the condition **in the EU** must **not be more than 5 in 10,000, and not more than 6.4/10,000 in the US**

→ **The number of patients for a disease to be accepted as a RD is clearly related to the population of each country or region** *(e.g. Malaria is a RD in EU and not in Africa)*

* Wakap et al. 2020 DOI: 10.1038/s41431-019-0508-0

THE EU ORPHAN REGULATION – a success story

Delivering treatments for up to 6.3 million patients with rare diseases

22. 1. 2000 EN Official Journal of the European Communities L 18/1

I

(Acts whose publication is obligatory)

REGULATION (EC) No 141/2000 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 16 December 1999
on orphan medicinal products

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission (1),

Having regard to the opinion of the Economic and Social Committee (2),

tions of competition and barriers to intra-Community trade;

(4) orphan medicinal products eligible for incentives should be easily and unequivocally identified; it seems most appropriate to achieve this result through the establishment of an open and transparent Community procedure for the designation of potential medicinal products as orphan medicinal products;

- Since 2000: 160+ new treatments authorised
- By 2019: 2100+ designations
- The Regulation raised the profile of rare diseases, built a community and networks
- EU Reference Networks (ERNs) improve the sharing of knowledge

THE RARE DISEASE MOONSHOT

At the current pace, it would take over 100 years to develop treatments for all rare conditions…

EURORDIS and EFPIA call for a Moonshot for basic and translational research for adult and paediatric rare disease

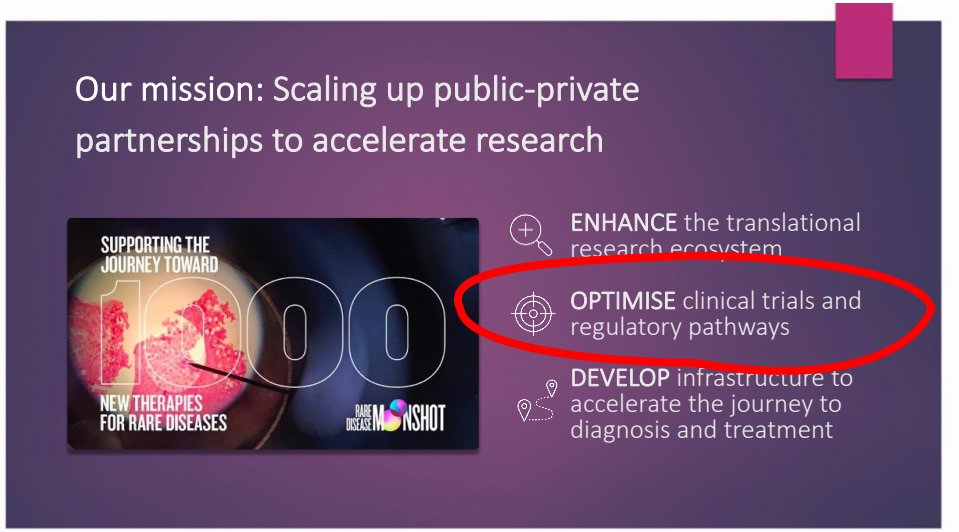
EFPIA has suggested a Moonshot to develop science for rare diseases, thus supporting innovation in underserved areas. Typically, a Moonshot refers to an open-science model aimed at making knowledge generated from scientific research transparent and accessible through shared collaborative networks. A recent example is the cancer Moonshot launched in 2016 with an ambition to reduce cancer deaths in the United States by 50%, by accelerating scientific discovery, fostering greater collaboration and improving data sharing[46].

In many rare and paediatric diseases, limited understanding of disease pathophysiology and of potential drug targets precludes any investment. The Moonshot for rare diseases aims to establish a mindset of concerted effort towards developing the basic science and accelerating the translational research that are prerequisites for clinical development[47].

This shared goal would encourage all stakeholders to work together on defined areas of priority based on better coordination of basic research, investment, and infrastructures. The model would be built on public-private partnerships, leveraging existing European initiatives such as the IMI and its successor, the Innovative Health Initiative (IHI), as well as enabling collaboration opportunities for industry in any Commission programme dealing with rare diseases (e.g., ERNs for rare disease and potential European Rare Disease Partnership in Horizon Europe).

This proposal has the potential of contributing to faster, better, and more efficient and coordinated development of innovative products. EURORDIS is fully supportive of this initiative; EURORDIS and EFPIA will actively partner to design and implement the Moonshot.

