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Rare diseases clinical trials toolbox - public resources and main considerations to set up a clinical trial on medicinal products for humans in Europe

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Abstract

Aim: Drug development programs in rare diseases face many challenges, such as the scarcity and geographic dispersion of patients, limited natural history data, the need for novel study designs, and sensitive outcome measures.

Over the past years, tools supporting clinical research have been developed in the context of different projects and for diverse purposes. Therefore, they have not yet been structured to encompass the conduct of rare disease (RD) clinical trials as a whole. To address this issue, the European Joint Program for Rare Diseases (EJP RD) has developed the Rare Diseases Clinical Trial Toolbox. This toolbox collates the accumulated knowledge (collectively termed "tools") generated by projects/organizations into a structured and guided instrument. By structuring and making resources discoverable, we aim to help RD clinical trialists and trial managers.

Methods: We have designed and developed a toolbox structured around the definition of the clinical trial pathway. It is organized into five domains. Each domain describes one or several activities to be considered throughout the clinical trial pathway. Selection criteria were then defined to include existing resources that are relevant to those activities. Rare disease-specific resources are highlighted as such and include those especially relevant to pediatric clinical research.

Results: The current version of the Toolbox includes 121 resources tagged as relevant to any of the 18 activities within the clinical trial pathway. Overall, 60% of all resources are relevant to any clinical trial while 40% are tagged as "rare disease-specific".

Conclusion: Access to public resources relevant to the development of clinical trials for rare diseases is sometimes challenged by limited awareness and/or the absence of an adequate framework that enables their findability. This Toolbox aims to build a framework supporting the optimal use of existing tools.

Keywords: Rare diseases, clinical trial, pediatric, toolbox, resources, academic-sponsored, investigator-initiated

INTRODUCTION

Drug development programs in rare diseases (RDs) face many challenges, some of which differ from those facing researchers working on common diseases, such as the lack of clinical research experts, the scarcity and geographic dispersion of patients, limited natural history data, the need for novel study designs, and sensitive outcome measures[1-4]. In the RD context, multinational, multi-center clinical trials are required to achieve sufficient recruitment and provide added value by promoting global standards of care and increasing the applicability of the research findings. International collaboration is nevertheless constrained by scientific, ethical, financial, and regulatory considerations. Different sponsors may have varying capacities to address these constraints, leading to divergent collaborative patterns.

Commercially sponsored clinical trials play a central role in bringing most new drugs to market. However, these clinical trials only assess the safety and efficacy of drugs that are chosen by the commercial entity which funds the entire process. Non-commercial or academic investigator-initiated trials, therefore, have their own specific significance, often focusing on new or refining indications of available treatments and optimizing therapeutic strategies[5,6] that do not contribute to significant financial gain to the pharmaceutical industry.

In contrast to industry-sponsored trials, academic-sponsored trials face a number of challenges, including: (a) lack of funding or flexible, long-term financial support covering unexpected issues that arise during the trial; (b) inadequate infrastructure to plan and execute the trial, including a working quality management system; (c) insufficiently structured processes to facilitate academic collaborations, and a lack of platforms to discuss and solve issues related to academic trials that result in difficulties accessing the right partner assisting on the operational management [usually provided by contract research organizations (CROs) for industry-sponsored trials][7].

Academic sponsors and investigators end up involved not only in the scientific aspects of the research, but also in navigating the operational coordination and management.

With this Rare Diseases Clinical Trials Toolbox[8], we aim to provide a guide for researchers, charities, and other academic trial stakeholders embarking on the setup of clinical trials for rare diseases. We describe a clinical trial pathway highlighting common activities, issues, and considerations at each development stage, and provide guidance to available relevant tools to make them discoverable.

METHODS

Five steps were followed to develop the Toolbox [Figure 1].

