**A checklist with questions that can assist you in your repurposing drug development program**

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| **Concept** | **Areas to be covered**  | **Building Blocks** | **Your notes <to be provided by the potential drug developer>** |
| 1. Describe the research at the basis of the repurposing hypothesis
 | * Which stage of your drug development program are you in?
* Have you already identified the drug substance?
* Have you identified the drug target/molecular pathway?
* Have you validated that the target can be modulated to induce/exert a desired pharmacological/clinically meaningful effect?
* Have you developed a Target Patient Value Profile (TPVP)?
 | * I431 – Target Patient Value Profile
* I129 – Remedi

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| * E142 – EATRIS
* E144 – REMEDi4ALL
* I449 – REPO4EU
* I436 – Chemical compound databases
* I437 – Network databases
* I440 – In silico models for screening for drug repurposing candidates
* I441 – Machine learning & data mining
* I442 – Competitive intelligence
* I443 – Drug prioritization analysis
* I143 – EU openscreen
* I450 – Drug discovery platform
* I452 – Generics
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| 1. Describe the existing disease knowledge, gaps and population
 | * How much knowledge already exists about the disease, such as:
	+ Natural History
	+ Retrospective and prospective disease registries
	+ Patient population/subpopulations (genotypic and/or phenotypic heterogeneity)
	+ Current standard of care practices
	+ Presently available therapeutic interventions
	+ Treatments (approved/not approved/under development)
	+ Prognosis
	+ Etiology
	+ Diagnosis
	+ Comorbidities
	+ Prevalence/incidence
	+ Subpopulations
	+ Availability of animal models or other clinically relevant models
	+ Total costs of the disease on families/healthcare system(s)
* Are you aware of sources of data compiling this knowledge and do you know how to access them?
* Are the available data fit for use in a regulatory dossier?
* Have you considered if it fulfills an unmet medical need?
 | * I418 – Natural History Studies
* I419 – Registries for Rare Diseases
* I413 – Biomarkers Development
* I414 – Patient preference studies
* I514 – Patient Centered Outcome Measures
* I416 – Companion Diagnostics
* I417 – Bio-assays
* I406 – Tissue Chip for Drug Screening Program
* I455 – Clinical Trials database
* I408 – BBMRI-ERIC
* I433 – CURE ID
* I434 – Off-label use
* I455 – How to develop pricing models for repurposing
* I460 – Data outside the public domain
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| 3. Describe in more detail the standard of care and its potential evolution | * Are you aware of other molecules or therapies that could change the standard of care for this disease?
* Are there guidelines and (some) consensus on how to diagnose, monitor and treat patients with this disease?
* Are there important variations in treatment/standard of care across countries or geographic regions?
* What does the development landscape look like for the next 10 years?
 | * I433 – CURE ID
* I434 – Off-label use
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| 4. Describe the pharmacologic substance of interest | * Do you have direct access to the medicinal drug product and/or drug substance? Is the product still available on the market? Is the product licensed/currently under patent?
* What type of evidence have you generated already and/or which data is available in the literature to support the safe and effective use in this new indication? Are there ongoing development programmes in this indication or in this disease with this substance? How are they progressing?
	+ Screening EMA for Orphan Drug Designation / FDA Orphan Drug Designation / PMDA? Either for the active substance, or for the same disease.mah
	+ EudraCT Clinical Trial Database; clinicaltrials.gov
	+ Clinical review available from sources such as CT “Cochrane Handbook for Systematic Reviews of Interventions” or PubMed-indexed publications
* In case the drug has been withdrawn from the market or abandoned, what was the reason? In case the drug has previously been investigated in clinical studies but not approved, what was the reason?
* Do you know how to mitigate the safety risk in case it has been withdrawn due to a rare adverse event?
 | * I462 – Public-private partnerships
* I434 – Off-label use
* I455 – Clinical Trials database
* I453 – Drug databases
* I454 – Combination of drugs
* I433 – CURE ID
* I435 – Cure Drug Repurposing Collaboratory
* E144 – REMEDi4ALL
* E145 – LifeArc Repurposing Medicines Toolkit
* U230 – ROADMAP
* I447 – How to maintain a literature archive
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| 5. Describe the freedom to operate | * Do you have access or can gain access to raw data, such as:
	+ Individual patient data from (past) clinical trials
	+ Investigator’s brochure
	+ Non-clinical toxicology data
	+ Drug manufacturing data (in case of previously approved but abandoned/off-market drugs)
* Do you have any knowledge on the patent status of the medicinal drug product / drug substance, in general and/or for any specific therapeutic use? If yes, using which source of information?
* Have you or your institution filed a patent application for these data? Or are you or your institution planning to file a patent application?
* Have you identified a legal expert that can support you in this?
* Did you request or schedule any freedom to operate analysis based on regulatory and/or patent information? If yes, for which specific therapeutic use and in which countries?
* Has the medicinal/drug product been on the market for more than 10 years?
* If applicable, did you contact the marketing authorisation holder?
* If applicable, did you contact your national health authorities?
