101057442 – REMEDi4ALL

Building a Sustainable European Innovation Platform to Enhance the Repurposing of medicines for All

WP7 – Clinical development & implementation

D7.1 Report on services, expertise barriers in the clinical development

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Definitions

- **Clinical trials** are scientifically controlled studies undertaken in humans to establish or confirm the safety and effectiveness of investigational medicinal products (IMPs). ***(EU)***
- **Non-clinical (or pre-clinical) development phase** primarily aims to identify which candidate therapy has the greatest probability of success, assess its safety, and build solid scientific foundations before transition to the clinical development phase. ***(EUPATI)***
- **Health Technology Assessment (HTA)** summarises information about medical, economic, social and ethical issues related to the use of a health technology. ***(NIH)***
- **Grant Agreement**. The agreement signed between the beneficiaries and the HADEA for the undertaking of the REMEDi4ALL project, with agreement nº 101057442.
- **Project**. The sum of all activities carried out in the framework of the Grant Agreement and its Annexes.
- **Work plan**. Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in the Grant Agreement.

Abbreviations

Acronym/ Abbreviation	Meaning
CSA STARS	
DF-HTA	Development-focused HTA
EMA	European Medical Agency
ECRIN	European Clinical Research Infrastructure Network
EU	European Union
EJP RD	EuropeanJoint Program on Rare Diseases
ERN	European Reference Network
ERICA	European Rare disease research Coordination and support Action Consortium
EURORDIS	European Organisation for Rare Diseases
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HE	Horizon Europe
HE&OR	Health economic and outcomes research
(e)HTA	(early) Health Technology Assessment
ICF	Informed Consent Form
IMI **IHI**	Innovative Medicines Initiative Innovative Health Initiative
IP	Intellectual Property
IRDIRC	International Rare Diseases Consortium
MAA	Marketing Authorisation Application
RDP	Repurposing Development Plan
ROI	Return On Investment
RWE	Real World Evidence
SRI	Syreon
STAMP	EC expert group on Safe and Timely Access to Medicines
TPP	Target Product Profile
WP	Work package

Abstract

This report summarises the results of a mapping exercise to inventorise the available capacities and expertise to support clinical development for drug repurposing within the REMEDi4ALL consortium and closely related ecosystem. Challenges and barriers of the clinical development process were identified via literature search and in-depth interviews with Principal Investigators and Project Managers of the demonstrator projects. Based on the discussions with the demonstrators, mapped expertise and capacities within the consortium and ongoing work on identifying barriers related to policy and funding in other work packages (WP8, WP9), a gap analysis has been conducted to evaluate the maturity and readiness of the consortium to provide clinical development services to drug repurposing projects. Based on the past experiences, long standing portfolio to support clinical development and clinical operational services by ECRIN and available expertise available within the consortium, a blueprint to cover clinical aspects of the Repurposing Development Plan is provided to smoothly navigate the clinical development process from end to end, which can be adaptable to any drug repurposing project.

1. Introduction

Within the REMEDi4ALL consortium, work package 7 (WP7) aims to develop and implement an operational clinical development process, shaped by the experiences gained through the demonstrator projects and testing its operational capacity with user projects from M36. WP7 has the following tasks to perform within the defined timelines of the project:

Task 7.1 Inventory and gap analysis of capacities and resources for clinical development, identification of barriers **(M1-M10)**

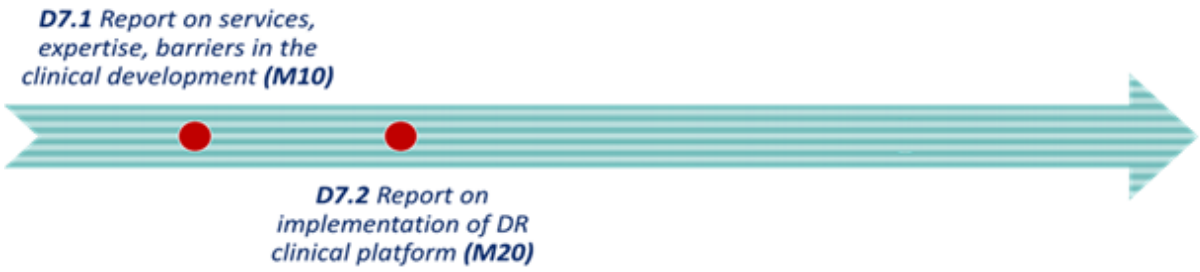
Task 7.2 Develop the operational capacity for clinical development and implementation **(M11-M60)**

Task 7.3 Demonstrator trials to assess and refine the operational capacity **(M18-M60)**

Output of the tasks will be presented in two different deliverables (Figure 1).

Figure 1: WP7 deliverables and timelines

Drug repurposing is a promising field to cater the needs of the patient population suffering from unmet medical needs, particularly in rare diseases. However, the path fulfilling these promises contains



numerous challenges. Considering the nature and advancement of these challenges is pivotal in establishing a successful clinical development plan for repurposing projects. The clinical development plan defines the route for the clinical program, including an overview of essential dates required for key decision points, as well as a projection of the (human) capital required to execute the plan. Challenges previously identified provide a strong basis to start developing a clinical development plan with the aim of minimizing already existing hurdles and overseeing expected hurdles. The clinical drug repurposing development plan describes a process that is project specific and will evolve along with the availability of new results. A clinical development plan is a strategic document that serves as a blueprint of a drug's complete clinical research strategy. It is a roadmap including all the processes and techniques to bring the drug from its early stage of discovery eventually to patients and ensures that all the multi-disciplinary teams involved are working in harmony to achieve the same goal.

As a starting point of WP7 activities to establish an operational clinical development plan and strategy, adaptable to different drug repurposing projects within the REMEDi4ALL framework, it is crucial to first understand what kind of resources and expertise the REMEDi4ALL consortium can currently offer. Demonstrator projects are centric to guide the way. Understanding the needs of the demonstrator projects at each step, supporting them with resources available within the consortium and expanding the framework by onboarding different collaborators to facilitate their progress will strengthen the consortium. This continuous testing is crucial to create a mature and sustainable

platform. Through the demonstrator and user projects, the operational capacity of the clinical development plan will be tested and optimised.

Within REMEDi4ALL, the focus is not only on the repurposing of already marketed medicinal products, but also on the repositioning of investigational drugs substances that have proven to be safe in humans and identified through screening to find new targets for unmet medical needs. The complete clinical development plan will be strategically aligned with the non-clinical aspects described in the overall Repurposing Development Plan (template provided by WP2) with the aim of bringing the repurposed drug all the way to the market and ensuring patient access. A tight collaboration with the preclinical work packages within the REMEDi4ALL consortium is pursued *(**WP4** Research data, tools and in silico discovery, **WP5** In vitro discovery services, **WP6** Preclinical development & validation)* with patient-centric planning "with the end goal in mind" (WP1) as a paramount activity to guide repurposing projects already from an early phase.

Another important aspect to be considered during the clinical development phase encompasses Health Technology Assessment (HTA). An early HTA (eHTA) can already address different reimbursement scenarios for repurposed medicines and will help to define the criteria to enable well-informed Go/No Go milestones during development. This will lead to better use of resources and flag possible hurdles in an early stage. Within REMEDi4ALL, WP8 has developed and implemented an eHTA approach for the demonstrator projects (included as part of ANNEX).

Aims of the deliverable 7.1

The deliverable aims to:

- Identify the barriers and challenges in clinical development (based on literature).
- Identify the barriers and challenges faced and expected by the demonstrator projects.
- Map the current operational capacity of the REMEDi4ALL consortium linked to clinical development for drug repurposing.
- Develop a guiding pathway for conceptualising a clinical development plan.

2. Methods

2.1 Development of a survey to map the capacities, resources, and expertise available within REMEDi4ALL consortium and close collaborators

A survey was designed using **RedCap** (https://www.project-redcap.org/) and disseminated among all consortium members and close collaborators. One response from each institution was recorded. The survey covered services linked to three main stages of clinical development process: clinical development, clinical operations, and post clinical (see Table 1). The survey is available in Annex 1.

2.2 Identification of barriers and challenges in clinical development for drug repurposing

The barriers and challenges identified in selected published literature were compiled using 10 publications aiming to identify and address barriers specific to drug repurposing and related to conducting clinical trials in general (see Table 1). These pre-identified barriers and challenges were integrated in the interview guide (Annex 2) created for the demonstrator interviews.