EFPIA-EURORDIS paper



The Moonshot is **a commitment and collaboration** between players in the translational and clinical research ecosystem to boost working in partnership (public-private, private-private) where they can accelerate the journey to new therapies for patients with rare diseases for whom white spots (no research, no solutions) exist

The collective objective is **to identify the gaps that are best addressed with industry collaboration and know-how and remove barriers for PPP collaborations**.

It aims to **simplify and facilitate** communication between translational and clinical research players and initiatives

It **complements**, **leverages** and **enhances** ongoing efforts

It **triggers new initiatives** where needed, explore how to upscale existing ones help filling pipelines with new solutions, and accelerate the journey to diagnosis and treatment.

It **is a response to the call for a paradigm change**

RARE DISEASE MOONSHOT

SCALING UP PUBLIC-PRIVATE PARTNERSHIPS TO ACCELERATE RESEARCH IN RARE DISEASES

Do you want to know more about the Moonshot coalition?

RARE DISEASE MOONSHOT
SCALING UP PUBLIC-PRIVATE PARTNERSHIPS
TO ACCELERATE RESEARCH IN RARE DISEASES

Where are we now?

Call Launch to public sector - 27th July '23

Deadline of applicant submission – 8th Nov '23

Confirmation of winning bid – 24 Jan '24

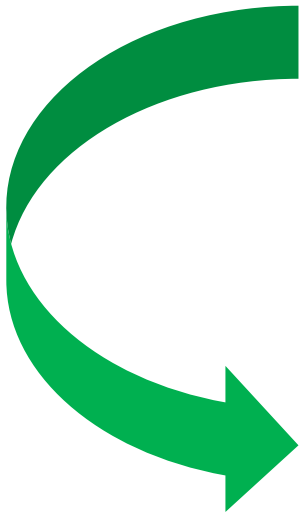
Joint proposal creation – Jan to Apr '24

Full Stage 2 proposal submitted – 23 Apr '24

Kick off meeting – January 9-10

5 years project

Establishing novel methodological approaches to improve clinical trials for rare/ultra-rare diseases (IHI Call 4/Topic 4



- Coordinator: Prof. Ralf-Dieter Hilgers; Sigmund Freud University, Austria
- Project Leader: Dr Solange CORRIOL-ROHOU, MD, PhD

innovative health initiative

Realise RD

compRehensive mEthodological and operational Approach to cLinical trIalS in ultra-rarE Diseases

Consortium

26 public partners
11 private partners
13 associated private partners

innovative health initiative

COCIR

efpia

EuropaBio

MedTech Europe
from diagnosis to cure

Vaccines Europe

Co-funded by the European Union

RealiseD objectives

RealiseD will implement a collaborative and compRehensive mEthodological Approach to cLinical trialS in (ultra-)rarE Diseases, enabling faster therapeutic development while balancing the need for timely development and regulatory compliance with the level of evidence realistically attainable in a constrained environment.

To achieve its goals, the RealiseD consortium has formulated objectives, supported by one or more of the WPs, and fully aligned with the expectations cited in the IHI Call 4/Topic 4: Establishing novel approaches to improve clinical trials for rare/ultra-rare diseases.