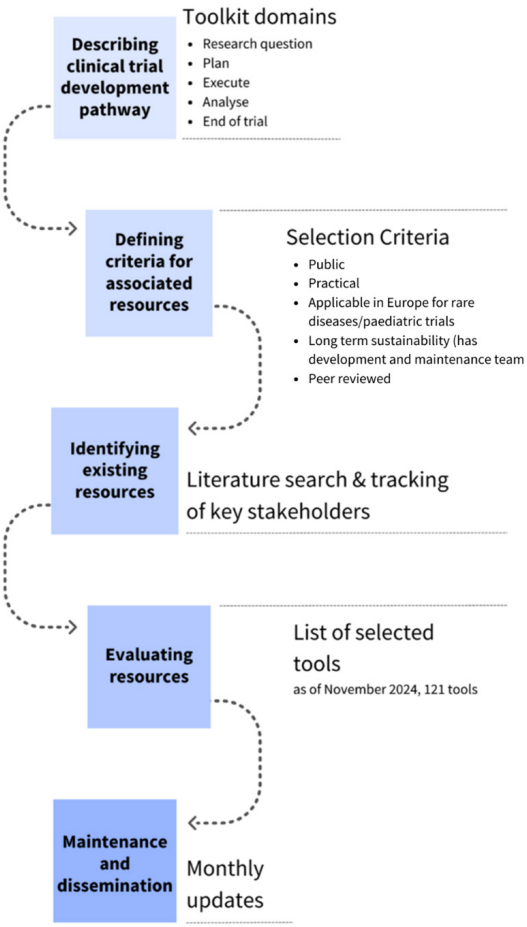

Figure 1. Outline of the steps taken for the development and implementation of the RD Clinical Trials Toolbox. RD: Rare disease.

Step 1- describing the clinical trial development pathway

The Toolbox does not aim to be a database of existing resources, but to classify and structure them in the context of the different processes and activities to be considered while setting up a clinical trial. Thus, the first step was defining the clinical trial pathway that would frame existing resources.

A clinical trial pathway outlines the steps a single clinical trial follows from conception to completion. Three disease-agnostic, clinical research experts were consulted to determine the most appropriate pathway. Thus, five main domains were chosen to define the clinical trial pathway:

• Research question

• Planning

• Execution

• Analysis

• End of the trial

For each domain, we defined several activities that occur through the trial pathway and that need to be considered while planning and conducting clinical trials, regardless of the therapeutic area [Figure 2].

The clinical trial pathway was finally set up as an outline of 18 activities grouped into 5 main domains [Figure 2]. The Toolbox makes a detailed description of each activity, and any necessary considerations related to rare disease specificities are provided; Table 1 shows an example.

Table 1. Example of clinical trial pathway domain/activity showing associated descriptions and resources

Clinical trial pathway	Research question
Activity	Define a question
Description and main considerations	Definition including considerations on why research question is important Research question based on PICO model (Population, Intervention, Comparison, Oucomes)
Resources (disease agnostic)	4 tools: • Clinical trial decision tool • Cochrane PICO search • Patient engagement × 2
Resources (rare disease specific)	1 tool: Rare disease patient engagement

Step 2- defining the criteria for associated resources

Each domain and activity are further elaborated on through the identification of existing resources that are relevant to the specific step.

The following Scope and Selection criteria were defined to select relevant tools:

• Public: Associated resources are in the public domain, i.e., documents, guidance notes, templates, and other research outcomes developed in the context of previous research projects, and/or developments of relevant clinical research stakeholders such as research infrastructures, universities, and patient organizations

• Peer-reviewed: Research articles published in scientific journals

• Selected tools, standards, and guidelines must be of importance to clinical trials and with a special focus on rare diseases clinical research. Tools that are non-rare-disease-specific are eligible if still relevant to the setup of clinical trials for rare diseases

• Practical: To be used/applied in the context of one or more of the activities described in the Clinical Trial pathway