* Are you aware of entities that are pursuing active development for this, or another indication for this active substance and/or drug product? If yes, from which source of information (company / institutional website, scientific publication or conference, patent or scientific database)?
 | * I462 – Public-private partnerships
* I455 – Clinical Trials database
* E142 – EATRIS
* E145 – LifeArc Repurposing Medicines Toolkit
* U230 – ROADMAP
* I143 – Newfound Initiative
* I148 – Engaging with MA holders
* I163 – Pre-competitive space working
* I444 – How to search and use IP and legal databases
* I445 – Patent framework of Drug Repurposing
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| 6. Describe the expected sources of funding | * Do you have an estimate of what the total cost of bringing the substance to market will be?
* Which sources of funding do you envisage to mobilize to cover the whole development and to bring the substance to market?
* Did you obtain funding already? If so, for which aspects? Do you have a funding plan going forward?
 | * E120 – MoCA
* E121 – EUNetHTA
* I448 – Funding resources for drug repurposing
* E123 – European Commission funded programs and resources
* E124 – European Joint Programme for Rare Diseases
* U226 – NIH Initiatives
* J312 – AMED funded programs
* I455 – How to develop pricing models for repurposing
* I404 – Crowd funding
* I420 – Private funding
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| 7. Describe the development needs for that specific indication | * Do you plan to adjust the dose of the drug for the new indication (i.e., different from current registered forms/regime for known indication)? Would toxicity safety data are available and are they sufficient?
* Do you plan to develop a different formulation for the new indication (i.e., from a cream to a tablet, or from injection to nasal spray, etc.)?
* Do you intend to target a different age group/population for the new indication (e.g., exposing the drug to children instead of adults)?
* Do you intend to use a (novel) combination of two (or more) drugs? If so, consider use of predictive in silico tools to analyze synergistic drug effects (efficacy) and possible drug-drug interactions (safety).
* Have you verified the reproducibility of the initial research findings in an independent lab/experiment or confirmatory screen/animal model? For instance, to ensure the quality and read out were robust/relevant to confirm the repurposing hypothesis.
* Have you verified the initial research findings by comparing effects observed when testing compounds/drugs that have similar structure and/or target the same biological effector of the candidate drug?
 | * I457 – Dose Finding
* E142 – EATRIS
* I143 – Newfound Initiative
* E144 – REMEDi4ALL
* I456 – PKPD Modelling in children
* I458 – new formulation of drugs
* I459 – safety data across indications
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| 8. Describe your regulatory strategy | * Did you check the regulatory requirements before starting human studies (in particular in case of drug repurposing approaches involving dose/formulation/target population adjustments)?
* Which countries are you seeking regulatory approval in and have you consulted with national regulatory authorities in each country?
* Did you apply, or have you obtained, an orphan drug designation (ODD)?
* Have you considered seeking (early) regulatory scientific advice from a regulatory authority?
* Did you consider leveraging publicly available information and/or modeling and simulation to reduce or eliminate future clinical studies for the new indication?
* Did you complete the necessary documentation to enter human development phase (e.g., Investigational Medicinal product dossier, Investigator’s brochure, Clinical trial application) and obtain (ethical) approval from the institutional review board (IRB)?
 | * E142 – EATRIS
* E144 – REMEDi4ALL
* E136 – Darwin-EU
* E137 – PUMA
* E138 – ILAP
* E139 – EMA pilot project to support academia
* E140 – STAMP initiative
* U229, U231, U232 – Initiative updating old labels
* E141 – STARS
* I446 – Regulatory framework of Drug Repurposing
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| 9. Describe how the drug will be made available to patients down the road after successful development | * Have you considered the possibilities / (dis)advantages of on-label vs. off-label repurposing approaches?
* How have you arranged patient involvement (at an early stage)?
* Equity/market access (in particular for drug repurposing there is information already on current market and could identify bottlenecks early - where is the target population and what does the drug access/reimbursement landscape look like for that specific country/region?)
* Have you conducted Health economics/technology assessment?
* Have you evaluated reimbursement options (knowledge on current drug/indication combination/pricing may provide a good starting point for planning engagement with health insurance companies/government payers)?
 | * I434 – Off-label use
* U223 - NCAT Toolkit for Patients-Focused Therapy Development
* I435 – Cure Drug Repurposing Collaboratory
* I143 – Newfound Initiative
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| 10. Summarise your planned interactions and expected collaboration at the different stages of the development plan | * Have you established relationships with (a) patient organization(s) and do you have support from a patient organization, based on the patients needs?
* Have you made an arrangement for business collaboration with a/the Marketing authorisation holder?
* Did you identify other key stakeholders, such as investigators, Key Opinion Leaders (KOL)?
* Have you developed a global regulatory strategy, based on the requirements of Regulatory Agencies (EMA, FDA, PMDA, etc.)?
* Have you evaluated requirements of national HTA agencies for reimbursement?
 | * I148 – Engaging with MA holders
* I163 – Pre-competitive space working
* I462 – Public-private partnerships
* I435 – Cure Drug Repurposing Collaboratory
* E146 – Engaging with HTA
* E142 – EATRIS
* I143 – Newfound Initiative
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