Table 1: Clinical development services mapped using survey

Clinical Development	Clinical Operations	Post Clinical Services
• Support in developing funding proposals • Support in networking to the funding agencies • Support in engaging patients/participants • Support in networking with the investigators • Support in investigator selection	• Regulatory approvals (national) • Regulatory approvals (EU) • Clinical trial coordination and project management (national) • Clinical trial coordination and project management (EU)	• Support in developing Marketing authorization application (MAA) • HTA assessment • Support in gathering Real World Evidence (RWE)
• Support in Clinical trial design planning • Support in protocol development • Support in adaptable Informed Consent Form development • Peer review protocol evaluation • Scientific advice	• Quality management including clinical trial monitoring and auditing (national) • Quality management including clinical trial monitoring and auditing (EU) • Safety management and reporting (national) • Safety management and reporting of the trial (EU) • Clinical trial data management	
• Sponsorship • Support in clinical trial site feasibility studies • Trial database setup • Support in development of monitoring plan • Support in developing data management plan • Orphan drug designation	• Drug Formulation development • Placebo development • Drug Formulation and placebo distribution (national) • Drug Formulation and placebo distribution (EU) • Support in trials' Bio-samples management (national) • Support in trials' Bio-samples management (EU)	

In depth interviews, lasting 90-120 minutes were conducted with three Demonstrator project leads (Demonstrator 10.2, Demonstrator 10.3, and Demonstrator 10.4) following the interview guide (Annex 2) via Zoom (see Table X). Demonstrator project 10.1 team was excluded from the interviews because the project is not in the clinical phase yet and hence, out of scope . Interviews were focused on the following aspects linked to clinical development and implementation:

- Current phase of the project
- Clinical phase set up
- Project management
- Challenges faced during the process and how they were overcome
- Challenges to expect
- Support provided by REMEDi4ALL platform and its impacts on the project
- Support expected from the REMEDi4ALL platform in the future

Recorded interviews were transcribed and coded using the software **dedoose** (https://www.dedoose.com/). Qualitative data was analysed using a mixed approach (inductive thematic analysis and narrative analysis). Using codes, themes encompassing challenges and barriers at different steps of the clinical development were extracted.

In parallel, WP8 conducted interviews with the consortium partners to identify policy barriers linked to repurposing projects and WP9 conducted interviews to identify funding barriers. Data analysis of WP8 and WP9 interviews are still ongoing. However, we worked together with leaders of WP8 and WP9 to include in this deliverable the policy and funding barriers identified so far. A more in-depth analysis of these barriers will be produced by the respective work packages.

	Old indication (s)	Repurposing concept	Disease area / new indication
Demonstrator 1: *Crizotinib Rimcazole*	Oncology, schizophrenia	Discovery and preclinical target validation for inhibition of viral replication	Infectious diseases – Covid-19
Demonstrator 2: *Valproic acid Simvastatin*	Epilepsy, depression, cardiovascular disease	Preclinical dose finding and PhI/II PoC study combination therapy with Gemcitabine and Taxol (ABX)	Cancer - Pancreatic cancer (mPDAC)
Demonstrator 3: *Tazarotene*	Psoriasis, acne vulgaris	PoC study in ultra-RD using drug identified by HTS screen	Rare disease – multiple sulfatase deficiency (MSD)
Demonstrator 4: *Losartan*	Hypertension	Dose finding for safe and efficient TGFB reduction	Rare – disease – Osteogenesis imperfecta (OI)

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Demonstrator 4: ***Losartan***	Hypertension	Dose finding for safe and efficient TGFB reduction	Rare disease – Osteogenesis imperfecta (OI)

Table 2: Summary of Demonstrator projects

3. Results and Discussion

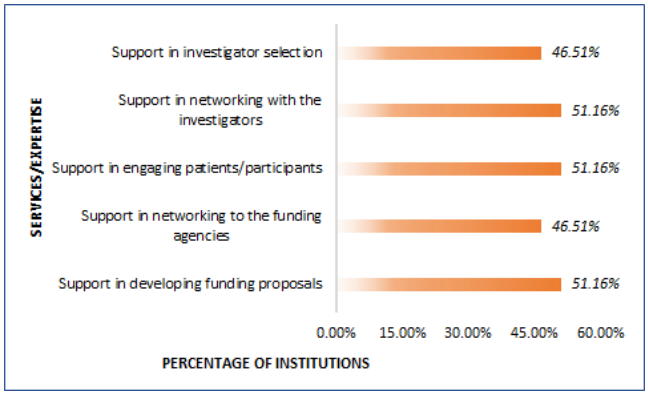
3.1 Services, expertise, and capacities currently available within the REDMEDi4ALL consortium to support clinical development of drug repurposing project

The analysis of survey responses provided a broader picture of the clinical development landscape within the REMEDi4ALL consortium and its associated partners. 43 institutions responded by listing their complete expertise and services that can be made available to support the current demonstrator projects and future user projects.

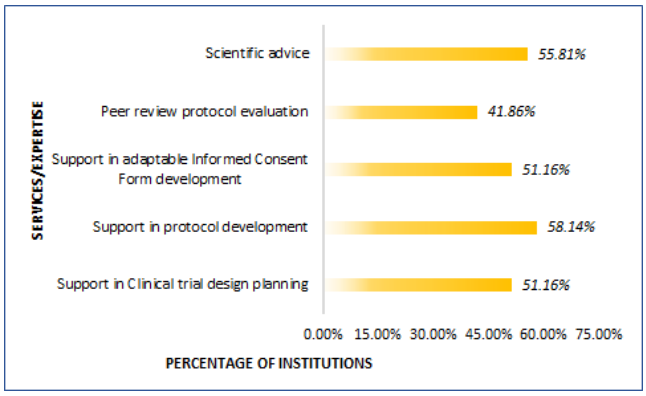
The expertises are divided in three categories in the clinical development process (excluding preclinical work); clinical development, clinical operations, and post clinical services (see Table 1). Results from the survey show that the percentage of institutions involved in each task is around 50%, indicating that the services are dispersed among the institutions. The most valuable aspect of the survey at this stage of the construction of the platform is the qualitative identification of the services that REMEDi4ALL consortium is able to deliver.

3.1.1 Capacity for clinical development services

Different expertise to support and/or carry out different clinical development tasks have been ideintified in 88% of the institutions. It is anticipated that future user projects can be served with single or multiple supporting tasks can be provided by one or more institutions if needed (see Figure 2a, 2b, 2c).



2(a) institution providing networking and patient engagement related tasks.



2(b) institutions supporting development of scientific documents and trial designs.

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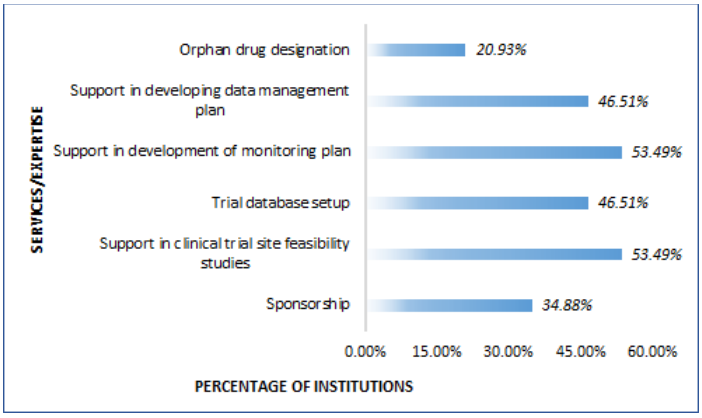


2(c) institution supporting trial set up tasks.

Figure 2: *Proportion of institutions (n=43) providing clinical development tasks*

Of note, four institutions hold the capacities to support *all* the services which raises the question if (academic) repurposing projects may be served in a more cost-effective manner, e.g., as designated 'expert centres' with coordinating capabilities to setup and integrate consistent workflows and optimise project resources. However, the service dissemination level (national vs EU vs outside EU) should be carefully considered as a potentially limiting factor. Only two institutions out of four (*SERVICIO MADRILENO DE SALUD Spain, VectorB2B Portugal*) can support services outside national boundaries in EU and only one (*VectorB2B Portugal*) can extend services outside EU boarders. Remarkably, 28 institutions (65%) can extend their services linked to one or multiple clinical development tasks across boarders within the EU which ensures that there is enough capacity to handle international repurposing projects in the clinical phase involving more than one EU countries.As per the survey results, two areas require a focused coordination in the consortium: orphan drug designation support and defining sponsorship/co-sponsorship roles. Currently nine institutions out of 43 have expertise to deliver orphan drug designation strategies and pathways, including EURORDIS, a key player in EU rare disease network. In the EU, the rare disease network is well defined through the ERNs and close netted with EMA backing certain initiatives like European Joint Programme on Rare Diseases (EJP RD), European Rare disease research Coordination and support Action Consortium (ERICA) and International Rare Diseases Research Consortium (IRDiRC). Considering the potential of drug repurposing approach towards the development of treatments for rare diseases, one strategic action could be for WP12 in the REMEDi4ALL consortium to approach these platforms to identify and take on board their expertise; this could help structure the needs of repurposing projects linked to the regulatory and policy fragments of the orphan drug designation.

Another important sphere requiring legal and regulatory focus is establishing well defined sponsor and co-sponsor roles in academic settings, specially for multinational projects. Also, the lack of experience and/or scarce knowledge on legal issues has been identified as a challenge by one of the demonstrator projects (c.f. 3.3.3).

3.1.2 Capacity for clinical operations services

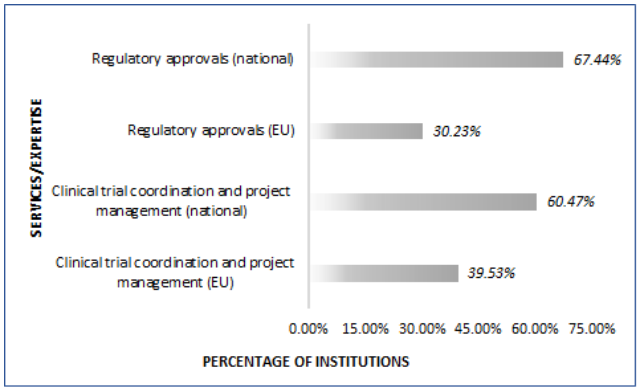
38 institutions (88%) have capacities to coordinate different aspects of the clinical operations (see Table 1), each institution encompassing single or multiple tasks (see Figure 4). Three institutions (7%)

can provide all the mentioned services and two of them (*VectorB2B Portugal, Dompé farmaceutici S.p.A. Italy*) can extend these services outside the EU borders.