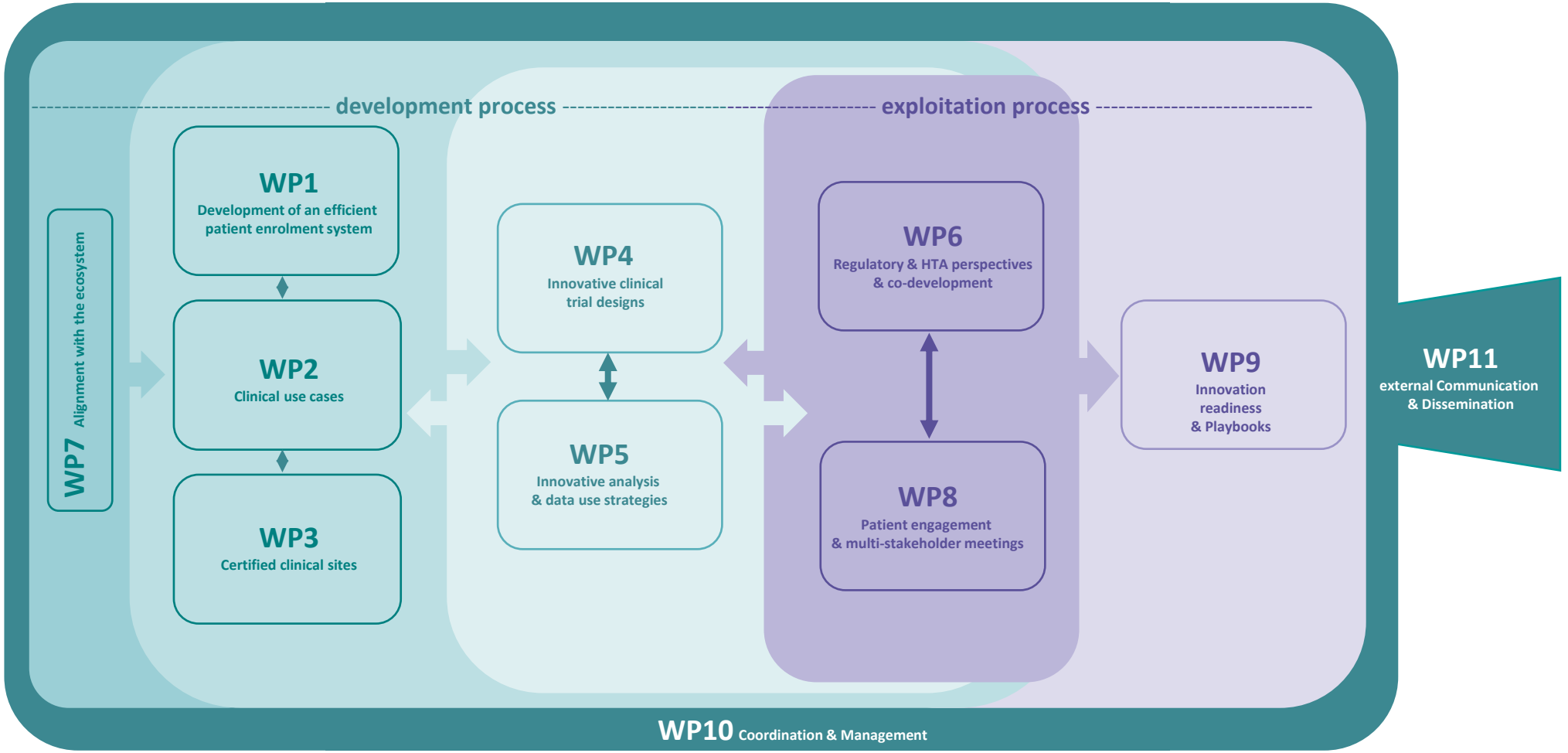
The scientific and operational objectives are as follows:

1. To enable patient referral strategies to minimize risk of enrolment failure for trials in (U)RD.
2. To address the main hurdles of CT conception in (U)RD diseases and to articulate the need for innovation in CT methodologies based on 4 use cases.
3. To provide a framework for centre certification.
4. To evaluate and optimise various aspects of CT designs for (U)RD, allowing comparative assessment. To enable quantitative comparison of various designs by developing models and assessment functions.
5. To develop methodology to maximally extract information from the available patients, on multiple and longitudinal outcomes; to enrich this knowledge base with an array of relevant additional sources including, in particular, natural history studies, from related indications, from real-word data, and from multiple sources; to develop user-friendly, stable, and precise inference methods for sparse data.
6. To develop regulatory science-based evidence, thereby integrating relevant Horizon Europe framework results, and to implement qualification pathways; to design and experiment with novel regulatory pathways
7. To ensure and maximize the alignment between RealiseD work, outputs and outcomes and the overall RD ecosystem including the future European partnership on rare diseases (ERDERA) as well as other relevant initiatives, infrastructures, or projects.
8. To ensure a patient-centric approach and enable the co-creation process throughout the whole workflow, with input of all stakeholders, thus maximising the relevance and subsequent buy into methodological /operational innovative approaches developed.
9. To create and make accessible to the RD community playbooks that contain tools, methodological products, and other resources for facilitating an efficient design and adoption of innovative methodological approaches for CT and (U)RD following a co-creation approach that will foster active engagement of project partners.