• Applicable in Europe and for rare diseases trials*

• Long-term sustainable: has a development and maintenance team

*National, regional, or institutional resources for rare diseases or a specific single disease entity, or commercial resources are excluded from the selection, although also acknowledged as being very important. The current version of the Toolbox has been developed to geographically cover the European Union (as per

applicable regulation) and to focus on medicinal products for human use. Although it is acknowledged that medical devices and advanced therapy products are especially relevant to rare disease research, the applicable guidelines (manufacturing) of clinical studies/trials for these investigational products are still complex and not fully harmonized in Europe and beyond. The recent implementation of the Clinical Trials Regulation[9] works to harmonize the clinical trial regulatory landscape in Europe for medicinal products. Thus, we have considered that the selected scope of medicinal products for human use was best suited for the initial version of the Toolbox, which is planned to cover other interventions [Advanced Therapy Medicinal Products (ATMP), medical devices] in the future. Within the clinical trials pathway, the breadth of the toolbox extends from the initial trial design to final trial results reporting and dissemination.

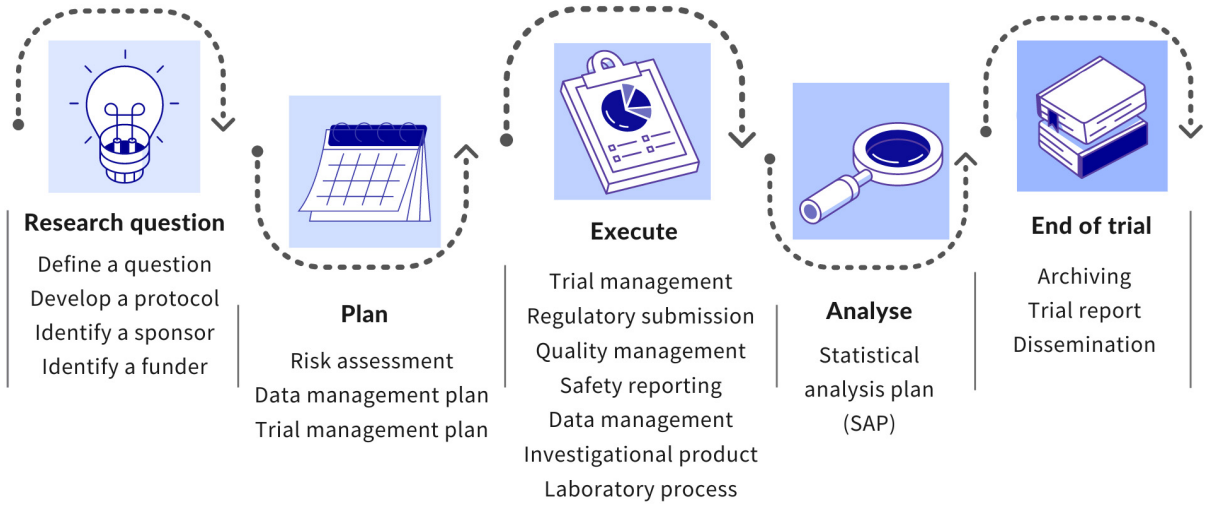

Figure 2. RD Clinical Trial Toolbox pathway. RD: Rare disease.

Step 3- identifying tools

A comprehensive (including all or nearly all elements according to the eligibility criteria) search in English was performed by a clinical research expert to identify potential tools that have been developed within publicly funded projects and/or by research infrastructures and organizations dedicated to clinical research, using the toolbox domains and activities as keywords. In addition to international and European guidelines, main sources of information include current and past research programs for rare diseases (including pediatrics) [International Rare Diseases Research Consortium (IRDiRC), European Joint Program for Rare Diseases (EJP RD), Paediatric Clinical Research Infrastructure Network (PedCRIN)], European research infrastructures [European Strategy Forum on Research Infrastructures (ESFRI) roadmap], organizations promoting patient engagement [European Patients Academy on Therapeutic Innovation (EUPATI), European Organization for Rare Diseases (EURORDIS)]. The identified tools were then matched against the above-mentioned selection criteria.

