Drug Repurposing Guidebook

Building Block I455

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

ITEM	DESCRIPTION
Building Block (BB) Title	Clinical trial databases
References	https://clinicaltrials.gov/ , https://www.clinicaltrialsregister.eu
Description	The registration and posting of clinical trials (CT) in public databases is a widespread requirement in international standards, federal, national and European regulations. CT databases contain information submitted by sponsors and inform users about ongoing clinical trials. • **ClinicalTrials.gov** is commonly referred to as a "registry and results database" of privately and publicly funded clinical studies conducted around the world. It is a US government web-based resource maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH). The ClinicalTrials.gov study registry was launched in February 2000 in response to US federal law requiring the NIH to “establish, maintain, and operate a data bank of information on clinical trials for drugs for serious or life-threatening diseases and conditions . . . in a form that can be readily understood by members of the public”. The US Food and Drug Administration Amendments Act of 2007 (FDAAA) further extended the scope and legal requirements of the ClinicalTrials.gov registry, and mandated the creation of a results database, which became operational in September 2008. ClinicalTrials.gov currently includes 426,776 research studies in all 50 US states and in 221 countries. • **EudraCT** (European Union Drug Regulating Authorities Clinical Trials Database) is the EU’s electronic database of clinical studies conducted in the European Union (EU) and European Economic Area (EEA). Studies that are conducted entirely outside of the EU are also required to have

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	results posted if they are part of a Paediatric Investigation Plan (PIP). EudraCT is confidential and accessible only to the national competent authorities (NCA) of the different Member States. The **EU Clinical Trials Register** (EUCTR) website was launched to provide the public with information held in the EudraCT database. The content and level of detail of this information is set out in the European Commission guideline and in its technical guidance. As of July 2014, it became mandatory for sponsors to post clinical trial results in the European Clinical trials Database. EudraCT is managed by the European Medicines Agency (EMA). The EU Clinical Trials Register currently displays 42663 clinical trials, of which 7022 are clinical trials conducted with subjects less than 18 years old.
Category	Clinical development, including extrapolation of efficacy and safety data
Type of BB	Development resource
Geographical scope	International
Availability	Users include study sponsors and data providers, researchers, patients, general public.
Scope of use	Clinical Trials databases are very useful tools with different objectives: - For researchers: they help them stay up to date on developments in their fields, find collaborators and identify unmet needs - For patients: they allow them to identify recruiting studies dealing with their conditions and learn about new treatments, as well as potentially identify results from trials that may inform their treatment - For sponsors and study record managers: they allow the registration of clinical studies and the submission of results after study completion
Stakeholders involved	Industry, EMA, National Competent Authorities in EU Member States, FDA, NIH, governments

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Enablers/ Requirements	To protect public health and foster innovation, sponsors are obliged to register their trials and submit summary results in CT databases. The mandatory submission of the results is the direct responsibility of the sponsors. Result-related information has to be posted within one year after the end of a clinical trial (6 months for paediatric trials) according to the European Commission Guideline 2012/302 03/EC1. The maximum time a clinical trial result can be delayed is two years from the date the Certificate of Delay (COD) is submitted, for a total of three years in ClinicalTrials.gov.
Output	CT databases are regularly updated at different points in the drug lifecycle; study records indicate the trial protocol and provide results where available. CT can be searched by status (initiated, ongoing, completed), disease, country or by other terms. ClinicalTrials.gov includes different types of CT (interventional; observational; expanded access) while all trials registered on EU CTR are interventional CT. Phase 1 trials conducted solely in adults and which are not part of a PIP are not public in the EU CTR. Phase I trials are not required to have results posted on Clinical Trials.gov.
Best time to apply and time window	Studies are registered at the start of the study, then updated as the study is conducted. Once a study is completed, summary results can be entered. Earlier versions of study records remain accessible.
Expert tips	The CT databases do not currently provide a way to identify **Drug Repurposing studies** systematically, with the exception of searches of specific drugs which are known to be repurposed. DR consists of investigating existing drugs for new therapeutic indications and is often presented as offering various advantages over traditional development of a new drug such as fewer risks, lower costs, and shorter timelines. For many reasons, the introduction of such an item could be relevant in CT databases. PROs • CT databases are a **key source of information** for clinicians, researchers, patients, the general public and industry; they help - assist patients in finding clinical trials that might be relevant to their medical condition - facilitate enrollment

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	- allow for tracking of the progress of trials • CT databases have been developed to **address structural problems** including non-publication of trial results, selective reporting of results in trial publications and duplication of research. • CT databases lead to increased **clinical trial transparency** by providing a free and accurate search of clinical trials CONs • **No guarantee for scientific accuracy:** study sponsors and data providers are responsible for ensuring that their submitted information is accurate and complete. • Not all listed studies are **regulated and/or reviewed** by the U.S. Food and Drug Administration, EMA or other governmental entities. There is limited quality control review for apparent errors, deficiencies, or inconsistencies. • Posted records **may contain incomplete information** In 2018, ClinicalTrials.gov contained registration information for nearly 270 000 studies in over 200 countries and had posted summary results information for only 30 000 registered studies. https://doi.org/10.1136/bmj.k1452 Efforts to increase timely reporting of results in ClinicalTrials.gov have not been very successful. • **Specificities of EudraCT/EUCTR** Sponsors needs to liaise with each and every relevant National Competent Authorities in EU Member States directly and on EUCTR each trial is broken down into separate 'protocols' specific to each Member State. For example, if a trial is run in France, Belgium and Germany then the registry holds three protocols, each with its own completion status. There is no headline completion status that covers the entire trial. • **Discrepancies between registries**. According to a cross-sectional study of 10,492 trials registered on both ClinicalTrials.gov and the European Union Clinical Trials Register (EUCTR) published in 2018 https://www.medrxiv.org/content/10.1101/2021.06.29.21259627v1.full trial completion status on registries was partially inaccurate. "33.9% of dual-registered trials listed as 'ongoing' on EUCTR were listed as 'completed' on ClinicalTrials.gov".