Realise D

compRehensive mEthodological and operational Approach to cLinical trIalS in ultra-rarE Diseases

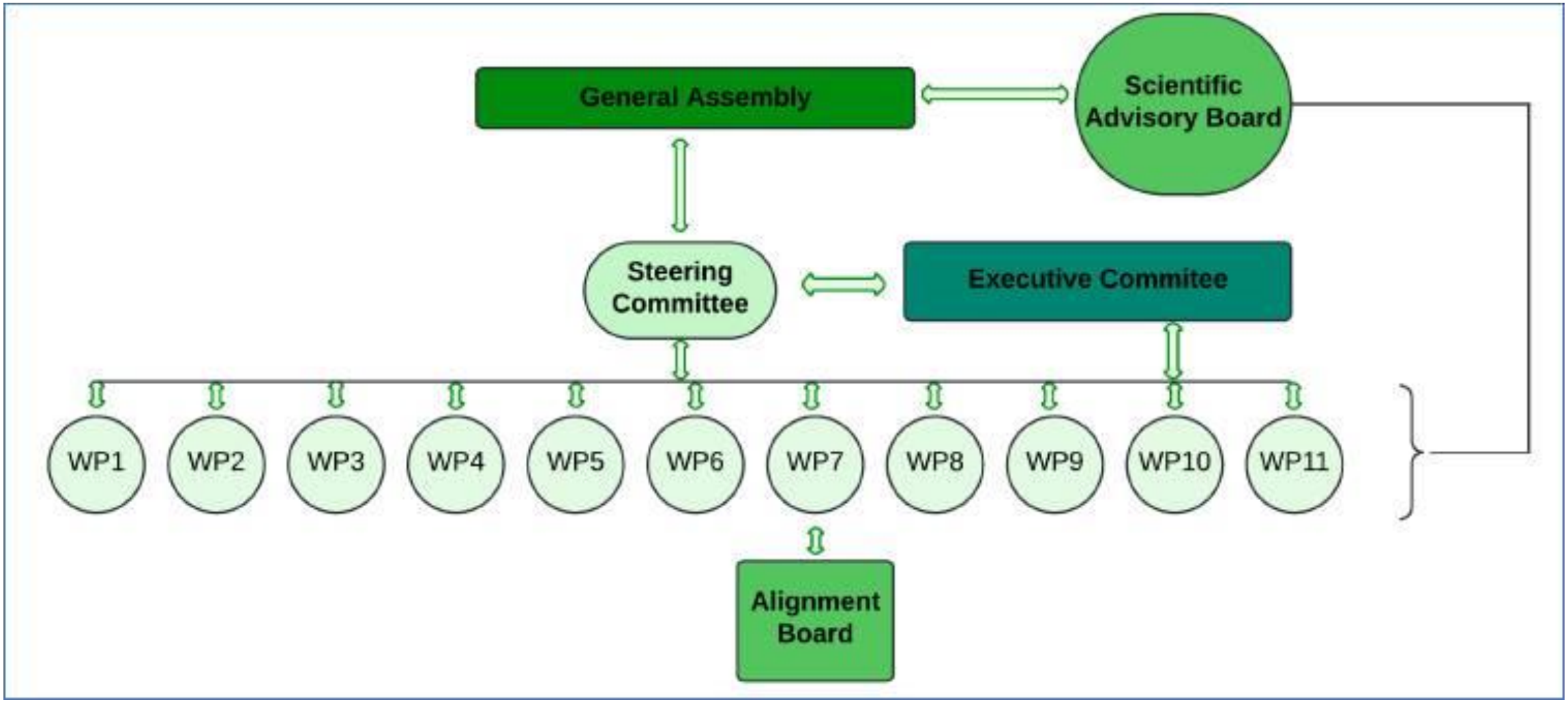
Structure



Realise D

compRehensive mEthodological and operational Approach to cLinical trIalS in ultra-rarE Diseases

Governance



Private partners' Perspectives

Let's be bold and ambitious → work beyond the state of the art, and consider innovative approaches, which will have also to be considered not only as useful but also acceptable by both regulators and HTA bodies.

- Selecting existing tools and methods to address research question when designing a trial will be quite important, as well as developing new ones.

Ref. Ares(2023)7602356 - 09/11/2023

Realise D

compRehensive mEthodological and operational Approach to cLinical trIalS in ultra-rarE Diseases

Expected Outcomes

Playbooks for novel CTs for rare diseases /clusters of diseases, to be also used for education/ training; co-created with and validated by regulators, HTA bodies and patients, including:

- Good practice recommendations and expert advice for multinational innovative studies, study protocols, EHRs driven registries and longitudinal natural history studies;
- Standardized processes across all disease areas, countries and sites for fast and reliable feasibility processes, allowing for example for early feasibility assessment to support design of feasible development programmes. Effectiveness assessment of optimised CT designs as compared to the 'gold-standard' CT design for rare diseases.
- Information to support clinical research network set up to conduct innovative trials including e.g., RWE, remote elements …

Certified/qualified CT sites

Structured and predictable system of referral of patient (physically and virtually) to expert centres

Alignment and complementarity with the EU Rare Diseases Partnership and other relevant PPPs to create synergies and avoid overlaps.

innovative health initiative

Realise D

compRehensive mEthodological and operational Approach to cLinical trIalS in ultra-rarE Diseases

Multi-stakeholder collaboration

Building on what exists
Filling the gaps where needed
Complementary with ….

