# Orphan Drug Development Guidebook

## Building Block I421

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 |
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| Building Block (BB) Title | Alternative designs for Small Population Trials |
| References | 1. https://www.ema.europa.eu/documents/scientific-guideline/guideline-clinical-trials-small-populations_en.pdf<br>2. https://www.ema.europa.eu/documents/scientific-guideline/draft-ich-e11r1-guideline-clinical-investigation-medicinal-products-pediatric-population-step-2b_en.pdf<br>3. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-rare-diseases<br>4. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm614641.pdf<br>5. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm629579.pdf<br>6. https://www.nap.edu/catalog/10078/small-clinical-trials-issues-and-challenges<br>7. Day S, Jonker AH, Lau LPL, et al. Recommendations for the design of small population clinical trials. Orphanet J Rare Dis. 2018 Nov 6;13(1):195.<br>8. Coping with small populations of patients in clinical trials: https://www.tandfonline.com/doi/full/10.1517/21678707.2014.93122 |
| Description | Recognizing the difficulties of clinical research in rare diseases, a number of general recommendations are available to select the most efficient study design for each medical condition or trial, and on potential adaptions of conventional designs to the low sample size scenario.<br><br>Within the multiple alternative trial designs available, master protocols allow to evaluate more than one or two treatments in more than one patient type or disease within the same overall trial structure. Particular cases include multi-arm trials, |

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| | platform trials, umbrella trials, and basket trials. These designs also allow for a collaborative approach where more than one sponsor may test their products in a single trial; use of a single control arm allows minimizing sample size and placebo exposure.<br><br>Low prevalence inherent to rare diseases results in lack of feasibility of large randomized trials as often required by conventional regulatory requirements. The use alternative designs suited to small populations may help in certain circumstances to gather the most robust evidence feasible from small datasets. In certain types of conditions, the use of master protocols for multiple-arms, umbrella, basket or platform trials, may be appropriate. |
| Category | Development Practices Building Block |
| Geographical scope | International |
| Availability | Applicants developing medicines for rare and non-rare diseases. |
| Scope of use | Sponsors and investigators may use the available guidance to plan the most efficient approach at the time of selection of the design of exploratory and confirmatory trials and the overall development plan.<br>Methods especially suited to the study of small populations should be considered early during the planning of clinical development, and especially for early trials.<br>Master protocol trials could be considered before reaching the clinical phase, whenever competitive intelligence suggests that several products might be developed independently for similar indications, and/or potentially predictive biomarkers might be applied to refine the target population and product indication.<br><br>Regulators will apply knowledge on alternative methods to their assessment at the time of scientific advice procedures and for assessment of marketing authorization applications.<br><br>Should be applied by:<br><br>• Sponsors should consider methods especially suited to the study of small populations early during the planning of clinical development. If master protocols are applicable, these should be considered during strategic discussions on clinical development of drug candidates.<br>• Clinical researchers, statisticians, other persons involved at any of the initial stages of clinical research planning should consider alternative options to classical designs that are suited to small populations. |

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| | • Ethics Committees assess the acceptability of the proposed approaches as regards to ability to conclude on proposed objectives and protection of subjects' rights and wellbeing.<br>• Patients provide input on the acceptability of the proposed approach and impact on their participation and interests.Regulators may be consulted at an early stage on acceptability of the approaches through Scientific Advice or similar procedures. Regulators assess the robustness and acceptability of data at the time of marketing regulatory applications. |
| Stakeholders | • Sponsors,<br>• Investigators,<br>• Any person involved in the strategic planning of clinical development,<br>• Ethic's Committees,<br>• Regulators,<br>• Patients. |
| Enablers/ Requirements | • Sponsors consider the applicability of alternative methods at the time of planning the clinical development of a drug candidate. If master protocols are suited involving products from other Sponsors, they approach at an early stage other companies potentially interested to coordinate and arrange any legal, economic and logistic issues.<br>• Investigators, statisticians and other persons involved in the trial contribute to study design and implement designs into study protocols and provide input during study conduction as required for any planned interim analysis or adaptions.<br>• Ethics Committees and regulators review the proposed protocol and issue authorizations for execution.<br>• Regulators provide input at early consultation and assess results as presented at the time of marketing authorization application / drug licensing. |
| Output | Clinical protocols implementing methodologies especially suited to the study of small populations. |
| Best time to apply and time window | The tool has its best use at the time of selection of the design of exploratory trials and planning of the overall development plan, ideally before first-into-human trials. Timely consideration very early during the process of drug development is necessary whenever coordination across companies or research groups is needed. |

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| Expert tips | **PROs**:<br>• The application of alternative designs suited to the study of small populations may reduce the requirements for sample size, improve the feasibility of clinical trials, increase the robustness of the data, and improve the ethical aspects of the trial, such as proportion of subjects exposed to placebo or potentially poor therapeutic options.<br>• Master protocols advantages may be expected once their set-up is complete. They may allow the use of a trial network with infrastructure in place to streamline trial logistics, improve data quality, and facilitate data collection and sharing, speeding-up the execution of clinical trials. Patients may be more efficiently screened, only once as compared to many times in independent trials and may have increased chances of participation into a relevant investigation.<br>**CONs**:<br>• The use of alternative designs or trial adaptions suited to the study of small populations may be a challenge to sponsors, because of regulatory perception of technical complexity and secondary reluctance to deviate from the double-blind randomized gold standard.<br>• Setting-up of trials under a master protocol approach may be long and costly, and requires good coordination and formal agreements between several sponsors for trial governance. Stakeholder coordination, infrastructure requirements, and complex trial design elements can extend the start-up time for a master protocol considerably, as compared with that for a single-purpose trial.<br>• Reluctance to share sensitive competitive information between sponsors may be a barrier to collaboration.<br>• While the exploratory setting in early development is less stringent as regards to multiplicity issues, multiple objectives may represent an issue when the objective of the trial is confirmatory, due to the extent of multiplicity adjustments required in a confirmative setting.<br>• Changes in the standard of care during the study conduct may require temporary interruption of recruitment to allow for implementation of changes in arms and design to include the new standard, to adapt the statistical analysis plans to new comparators, and may impact the potential for recruitment if an effective standard of care impacts the perception of medical need. |