Step 4- evaluating tools

Pre-identified resources fulfilling the selection criteria are categorized under the relevant domain and activity of the clinical trial pathway. The relevance of each resource in relation to the associated domain/activity and rare disease specificity is described. Selected resources are accessible at their original location using public links. Tools developed within EU-funded projects are accessible in the long term through the EU CORDIS website[10]. In the context of this Toolbox, evaluation refers to assessing the suitability of the resources for inclusion as tools, rather than making any statement on the usefulness, quality, or robustness

of the tools eventually selected.

The Toolbox described in this manuscript aims to collate the accumulated knowledge, experience, and resources (collectively termed "tools") generated by various projects, organizing them within a well-defined clinical trials pathway to make them discoverable.

Step 5- maintenance and dissemination

The Toolbox is a living tool; hence, new or currently unidentified resources that come to light will be added as required to the appropriate domain/activity. The Toolbox is hosted on the European Clinical Research Infrastructure Network (ECRIN) website[8]. It has been labeled as an IRDiRC recognized resource and is accessible through the IRDiRC website[11].

RESULTS

The current version of the toolbox outlines 18 activities and 121 linked tools[12]. These tools are distributed across the 18 activities, with a higher concentration of resources in some areas and some gaps in others [Figure 3].

A short tutorial/instructional video has been developed to help users navigate the Toolkit[13]

The domain "execute" contains the most tools, 50% (61), followed by the domain "research question" with 39 tools.

Among the resources addressing activities linked to the "execution" of the trial, 15 are rare disease-specific, 24 address trial management, 8 provide insights on data management, and 8 cover safety reporting.

In the "research question" domain, the most represented activity is "develop a protocol" with 30 tools, of which 16 are rare disease-specific.

The Toolbox includes a variety of resources. Of these, 37% (45 resources) are guidelines, while 9% (11 resources) are recommendations [Figure 4].

Overall, 60% of all resources are relevant to any clinical trial within the scope of the toolbox, while 40% are tagged as "rare disease-specific". From the latter, 14 resources are guidelines and six resources are recommendations that have been developed to fine-tune more general guidelines considering specificities of pediatrics trials (pharmacokinetics and ethics) and rare diseases (small number and/patients' heterogeneity).

DISCUSSION

A recent analysis of six use cases[4] describes obstacles hindering the development of academic-sponsored clinical trials for rare diseases, highlighting the high number of hurdles related to operational management. Academic sponsors and investigators end up getting involved not only in the scientific aspects of the research, but also having to navigate regulatory aspects, operational coordination, and management themselves. Better information about existing resources such as research infrastructures, clinical research programs, and counseling mechanisms is needed to support and guide clinicians and sponsors through the many challenges related to the setup of academic-sponsored multinational trials. Over the past years, research, policy, regulatory initiatives and resources have been introduced to expedite drug development for rare diseases[14]. Nevertheless, these tools have been developed in the framework of different projects and for