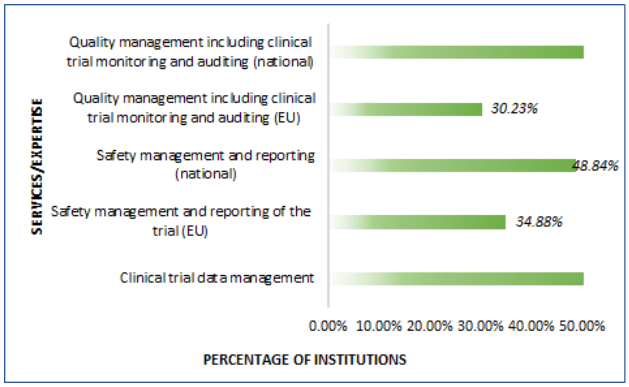
Support for regulatory approvals, clinical trial coordination and project management, quality management services and safety reporting at national level can be provided by nearly half of the institutions and can be extended across borders in the EU through certain associated partner institutions extending into the wider network (see Figure 3). ECRIN can coordinate these services across EU including 13 ECRIN member and observer countries[1] with its network of over 120 clinical trial units (CTUs) across Europe.

One essential aspect often linked to the repurposing of existing drug substances is formulation development in case the approved and available formulations cannot be used for the new disease indication, or if no approved formulation is available. GMP production of new formulations and placebos are challenging (c.f. 3.3.4). Currently 8 institutions linked to the consortium can support formulation development and 6 could also develop placebo formulations (see Figure 3c). Continued mapping the formulation and placebo development expertise and capacities within the REMEDi4ALL Consortium and its extended network of service providers is \crucial to ensure enough critical mass.(see T 6.2.4 in WP6 Preclinical development & validation as des)

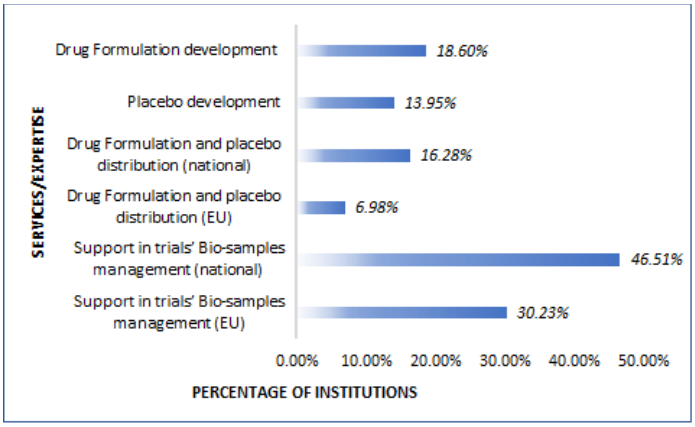
[1] *Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, Norway, Poland, Portugal, Spain, Switzerland, Slovakia*



3(a) institutions providing regulatory and clinical trial management services



3(b) institutions providing data and regulatory management services



***3(c)* institution supporting formulation, placebo and bio sample management tasks**

Figure 3: *Proportion of institutions (n=43) providing clinical operations' tasks*

3.1.3 Capacity for post clinical services

Health Technology Assessment (HTA) and gathering real world evidence (RWE) is imperative to successfully conclude drug repurposing projects as these activities are instrumental to build a Marketing Authorisation Application (MAA). REMEDi4ALL platform is building capacities to successfully integrate these services via different partners (see Figure 4). Objectives of WP8 (Improving the market access environment of DR) are dedicated to these tasks. Details on these will be presented in the deliverables produced by WP8.

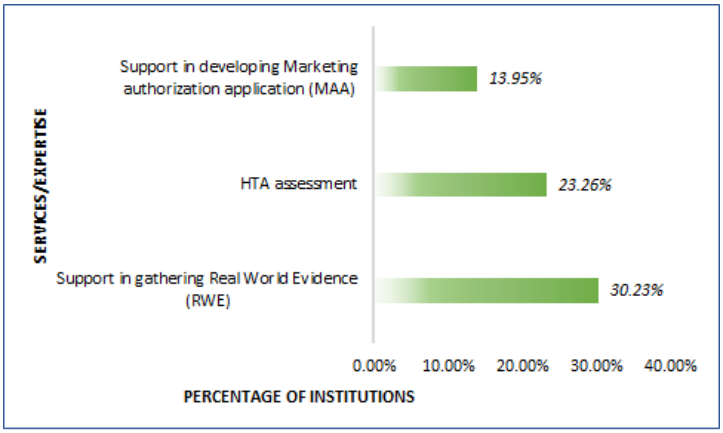


Figure 4: Proportion of institutions (n=43) providing post clinical services

3.2 Regulatory ecosystem specific to drug repurposing mapped by CSA-STARS

The CSA-STARS project has developed a comprehensive regulatory inventory of institutions in EU based on their area of expertise, including institutions holding drug repurposing expertise. It was developed with the aim of assisting European academic drug developers in finding regulatory affairs

support. The inventory lists various support services provided by national competent authorities, public actors and private entities and it could complement the REMEDi4ALL resources if needed.

3.3 Challenges and barriers identified for clinical development for drug repurposing

The main barriers identified through interviews conducted by WP7, WP8 and WP9 are summarized in Table 3.

3.3.1 Financial constraints

Limited funding options has always been an obstacle for academic driven drug development projects. Our findings indicate that, despite the opportunities to safe development costs, financial hurdles are also a major concern for clinical development projects encompassing drug repurposing. The funding landscape is evolving in EU with programs like Horizon Europe (HE), Innovative Health Initiative (IHI) etc., but the available funding calls are not enough to cater the needs of patients and equip academia and non-for-profit research infrastructures with all the financial resources to generate a mature MAA that enables a successful registration with patient access (e.g. through label extension). Funders do not yet consider drug repurposing as a mainstream activity of their funding programs. Increasing the success rate and cost-effectiveness of drug repurposing projects can build trust making more resources dedicated specifically to drug repurposing available.

In this context, public and other funding organizations seem to struggle to find a good balance in setting criteria for project selection based on the one hand the best patient and public health outcomes versus on the other hand the cost-effectiveness and potential benefits that could be achieved through drug repurposing (e.g. with currently available cheaper generics). Robust socio-economic models to assess the potential benefits of drug repurposing approaches are also lacking. This leads to investment in repurposed projects that are in advanced stages, with identified benefit-risk ratio, dose response relationship and other sound scientific metrics. However, less funding goes to the projects in earlier development phases such as reported by the demonstrator projects.

Below across the text are inserted several quotes from interviews with members of the Demonstrator Project Teams that highlight specific challenges encountered early in their project.

> *"…I mean, this study is recruiting 30 patients and it's costing 2.1 million euros…I mean where you are going to find funders that feel that it's worth spending 2.1 million on a rare disease…"*
>
> ***Demonstrator project***

> *"….You look at the funding models that are being applied by pharma companies. They are acting in a risk adverse manner and, they are waiting to see which of the biotechs actually produce the drug that works. And then buy them; but you know that is their business."*
>
> ***Demonstrator project***

Table 3: Main barriers to clinical development of repurposed drugs identified in literature and in REMEDi4ALL consortium

Barriers Identified	Details	Identified in literature	Identified by demonstrators, funders/consortium members
Funding/Funding mechanisms	Limited funding calls including drug repurposing	Kato et al. (2015)[1], Pushpakom et al. (2018)[2], Djurisic et al. Trials (2017)[3], Alemayehu et al. (2018)[4]	Demo 3, Demo 4, WP8/9
	Restrictive cross border funding	del Alamo et al. (2022)[5], Djurisic et al. Trials (2017)[3]	Demo 4
	Poor understanding of funding mechanism and allocation by clinical research teams	del Alamo et al. (2022)[5], Alemayehu et al. (2018)[4]	Demo 2, Demo 4, Demo 3, WP8/9
	Difficult to find a compromise between patient and public health outcomes vs best value for money for funders	Krishnamurthy et al. (2022)[6], Kato et al. (2015)[1]	WP8/9, Demo 3, demo 4
	Limited resources and expertise to search for funding at different phases	del Alamo et al. (2022)[5], Krishnamurthy et al. (2022)[6], Alemayehu et al. (2018)[4]	WP8/9, Demo 3, Demo 4
	Funding required from multiple sources to fund a complete project	del Alamo et al. (2022)[5], Krishnamurthy et al. (2022)[6]	Demo 2; demo 4, WP8/9
	Funding for rare disease is a challenge	del Alamo et al. (2022)[5]	WP8/9; Demo 3, Demo 4
	Funding difficult for projects in early phase		Demo 2, demo 3, Demo 4

