Orphan Drug Development Guidebook

Building Block I424

This document defines the content of the Building Block created for each identified tool, incentives, initiative or practice introduced by public bodies or used by developers to expedite drug development in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	Ethic's Committees assessment of protocols for trials with orphan medications
References	https://www.coe.int/t/dg3/healthbioethic/activities/02_biomedical_research_en/Guide/Guide_EN.pdf https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/research-ethics-committee-members-area/guidance-and-policy-for-rec-members/ https://doi.org/10.1016/j.clinthera.2014.01.013
Description	To improve the quality of data supporting regulatory evaluation and clinical use of orphan medications, the ethical assessment of clinical trials in orphan populations should be done by experienced committees, which should ensure that all relevant aspects on patient protection are present, but also that the trials apply robust methodology and the most efficient clinical design able to conclude on the efficacy and safety of the studied treatments. Protocols of clinical trials studying orphan medications raise particular difficulties at the time of ethical assessment by ethic's committees or Institutional Review Boards. Ethical assessment of clinical trials in orphan diseases should be done by experienced committees, and should ensure that all relevant aspects of this particular type of trial is properly assessed. Trials in RD are often conducted in vulnerable populations (children or disabled), use uncommon methodologies due to the scarcity of eligible population, use biomarkers due to lack of power to assess clinical end-points, lack information on populations to support dose selection or apply modelling from other populations

	or diseases to that purpose, and face concerns on placebo use in severe conditions with no available alternatives. Often marketing authorizations are granted based on early evidence of efficacy when the severity of the condition is high and there are no available alternatives. Because of this, it is required that investigators apply the most efficient clinical design able to conclude on causality even in very early or preliminary clinical studies. There are general guidances and procedures for Ethical review of research, such as the one in UK, and similar documents in other countries: https://www.hra.nhs.uk/planning-and-improving-research Also, some EMA and other guidance for ethical assessment of paediatric trials can be found e.g.: https://www.ema.europa.eu/en/documents/report/ethical-considerations-paediatric-trials_en.pdf Guidance on methods and general approach to study design in small populations is also available: https://www.ema.europa.eu/documents/scientific-guideline/guideline-clinical-trials-small-populations_en.pdf https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm458485.pdf However, guidance for ethical assessment of trials specifically in rare diseases are currently unavailable but there is a growing literature e.g.: ue. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5764070/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7568613/The duration of the tasks related to study drafting and protocol submission is dependent on the sponsor and investigators and does not have a predetermined duration. Tasks related to ethical assessment by committees are of variable duration across countries and may depend on the type of applications and products, ranging between 30 and 120 days.
Category	Development Practices Building Block
Geographical scope	International
Availability	Applicants developing medicines for rare and non-rare diseases.

Scope of use	During protocol design and assessment, to ensure that ethical, safety and practical aspects are considered, and that relevant outcomes are included in the trial. Should be applied by: • Clinical researchers at the initial stages of clinical research planning Ethic's committee members at the time of authorization of a trial, and during the follow-up of the study. The BB may be used by investigators at the time of designing a trial and writing a protocol and by Ethic's Committees members to guide the assessment of clinical research in patients with orphan diseases.
Stakeholders	• Clinical researchers, • Members of Ethic's Committees, • Authorities responsible to qualify/recognize/audit Ethic's Committees
Enablers/ Requirements	- Investigators should use the BB at the time of drafting the study protocol in rare diseases (RD) - The sponsor submits the study protocol in RD to Ethic's Committee for review -
Output	Ethical review of a clinical trial in RD by IRBs/Ethic's committee include specific considerations for RD.
Best time to apply and time window	The tool has its best use by the time a trial is being conceived and designed, and at the time of assessing a trial before start.
Expert tips	The process begins when investigators decide that a clinical trial is required to test a working hypothesis. The investigators draft a protocol and work in teams with statisticians, methodologists, other clinicians and investigators and patients to gather multidisciplinary input. A number of tools such as guidances and check-lists may help to improve the protocol quality and consistency.

	The sponsor of the trial is responsible to gather all the required documentation and submits the study for review and approval by both the regulatory body and the ethic's committee; each has the responsibility to assess key aspects of the trial to ensure compliance with regulation and laws, as well as ethical principles of research involving human beings. The ethic's committee liaises with members and, where required, external experts, to prepare the evaluation report. To that purpose, Standard Operating Procedures, relevant guidances and check-lists are applied. The project is discussed in a meeting and a list of questions or comments is sent to the sponsor for amendment or clarification. Once (if) resolved, an authorization is issued when appropriate, within the pre-established timelines as set by regional/local regulation. PROs: – Availability of ethical and methodological standards will improve the quality of data supporting regulatory evaluation and clinical use of orphan medications. – Application of standards during design and review should ensure that all relevant aspects on patient protection are present, but also that the trials apply robust methodology and the most efficient clinical design able to conclude on the efficacy and safety or the studied treatments. CONs: – It is difficult to reflect all possible situations in a single guidance given the variety of clinical situations and methods potentially applicable to study them, and thus there is risk of incompleteness.