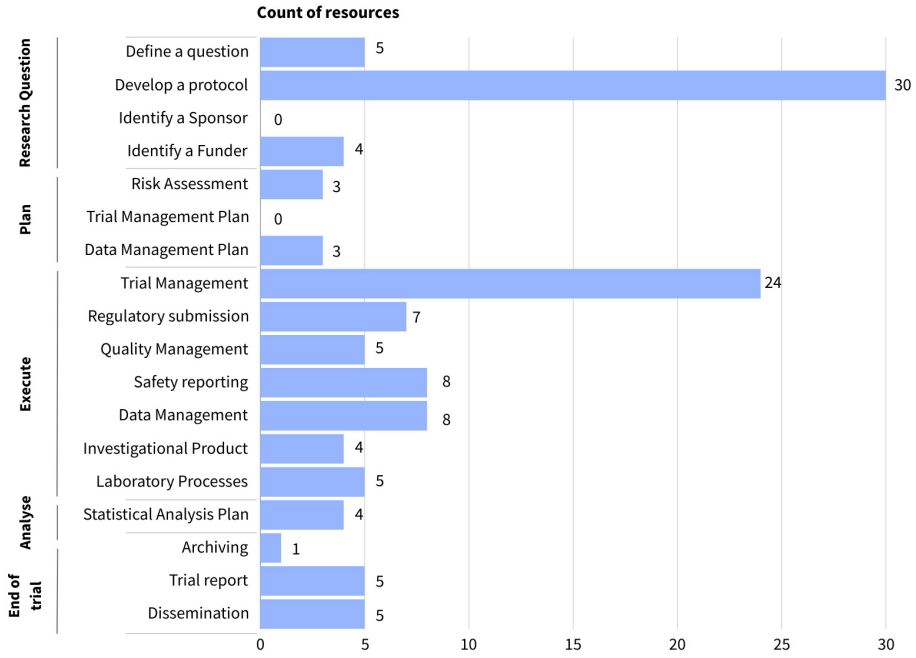

Figure 3. Number of resources in the Toolbox per domain and activity at key steps of the clinical trial pathway.

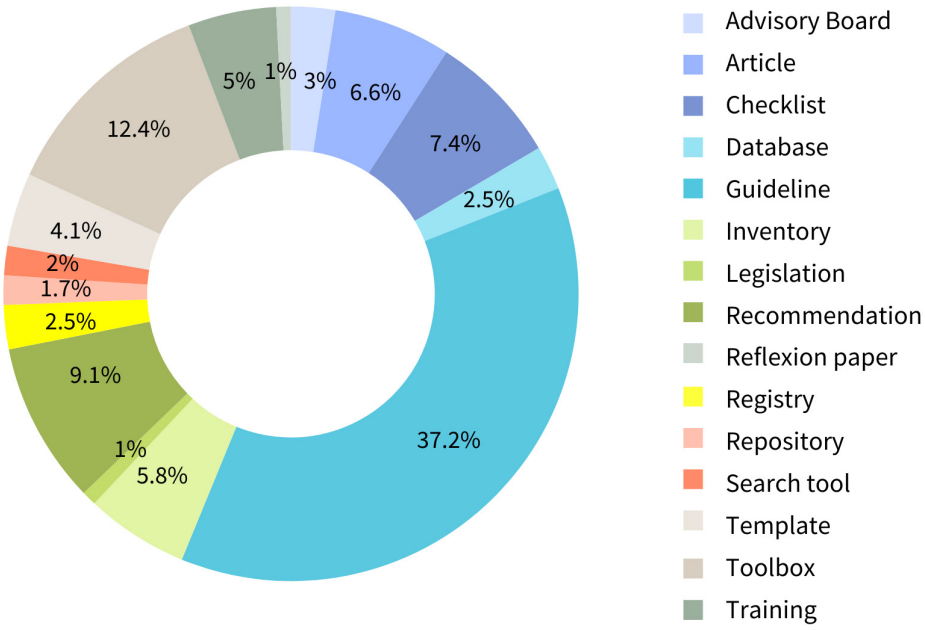

Figure 4. Representation of the different types of resources in the RD Clinical Trials Toolbox. RD: Rare disease.

different purposes; therefore, they have not yet been collated and structured to support the conduct of a clinical trial as a whole. To address this issue, the EJP RD has developed the Rare Diseases Clinical Trial Toolbox. This Toolbox aims to build a framework in which existing tools applicable to the development of clinical trials for rare diseases can be presented.

Existing toolboxes

Practical advice to researchers in designing and conducting trials has been previously published as guidelines, toolboxes, guidebooks, *etc.* Addressing different goals, they differ mostly in their scope and format.

In the USA, the NIH maintains a clinical research study investigator's toolbox[15], a Web-based informational repository for investigators and staff involved in clinical research. This toolbox contains templates, sample forms, guidelines, regulations, and informational materials to assist investigators in the development and conduct of high-quality clinical research studies in the USA. It applies a very practical approach, with a focus on providing examples of procedures and templates for general clinical research, without a specific outline for clinical trials.

In Europe, the NIHR Clinical Trials Toolkit was developed in 2003 by the UK Medical Research Council (MRC) and the UK Department of Health[16] as a tool to guide investigators embarking on a clinical trial through the regulatory and governance requirements. The NIHR Clinical Trials Toolbox is a good starting point for trialists and trial managers to ensure all legal obligations are met and presents the information as a structured Roadmap, but with a strong focus on the UK Clinical Trials Regulation and national specificities.