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	Funding difficult for generic repurposed drugs	Breckenridge et al. (2018)[7]	Demo 2
Intellectual Property (IP)	Lack of IP protection	Fetro et at. (2020)[8], Krishnamurthy et al. (2022)[6], Breckenridge et al. (2018)[7], A. TALEVI AND C. L. BELLERA (2019)[9], Pushpakom et al. (2018)[2]	Demo 2, Demo 3
	Difficult to engage IP protected compounds specially from pharmaceutical companies in repurposing projects	Breckenridge et al. (2018)[7], Krishnamurthy et al. (2022)[6]	
Data accessibility	Reluctance from industry to provide access to their data (clinical trials, pre-clinical, chemical libraries etc.)	Krishnamurthy et al. (2022), A. TALEVI AND C. L. BELLERA (2019), Pushpakom et al. (2018), Breckenridge et al. (2018)	Demo 3
Limited expertise	Limited understanding of the complete drug development process as the major focus is given to conducting a trial from scientific point only		Demo 3, Demo 2
	Inadequate understanding of disease/drug specific trial methodology and protocol development (frequent for rare disease repurposing projects)	del Alamo et al. (2022)[5], Djurisic et al. Trials (2017)[3], Kempf et al. (2017)[10]	Demo 3
	Limited expertise in choosing an appropriate trial design due to lack of available registries orchestrating patient reported outcomes measures in specific disease areas	del Alamo et al. (2022)[5], Djurisic et al. Trials (2017)[3], Kempf et al. (2017)[10]	Demo 3
	Limited experience and/or Inadequate understanding of the sponsor's and/or co-sponsor roles and responsibilities by academic institutions	del Alamo et al. (2022)[5], Djurisic et al. Trials (2017)[3]	Demo 4

Drug procurement	For generic drugs it is difficult to get the drug from single vendor to avoid bias in multinational trials		Demo 2
Lack of interest from industry	Low Return On Investment (ROI) and/or possible high liability costs in particular for repurposing projects involving generic drugs, drugs with limited patent life, drugs for rare diseases, previously failed drugs, etc	Krishnamurthy et al. (2022)[6], Breckenridge et al. (2018)[7], Kato et al. (2015)[1], Fetro et at. (2020)[8]	Demo 2, Demo 3, Demo 4
	Companies are least interested in the repurposing projects outside of their focused disease area and in projects in early phase of development	Krishnamurthy et al. (2022)[6], Breckenridge et al. (2018)[7], Pushpakom et al. (2018)[2]	Demo 2, Demo 3, Demo 4
Regulatory and legal barriers	Non harmonised regulatory and legal setup within each country and/or EU makes implementation of projects at various steps complex and less efficient (funding, protocol and ICF development, regulatory and ethical approvals, legal contracts etc)	Djurisic et al. Trials (2017)[3], Alemayehu et al. (2018)[4], Kempf et al. (2017)[10]	Demo 2, Demo 4
	No specific regulatory and legal guidance available to institutions and infrastructures working on drug repurposing projects	Fetro et at. (2020)[8]	Demo 2, Demo 3
	No specific investment framework within regulatory bodies exist to address low ROI issues	Breckenridge et al. (2018)[7]	WP8/9, Demo, 2, Demo 4
	Too bureaucratic approach to evaluate the projects hide their scientific potential		Demo 2
Non collaborative research environment	Despite having expertise, institutions (academic, industrial, government, non-government, regulatory bodies, funding bodies) are not aligned	Krishnamurthy et al. (2022)[6], Breckenridge et al. (2018)[7], A. TALEVI AND C. L. BELLERA (2019)[9], Fetro et at. (2020)[8], Pushpakom et al. (2018)[2], Djurisic et al. Trials (2017)[3]	Demo 2, Demo 3,

	on specific frameworks which create loopholes in focused clinical development initiatives		
Formulation and placebo development	New formulation development as per GMP for repurposed drugs is challenging and time consuming		Demo 3
	Commercially developed placebos are expensive and limited companies to provide	Krishnamurthy et al. (2022)[6], Djurisic et al. Trials (2017)[3]	

Another important aspect that gives rise to funding constraints are the restrictions in sharing of funds across the border. Country-specific restrictions on granted funds makes it difficult to set up multinational projects to align and harmonize best scientific interests. As a result of BREXIT, collaborations between EU and UK have been negatively impacted leaving administrative tasks more complicated involving sharing of HORIZON 2020 funds as identified by Demonstrator project 10.4. Apart from cross-border funding restriction issues, the understanding of the funding models and movement of money within different partners in multi-national set up is tedious. Academic sponsors and investigators lack financial expertise to understand complex funding mechanisms and resources to locate and approach development phase-specific funders.

Drug repurposing holds potential for rare medical conditions, but this potential is not yet explored extensively due to low interest of funding bodies in rare diseases. This is partly due to the overall failure rates in drug development. It is known that poorly known disease natural histories pose a great risk for the failure of projects seeking therapeutic solutions for rare disease, even at advanced stages.

3.3.2 Intellectual property and data accessibility

Pharmaceutical companies patent numerous compounds in their pipeline for a single project. This in turn creates a good store of shelved compounds which fail to make it to the final stages of the respective projects. Engaging these shelved compounds protected by patents poses a challenge as it requires obtaining a license. On the other hand, limited patent time left for compounds dropped in later stages could make investors (re-)consider the limited return on investment (ROI). These considerations are largely influenced by the size and number of profit-sharing stakeholders of the company.

Classical IP protection paths and regulatory data exclusivity aer not always within reach for the protection of repurposed drugs. Established IP protection laws are strongly based on the novelty of the invention which may be difficult to prove with repurposed drugs already on the market (e.g through a method of use patent). The use of an existing drug for a new indication sometimes is already hinted in the literature and may be scarcely looked upon during the discovery phase of the compound, or during pre-clinical assessments. ‘Second or further medical use of known pharmaceutical products’ type patent can address some of these issues but it requires robust scientific data to prove efficacy of the drug and novelty of the new indication under established IP laws. Consequently, the patentees must make sure that if the new indication is not already disclosed in the public literature.

Besides patent protection, data accessibility is another issue linked to industry generated data. Pharmaceutical companies are hesitant to give access to their data related to the projects which are no longer ‘live’. Demonstrator project 10.3 project is a prime example where the REMEDi4ALL platform has successfully negotiated the access to data of the pharmaceutical development, preclinical safety and efficacy asessments and clinical trials historically performed by Allergan for tazarotene (Tazorac, Allergan, Inc.) twenty years ago. Pharmaceutical companies often become anxious when third parties become successful in using their compound and/or (re-)formulated drug as it may reveal potential shortcomings of

their assets. In addition, there are no incentives for industry to disclose research data of shelved compounds, which is a huge, unlocked potential when it comes to data accessibility.

Below across the text are inserted several quotes from interviews with members of the Demonstrator Project Teams that highlight specific challenges encountered early in their project.

"The oral formulation has not been approved by the FDA and it was in 2004……after this Allergan stopped the entire project. And so it was a Sleeping Beauty, all the files and data are still available with the company, but not publicly available….until EATRIS and selected REMEDi4ALL partners managed to settle a (sub-)license agreement to provide access to the data"

Demonstrator

https://remedi4all.org/eatris-and-the-remedi4all-consortium-to-initiate-new-study-to-advance-potential-treatment-for-ultra-rare-disease/

3.3.3 Lack of specific expertise

A complete understanding of the clinical development process is limited in academia where the major focus is on knowledge generation, education and generating scientific output through peer-reviewed and open access publications. Hence, academic staff needs to gain experience in the multidisciplinary approaches through collaboration with private partners and specified trainings in strategic areas of the drug development process. For example, compiling documents for regulatory filing, project management, coordination of all the institutions involved, regulations, marketing authorization aspects, HTA aspects, defining roles like sponsor and co-sponsor etc. require specific translational skills that are professionalised in industry, but harder to find in academic institutions.

Insufficient experience of choosing proper trial designs, trial methodology and protocol development are highlighted by Demonstrator projects. Proper identification of the end points, trial methodology and clinical trial design based on the available data is crucial for designing efficient repurposing projects. However, in disease specific areas such as rare diseases, it is very difficult due to lack of registries orchestrating patient reported outcome measures.

"…I have an overview of how clinical trials are conducted, but you know I'm definitely not an expert in setting up the clinical trial or even the clinical trial protocol …."

Demonstrator

3.3.4 Reformulation hurdles

When drug repurposing projects involve formulations that are different from those available on the market, reformulation becomes a complete scientific project of its own. It requires onboarding of specific expertise in drug formulation development and additional pre-clinical work to assess the pharmacological aspects specific to formulation type. This substantially increases the overall development costs of the project. Furthermore, GMP manufacturing of the formulations in different dosage strengths than those marketed is quite challenging and subject to the availability of regulatory defined premises and quality controlled manufacturing steps, which necessitates the onboarding of dedicated expertise.

"…, it is the drug formulation, that is for me the big biggest challenge because it is not the classic the classical repurposing for me….."