ERDERA

EUROPEAN RARE DISEASES RESEARCH ALLIANCE

The EU Rare Disease Partnership

Some initiatives of interest ….

Some PPPs* to Advance Paediatric Research

*Public Private Partnerships

How IHI can contribute?

Challenges and opportunities in regulatory science that could be addressed by a cross-sectoral public-private partnership like IHI.

- Paediatrics is an area where more public-private collaborative projects and possibly an integrated programme are needed, in order to address specific challenges and be as transformational as IMI projects such as ITCC-P4 and c4c. These include:
  - sustainable framework/infrastructure to stimulate and speed up the paediatric development for medicines, diagnostics, and devices; to this end the concept for a paediatric accelerator could be very highly valuable. Scientific robustness will be key;
  - improve the current situation with paediatric medical devices and consider how pre-competitive projects could help with paediatric devices and combination products;
  - how to close research gaps that when closed will make necessary investigations much more efficient, for instance to facilitate the implementation of the mode of action mechanism concept as proposed in the revision of the EU pharmaceutical legislation and to address the specific needs in neonatology and other therapeutic areas.
- Collaboration is key and a programmatic approach should be considered to advance regulatory science in paediatrics through several complementary projects.

https://www.ihi.europa.eu/sites/default/files/uploads/Documents/ProjectResources/RegulatoryScienceSummit_Feb2024_Report.pdf

11 projects funded under Horizon Europe

Among these projects:

- INVENTS is working on creating a comprehensive framework to improve the evaluation, assessment, and regulatory decision-making processes of new medicines targeting rare diseases, including paediatric rare diseases
- ERAMET aims to provide an integrated approach to support developers' and regulators' decision-making in the field of paediatric and orphan drug development

Horizon Europe EU funded projects: Rare Disease Day: discover 11 new projects funded under Horizon Europe - European Commission (europa.eu)

ACT EU: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/accelerating-clinical-trials-eu-act-eu

Horizon Europe Funded Projects

EU-RAS	• EUropean network for neurodevelopmental RASopathies
GEREMY	• Gene Therapy for treatment of rare inherited Arrhythmogenic Cardiomyopathy
MAGIC	• Next-generation models and genetic therapies for rare neuromuscular diseases
NANEMIAR	• Nanomedicine Approach to Normalize Erythrocyte Maturation in Congenital Anemia by messenger RNA
RESTORE VISION	• Novel advanced and repurposed therapeutics for vision restoration in a group of severe rare ocular surface diseases: from validation to first clinical investigations
SIMPATHIC	• Accelerating drug repurposing for rare neurological, neurometabolic and neuromuscular disorders by exploiting SIMilarities in clinical and molecular PATHology
TheRaCil	• Therapies for Renal Ciliopathies
DREAMS	• Drug REpurposing with Artificial intelligence for Muscular disorderS
LightCure	• Light for double specificity and efficacy without burden