At the international level, but with a clear focus on a specific disease, the Malaria Clinical Trials Toolbox[17] is presented as a pathway with a step-by-step guide for researchers on how to plan, design, execute, and interpret malaria clinical trial results.

In the field of Rare Diseases, IRDiRC has developed and published the Orphan Drug Development Guidebook (ODDG)[14], a patient-focused guidebook that describes the available tools, incentives, resources, and practices for developing traditional and innovative drugs/therapies for rare diseases and how to use them best. Structured as factsheets, the ODDG guides users through the full orphan drug development process, including regulatory pathways, Health Technology Assessment (HTA) and reimbursement, early access and development practices and resources at the international level.

With a different focus, the Rare Diseases Clinical Trial Toolbox integrates some of the tools already included in these previous initiatives and incorporates them, together with other resources, in a guided, practical structure as defined by the clinical trial pathway.

The current version of the Rare Diseases Clinical Trial Toolbox is primarily focused on Clinical Trials of Investigational Medicinal Products (CTIMPs) in the EU and the regulatory environment and requirements associated with these.

Generic clinical trial tools

Although rare diseases may present unique clinical problems, some of the methodological and operational challenges to studying health outcomes are common for other disease areas. Indeed, generic guidelines relevant to rare diseases clinical trial design include the International Council for Harmonization (ICH) general guidelines[18] and the main Standard Protocol Items: Recommendations for interventional trials (SPIRIT) statement[19,20]. Fine-tuned versions for pediatrics and/or rare disease guidelines have subsequently been published as a complement to these specific guidelines. Other relevant resources, such as a clinical trials registry/metadata repository, are still missing their "rare diseases"-specific version. Thus, by presenting all relevant tools in a structured framework, the Toolbox contributes to avoiding duplication and to uncovering possible gaps.

Rare disease-specific tools

Previous works have highlighted the need for specific methodologies for enabling meaningful data generation from trials in small populations and designing outcome measures that are focused on and relevant to patients[3,21]. Indeed, several resources aiming to fill this gap include outcomes of the EU-funded projects IDEAL, ASTERIX, and INSPIRE[22-24] regarding novel trial designs or the Patient Reported Outcome Measures (PROM) repository developed by the ERICA project[25]. Other interesting initiatives aiming to provide support for rare diseases/pediatric populations include advisory boards for patient involvement (EURORDIS) and Informed Consent Guidelines.

Informed consent guidelines- a use case

For investigators interested in setting up clinical trials for medicinal products for rare diseases in the pediatric population in Europe, several complementary resources are available through the RD Toolbox:

The Informed consent form (ICF) template, developed by the EU co/funded Do-it project, covers all the information to be included in a general informed consent, complying with Clinical Trials Regulation (CTR) and General Data Protection Regulation (GDPR) rules.

The European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA's) Working Group on Ethics has developed guidelines for developing ICFs on pediatric trials. The Assent/Informed Consent Guidance for Paediatric Clinical Trials with Medicinal Products in Europe developed by Enpr-EMA's Working Group on Ethics is intended to be used as an overview tool of the contents for assent/informed consent forms for all stakeholders (such as patients, sponsors, and investigators) to support the conduct of high-quality pediatric clinical trials in Europe. This tool would serve as a complement to adapt the Do-it general template to clinical research in children.

The GA4GH and IRDiRC projects have developed the Consent Toolkit, with sample consent clauses for clinical genomics research on rare diseases.

In addition to these three complementary resources - aiming to assist researchers in the development of an appropriate ICF, other tools intend to support investigators in the informed consent process:

The PedCRIN tool "Neonatal trials and informed consent", which provides a checklist of practical points to consider when talking to parents about the possible inclusion of a neonate into a clinical trial.

The guideline "Ethical considerations for clinical trials on medicinal products conducted with minors" includes, rather than a template/clauses for ICF, recommendations on the process of informed consent, describing who, how, and when they should be involved in the process.