Demonstrator

3.3.5 Regulatory and legal constraints

The EU commission and its regulatory bodies in the EU have drug repurposing on their radar via projects like REMEDi4ALL, REPO4EU, SIMPATHIC, DRUGtrain and the STAMP initiative. Yet, specific regulatory and legal reforms are still missing to guide these initiatives and developing a regulatory friendly ecosystem for repurposing projects. Without establishing these necessary reforms, productive output of repurposing initiatives and individual projects will remain limited, and no answers can be found for the issues linked to IP protection, ways to ensure a path for investors regarding ROI, etc. In this regard, the new draft EU pharma legislation (https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en) offers potentially interesting avenues with a more prominent role for the 'public sponsor' as proposed in Art. 48 and 84 of the regulation and directive.

Lack of harmonisation among regulatory bodies at both national and EU levels complicates the operational side of clinical development process for drug repurposing projects. Country-specific and even institution specific laws towards allocation of internal or external funding is hampering the academic sector with limited expertise to understand the complex regulatory and legal ecosystem. Furthermore, projects are not able to meet the timelines defined due to differences in common document development and country specific adaptations as per each country's laws e.g.:

- protocol development
- informed consents
- patient protection and liability clauses

- legal contracts (sponsorship, co-sponsorship, site agreements, material transfer agreements, etc.).

Additionally, ethical and regulatory approval requirements and paths differ from country to country. As an example, within some countries ethical approval is required from more than one ethics committee leading to multiple rounds of - sometimes conflicting - reviews. To sum up, this convoluted net of regulatory systems is putting pressure not only on regulatory and legal frameworks but also on scientific bodies that become too bureaucratic towards planning and assessment of the scientific projects. Consequently, the real potential of many of the repurposing projects is not achieved.

These issues cannot be bridged by discussions within single entities, it requires a collaborative approach between all the stakeholders (regulatory bodies, academia, industry, legal entities etc). These issues seek solution based on understanding the needs of each stakeholder involved.

3.3.6 Uncoordinated research and regulatory ecosystem

One critical aspect important to sustainability of the focused frameworks like REMEDi4ALL is coordination and onboarding of all the stakeholders, that is currently still missing. Expertise is present in the relevant fields but is scattered and lacks clear ownership and mechanisms for coordination. CSA-STARS project mapped the regulatory ecosystem in EU included a mapping of institutions that are able to support repurposing projects. But this inventory as such does not per se activate those institutions to contribute to the drug repurposing ecosystem in an aligned manner to tackle the systemic barriers.

In the repurposing field, groups are working on specific diseases like cancer or rare conditions. Coordinated funding networks that match these thematic research areas are explored through projects like ERA4Health, and in REMEDi4ALL, but are still scarce for drug repurposing. The required experts in specific parts of the drug development processes are scattered around Europe, however, there is an opportunity to improve this under REMEDi4ALL, to support specific projects by identifying and coordinating (rather than fully onboarding these resources) supported with a well-constructed collaborative model to a capable of onboarding all the relevant stakeholders and expertise.

4. Guiding clinical development plan strategy for drug repurposing projects

Section 3 in this report has listed several resources available to the Consortium that are required for the planning and execution of repurposing projects in the clinical development phase. In this section, more details are provided to compile the clinical phase of the RDP, using these resources.

The main elements of the overall RDP are described in WP2 (D2.2), where the following key components are highly integrated with the clinical development plan (Figure 5):

- Development of a Target Product Profile (TPP)
- Clearly defined scientific rationale
- Clearly defined path to market including eHTA plan
- Key results from non-clinical discovery
- Key results from preclinical development
- Complete clinical trials planning
- Marketing Authorization strategy
- Post marketing strategy
- Milestones
- Gantt chart or high-level timelines
- Risk assessment and risk mitigation plans

Working strategy for a development plan can be split in 3 phases:

- Preparation phase
- Execution phase
- Surveillance and communication phase

Non-clinical discovery

This section of the clinical development plans the DR hypothesis, i.e., the rationale of choosing the existing drug substance or drug product to be repurposed for the respective new disease or indication. Data included in this section can depend on the current status of the project. For the projects involving repurposing the existing compound to newly ideintified targets from screening it can be an extensive section detailing all the experimental or in silico work carried out. Alternatively, for projects with already marketed or investigational drugs, data on clinical observations and real-world evidence (RWE) can be incorporated from already available filings, registries or published work.

In the REMEDi4ALL platform, two work packages including experts from various institutions are dedicated to such discoveries; **WP4** Research data, tools and in silico discovery and **WP5** In vitro discovery services.

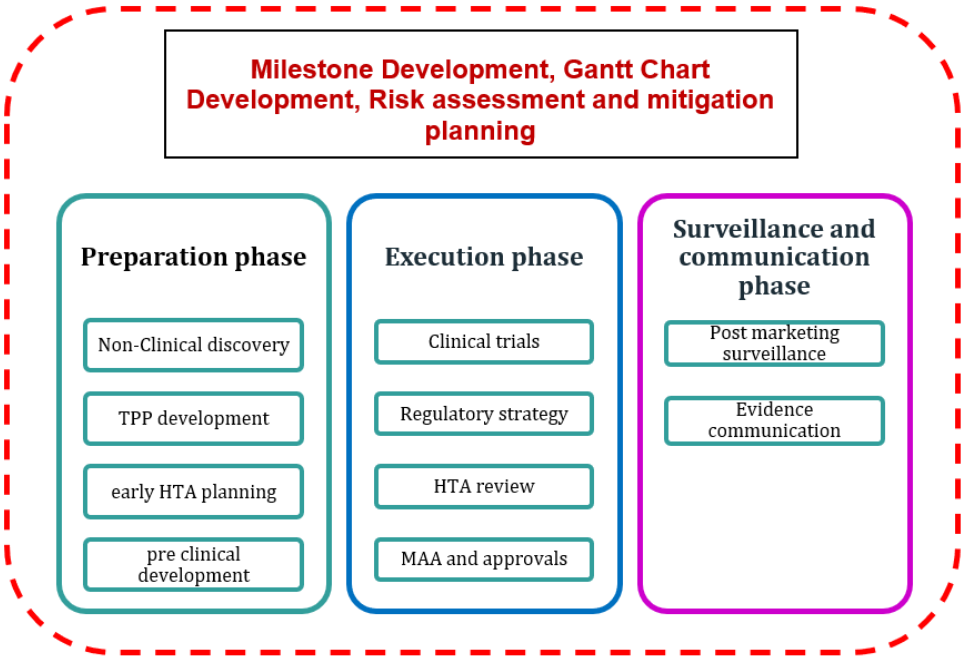

Figure 5: phases of clinical development plan

Target Product Profile development

Development of a TPP is a key first step to take. It is defining an endpoint or a destination which holds all the key attributes of the final drug to be marketed. This is a crucial document which guides the design of all other activities, like pre-clinical and clinical designs and aims to collect as robust information as possible required to assess whether the drug meets the desired characteristics. This leads towards a focused plan for answering critical questions at early stages and defines the critical development path.

TPP is a live document evolving with the availability of information as the project advances. It drives key investment decisions, for example, given the safety profile of the repurposed compound, e.g. whether it can continue towards exploratory Phase I human trial, a Phase II proof of concept trial or a pivotal Phase III clinical trial or not.

Core elements of the TPP include:

- Research question

- Targeted new indication or disease
- Targeted patient/participant population
- Clinical safety
- Therapeutic efficacy
- Formulation (in case of repurposed drugs if new formulation or different dosage strength etc)
- Dosing regimens (in case of repurposed drugs same dose or different dose with rationale)
- Clinical pharmacology and nonclinical toxicology
- Contraindications or precautions etc.
- Cost
- Patient access requirements
- Any other element that is specific to addressing the unmet medical needs of the specific patient population

Early HTA planning

While traditionally HTA is used to evaluate the value of technologies after launch to support reimbursement and formulary listing decisions of payers, this methodology and approach can also support decisions in the development phase of health technologies. Moreover, HTA can be used to support evidence-informed decisions throughout the entire life cycle of health technologies (see Figure 6). The literature calls this approach early health technology assessment (eHTA) or development-focused HTA (DF-HTA). REMEDi4ALL uses the eHTA terminology in this report and in subsequent activities consistently. The main differences between the features of eHTA compared with traditional HTA, beyond its timing in the technology lifecycle, include the stakeholder profile (manufacturers, product innovators/developers, public/private funding organisations, patient organizations), the limited availability of clinical evidence (from pre-clinical studies or in silico screening), and the way eHTA can inform decision-makers and influence decisions in the development process.