European Commission

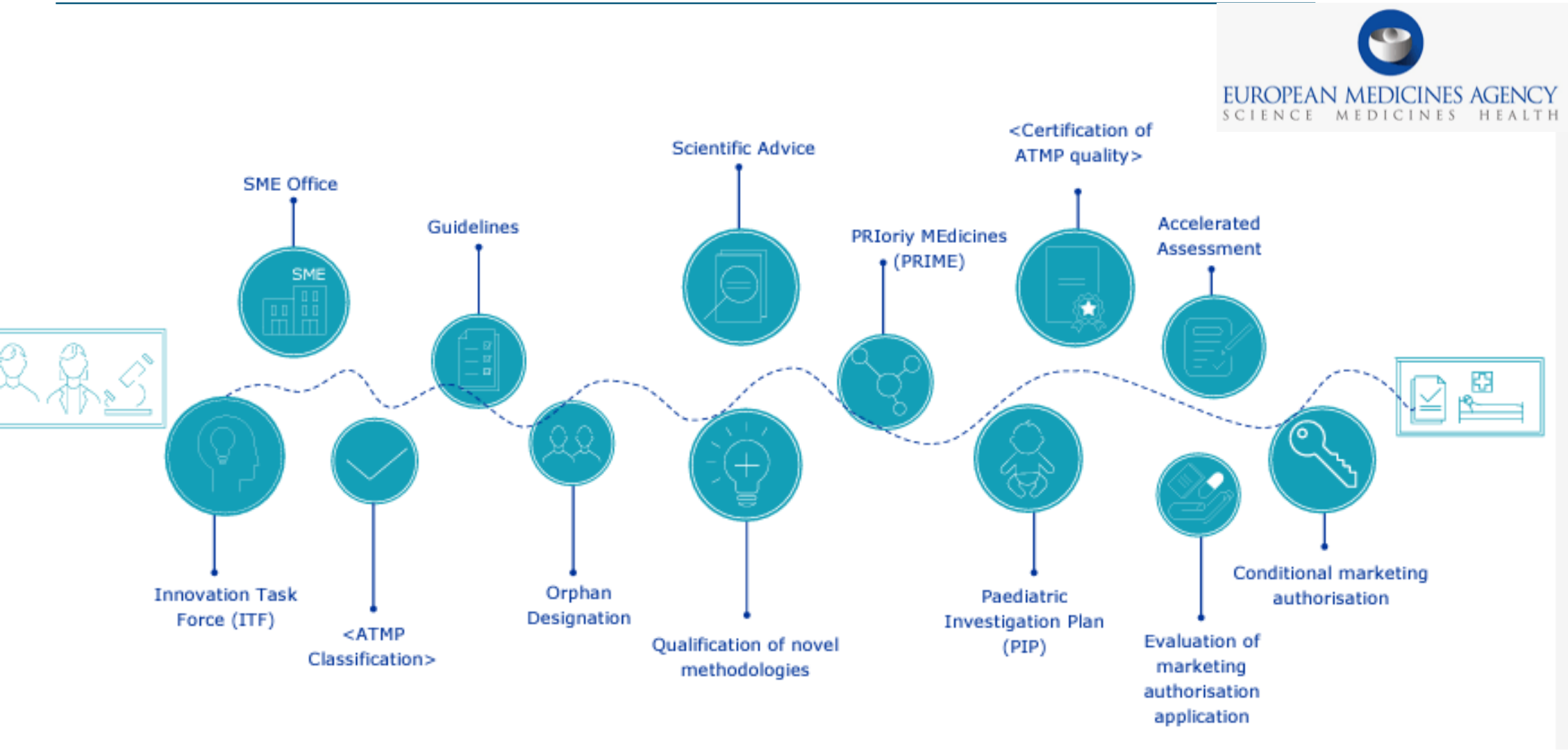
Conect4Children Stichting (c4c-S)

- c4c-S is a unique pan-European network that offers a faster and more efficient way to design, set up and conduct regulatory-grade patient-centric paediatric trials covering all ages and therapeutic areas.

- c4c-S was founded in April 2023 as a spin-off of the IMI2 project c4c, a one-of-a-kind collaboration, bringing together 36 academic and 10 industry partners as well as around 500 affiliated partners. Together, capacity has been built up for the implementation of multinational paediatric trials in Europe, ready to support the next generation of paediatric therapies.

- C4c offers Expert Advice, site identification, site feasibility, and study support

Innovation and support - available tools



Some clinical research networks

c4c-Stichting: a pan-EU Paediatric CT Network to Improve Infrastructure and Facilitate Development of Medicines for Children in Europe

Pediatric Rare Disease Clinical Trials and Treatment Network

SIOP Europe
the European Society for Paediatric Oncology

ITCC
INNOVATIVE THERAPIES FOR CHILDREN AND ADOLESCENTS WITH CANCER

CHILDREN'S ONCOLOGY GROUP

North America, Australia, New Zealand

Single point of contact for your clinical research in France and Europe, whether you are in industry or academia.

EU Network of Excellence for Paediatric Research

Accelerating trials in the EU

- An EC-HMA-EMA initiative launched in January 2022 with the aim of further developing the EU as a competitive centre for innovative clinical research.
- A business change initiative outlining 10 priority actions to transform the EU clinical research environment in support of medical innovation and better patient outcomes
- The ACT EU 2022 – 2026 multi-annual workplan was adopted in August 2022

The value of Public Private Partnerships Multistakeholders collaboration

- **Public Private collaboration** bringing together all involved in **drug development**, and who are now used to work together in the pre-competitive space
- To address complex areas, relevant to public health needs
- **Generate high-quality science**
- European focus but global impact

THANK YOU!