Annex 2: Reverse Planning Template

When you plan in reverse, you start with your end goal and then work your way backwards from there to develop a plan of action. Working backwards in this way can give you a much clearer picture of what and how much must be accomplished during each phase of a project. It can also help you identify and avoid unnecessary activities.

Phase	What to do	What you should know for rare diseases
TPP A target product profile (TPP) is a document that outlines the desired 'profile' or characteristics of all relevant information needed in validating product development	Envision and briefly describe the target scenario of the primary indication of the TPP/marketed product	
Clinical Phase III The aim is to determine a drugs therapeutic efficacy (25-30% pass this phase). Typically, 300-3000 people with specific disease are included in this trial. Outcome: Determine a drugs therapeutic efficacy (25-30% of drugs pass this phase)	Envision and briefly describe the pivotal clinical phase III trials need to apply for a marketing authorisation the primary indication of the marketed product. Ask yourself: “What is the ideal patient population for phase III?” “Can we test against placebo or comparator products?” “How many patients will be needed to show efficacy and safety (and also to identify rare side effects, if applicable)?” Based on incidence and prevalence in the indication of interest, how long will a phase III trial last and how many sites need to be enrolled?” “How much study material will we need or testing?”	Often enrol small samples, and often with high inter-individual variability in clinical course, and patients often are spread out all over the world. FDA proposes a trial regimen with a safety cohort operating at the same time as the efficiency trial. Natural history and patient registries can be used to identify key milestones in diseases progression, determine clinical meaningful difference, develop inclusion/exclusion criteria.

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Clinical Phase II 100-300 participants with specific disease (therapeutic dose) Outcome: Estimate efficacy and side-effects (Success rate ~ 33%)	Envision and briefly describe the cornerstones of the phase II clinical programme when considering TPP and phase III in order to show efficacy in a dedicated patient cohort. Ask yourself: “What is the ideal patient population for phase II?” “Can we test against placebo or comparator products?” “How many patients will be needed to show efficacy?” “Suitable secondary endpoints and exploratory parameters?” “How much study material will we need or testing?”	In rare diseases, many of which cause a shortened lifespan, there are ethical concerns about placebo-controlled trials, parents may be reluctant to enroll their child in a trial where he or she may receive a placebo rather than the intervention under study. Patients are more willing to participate if they have an open-label or crossover design option, rather than a randomized, placebo-controlled trial.
Clinical Phase I 10 to 100 healthy volunteers (sub-therapeutic with ascending doses) Outcome: Dose-ranging to determine if it is safe to test for efficacy (Success rate ~70%)	Envision and briefly describe the cornerstones of the (First-in-Man, FiM) phase I clinical programme when considering the previous planning phases in order to show safety in healthy volunteers. Ask yourself: “Healthy volunteers or patients required?” “Open-label? Controlled?” “What is the optimal dose, what is the dose range?” “What is the route of administration?” “Suitable secondary endpoints and exploratory parameters?” “How much study material will we need or testing?” “Is the study material for clinical phase I comparable to the non-clinical?”	Alternative trial design: Statistical techniques that maximize data from a small and heterogeneous group of subjects are needed. Precedent for approval of drugs with an orphan designation based on pivotal studies that are not randomized, placebo-controlled, or double-blind, with smaller trial sizes compared to studies of drugs without such a designation

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Non-clinical Programme (preclinical development) Preclinical studies objective is to provide detailed information about safety and efficacy of a drug and requires appropriate animal models that mimic human disease	Envision and briefly describe the cornerstones of the non-clinical programme when considering the previous planning phases in order to show safety in suitable animal models. Ask yourself: “What is the suitable animal model to show safety/efficacy?” “What are the analytical methods for characterizing pharmacokinetics and metabolic of the test substance?”	Most rare diseases are juvenile: Use juvenile animal models in reasonable cohort sizes in case of pediatric rare diseases Evaluation of the drug dosing and response considering the differences in the anatomy and physiology between adults and children. Adult disease: Using forward and reverse genetic manipulation in mice and occasionally with other animals. This approach although is expensive and time-consuming is now a fundamental experimental strategy. Cultured cells from mouse models of rare disease. Mice with humanized livers can be a boon in the case of drug toxicity testing No mice model: consider using zerbrafish, or use of human cells, both normal and those derived from patients with genetic defects.