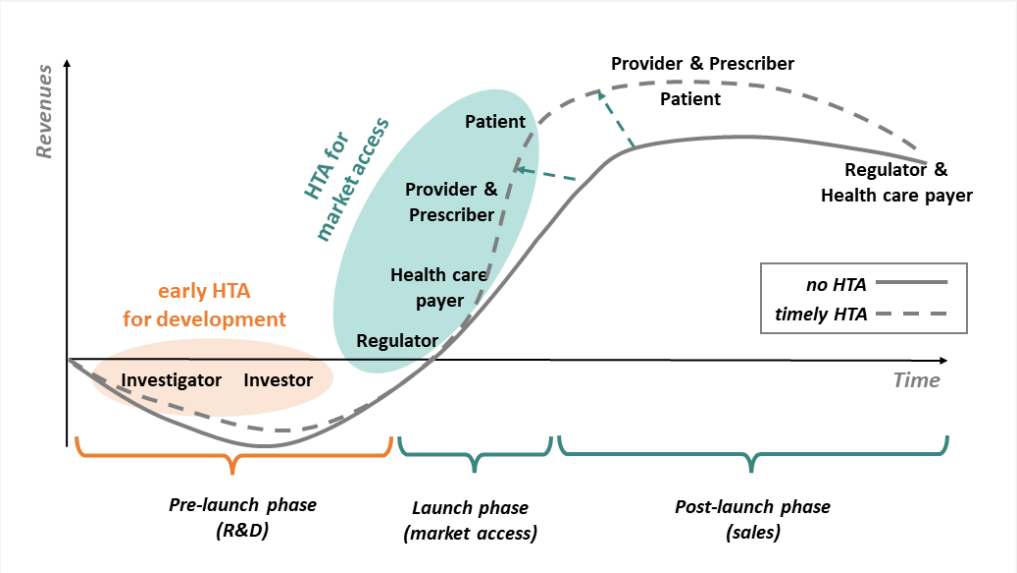

Figure 6: HTA supporting different phases of the lifecycle of a health technology. The figure also describes the different stakeholders (and decision-makers) in each phase (created by Zoltán Kaló).

A complete methodological approach and process for supporting demonstrator projects has been set up by the WP8 team. Details of the work done are available as ANNEX III and ANNEX IV.

Preclinical development

This section encompasses all the relevant details of in vitro and in vivo experimental strategy (rational for the choice of selected cell lines, animal models and species, toxicology studies etc.) including steps leading towards the lead candidate. For the repurposed drugs, data already available can be adapted, or else data may be augmented with the extended animal studies plan, in case of new formulation or dosage regimen.

The pre-clinical phase is a profound step to establish a Go/No-Go decision into the clinical studies in a regulatory compliant manner. Already before embarking on clinical studies, it should be ensured that the pre-clinical development a strategy is aligned with the regulatory requirements (e.g., supported with a data package that is generated in appropriate animal studies) If needed, these data can be refined with extended predictive models on the basis of the results of Phase I or Phase II studies.

Clinical study plan

This is a critical part of any clinical development plan and includes well-planned and well-designed first-in-human Phase I to Phase II “proof of concept” and pivotal Phase III trials. Clinical studies are generally more costly than preclinical studies, providing critical data on the safety and efficacy of new therapeutic interventions, including drug repurposing. Challenges in clinical operations (e.g., related to patient recruitment and retention, particularly in rare diseases) make the clinical phase the rate limiting phase of many projects. Therefore, it is key

to ensure a sound clinical trial design, and to choose the correct methodology to gain the scientifically sound answers to the research questions and criteria set in the TPP.

The clinical study plan summarizes the key aspects of each clinical trial phase:

- Overview of planned clinical activities (study phase, study objectives, duration of the studies, number of subjects in each phase, inclusion/exclusion criteria, study arms, comparators for non-inferiority trials, power calculations, dosing & dosing modelling strategies)
- Assessment of drug-drug interactions and synergies in drug combinations Toxicology and drug safety plan to support Phase II and Phase III studies
- Clearly defined clinical endpoints (primary & secondary), chosen methodology (clinical endpoint assays, data collection plan, statistical methods, etc.)
- Trial discontinuation criteria
- Set up of the trial (national/multinational, selected countries, selected sites including site feasibility studies)
- Project management of the trial within all partners
- Development of relative trial documents (protocol, Informed Consent Form (ICF), Monitoring plan, data management plan, and statistical analysis plan etc.)

Regulatory strategy

As described in section 3.3.5**,** regulatory strategy planning is often complicated and due to the lack of dedicated regulatory structures specific to drug repurposing projects. However, also for the clinical phase of drug repurposing certain key aspects are mandatory to address:

- Detailed understanding of the regulatory and ethical bodies to be included in the project.
- Finding the most efficient regulatory approval pathway based on detailed regulatory intelligence specific to the project. This can include looking at historic approvals for similar drugs, explore expedited approvals in case of urgent medical and/or obtaining orphan drug designation status.
- Good knowledge of expected timelines for ethical and regulatory approvals in each country involved.
- Expert analysis on key data and types of endpoints and safety considerations regulators are expecting to see at each phase.
- Preparing scientific advice and how to answer specific questions received from the regulatory and ethical bodies.

Post approval strategy

This step requires timely onboarding of health economic experts, HTA experts, health insurers, professional medical organisations and related governmental departments to map the

(competitive) market landscape and devise a strategy that results in a viable business model that ensures sustainable path to market and patient access.

Further, it involves Phase IV of the clinical study; gathering RWE data to look for possibility of extending the drug in further therapeutic indications and/or gathering additional efficacy data to compare the drug with its competitors to support health economic studies (reimbursements, patient benefits, health economic value etc.) in all different geographical regions to maximise patient access.

Milestone and timelines planning

Planning with the end-goal in mind is critical for the efficient and cost-effective execution of the project. Combined with all elements of the RDP, that also includes a patient engagement plan, clear Go/No Go milestone points can be defined for the clinical study plan to timely assess if the candidate drug can meet the requirements defined in the TPP. Such Go/No-Go criteria can be set with multi stakeholders involvement including relevant medical professionals, patients, statisticians, methodologists and regulators.

Setting up the proper timelines and stage gates gives a live perspective on the project progress, its achievements and enables key decision making and optimal use of resources towards regulatory approval.

Risk assessment and risk mitigation plan

Overall quality control of the clinical development plan depends on conducting a comprehensive risk assessment in each step of the process and identify mitigation measures on the identified risks during the development phase. It includes concrete risk mitigation strategies to tackle and address potential risks and address (rate-)limiting factors with the possibility of changing course of the clinical development plan as per the results acquired at each step.

5. Conclusions

Advancements in the drug repurposing field are progressing in academia, however, certain key challenges still need to be addressed. Most pertinent barriers to the clinical development process of drug repurposing include financial challenges, the complexity and lack of regulatory mechanisms specific for drug repurposing, data access barriers, a lack of suitable business models to attract industrial partners. The most promising approach towards reaching a middle ground with all these hurdles is to collaborate in a framework with the relevant experts from academia, funding bodies, patients, regulatory bodies and industries and engaging them together in real discussions and in making improvements towards a more sustainable future drug repurposing ecosystem. A successful clinical development plan implementation should also include proposals for mitigating these barriers, as the currently limiting factors in the clinical development process for drug repurposing.

The REMEDi4ALL consortium holds the required expertise to cater the needs of drug repurposing projects. However, finetuning of the consortium to best adapt to the requirements of the drug repurposing ecosystem is required and it is an evolving process based on the advancement of the project, maturation of the platform and gaining hands on experience with the demonstrator and user projects. Collaboration among all the WP partners and demonstrator projects and the DR community will be the key to optimise and successfully implement a tailored clinical operational workflow for drug repurposing

This project has received funding from the European Union's Horizon Europe research and innovation programme under grant agreement No 101057442. Views and opinions expressed in this disclaimer are those of the author(s) only. They do not necessarily reflect those of the European Union who cannot be held responsible for the information it contains.

ANNEXES Annex I: Survey to map the available expertise and resources within REMEDi4ALL Consortium.

Mapping services, expertise and tools available within REMEDI4ALL consortium and extended network for clinical development of repurposed drugs

Introduction:

REMEDI4ALL aims to establish Europe's leadership globally in the repurposing of medicines by creating a vibrant community of practice covering all relevant sectors and disciplines. REMEDI4ALL will establish and operate a permanent European research and innovation platform comprising the complete value chain for cutting edge, patient-focused repurposing, collaborating with users to execute high potential projects at any phase of development, upskilling all stakeholder groups through a comprehensive education and training portfolio, and advancing cross-sectoral policy dialogue with all relevant stakeholders and thought leaders. The tools and processes developed assembled in REMEDI4ALL will be validated in a portfolio of 4 ambitious preclinical and clinical phase demonstrators, representing high patient need in a variety of disease areas, including oncology, rare and infectious diseases.

Aim of the survey:

This questionnaire has been prepared with the aim of mapping available capacities, resources, tools and expertise for clinical development for drug repurposing within REMEDI4ALL consortium and extended network. The catalogue of services developed will be a model guide of services and expertise for the future users of the platform.

Data generated through this survey will be part of the REMEDI4ALL Deliverable 7.1 report under WP7 (Clinical development and implementation)

Timing:

The open consultation will be launched on 9 March 2023 and close on 10 April 2023.

This questionnaire will take around 15 - 20 minutes to complete.

[Attachment: "REMEDI4LL-Survey-Glossary.pdf"]

Section A. GENERAL QUESTIONS

Annex II: Interview guide to conduct interviews with the demonstrators

WP7/D7.1: Interview guide to conduct interviews with the demonstrators

Institution: ECRIN

Author: Sareema JAVAID

Summary of the trial

- Phase
- Design
- Disease
- Rare disease or not
- National or multinational etc

Set up of the trial

- Problems in cross border trial
- Effects of Brexit (when relevant)

PI network and investigators

- How did you find other investigators (someone you already worked with or new)
- Any platform to connect with the investigators?