This use-case exemplifies how resources that were initially targeted to different users - general trialists, pediatric investigators, and rare diseases investigators - are complementary in a general scenario of rare disease clinical research but would not be easily discovered out of the framework of this Toolbox.

Activities with limited tools

As noted earlier, it is also essential to understand where there are gaps in existing support. Two activities within the "Research Question" domain have none (Identify a sponsor) or limited (Identify a funder) identified resources. Within the "Plan" domain, no resources have been identified for the activity Trial management plan.

Identify a funder - While this may be a less pertinent problem for industry-funded trials, funding has been identified as a main challenge for academic clinical trials. In the rare diseases area, the small patient population can dampen commercial interest, making the need to address this challenge even more relevant. Indeed, public funding calls for multinational clinical trials might be scarce[6], difficult to identify and/or not suitable to support specific research questions.

Funders' communication channels aim to reach investigators and trialists; however, funding is often mostly restricted to the national level, making it difficult to identify opportunities for funding or the development of multinational trials. A comprehensive database on clinical trial funders in Europe is missing. Interestingly, EU co-funded programs like ERA4Health[26] are currently working on building capacity in conducting investigator-initiated clinical studies, with plans to map the funding landscape in Europe.

The current version of the RD Clinical Trial Toolbox includes four tools on the topic. Navigating Innovation & Research Opportunities ("NIRO")[27] and research funding database "ScientifyResearch"[28] have developed open, curated, and structured research funding databases to help researchers find funding opportunities. Although the scope of both tools is general research (with NIRO more focused on infectious diseases), their search engines enable users to narrow the search at the clinical trial level.

Trial management plan - Each clinical trial management plan should be customized to the specific trial, ensuring it aligns with sponsor policies, regulatory requirements, and best practices in clinical research. We speculate that some academic sponsors might have developed sponsor-specific management trial plan templates and not considered them relevant to the general public.

Identify a sponsor - For non-industry sponsored trials, the sponsor is usually the institution to which the investigator is affiliated, a research foundation, and/or a patient organization. A selection of these academic/public institutions have previous experience and specific personnel to work as sponsor's representatives, but in other cases, the coordinating investigator assumes the sponsor's role. To our knowledge, no database compiling information about academic sponsors exists and, unlike industry sponsors, academic institutions acting as sponsors are rarely present in European forums discussing clinical trial implementation. Interestingly, the current EU clinical trials transformation initiative, Accelerating Clinical Trials in the EU (ACT EU)[29] workplan, aims to establish a process to support academic sponsors to undertake large multinational clinical trials.

Conclusions

Academia plays a key role in the development of drugs for rare diseases[5], but sponsors and investigators leading these trials face a wide range of challenges that hinder patient's access to drugs. Over the past years, public funding has supported initiatives, projects, and organizations to make gap analyses and to develop resources supporting and guiding clinicians through the many challenges associated with the setup of academic-sponsored trials. Access to these public resources is sometimes challenged by limited awareness and/or the absence of an adequate framework that makes them findable. The RD Clinical Trial Toolbox is geared to support this community and provide a framework in which they can navigate the various tools that have been made available.

DECLARATIONS

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Hilgers, Rima Nabbout, and Agustin Arasanz Duque.

Authors' contributions

Participated in the design and development of the toolbox: del Álamo M, Klager S, Kubiak C, Esdaile M
Search, curate, and update the tools: del Álamo M, Esdaile M, Zafirova B
Drafted the initial version of the manuscript: del Álamo M, Zafirova B
Created the figures: Esdaile M, Karam S
All authors participated in the discussions, read and critically revised the manuscript for important intellectual content, and approved the final version for publication.

Availability of data and materials

All data supporting the findings of this study are available in the paper and on the following websites: https://ecrin.org/rare-diseases-clinical-trials-toolbox, https://imt.ejprarediseases.org/collection/clinical-trials-toolkit/. A list of all resources can be downloaded through all the above-mentioned websites.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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