Orphan Drug Development Guidebook

Building Block I412

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	Decentralized clinical trials
References	https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/future-topics/IndicativeTopic_RemoteTrials.pdf Planning decentralised trials **https://ctti-clinicaltrials.org/our-work/digital-health-trials/planning-decentralized-trials/** **Decentralized Clinical Trials for Drugs, Biological Products, and Devices Guidance for Industry, Investigators, and Other Stakeholders DRAFT GUIDANCE: 2023** **https://www.fda.gov/media/167696/download** Facilitating Decentralised Clinical Trials in the EU **https://www.ema.europa.eu/en/news/facilitating-decentralised-clinical-trials-eu**
Description	One of the identified key barriers to patients' participation in trials is geography and the distance to the clinical site, as well as the burden that participation represents to patients, including the duration and number of clinical visits. Decentralized trials aim to improve patient access to trials by enabling patient involvement from home or community care, increase the participation of more diverse populations, and enhancing data collection by combining the adoption of digital endpoints and telemedicine as applied to trials.

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	To that purpose, web-based platforms, tele-health, online patient diaries, e-informed consent programs, patient apps, wearables and systems adapted to capture data from electronic medical records are used to collect clinical information in the setting of clinical trials. The European Medicines Agency has identified amongst its strategic goals for 2025 to develop the regulatory framework for emerging clinical data generation. The specific goals include to develop methodology to incorporate clinical care data sources in regulatory decision-making, to modernize the GCP regulatory oversight to enable decentralized models of clinical trials coupled with direct digital data accrual, to develop the capability to assess complex datasets captured by technology such as wearables, and to facilitate training and understanding of healthcare professionals and patients to access and participate effectively in such trials. Similarly, the FDA has identified the use of decentralized, or virtual, or patient-centric clinical trials as a key development that would facilitate recruiting, enrolling and retaining participants in clinical studies, a major challenge and cost for study sponsors. FDA has established a formal working group on decentralized trials that is charged with developing guidance further outlining these approaches. Costs will be related to the project management required for coordination of the trials, and regulatory approval as in regular trials, plus the additional requirements for developing, validating, setting up and providing user support for specific tools used for data collection. Decentralized trials require a strong communication strategy to ensure compliance in execution and awareness of the trial to potential participants.
Category	Development Practices Building Block
Geographical scope	The BB is based on the availability of internet and the potential of remote virtual connection, thus is available globally.
Availability	There are a number of previous experiences in development, and tools and companies specialized in different aspects of decentralized trials, and projects focused on the subject.These initiatives are particularly important in assessing rare disease therapies affecting small patient populations. The extremely low prevalence of certain rare diseases means that patients are

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	scarce at a given site, are geographically disperse, and may have difficulties to reach the reference sites for trial participation (particularly for debilitating conditions). Long travelling for frequent visiting required for clinical trials represents a burden for families and a barrier to participation. Also, international trials with many centers require a high investment for setting up, and are costly in terms of monitoring. The use of information technologies may enable international collaborations of sites regardless of their distance, ease access to trial participation of larger numbers of patients, and remove barriers to recruit and visit patients living far from the reference sites. Also, the use of wearables, apps and tools for collecting patient reported outcomes may help to enrich the variety of clinical information by collecting patient's input on the benefits and risks of experimental treatments as a part of clinical trial data.
Scope of use	The BB can be used at the time of study planning and design, as a tool to manage practical issues related to the burden of visits, recruitment challenges, the duration of visits or those derived from the lack of access to geographically distant resources.
Stakeholders	Sponsors of clinical trials, clinical researchers and networks of clinical researchers, patients and patient's associations, members of Ethic's Committees, regulatory authorities.
Enablers/ Requirements	The BB may be considered in any clinical situation characterized by geographical dispersion of patients and/or clinical sites where the decentralization of the trial may be of benefit to ensure its feasibility.
Output	A clinical trial design and protocol that involves many sites and settings for the conduction of the study, with variable degrees of implementation of remote data capture for the assessment of efficacy, safety, quality of life or other relevant parameters, that may involve telemedicine and virtual visiting, applications, electronic records, wearables, web-based data capture or other tools.
Best time to apply and time window	The approach may start before or at the time of planning a clinical trial.

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Expert tips	A number of recommendations can be found in relevant literature and/or specialized societies – see references The process should begin early at the time of clinical trial planning, by considering the potential setting of the study to be widened from a few sites to a broader setting including smaller sites / primary care / other settings, and the number of visits that require physical attendance vs those that can be supported by the use of remote or virtual systems. The extent of application or use of any web based tools, apps, or other systems should be considered early in the development to allow for design and validation if required, and checking of acceptability for regulatory purposes should include not only ethic's committees but also regulatory authorities through scientific advice procedures. Issues such as accuracy and sensibility, robustness and privacy secureness must be properly addressed. Any tools used during the trials will require development, validation, setting up and training, and also a strong user support during the trial conduction. **PROs:** DCTs using telemedicine and other emerging and novel information technology (IT) services offer the potential for local HCPs to participate in clinical trials. This may provide several advantages compared to traditional clinical trials conducted at more centralized clinical trial sites, including the following: • The use of web-based systems for randomization may ease the connection of several sites that are physically distant into a single trial, and may be useful to reduce barriers and costs of international multisite clinical research in small populations. • Also, the use of remote monitoring technologies may also reduce the need for traditional on-site monitoring of each clinical site, while assuring the integrity of data needed to assess patient safety and product efficacy. • A potential benefit would be to reduce administrative and economic burdens on sponsors and investigators, while also permitting patients to receive treatments from community providers without compromising the quality of the study or the integrity of data. • Other potential benefits may include:

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	○ Faster trial participant recruitment. ○ Improved trial participant retention, which may reduce missing data, shorten clinical trial timelines, and improve data interpretability. ○ Greater control, convenience, and comfort for trial participants by offering at-home or local patient care. ○ Increased diversity of the population enrolled in clinical trials. An opportunity for home administration or home use of the Investigational Medicinal Product (IMP), which may be more representative of real-world administration/use post-approval. **CONs**: • Decentralized trials may be challenging for coordination, since dispersion of sites and an increased number of investigators open the room for heterogeneity in interpretation or application of study protocols. • Less human contact across the team and lower physical presence may require stronger systems to ensure robustness of methods. • Special attention should be paid to the treatment supply chain, since decentralized trials may pose challenges to the distribution, control and traceability of investigational medicinal products – the issue is less worrisome if trial medication is already approved. • A deep understanding of the data is needed; understand how it may be presented and how it should be analyzed to avoid errors or use of poor quality data biased or inaccurate information for decision making. • Guidelines on standards and validation of data and tools are needed to ensure they are robust enough for regulatory decision-making. • Secure mechanisms to protect patient confidentiality in line with data protection legislation will be critical for securing patient trust. • Apps and software can also pose potential risks. A flexible, risk-based framework that protects patients without blocking advance

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	of digital health will be required, that provides the necessary guarantees.