Funding

- Who is funding the trial
- How did you secure the funding
- Was it difficult to secure the funding
- Challenges in securing the funding
- Help in writing funding proposal
- Do you know any funding specific to drug repurposing
- Any help from WP9 funders network and research funding policy

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- Your expectations from the funding network or funding platforms

Trial design planning

- Any support
- How the trial was designed
- How the endpoints were set

Sponsorship

- Single sponsor or co-sponsorship
- Academic sponsor or industrial?
- Involvement of industrial sponsorship?
- Roles defined?
- Challenges

Protocol and ICF

- Support in protocol development
- Scientific peer review evaluation of the protocol (if yes, was it helpful?)
- Harmonization of protocol in all the countries?
- Need of master protocol designs specific to repurposing?
- ICF adaptations (mentioned in ICF about current uses of the drug?)

Site selection process

- How the sites were selected (site feasibility studies?)
- Site selection specific procedure?
- Site agreements challenges?

Trial database

- How the database was set up
- Challenges in trial database setup
- Harmonization of the database across different countries?

Monitoring manual

- Single manual?
- How was it developed?
- Challenges?

Patients/participants/public engagement

- How it has been done or forecast?
- Any support from the platform?
- Joined any groups/patients' organization groups?
- Participants' reservations? How they have been addressed or plan to address?
- Challenges?
- Suggestions?

Trial coordination and regulatory' approvals

- CTU or CRO?
- Project management of the trial?
- Monitoring and auditing of the trial?
- Challenges?
- Brexit effects?
- Support in regulatory approvals in different countries?
- SAE and SUSARs management in different countries?
- What kind of support is expected from regulators' specific to drug repurposing trials?
- Support required in producing study reports.
- What are the challenges?

Formulation and placebo development

- Original formulation used or new?
- How was the formulation developed and distributed?
- How was the placebo developed and distributed?
- Challenges in acquiring the product?
- Suggestions

Orphan drug designation

Trial data management

- Data management plan developed.
- Who developed the DMP?
- Challenges to expect?
- Suggestions?

Biosamples' management

- Plan?
- Handling of bio-samples cross boarders?
- Challenges?

Post trial services

- Plan to put the drug in market if trial becomes successful.
- Industrial involvement?
- Startup option?
- Funding support for MA?
- Support available for developing MAA?
- HTA assessment from Syreon?
- Perceived challenges in MA and HTA?

General challenges

General suggestions

Comments

Annex III: Early Health Technology Assessment (eHTA) support for demonstrator and user projects in clinical development process

As repurposing projects are often brought forward by resource-constrained investigators or investors (who may not be aware of the importance of eHTA), they often miss to consider early phase value judgement and reimbursement scenarios for repurposed medicines before moving ahead with or investing time and financial resources into a development program. Consequently, several repurposed medicines may reach the market without a solid market access strategy (including strategic pricing and payment model). Without preparedness for integration of the repurposed medicine into the system of health care financing, the new technology might be available and accessible only to a narrow group of patients, undermining the ultimate goal of drug repurposing, namely improving health gain for a broad range of patients in a "cost-effective" way.

As seen in **Figure 7**, the main users of eHTA in the development phase are innovators and funders of repurposed medicines. The objective of using eHTA depends on the funders' status:

- for commercial innovators and investors: to maximize the long-term financial return on investment from limited private R&D resources,
- for non-commercial innovators and funders: to maximize societal return on investment from limited public and non-profit budgets for R&D.

eHTA can inform a wide range of processes during the discovery and development phases of medicines, including initial judgement about fair pricing and payment models, go/no go decisions, selection/prioritisation of target patient groups, the listing of value drivers, contribution to trial design and evidence generation strategy. Several process frameworks exist already in the literature providing a stepwise guide on the methodologies to follow along the iterative process of eHTA, but there is no consensus yet on what eHTA refers to exactly. For drug repurposing projects, Syreon from WP8 has introduced an iterative eHTA process specifically developed for supporting drug repurposing projects from early drug discovery to drug development projects in pivotal clinical trial phases. It aims to:

(1) exploring (and quantifying) value propositions of investigational medicines,

(2) establishing payment models,

(3) facilitating evidence generation to support reimbursement applications,

(4) supporting crucial go/no go decisions throughout the entire R&D process.

1. Methodological approach and process in REMEDi4ALL

1.1 Justification

Using existing drugs to treat new diseases is an attractive approach to drug development since it comes with high hopes for a more affordable and faster solution to the unmet needs of patients. However, based on our previous research in the field, current HTA frameworks and pricing and reimbursement practices in Europe often hinder the timely market launch of repurposed medicines. In REMEDi4ALL, we wanted to make sure that repurposing projects receive the necessary health economic support in early development phases, so they might have better chances to reach positive reimbursement decisions in target healthcare markets after market authorization. eHTA is also a valuable tool to optimise development pathways, minimise the risk of failure at later stages of development and commercialization, optimise the allocation of R&D resources and generally, create value for the entire healthcare systems.

1.2 Scope of eHTA support for demonstrator and user projects

The eHTA support process starts with an **eHTA Scoping Review**, which is a structured data collection process about the drug repurposing project that includes an iterative discussion between the service providers (eHTA experts) and leaders of repurposing projects. The data collection is designed to gain clarity on the health economic profile of the repurposed drug, including the unmet medical need in the target indication, the potential value propositions, the key economic attributes built into the TPP, potential pricing scenarios and input to clinical trial design. Building on the eHTA Scoping Reviews - and depending on the phase of each repurposing project – further eHTA and HTA steps and support will be defined. Any further eHTA support will be well-tailored to the needs, the budget and the potential of the specific repurposing project. These possible HTA support activities throughout the entire life-cycle of drug repurposing are presented in **Figure 8.**

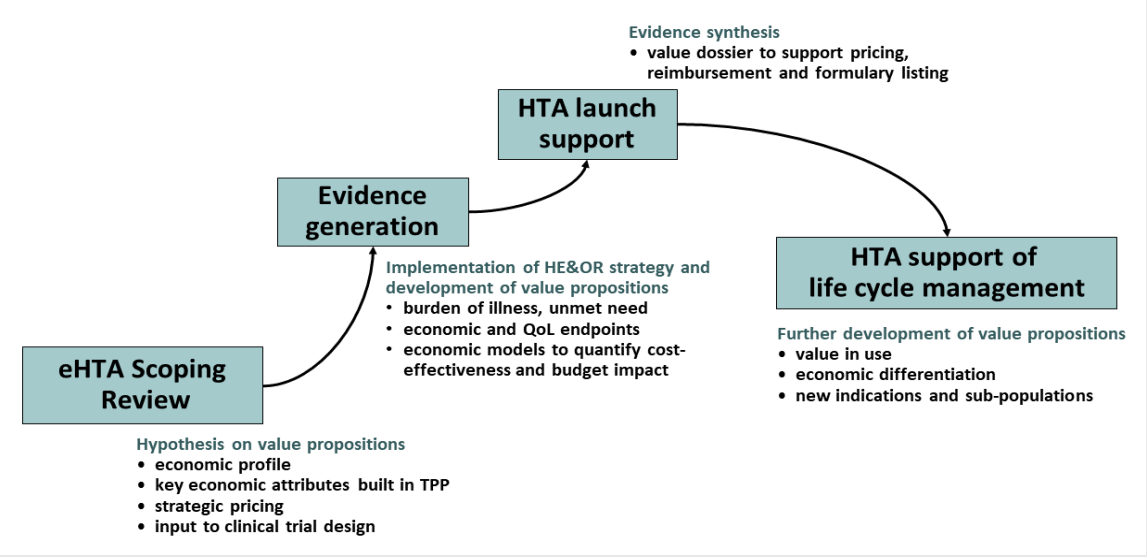


Figure 8: Building the value story throughout the life-cycle of repurposed drugs (created by Zoltán Kaló, SRI)

1.3 Steps of the eHTA Scoping Review

Step 1 - First Mentoring Meeting

The eHTA Scoping Review process starts with a mentoring meeting arranged between project owners and service providers (eHTA experts from SRI). It is an extensive virtual meeting, where repurposing project owners are asked to present a short summary of the target disease and repurposing hypothesis, provide a status update for the project, and describe any plans related to the future financing of the therapy after receiving market authorization. After this presentation, service providers present a general introduction to HTA and the eHTA approach, followed by a detailed introduction of the eHTA support process specifically applied within REMEDi4ALL. The project owners are introduced to the standardized documents to be filled out and the meeting is concluded by a long, unmoderated discussion, where project owners and service providers can ask questions or raise concerns.

Step 2 – Feedback from project owners

Following the first mentoring meeting, project owners receive a standardized feedback form, that guides them through the main questions and areas to explore during the review. The feedback form is structured around 5 main areas. These areas are presented in Annex IV.

First, project owners are asked to determine the degree of added value of their developed drug. In drug development, this can be captured by the added value, compared to already available therapeutic options in a specific target indication. The developed drug might bring (1) disruptive innovation (patients will be treated differently), (2) major incremental innovation (patient outcomes will significantly improve, but they will be treated similarly), (3) minor incremental innovation (patient outcomes will slightly improve, but they will be treated similarly) or might (4) not deliver improvement in patient outcomes. We encourage project owners to have an honest look at their developed technology and be ready to accept if the drug brings limited novelty since it could still deliver added value. A technology can still be successful if it provides the same benefits as the current gold standard, but it can be marketed at a lower price (a price advantage), or it is regionally not available or accessible (increase in patient access in regional markets), or it can be integrated to the provider chain (an advantage in vertical integration).

Second, project owners need to clarify their expectations on a reasonable payment model for the investigational repurposed medicine. In many cases, investigators of early-phase projects are not incentivized (or not trained) to consider different payment models in the long term, therefore when development decisions are made, they do not consider this aspect or are too optimistic about the attitude of payers (“payers will understand the importance and added value of our repurposed medicine”). REMEDi4ALL facilitates project owners to set realistic expectations about the future payment of the investigational repurposed medicine. If project owners decide to launch the medicine themselves, several potential purchasers and even more payment models exist, e.g.:

- **Third-party payer** *(e.g., reimbursement or centralized procurement by health insurance or national health service)*

- **Healthcare providers** *(hospitals, outpatient clinics, GPs)*
- **Patients** *(e.g., direct out-of-pocket payment)*
- **Health technology manufacturers** *(to support R&D or manufacturing)*

The project owner also has the opportunity to explore exit strategies, e.g., exit payment by investors before market entry. If project owners consider launching the technology themselves, the questions guide them to consider potential target countries, target providers, and target use (mono vs. combination therapy; prevention vs. treatment vs. rehabilitation; acute vs. chronic use).

Third, quantitative expectations for the benefits and risks of the investigational repurposed medicine have to be declared in a target product profile (TPP). The TPP outlines the expected 'profile' or characteristics of the medicines that are aimed to be used in a particular disease. In the TPP, project owners are asked to state the intended use, target populations and other desired quantitative attributes of the future products, including safety and efficacy. The TPP is a tool that helps explicitly outline the attributes of the future product and provides a basis for the conceptual value framework.

Fourth, the project owner should think about how the TPP can be translated to true value propositions for HTA agencies, healthcare payers or other purchasers. The framework should include all policy-relevant benefits that the medicine could deliver (*What is the promise for your purchasers?*). Project owners are encouraged to list any potential value proposition at this stage, however, to facilitate their elaboration, we also provide some options for potentially relevant value propositions, as the following:

Quality-adjusted life year gain

- efficacy (clinical improvement)
- survival
- safety and tolerability
- quality of life

1. **Improved value in use**
   - patient experience
   - the burden on healthcare professionals
   - geographical coverage in distant areas

2. **Cost-savings**
   - direct health care costs
   - direct costs on households
   - indirect costs
3. **Health system benefits**
   - supply reliability
   - product stability
   - vertical integration to the provider chain
4. **Societal benefits**

- productivity
- business continuity

Fifth, after elaborating on the payment model, TPP and the conceptual value framework project owners are asked to think about the necessary health economic and outcomes research (HE&OR) activities before launch (e.g., developing an economic model to prove that the product is cost-effective). A HE&OR strategy is a plan to maximise and demonstrate the economic value to healthcare payers. Project owners are asked to provide a detailed plan on the necessary activities, timing of deliverables and budget planning for the described HE&OR strategy.

The project owners are to fill in each component of the feedback form. If they need help at any stage of filling out the form, they can ask for consultation from the SRI team.

Step 3 - Consolidation of eHTA Scoping Review

Project owners send the completed form to SRI. The eHTA team reviews the responses and organizes an internal scoping review meeting to discuss draft eHTA recommendations. The draft eHTA Scoping Review report is sent to project owners, which includes a short description of the project, key conclusions and recommendations. Then, project owners will have an opportunity to discuss the draft report with the SRI team to finalize key conclusions and recommendations. The eHTA Scoping Review report will serve as a compass for further eHTA activities.

After the eHTA scoping Review process, eHTA support activities will be integrated and followed up on the monthly RDT meetings. The formal structure and process of following support activities are under development currently and will be described in detail in Deliverable *D2.3 - Operations handbook and services catalogue*, due in Month 24 of the project.

ANNEX IV: eHTA Feedback Form

Scoping eHTA to support value maximization & selection of payment model

[to be completed by project owners]

#1 – Degree of added value
Clarify your expectations of incremental benefit. Be honest with yourself!

1. disruptive innovation (patient will be treated differently)
2. major incremental innovation (patient outcomes will significantly improve, but they will be treated similarly)
3. minor incremental innovation (patient outcomes will slightly improve, but they will be treated similarly)
4. no improvement in patient outcomes

Don't be afraid to admit, if your technology has limited novelty.

A technology can still be successful, if it provides the same benefits as the current gold standard, but…

…it can be marketed with a lower price – an advantage in price

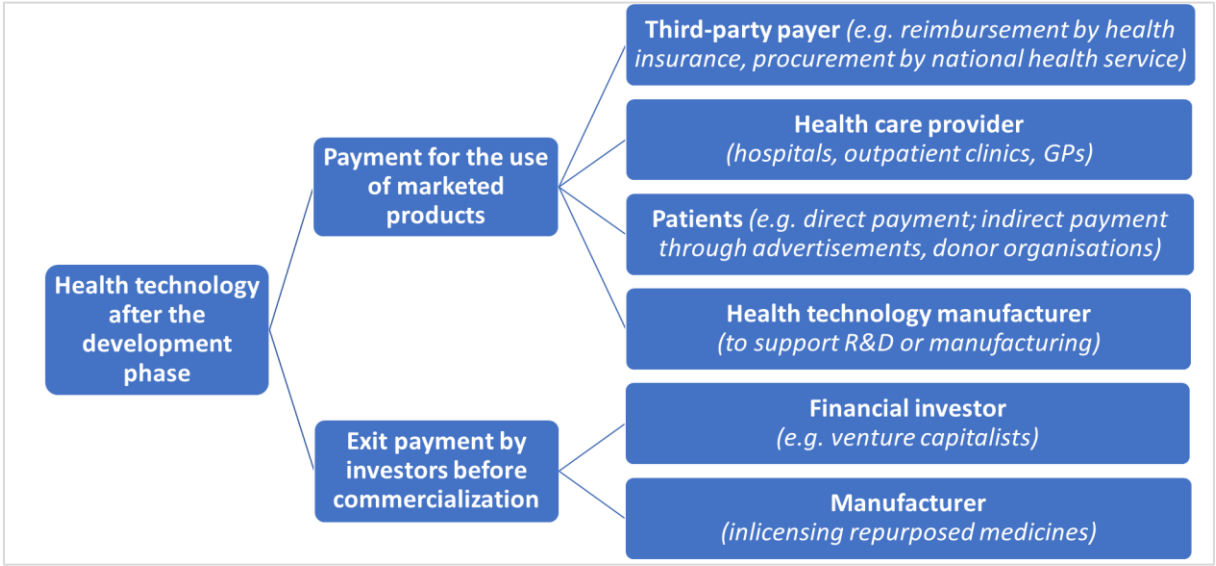
…it is regionally not available or accessible – advantage in regional markets

…it can be integrated into the provider chain – advantage in vertical integration

[Please provide a description here]

#2a – Payment model: Who will pay for your product?

Clarify your expectations of financing your product. We provided some options on the figure, but feel free to describe any additional options.



[Please provide a description here]

#2b - Payment model: If you plan to launch the repurposed medicine yourself

Please indicate your

1. *target countries*
2. *target providers*
3. *target use*
    - *mono vs. combination therapy (add-on)*
    - *prevention vs. treatment vs. rehabilitation*
    - *acute vs. chronic use*

[Please provide a description here]

#3 - Expected benefits of your product (target product profile - TPP)
Describe what are the quantitative expectations towards your project?

- A **Target Product Profile** (TPP) outlines the expected 'profile' or characteristics of a health technology that is aimed at a particular disease or diseases
- TPPs state intended use, target populations and other desired **quantitative** attributes of products, including safety and efficacy
- TPP guides product research and development (R&D) and is used as a planning tool that guides development towards desired characteristics
    - clinical trial strategy (choice of comparator)
    - clinical trial design (e.g., power calculation)
    - health economics strategy

[Please provide a description here]

#4 - Conceptual value framework

Understand how the TPP can be translated to true value propositions depending on who your buyer is: What is the promise for your purchasers? Which elements are relevant for your product? Please see some examples listed below, but feel free to add any additional value propositions.

5. **Quality-adjusted life year gain**
   - efficacy (clinical improvement)
   - survival
   - safety and tolerability
   - quality of life
6. **Improved value in use**
   - patient experience
   - burden on health care professionals
   - geographical coverage in distant areas
7. **Cost-savings**
   - direct healthcare costs
   - direct costs on households
   - indirect costs
8. **Health system benefits**
   - supply reliability

- product stability
- vertical integration to provider chain

9. Societal benefits

- productivity
- business continuity

#5 - Initial HE&OR (health economic and outcomes research) strategy

Once you have your payment model, TPP, and conceptual value framework, start to think about what the necessary activities before launch are (e.g., developing an economic model to prove the product is cost-effective). Think about allocating the necessary time and budget for these activities.

Health economics and outcomes research strategy: plan to maximise and demonstrate the economic value to health care payers.

- necessary activities
- timing of deliverables
- budget planning for HE&OR strategy

[Please provide a description here]

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